AZETIDINE DERIVATIVES USEFUL FOR THE TREATMENT OF METABOLIC AND INFLAMMATORY DISEASES

FIELD OF THE INVENTION

[0001] The present invention relates to novel compounds that antagonize GPR43 (FFAR2), a G-protein-coupled receptor that is involved in inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.

[0002] The present invention also provides methods for the production of these novel compounds, pharmaceutical compositions comprising these compounds, and methods for the prevention and/or treatment of inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases, by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0003] Fatty acids (FA) within triglycerides are the major source of energy storage in complex organisms and animals. Besides being an essential component of energy metabolism, FAs are involved in both intracellular and extracellular (autocrine and paracrine) and whole animal (endocrine) signaling processes. It is increasingly becoming evident that disturbances in FA metabolism are strongly associated with the pathogenesis of a large number of chronic conditions including the metabolic syndrome, inflammatory diseases and some cancers (Prentki *et al.*, 2008, Endocrine Review, 29(6), 647-676). Among FAs, the short chain fatty acids (SCFA, carbon lengh C_2-C_6) are mainly produced during anaerobic bacterial fermentation of fibers in the gut (Sellin *et al.*, 1999, News. Physiol. Sci, *14*, 58-64). It has been found that short chain fatty acids (SCFA) bind to GPR43 (also known as FFAR2) (Le Pouls *et al.*, 2003, The Journal of Biological Chemistry, 278, 28, 25481-25489; Brown *et al.*, 2003, The Journal of Biological Chemistry, 278, 13, 11312-11319). GPR43 expression has been shown in immune cells at least but not limited to polymorphonuclear leukocytes (PMN), purified neutrophils, peripheral blood mononuclear cells (PBMC), purified monocytes, eosinophils, and B lymphocytes ((Le Pouls *et al.*, 2003, The Journal of Biological Chemistry, 278, 28, 25481-25489; Brown *et al.*, 2003, The Journal of Biological Chemistry, 278, 13, 11312-11319; Stoddart *et al.*, 2008, Pharmacological Reviews, 60, 405-417); and also in other tissues that may play a role in the propagation of the inflammatory response (*e.g.* intestinal cells or endothelial cells, Dass *et al.*, 2007, Neurogastroenterl. Motil., 19:66-74; Karaki *et al.*, 2006, Cell Tissue Res., 324/353-360). Recently, short chain fatty acids (SCFAs) have been shown to play a central role in the development of inflammatory conditions such as colitis, arthritis and asthma in a GPR43-dependent manner (K.M. Maslowski *et al.*, 2009, Nature, *461*, 1282-1287; C. Sina *et al.*, 2009, The Journal of Immunology, *183*:7514-7522). GPR43 knock-out (KO) mice were protected against chronic dextran sodium sulfate (DSS)-induced colitis. In a chronic DSS model, GPR43 KO mice presented less severe colon inflammation than wild-type (WT) mice, with a reduction of infiltrated

polymorphonuclear leukocytes (PMN). The activity of granulocyte-specific MPO (myeloperoxidase) was reduced in GPR43 KO colon compared to WT colon, as well as TNFα levels. SCFA have been shown to induce neutrophil migration both *in vitro* with isolated neutrophilic granulocytes and *in vivo* in an inflamed air pouch model. GPR43 KO isolated neutrophilic granulocytes lost the ability to migrate in response to SCFAs, suggesting key function of GPR43 is neutrophilic granulocytes (C. Sina *et al.*, 2009, The Journal of Immunology, *183*:7514-7522).

[0004] GPR43 KO mice were protected from high fat diet (HFD)-induced obesity and dyslipidemia (Bjursell et al., 2011, Am. J. Physiol. Endocrinol. Metab. 300:(11) E211-E220). GPR43 KO mice presented higher lean body mass and lower body fat mass than compared to WT mice. Plasma adiponectin levels were increased in GPR43 KO mice as compared to littermate controls. The liver of GPR43 KO mice showed reduced triglyceride content. Moreover, insulin sensitivity was improved by GPR43 gene ablation as GPR43 KO mice displayed lower insulin levels, but normal glucose levels, in the oral glucose tolerance test. In addition the reduced macrophage content in GPR43 KO adipose tissue compared to WT mice indicated a protection from HFD induced adipose inflammation. Finally, GPR43 KO mice were also found to be protected from HFD-induced hypercholesterolemia. The improved metabolic profile observed under HFD in GPR43-deficient mice is likely explained, at least in part, by an increase in energy expenditure.

[0005] GPR43 was recently implicated in carcinogenesis (Hatanaka et al., 2010, Cancer Sci., 101:54-59). GPR43 expression (both mRNA and protein) was increased in digestive tract cancer tissues compared to normal digestive tract tissues. 3T3 cells infected with recombinant retrovirus encoding GPR43 and treated with acetate shown a pronounced increase in proliferation. 3T3 cells infected with recombinant retrovirus encoding GPR43 were tested for tumorigenicity in athymic nude mice. Tumor formation was apparent with 4 tumors developped for 4 injections, similar to 3T3 cells infected with recombinant retrovirus encoding v-Ras (8/8 tumor/injection), but in opposition to 3T3 cells infected with empty virus (0/8 tumor/injection).

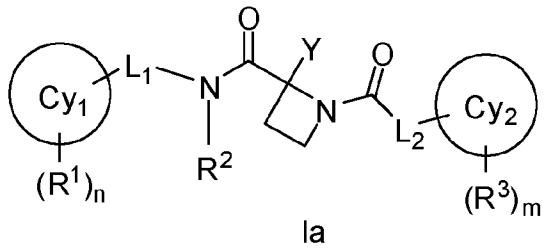
[0006] Therefore, the present invention provides novel compounds, processes for their preparation and their use in the preparation of a medicament for the treatment of inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.

SUMMARY OF THE INVENTION

[0007] The present invention relates to novel compounds that antagonize GPR43 and that are potentially useful for the treatment of inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell

functions, cardiometabolic diseases, and/or proliferative diseases, by administering a compound of the invention.

[0008] In a first aspect of the invention, a compound of the invention is provided having a Formula Ia:



Ia

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is

- C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano), or
- C_{1-4} alkenyl comprising 1 double bond;

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,

- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more groups independently selected from halo or phenyl), C_{1-6} thioalkoxy, phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, C(=O)-C_{1-4} alkoxy and CN);

R^4 is

- OH,
- C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- $NR^{4a}R^{4b}$, or
- $NHSO_2R^{4c}$;

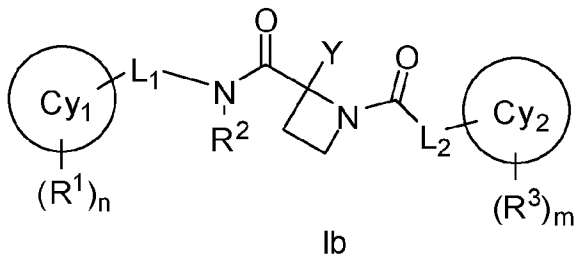
each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2.

[0009] In a further aspect of the invention, a compound of the invention is provided having a Formula Ib:



Ib

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano);

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups;

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more groups independently selected from halo or phenyl), phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, $C(=O)$-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- $-NR^{4a}R^{4b}$, or
- $-NHSO_2R^{4c}$;

each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2.

[0010] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. Moreover, a compound of the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein is pharmaceutically acceptable as prepared and used. In this aspect of the invention, the pharmaceutical composition may additionally comprise further active ingredients suitable for use in combination with a compound of the invention.

[0011] In another aspect of the invention, this invention provides novel compounds of the invention for use in therapy.

[0012] In a further aspect of the invention, this invention provides a method of treating a mammal susceptible to or afflicted with a condition from among those listed herein, and particularly, such condition as may be associated with aberrant GPR43 activity and/or aberrant GPR43 expression and/or distribution of GPR43, for example inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[0013] In a further aspect, the present invention provides a compound of the invention for use in the treatment or prevention of a condition selected from those listed herein, particularly such conditions as may be associated with aberrant GPR43 activity and/or aberrant GPR43 expression and/or distribution of GPR43 such as inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.

[0014] In additional aspects, this invention provides methods for synthesizing a compound of the invention, with representative synthetic protocols and pathways disclosed herein.

[0015] Accordingly, it is a principal object of this invention to provide a compound of the invention, which can modify the activity of GPR43 and thus prevent or treat any conditions that may be causally related thereto.

[0016] It is further an object of this invention to provide a compound of the invention in order to treat or alleviate conditions or diseases or symptoms of same, such as inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases, that may be causally related to the activity and / or expression and/or distribution of GPR43.

[0017] A still further object of this invention is to provide pharmaceutical compositions that may be used in the treatment or prevention of a variety of disease states, including the diseases associated with aberrant GPR43 activity and/or aberrant GPR43 expression and/or distribution of GPR43 such as

inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.

[0018] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0019] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0020] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term 'substituted' is to be defined as set out below. It should be further understood that the terms 'groups' and 'radicals' can be considered interchangeable when used herein.

[0021] The articles 'a' and 'an' may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example 'an analogue' means one analogue or more than one analogue.

[0022] 'Alkyl' means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, and 1,2-dimethylbutyl. Particular alkyl groups have between 1 and 4 carbon atoms.

[0023] 'Alkoxy' refers to the group O-alkyl where the alkyl group has the specified number of carbon atoms. Particularly alkoxy refers to $-O-C_1-C_6$ alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0024] 'Amino' refers to the radical $-NH_2$.

[0025] 'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, mono-cyclic or poly-cyclic that includes the number of ring members specified. Particular aryl groups have from 6 to 10 ring members. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

[0026] 'Carbamoyl or amido' refers to the radical $-C(O)NH_2$.

[0027] 'Carboxy' refers to the radical -C(O)OH.

[0028] 'Cycloalkyl' refers to cyclic non-aromatic hydrocarbyl groups having the number of carbon atoms specified. Particular cycloalkyl groups have from 3 to 7 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0029] 'Cyano' refers to the radical -CN.

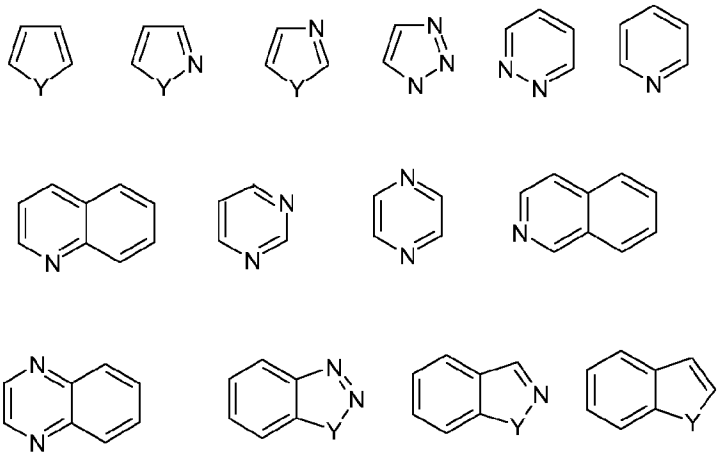
[0030] 'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[0031] 'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, e.g. heteroalkyl, cycloalkyl, e.g. heterocycloalkyl, aryl, e.g. heteroaryl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0032] 'Heteroaryl' means an aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms and the number of ring members specified. Particular heteraryl groups have 5 to 10 ring members, or 5 to 6 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and

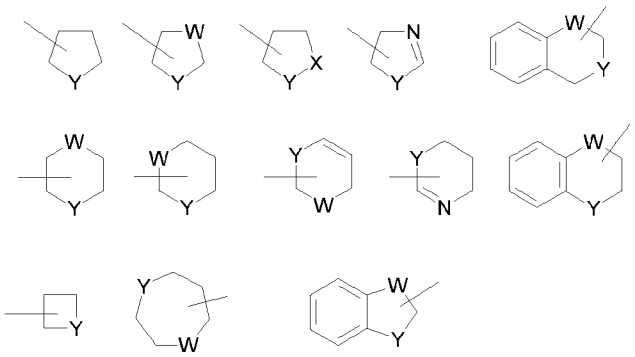
pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[0033] Examples of representative heteroaryls include the following:



wherein each Y is selected from >C=O, N, O and S.

[0034] As used herein, the term 'heterocycloalkyl' refers to a stable heterocyclic non-aromatic ring and/or including rings containing one or more heteroatoms independently selected from N, O and S, fused thereto wherein the group contains the number of ring members specified. Particular heterocycloalkyl groups have 4-10 ring members or 5 to 7 ring members, or 5 to 6 ring members. The heterocycloalkyl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heterocycloalkyl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heterocycloalkyl ring contains at least one ring nitrogen atom. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CH_2, NH, O and S; and each Y is selected from NH, O, CO, SO_2, and S.

[0035] 'Hydroxy' refers to the radical -OH.

[0036] 'Nitro' refers to the radical $-NO_2$.

[0037] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

[0038] 'Thiol' refers to the group -SH.

[0039] 'Thioalkoxy' refers to the group $-SR^{10}$ where R^{10} is an alkyl group with the number of carbon atoms specified. Particular thioalkoxy groups are where R^{10} is a C_1-C_6 alkyl. Particular alkoxy groups are thiomethoxy, thioethoxy, n-thiopropoxy, thioisopropoxy, n-thiobutoxy, tert-thiobutoxy, sec-thiobutoxy, n-thiopentoxy, n-thiohexoxy, and 1,2-dimethylthiobutoxy. Particular thioalkoxy groups are lower thioalkoxy, i.e. with between 1 and 6 carbon atoms. Further particular thioalkoxy groups have between 1 and 4 carbon atoms.

[0040] As used herein, term 'substituted with one or more' refers to one to four substituents. In one embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

[0041] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[0042] 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0043] 'Pharmaceutically acceptable salt' refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid,

pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[0044] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0045] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention,which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0046] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0047] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[0048] 'Therapeutically effective amount' means the amount of a compound of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0049] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[0050] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0051] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[0052] As used herein the term 'inflammatory condition(s)' refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, gout, allergic airway disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and related diseases involving cartilage, such as that of the joints. Partcicularly the term refers to rheumatoid arthritis, osteoarthritis, allergic airway disease (e.g. asthma) and inflammatory bowel diseases.

[0053] As used herein, the term 'infectious diseases' refers to bacterial infectious diseases and includes but is not limited to conditions such as sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving Yersinia, Salmonella, Chlamydia, Shigella, or enterobacteria species.

[0054] As used herein the term 'autoimmune disease(s)' refers to the group of diseases including obstructive airways disease (including conditions such as COPD (Chronic obstructive pulmonary disease)), asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantily asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), multiple sclerosis, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, psoriasis, systemic lupus erythematosis, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[0055] As used herein, the term 'diseases involving impairment of immune cell functions' includes conditions with symptoms such as recurrent and drawn out viral and bacterial infections, and slow

recovery. Other invisible symptoms may be the inability to kill off parasites, yeasts and bad bacteria in the intestines or throughout the body.

[0056] As used herein the term 'cardiometabolic disorders' refers to diseases or disorders of the internal body chemistry that triggers the body's metabolism. The term metabolic disorders usually does not include hormonal disorders or endocrine disorders which refer to the interactions between body glands and hormones, and includes but is not limited to conditions such as dyslipidemia, hypercholesterolemia, hypertriglyceridemia, Obesity, metabolic syndrome, atherosclerosis, Type II diabetes, pre-diabetes, insulin resistance, heart disease, stroke, hypertension, perivascular disease.

[0057] As used herein the term 'proliferative disease(s)' refers to conditions such as cancer, myeloproliferative disorders (e.g. polycythemia vera, essential thrombocytosis and myelofibrosis), leukemia, multiple myeloma, psoriasis, restenosis, sclerodermitis or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

[0058] As used herein, the term 'cancer' refers to a malignant or benign growth of cells in skin or in body organs, for example but without limitation, breast, prostate, lung, kidney, pancreas, stomach or bowel. A cancer tends to infiltrate into adjacent tissue and spread (metastasise) to distant organs, for example to bone, liver, lung or the brain. As used herein the term cancer includes both metastatic tumour cell types, such as but not limited to, melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, and mastocytoma and types of tissue carcinoma, such as but not limited to, colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, renal cancer, gastric cancer, glioblastoma, primary liver cancer, ovarian cancer, prostate cancer and uterine leiomyosarcoma.

[0059] As used herein the term 'leukemia' refers to neoplastic diseases of the blood and blood forming organs. Such diseases can cause bone marrow and immune system dysfunction, which renders the host highly susceptible to infection and bleeding. In particular the term leukemia refers to acute myeloid leukaemia (AML) and acute lymphoblastic leukemia (ALL).

[0060] As used herein the term 'degenerative disorders' refers to is a disease in which the function or structure of the affected tissues or organs will progressively deteriorate over time, whether due to normal bodily wear or lifestyle choices such as exercise or eating habits. Degenerative disorders include for example but without limitation, Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, Alzheimer's disease, Parkinson's disease, multiple system atrophy, Niemann Pick disease, atherosclerosis, progressive supranuclear palsy, cancer, Tay-Sachs disease, diabetes, heart disease, keratoconus, inflammatory bowel disease (IBD), prostatitis, osteoarthritis, osteoporosis, rheumatoid arthritis, Huntington's disease, or chronic traumatic encephalopathy. In particular, herein the term 'degenerative disorders' refers to diabetesinflammatory bowel disease (IBD), osteoarthritis, osteoporosis, or rheumatoid arthritis.

[0061] 'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, and the solvates of the pharmaceutically acceptable salts where the

context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0062] When ranges are referred to herein, for example but without limitation, C_{1-6} alkyl, the citation of a range should be considered a representation of each member of said range.

[0063] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particular such prodrugs are the C_1 to C_8 alkyl, , and substituted or unsubstitutedC_{6-10} aryl, esters of the compounds of the invention.

[0064] As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0065] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0066] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[0067] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the

molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[0068] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[0069] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

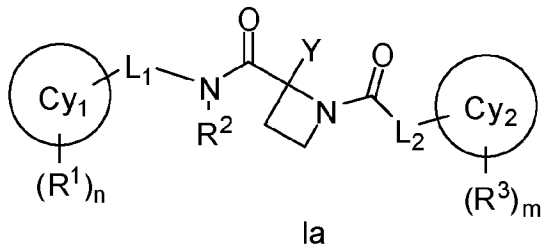
[0070] The compounds of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

[0071] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

THE COMPOUNDS

[0072] The present invention relates to novel compounds that antagonize GPR43 and that may be potentially useful for the treatment of inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention and methods for treating diseases involving inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases by administering a compound of the invention. A compound of the invention is an inhibitor of GPR43.

[0073] In a first aspect of the invention, a compound of the invention is provided having a Formula Ia:



Ia

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is

- C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano), or
- C_{1-4} alkenyl comprising 1 double bond;

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more groups independently selected from halo or phenyl), C_{1-6} thioalkoxy, phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, $C(=O)$-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),

- $-NR^{4a}R^{4b}$, or
- $-NHSO_2R^{4c}$;

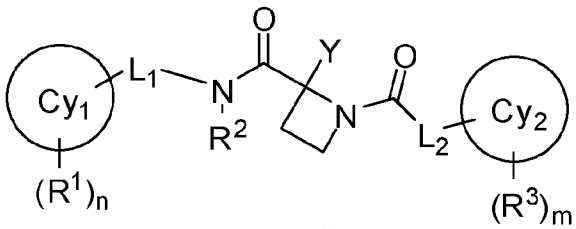
Each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2.

[0074] In a further aspect of the invention, a compound of the invention is disclosed having a Formula Ib:



Ib

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano);

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,

- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more groups independently selected from halo or phenyl), phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, $C(=O)$-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- $-NR^{4a}R^{4b}$, or
- $-NHSO_2R^{4c}$;

Each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

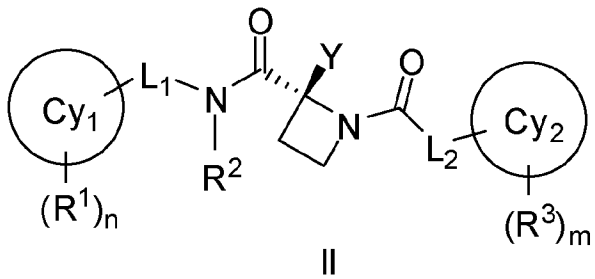
R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2.

[0075] In one embodiment, a compound of the invention is according to Formula Ia or Ib, wherein L_2 is a single bond, NR^e or CR^cR^d.

[0076] In one embodiment, a compound according to Formula Ia or Ib is according to Formula II:



II

,

wherein L_1, L_2, R^1, R^2, R^3, Cy^1, Cy^2, R^a, R^b, R^c, R^d, R^e, Y, n, and m are as described above.

[0077] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein L_1 is a single bond.

[0078] In another embodiment, a compound of the invention is according to Formula Ia, Ib or II, wherein L_1 is CR^aR^b, and wherein each R^a and R^b group is independently selected from H and C_{1-4} alkyl. In a particular embodiment, each R^a and R^b group is independently selected from H, Me, Et, Pr, and iPr.

[0079] In another embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein L_1 is CR^aR^b, and wherein R^a is H or C_{1-4} alkyl and R^b is H. In a particular embodiment, R^a is H, Me, Et, or Pr, and R^b is H. In more particular embodiment, R^a and R^b are both H.

[0080] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Y is C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one ore more halo), C_{1-4} alkoxy, halo or cyano). In a particular embodiment, Y is C_{1-4} alkyl optionally substituted with one group selected from fluoro, OH, and phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo or cyano).

[0081] In another embodiment, compound of the invention is according to Formula Ia, Ib, or II, wherein Y is C_{1-4} alkyl substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one ore more halo), C_{1-4} alkoxy, halo or cyano). In a particular embodiment, Y is C_{1-4} alkyl substituted with one group selected from fluoro, OH, and phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one ore more halo), C_{1-4} alkoxy, halo or cyano). In a more particular embodiment, Y is Me, Et, Pr or iPr, substituted with one or more groups selected from fluoro, OH, and phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one ore more halo), C_{1-4} alkoxy, halo or cyano). In a further particular embodiment, Y is Me, substituted with OH, or phenyl (optionally substituted with one or more C_{1-4} alkyl (optionally substituted with one ore more halo), C_{1-4} alkoxy, halo or cyano). In a most particular embodiment, Y is $-CH_2-Ph$ or $-CH_2-OH$. In a further most particular embodiment, Y is $-CH_2-Ph$.

[0082] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Y is C_{1-4} alkyl. In a most particular embodiment, Y is Me, Et, Pr, or iPr. In a further most particular embodiment, Y is Me.

[0083] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Cy_1 is C_{6-10} aryl. In a particular embodiment, Cy_1 is phenyl or naphthyl. In a most particular embodiment, Cy_1 is phenyl.

[0084] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein the subscript n is 1 or 2. In a particular embodiment, the subscript n is 1 or 2, and each R^1 group is independently selected from halo, and C_{1-4} alkyl optionally substituted with one or more halo. In a more particular embodiment, the subscript n is 1 or 2, and each R^1 group is independently selected from F, Cl, Me, Et, iPr, i-Bu, t-Bu and CF_3.

[0085] In another embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein the subscript n is 1. In a particular embodiment, the subscript n is 1, and each R^1 group is independently selected from halo, and C_{1-4} alkyl optionally substituted with one or more halo. In a more particular embodiment, the subscript n is 1, and R^1 group is independently selected from F, Cl, Me, Et, iPr, and CF_3. In a most particular embodiment, the subscript n is 1, and R^1 group is Cl or CF_3. In a further most particular embodiment, the subscript n is 1 and R^1 group is Cl.

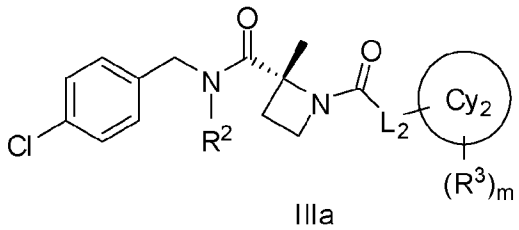
[0086] In another embodiment, a compound of the invention is according to Formula Ia, Ib, or II, the subscript n is 1, and R^1 group is OCF_3.

[0087] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Cy_1 is 5-10 membered heteroaryl. In a particular embodiment, Cy_1 is benzofuranyl, benzothiophenyl, indazolyl, indolyl, or benzothiazolyl.

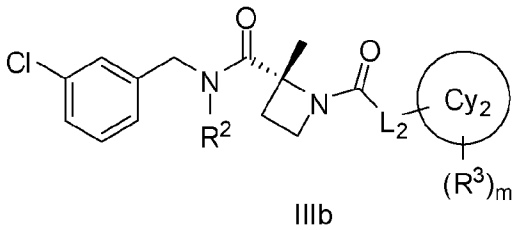
[0088] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Cy_1 is C_{6-10} aryl, and the subscript n is 0. In a particular embodiment, Cy_1 is phenyl or naphthyl, and the subscript n is 0.

[0089] In one embodiment, a compound of the invention is according to Formula Ia, Ib, or II, wherein Cy_1 is 5-10 membered heteroaryl, and the subscript n is 0. In a particular embodiment, Cy_1 is benzofuranyl, benzothiophenyl, indazolyl, indolyl, or benzothiazolyl, and the subscript n is 0.

[0090] In one embodiment, a compound of the invention is according to Formula Ia, Ib or II, wherein the compound is according to Formula IIIa or IIIb:



IIIa



IIIb

,

wherein R^2, L_2, Cy_2, R^3 and m are as described in any one of the embodiments above.

[0091] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is H.

[0092] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups. In a particular embodiment, R^2 is C_{1-4} alkyl optionally substituted with one R^{2a} group. In a particular embodiment, R^2 is C_{1-4} alkyl. In a more particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu. In an even more particular embodiment, R^2 is Me.

[0093] In a further embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group. In a more particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one or more R^{2a} groups. In a most particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one R^{2a} group.

[0094] In an even further embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is OH, CN, or C_{1-6} alkoxy. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is OH, CN, or C_{1-6} alkoxy. In a more particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one or more R^{2a} groups, wherein R^{2a} is OH, CN, or C_{1-6} alkoxy. In a most particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one R^{2a} group, wherein R^{2a} is OH, CN, or C_{1-6} alkoxy. In an even most particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one R^{2a} group, wherein R^{2a} is OH, CN, or OMe. In a further even most particular embodiment, R^2 is $-CH_2$-CN, $-(CH_2)_2$-OH, $-(CH_2)_2$-CN,$-(CH_2)_2$-OMe, $-CH_2-CH(CH_3)$-OH, or $-(CH_2)_3$-OH.

[0095] In an even further embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is COR^4. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$. In a more particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$. In a most particular embodiment, R^2 is Me, Et, Pr, iPr, Bu, or iBu, each of which is substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$.

[0096] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is $C(=O)R^4$, wherein R^4 is OH, or C_{1-6} alkoxy. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$, wherein R^4 is OH, or C_{1-6} alkoxy. In a more particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$, wherein R^4 is OH, or OMe, or OEt. In an even more particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $-C(=O)R^4$, wherein R^4 is OH.

[0097] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is $C(=O)R^4$, and R^4 is $NR^{4a}R^{4b}$. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$, and R^4 is $NR^{4a}R^{4b}$.In a particular embodiment, each of R^{4a} and R^{4b} is independently selected from H, C_{3-7} cycloalkyl or C_{1-4} alkyl. In a most particular embodiment, each of R^{4a} and R^{4b} is independently selected from H, cyclopropyl, Me, Et, Pr, or iPr.

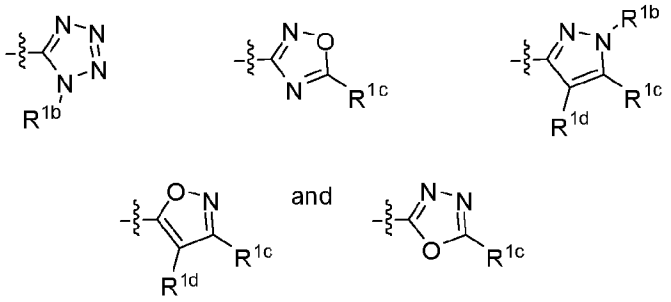
[0098] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is $C(=O)R^4$, wherein R^4 is $NHSO_2R^{4c}$. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $C(=O)R^4$, and R^4 is $NHSO_2R^{4c}$. In a more particular embodiment, R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo). In a most particular embodiment, R^{4c} is Me, phenyl or CF_3.

[0099] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is

$S(O)_2R^4$. In a particular embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $S(O)_2R^4$. In a more particular embodiment, R^4 is *N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, or oxo). In a most particular embodiment, R^4 is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is optionally substituted with one or more independently selected C_{1-6} alkyl, or oxo.

[00100] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more independently selected R^{2a} groups, wherein R^{2a} is $S(O)_2R^4$. In a particular embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one R^{2a} group, wherein R^{2a} is $S(O)_2R^4$. In a more particular embodiment, R^4 is $NR^{4a}R^{4b}$, wherein each of R^{4a} and R^{4b} is independently selected from H, or C_{1-4} alkyl. In a most particular embodiment, R^4 is $-NH_2$, NHMe, or NMe_2.

[00101] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one or more 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl). In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one group selected from:



,

wherein R^{1b} is H, or C_{1-4} alkyl; R^{1c} is OH, or C_{1-4} alkoxy; and R^{1d} is H, F, or C_{1-4} alkyl.

[00102] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^{1b} is H, Me, or Et.

[00103] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^{1c} is OH, OMe, or OEt.

[00104] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^{1d} is H, F, Me, or Et.

[00105] In a particular embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein R^2 is $-CH_2$-COOH, $-CH_2$-COOMe, $-CH_2$-COOEt, $-(CH_2)_2$-COOH, $-(CH_2)_2$-COOMe,$-(CH_2)_3$-COOH, $-(CH_2)_3$-SO_2NH_2, or $-(CH_2)_3$-SO_2NHMe. In a more particular embodiment, R^2 is $-(CH_2)$-COOH, $-(CH_2)_3$-COOH, $-(CH_2)_3$-SO_2NH_2, or $-(CH_2)_3$-SO_2NHMe.

[00106] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein R^2 is $-CH_2$-CN, $-(CH_2)_2$-CN, or $-(CH_2)_3$-CN.

[00107] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein R^2 is $-CH_2$-CONHMe, $-(CH_2)_2$-CONHMe, or $-(CH_2)_3$-CONHMe.

[00108] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein R^2 is $-CH_2$-$CONMe_2$, $-(CH_2)_2$-$CONMe_2$, or $-(CH_2)_3$-$CONMe_2$.

[00109] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein R^2 is $-CH_2$-OMe, $-(CH_2)_2$-OMe, or $-(CH_2)_3$-OMe.

[00110] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein R^2 is $-CH_2$-$NHSO_2Me$, $-(CH_2)_2$-$NHSO_2Me$, or $-(CH_2)_3$-$NHSO_2Me$.

[00111] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein Cy_2 is C_{6-10} aryl. In a particular embodiment, Cy_2 is phenyl, or naphthalene. In a more particular embodiment, Cy_2 is phenyl.

[00112] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein Cy_2 is 5-10 membered heteroaryl. In a particular embodiment, Cy_2 is thiophenyl, benzothiophenyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl, or indolyl.

[00113] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein the subscript m is 1 or 2. In a particular embodiment, the subscript m is 1 or 2, and each R^3 group is independently selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more halo, or phenyl), phenyl or CN. In a more particular embodiment, the subscript m is 1 or 2, and each R^3 group is independently selected from F, Cl, Br, Me, CF_3, and OMe.

[00114] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein the subscript m is 1. In a particular embodiment, the subscript m is 1, and R^3 group is a phenyl optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), CN, C_{1-6} alkoxy, and $C(=O)$-C_{1-4} alkoxy. In a more particular embodiment, the subscript m is 1, and R^3 is selected from phenyl, 4-F-phenyl, 3-Cl-phenyl, 3-CN-phenyl, 4-CN-phenyl, 4-OMe-phenyl, 2-Me-phenyl, 2-CF_3-phenyl, and 3-COOMe-phenyl.

[00115] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein the subscript m is 0.

[00116] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein L_2 is a single bond.

[00117] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein L_2 is $-CR^cR^d$-, wherein each of R^c and R^d are independently selected from H, or C_{1-4} alkyl. In a particular embodiment, L_2 is $-CR^cR^d$-, and each of R^c and R^d are independently selected from H, Me, and Et. In another particular embodiment, L_2 is $-CR^cR^d$-, wherein R^c is H, and R^d is selected from H, or C_{1-4} alkyl. In a more particular embodiment, L_2 is $-CR^cR^d$-, wherein R^c is H, and R^d is selected from H, Me, and Et. In a most particular embodiment, L_2 is $-CH_2$-.

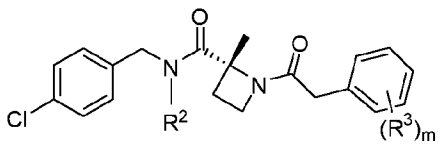
[00118] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein L_2 is $-CR^cR^d$-, wherein R^c and R^d together with the carbon on which they are attached, form a C_{3-7} cycloalkyl ring. In a particular embodiment, L_2 is $-CR^cR^d$-, wherein R^c and R^d together with the carbon on which they are attached, form a cyclopropyl ring.

[00119] In one embodiment, a compound of the invention is according to Formula Ia-IIIb, wherein L_2 is .

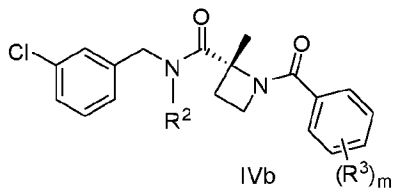
[00120] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein L_2 is –O-.

[00121] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein L_2 is $-NR^e$, wherein R^e is C_{1-4} alkyl. In a particular embodiment, R^e is Me, Et, Pr, iPr. In a more particular embodiment, R^e is Me.

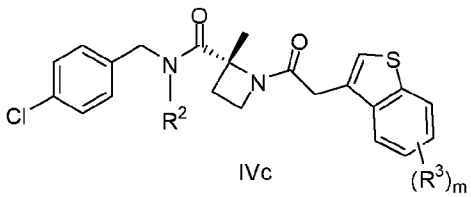
[00122] In one embodiment, a compound of the invention is according to any one of Formulae Ia-IIIb, wherein the compound is according to Formula IVa, IVb, IVc, or IVd:



IVa

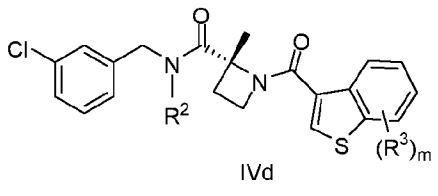


IVb



IVc

or



IVd

,

wherein R^2, R^3, and m are as described in any one of the embodiments above.

[00123] In one embodiment, a compound of the invention is according to Formula IVa-IVd, wherein the subscript m is 1 and R^3 is Cl.

[00124] In one embodiment, a compound of the invention is according to Formula IVa-IVd, wherein the subscript m is 0.

[00125] In one embodiment, a compound of the invention is according to any one of Formulae I-IVd, wherein R^2 is $-CH_2$-COOH, $-(CH_2)_2$-COOH, or $-(CH_2)_3$-COOH.

[00126] In one embodiment, a compound of the invention is selected from the following compounds:

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide,

2-(4-Chloro-benzylcarbamoyl)-2-methyl-azetidine-1-carboxylic acid 4-chloro-phenyl ester,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-phenyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-methyl-benzyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethyl-benzyl)-amide,

1-[2-(3-Iodo-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(2-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(4-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,4-Difluoro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

2-Methyl-1-(2-naphthalen-2-yl-acetyl)-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(4'-Fluoro-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(2-Benzyloxy-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(2-Iodo-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Difluoro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-(2-Biphenyl-4-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3'-Chloro-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3'-Cyano-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(4'-Methoxy-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(4'-Cyano-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

2-Methyl-1-[2-(2'-methyl-biphenyl-4-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

methyl 4'-(2-(2-((4-chlorobenzyl)(methyl)carbamoyl)-2-methylazetidin-1-yl)-2-oxoethyl)biphenyl-3-carboxylate,

1-(2-Biphenyl-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

2-Methyl-1-[2-(2'-trifluoromethyl-biphenyl-3-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3'-Chloro-biphenyl-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-bromo-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-isopropyl-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-tert-butyl-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2,4-dimethyl-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-isobutyl-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-ethyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2,4-dichloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethoxy-benzyl)-amide,

1-[2-(3'-Methoxy-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-bromo-benzyl)-methyl-amide,

1-[2-(2,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-3-fluoro-benzyl)-methyl-amide,

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-methyl-benzylamide,

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-trifluoromethyl-benzylamide,

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethyl-benzyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyclopropyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-ethyl)-amide,

((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid methyl ester,

((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid,

N-(4-chlorobenzyl)-N,2-dimethyl-1-(3-methylbenzofuran-2-carbonyl)azetidine-2-carboxamide,

1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 3-methyl-benzylamide,

N-(4-chlorobenzyl)-1-(1-(2,4-dichlorophenyl)cyclopropanecarbonyl)-2-methylazetidine-2-carboxamide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methylcarbamoylmethyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-dimethylcarbamoylmethyl-amide,

(S)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methoxy-ethyl)-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid ethyl ester,

[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(3-methyl-benzyl)-amino]-acetic acid,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-acetic acid methyl ester,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid,

3-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester,

4-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid methyl ester,

4-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid,

3-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-acetic acid,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-ethyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyanomethyl-amide,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-methyl-benzyl)-amino]-acetic acid,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-hydroxy-propyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-carbamoyl-ethyl)-(4-chloro-benzyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-propyl)-amide,

(R)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester,

(R)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid carbamoylmethyl-(4-chloro-benzyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(1H-tetrazol-5-ylmethyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-cyano-ethyl)-amide,

[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid,

[[1-(2-Benzo[d]isoxazol-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(isopropylcarbamoyl-methyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyclopropylcarbamoylmethyl-amide,

((4-Chloro-benzyl)-{(S)-1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid,

((4-Chloro-benzyl)-{(R)-1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-morpholin-4-yl-2-oxo-ethyl)-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyanomethyl-amide,

[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-hydroxymethyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid ethyl ester,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide,

2-Methyl-1-[2-(1-methyl-1H-indol-3-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(5-Chloro-benzo[b]thiophen-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(5-Methyl-benzo[b]thiophen-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-oxo-2-trifluoromethanesulfonylamino-ethyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methanesulfonylamino-2-oxo-ethyl)-amide,

[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indol-6-ylmethyl)-amino]-acetic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-cyano-propyl)-amide,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-cyano-propyl)-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(1H-tetrazol-5-yl)-propyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-acetylamino-ethyl)-(4-chloro-benzyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methanesulfonylamino-ethyl)-amide,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-benzenesulfonylamino-2-oxo-ethyl)-(4-chloro-benzyl)-amide,

1-(2-Benzo[b]thiophen-4-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(4-Fluoro-naphthalen-1-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-amide,

1-(2-Benzo[b]thiophen-2-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(1H-tetrazol-5-yl)-ethyl]-amide,

[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indazol-6-ylmethyl)-amino]-acetic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,3,4]oxadiazol-2-ylmethyl)-amide,

1-(Benzo[b]thiophene-5-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide,

4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indol-6-ylmethyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethyl)-amide,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-1H-pyrazol-3-yl)-ethyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-1-methyl-1H-pyrazol-3-yl)-ethyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-ethoxy-1-methyl-1H-pyrazol-3-yl)-ethyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,3,4]oxadiazol-2-yl)-ethyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-ethoxy-1H-pyrazol-3-yl)-ethyl]-amide,

1-(benzofuran-5-carbonyl)-N-(4-chlorobenzyl)-N,2-dimethylazetidine-2-carboxamide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide,

4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indazol-6-ylmethyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[4-(4-methyl-piperazin-1-yl)-4-oxo-butyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-dimethylcarbamoyl-propyl)-amide,

1-(2-naphthoyl)-N-(4-chlorobenzyl)-N,2-dimethylazetidine-2-carboxamide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid,

4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-hydroxy-isoxazol-5-ylmethyl)-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-1H-pyrazol-3-ylmethyl)-amide,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-5-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid,

4-[[1-(2-Benzo[b]thiophen-4-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid,

1-(benzo[b]thiophene-5-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-morpholino-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-morpholino-4-oxobutyl)azetidine-2-carboxamide,

1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide,

ethyl 4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(4-(trifluoromethyl)benzyl)azetidine-2-carboxamido)butanoate,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester,

ethyl 4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoate,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid ethyl ester,

4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide,

3-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester,

3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid ethyl ester,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid ethyl ester,

3-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid,

3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide,

4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(4-trifluoromethyl-benzyl)-amino]-butyric acid,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid,

4-((3-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid,

4-(Benzofuran-6-ylmethyl-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid,

4-{[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid,

4-{[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid,

4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester,

1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide,

4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2,4-dimethoxy-benzylsulfamoyl)-propyl]-amide,

3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide,

3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid methyl ester,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid methyl ester,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid methyl ester,

3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid,

4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-imidazo[1,2-a]pyridin-7-ylmethyl-amino}-butyric acid,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2,4-dimethoxy-benzylsulfamoyl)-propyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(morpholine-4-sulfonyl)-ethyl]-amide,

1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(4-methyl-piperazine-1-sulfonyl)-propyl]-amide,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide,

4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzothiazol-5-ylmethyl-amino}-butyric acid,

4-{[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-benzothiazol-5-ylmethyl-amino}-butyric acid,

4-(Benzothiazol-5-ylmethyl-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-(3-sulfamoyl-propyl)-amide,

3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid,

1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide,

4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-sulfamoyl-ethyl)-amide,

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methylsulfamoyl-ethyl)-amide,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-phenyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-ethyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 3,5-dimethyl-phenyl ester,

4-{[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-[(R)-1-(4-chloro-phenyl)-ethyl]-amino}-butyric acid,

4-{[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-[(S)-1-(4-chloro-phenyl)-ethyl]-amino}-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-benzyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

4-{(4-Chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid,

4-((4-Chloro-benzyl)-{1-[(3,5-dimethyl-phenyl)-methyl-carbamoyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid,

2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 2-chloro-phenyl ester,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-isopropyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-propyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid,

2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid o-tolyl ester; and

1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-phenyl)-(3-sulfamoyl-propyl)-amide.

[00127] In another embodiment, a compound of the invention is selected from the following compounds:

(R)-1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-methyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

4-(N-(4-chlorobenzyl)-1-((2-fluorophenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-((benzo[b]thiophen-3-yloxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-1-((2-methoxyphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-1-((2,4-dimethylphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-2-methyl-1-((2-(trifluoromethyl)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid,

4-(1-((2-chloro-5-methoxyphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-isopropyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

4-(N-(4-chlorobenzyl)-1-((3-methoxyphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-fluorobenzyl)azetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methylbenzyl)azetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methoxybenzyl)azetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-(trifluoromethyl)benzyl)azetidine-2-carboxamido)butanoic acid,

4-(1-((2-chloro-4-methylphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-((2-chloro-4-methoxyphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-chlorobenzyl)azetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-2-methyl-1-((4-(trifluoromethyl)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-2-methyl-1-((4-(methylthio)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

2-allyl-1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-2-benzyl-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

(R)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)-2-propylazetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-isopropyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorophenyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

4-(1-((2-bromophenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-((2-chloro-5-(trifluoromethyl)phenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-1-(1H-indole-1-carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(N-(4-chlorobenzyl)-1-((2,4-dichlorophenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-((2-chloro-4-fluorophenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid,

1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-fluorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methoxybenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(2-fluorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide,

(R)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

(S)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorophenyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(2-methoxybenzyl)azetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorophenyl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(6-chloropyridin-3-yl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(5-chloropyridin-2-yl)-2-methylazetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(3-(trifluoromethyl)phenyl)azetidine-2-carboxamido)butanoic acid,

4-(1-(benzo[b]thiophene-3-carbonyl)-N-(4-chloropyridin-2-yl)-2-methylazetidine-2-carboxamido)butanoic acid, and ,

4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(pyridin-2-yl)azetidine-2-carboxamido)butanoic acid.

[00128] In one embodiment, a compound of the invention is 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid.

[00129] In another embodiment, a compound of the invention is not 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid.

[00130] In one embodiment a compound of the invention is not an isotopic variant.

[00131] In one aspect a compound of the invention is present as the free base.

[00132] In one aspect a compound of the invention is a pharmaceutically acceptable salt.

[00133] In one aspect a compound of the invention is present as the free base or a pharmaceutically acceptable salt.

[00134] In one aspect a compound of the invention is a solvate.

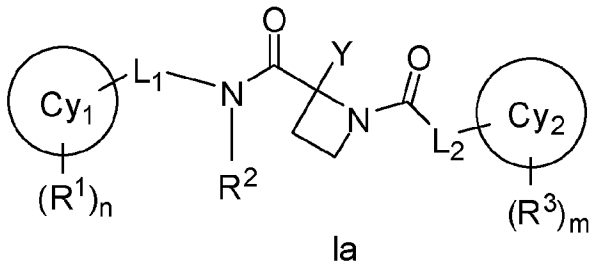
[00135] In one aspect a compound of the invention is a solvate of a pharmaceutically acceptable salt of the compound.

[00136] In certain aspects, the present invention provides prodrugs and derivatives of a Compound of the Invention according to the formulae above. Prodrugs are derivatives of a compound of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[00137] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

CLAUSES:

Clause 1. A compound of the invention according to Formula Ia:



Ia

,

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is

- C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano), or
- C_{1-4} alkenyl comprising 1 double bond;

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more halo, or phenyl), C_{1-6} thioalkoxy, phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, $C(=O)$-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- $-NR^{4a}R^{4b}$, or
- $-NHSO_2R^{4c}$;

Each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

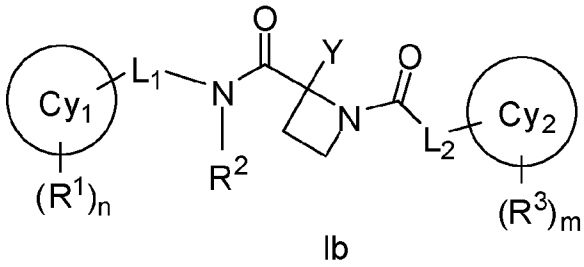
R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2;

or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

Clause 2. A compound of the invention according to Formula Ib:



Ib

,

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is $-C_{1-4}$ alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano);

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,

- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or
- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more halo, or phenyl), phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, $C(=O)$-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- $-NR^{4a}R^{4b}$, or
- $-NHSO_2R^{4c}$;

Each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

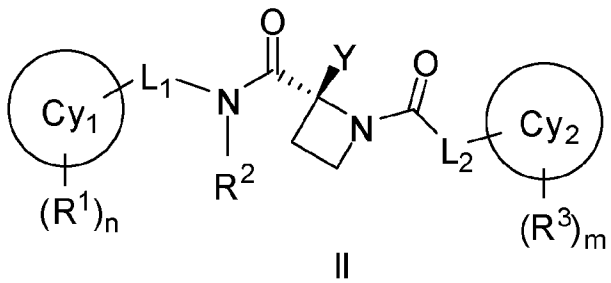
R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2;

or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

Clause 3. A compound of the invention according to clause 1 or 2, wherein the compound is according to Formula II:



II

,

wherein L_1, L_2, R^1, R^2, R^3, Cy^1, Cy^2, R^a, R^b, R^c, R^d, R^e, Y, n, and m are as described in clause 1 or 2.

Clause 4. A compound of the invention according to clause 1, 2 or 3, wherein L_1 is a single bond.

Clause 5. A compound of the invention according to clause 1, 2 or 3, wherein L_1 is CR^aR^b.

Clause 6. A compound of the invention according to clause 5, wherein R^a is H or C_{1-4} alkyl and R^b is H.

Clause 7. A compound of the invention according to clause 6, wherein R^a and R^b are both H.

Clause 8. A compound of the invention according to any one of clauses 1-7, wherein Y is Me, Et, Pr, iPr, or $-CH_2-Ph$.

Clause 9. A compound of the invention according to clause 8, wherein Y is Me.

Clause 10. A compound of the invention according to any one of clauses 1-9, wherein Cy_1 is phenyl.

Clause 11. A compound of the invention according to any one of clauses 1-10, wherein n is 1 or 2

Clause 12. A compound of the invention according to clause 11, wherein n is 1.

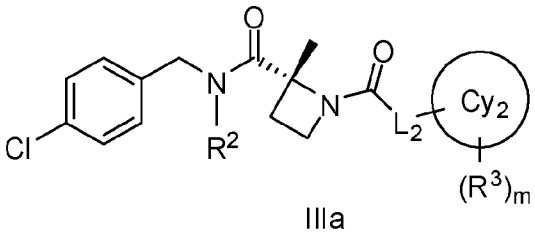
Clause 13. A compound of the invention according to clause 1-12, wherein each R^1 group is independently selected from halo, and C_{1-4} alkyl optionally substituted with one or more halo.

Clause 14. A compound of the invention according to clause 13, wherein each R^1 group is independently selected from F, Cl, Me, Et, iPr, and CF_3.

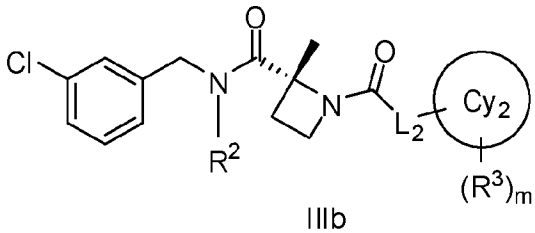
Clause 15. A compound of the invention according to any one of clauses 1-9, wherein Cy1 is benzofuranyl, benzothiophenyl, indazolyl, indolyl, or benzothiazolyl.

Clause 16. A compound of the invention according to any one of clauses 1-10 or 15, wherein n is 0.

Clause 17. A compound of the invention according to clause 1, 2 or 3, wherein the compound is according to Formulae IIIa or IIIb:



IIIa



IIIb

wherein R^2, L_2, Cy_2, R^3 and m are as described in clause 1 or 2.

Clause 18. A compound of the invention according to any one of clauses 1-17, wherein R^2 is H

Clause 19. A compound of the invention according to any one ofclauses 1-17, wherein R^2 is C_{1-4} alkyl.

Clause 20. A compound of the invention according to clause 19, wherein R^2 is Me, Et, Pr, iPr, Bu, or iBu.

Clause 21. A compound of the invention according to any one of clauses 1-17, wherein R^2 is C_{1-4} alkyl substituted with OH, CN, or C_{1-6} alkoxy.

Clause 22. A compound of the invention according to clause 1-17, wherein R^2 is C_{1-4} alkyl optionally substituted with one or more $C(=O)R^4$.

Clause 23. A compound of the invention according to clause 22, wherein R^4 is OH, or C_{1-6} alkoxy.

Clause 24. A compound of the invention according to clause 22, wherein R^4 is $NR^{4a}R^{4b}$, wherein each of R^{4a} and R^{4b} is independently selected from H, C_{3-7} cycloalkyl or C_{1-4} alkyl.

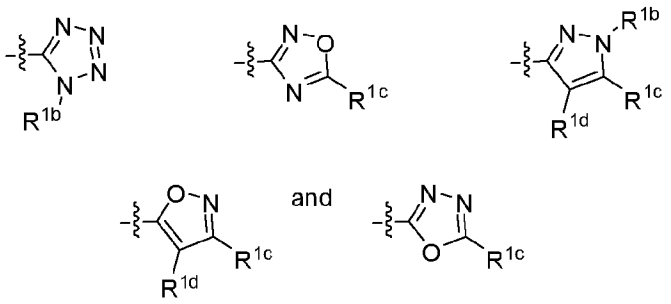
Clause 25. A compound of the invention according to clause 22, wherein R^4 is $NHSO_2R^{4c}$, wherein R^{4c} is Me, phenyl or CF_3.

Clause 26. A compound of the invention according to clause 1-17, wherein R^2 is C_{1-4} alkyl optionally substituted with $S(O)_2R^4$.

Clause 27. A compound of the invention according to clause 26, wherein R^4 is *N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more idependantly selected C_{1-6} alkyl, or oxo).

Clause 28. A compound of the invention according to clause 26, wherein R^4 is $NR^{4a}R^{4b}$, wherein each of R^{4a} and R^{4b} is independently selected from H, or C_{1-4} alkyl.

Clause 29. A compound of the invention according to clause 1-17, wherein R^2 is C_{1-4} alkyl substituted with one:



,

wherein R^{1b} is H, or C_{1-4} alkyl; R^{1c} is OH, or C_{1-4} alkoxy; and R^{1d} is H, F, or C_{1-4} alkyl.

Clause 30. A compound of the invention according to clause 1-17, wherein R^2 is C_{1-4} alkyl optionally substituted with $NHC(=O)R^5$, $NHSO_2R^5$.

Clause 31. A compound of the invention according to clause 30, wherein R^5 is Me, Et, or CF_3.

Clause 32. A compound of the invention according to clauses 1-17, wherein R^2 is $-(CH_2)$-COOH, $-(CH_2)_3$-COOH, $-(CH_2)_3$-SO_2NH_2, or $-(CH_2)_3$-SO_2NHMe.

Clause 33. A compound of the invention according to any one of clauses 1-32, wherein Cy_2 is phenyl, or naphthalene.

Clause 34. A compound of the invention according to any one of clauses 1-32, wherein Cy_2 is 5-10 membered heteroaryl.

Clause 35. A compound of the invention according to clause 34, wherein Cy_2 is thiophenyl, benzothiophenyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl or indolyl.

Clause 36. A compound of the invention according to any one of clause 1-35, wherein m is 1 or 2.

Clause 37. A compound of the invention according to clause 35, wherein each R^3 group is independently selected from F, Cl, Br, Me, CF_3, and OMe.

Clause 38. A compound of the invention according to any one of clause 1-35, wherein m is 0.

Clause 39. A compound of the invention according to any one of clauses 1-38, wherein L_2 is a single bond.

Clause 40. A compound of the invention according to any one of clauses 1-38, wherein L_2 is $-CR^cR^d-$, and wherein each of R^c and R^d are independently selected from H, Me, and Et.

Clause 41. A compound of the invention according to any one of clauses 1-38, wherein L_2 is $-CR^cR^d-$, and wherein R^c is H and R^d is H or C_{1-4} alkyl

Clause 42. A compound of the invention according to clause 41, wherein L_2 is $-CR^cR^d-$, and wherein R^c is H and R^d is H, Me, or Et.

Clause 43. A compound of the invention according to clause 41, wherein L_2 is $-CH_2-$.

Clause 44. A compound of the invention according to any one of clauses 1-38, wherein L_2 is –O-.

Clause 45. A compound of the invention according to any one of clauses 1-38, wherein L_2 is $-NR^e$.

Clause 46. A compound of the invention according to clause 45, wherein R^e is Me.

Clause 47. A compound of the invention according to clause 1, wherein the compound is 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid; or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salt.

Clause 48. A pharmaceutical composition comprising a compound of the invention according to any of clauses 1-49, and a pharmaceutically acceptable carrier.

Clause 49. The pharmaceutical composition according to clause 48 comprising a further therapeutic agent.

Clause 50. The use of a compound of the invention according to any of clauses 1-47 in the manufacture of a medicament.

Clause 51. A compound of the invention according to any of clauses 1-47 for use as a medicament.

Clause 52. A method for the treatment or prophylaxis of inflammatory inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases, comprising administering a prophylactically or therapeutically effective amount of a compound of the invention according to any one of clauses 1-47, or a composition of any of clauses 48-49.

Clause 53. A method according to clause 52, wherein the condition or disease involves an inflammatory condition.

Clause 54. A method according to clause 53, wherein the inflammatory condition is rheumatoid arthritis.

Clause 55. A method according to clause 53, wherein the inflammatory condition is inflammatory bowel disorders.

Clause 56. A method according to clause 52, for the treatment or prophylaxis of cardiometabolic diseases.

Clause 57. The method according to clauses 52-56, wherein compound of the invention according to clause 1-48 is administered in combination with a further therapeutic agent.

Clause 58. The compound of the invention according to any one of clauses 1-48, or the pharmaceutical composition according to clauses 49 or 50, for use in the treatment or prophylaxis of

inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.

Clause 59. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of rheumatoid arthritis.

Clause 60. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of inflammatory bowel disorders.

Clause 61. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of cardiometabolic diseases.

Clause 62. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of COPD or vasculitis.

Clause 63. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of gout.

Clause 64. The compound of the invention or the pharmaceutical composition according to clause 58, for use in the treatment of sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving Yersinia, Salmonella, Chlamydia, Shigella, or enterobacteria species.

Clause 65. The compound of the invention according to anyone of clauses 1-64, wherein the compound is present as the free base.

Clause 66. The compound of the invention according to anyone of clauses 1-64, wherein the compound is present as a pharmaceutically acceptable salt.

Clause 67. The compound of the invention according to anyone of clauses 1-64, wherein the compound is present as the free base or a pharmaceutically acceptable salt.

Clause 68. The compound of the invention according to anyone of clauses 1-64, wherein the compound is present as a solvate.

Clause 69. The compound of the invention according to anyone of clauses 1-64, wherein the compound is present as solvate of a pharmaceutically acceptable salt of the compound.

PHARMACEUTICAL COMPOSITIONS

[00138] When employed as a pharmaceutical, a compound of the invention is typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, a compound of the invention is administered in a pharmaceutically effective amount. The amount of a compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound - administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00139] The pharmaceutical compositions of the invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, and

intranasal. Depending on the intended route of delivery, a compound of this invention is preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00140] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, a compound of the invention is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00141] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00142] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00143] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[00144] A compound of the invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00145] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[00146] A compound of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[00147] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[00148] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active amide compound per tablet) in a tablet press.

Formulation 2 - Capsules

[00149] A compound of the invention may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active amide compound per capsule).

Formulation 3 - Liquid

[00150] A compound of the invention (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient water may then be added with stirring. Sufficient water may be then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

[00151] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active amide compound) in a tablet press.

Formulation 5 - Injection

[00152] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[00153] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of a compound of the invention (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

METHODS OF TREATMENT

[00154] A compound of the invention may be used as a therapeutic agent for the treatment of conditions in mammals that are causally related or attributable to aberrant activity of GPR43 and/or aberrant GPR43 expression and/or aberrant GPR43 distribution. Accordingly, a compound of the invention and pharmaceutical compositions of the invention find use as therapeutics for preventing and/or treating inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases, in mammals including humans.

[00155] In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with an inflammatory condition. The methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or a compound of the invention herein described. In a specific embodiment, the inflammatory condition is selected from rheumatoid arthritis, osteoarthritis, gout, allergic airway disease (e.g. asthma) and inflammatory bowel disease.

[00156] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of an inflammatory condition. In a specific embodiment, the inflammatory condition is selected from rheumatoid arthritis, osteoarthritis, gout, allergic airway disease (e.g. asthma) and inflammatory bowel disease.

[00157] In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with an infectious disease, in particular sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving Yersinia, Salmonella, Chlamydia, Shigella, or enterobacteria species. In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of an infectious disease, in particular sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving Yersinia, Salmonella, Chlamydia, Shigella, or enterobacteria species.

[00158] In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with an autoimmune disease. The methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or a compound of the invention herein described. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, psoriasis, systemic lupus erythematosis, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[00159] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of an autoimmune disease. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, psoriasis, systemic lupus erythematosis, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[00160] In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with a metabolic disease. The methods comprise administering an

effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or a compound of the invention herein described. In a specific embodiment, the metabolic disease is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, obesity, metabolic syndrome, atherosclerosis, Type II diabetes, pre-diabetes, insulin resistance, heart disease, stroke, hypertension, and perivascular disease.

[00161] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of a metabolic disease. In a specific embodiment, the metabolic disease is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, obesity, metabolic syndrome, atherosclerosis, Type II diabetes, pre-diabetes, insulin resistance, heart disease, stroke, hypertension, and perivascular disease.

[00162] As a further aspect of the invention there is provided a compound of the invention for use as a medicament especially in the treatment or prevention of the aforementioned conditions and diseases. Also provided herein is the use of the compound in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases.

[00163] A particular regimen of the present method comprises the administration to a subject in suffering from an inflammatory condition, of an effective amount of a compound of the invention for a period of time sufficient to reduce the level of inflammation in the subject, and preferably terminate, the processes responsible for said inflammation. A special embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject patient suffering from or susceptible to the development of inflammatory condition , for a period of time sufficient to reduce or prevent, respectively, inflammation of said patient, and preferably terminate, the processes responsible for said inflammation.

[00164] Injection dose levels range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[00165] For the prevention and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of a compound of the invention, with particular doses each providing from about 0.1 to about 10 mg/kg and especially about 1 to about 5 mg/kg.

[00166] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[00167] When used to prevent the onset of a condition, a compound of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a

particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[00168] A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compounds that demonstrate the same or a similar therapeutic activity, and that are determined to be safe and efficacious for such combined administration. In a specific embodiment, co-administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

[00169] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of an inflammatory condition; particular agents include, but are not limited to, immunoregulatory agents e.g. azathioprine, corticosteroids (e.g. prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, Mycophenolate Mofetil, muromonab-CD3 (OKT3, e.g. Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

[00170] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of arthritis (e.g. rheumatoid arthritis); particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, auranofin, sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, and cyclosporin), and biological DMARDS (for example but without limitation Infliximab, Etanercept, Adalimumab, Rituximab, and Abatacept).

[00171] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of autoimmune diseases; particular agents include but are not limited to: glucocorticoids, cytostatic agents (e.g. purine analogs), alkylating agents, (e.g nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others), antimetabolites (e.g. methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (e.g. dactinomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies(e.g., anti-CD20, anti-CD25 or anti-CD3 (OTK3) monoclonal antibodies, Atgam® and Thymoglobuline®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (e.g. IFN-β), TNF binding proteins (e.g. infliximab (Remicade™), etanercept (Enbrel™), or adalimumab (Humira™)), mycophenolate, Fingolimod, and Myriocin.

[00172] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of infectious diseases; particular agents include but are not limited to antibiotics. In a particular embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of infections of any organ of the human body; particular agents include but are not limited to: aminoglycosides, ansamycins, carbacephem, carbapenems, cephalosporins, glycopeptides, lincosamides, macrolides, monobactams, nitrofurans, penicillins, polypeptides, quinolones, sulfonamides, tetracyclins, anti-mycobacterial agents, as well as chloramphenicol, fosfomycin, linezolid, metronidazole, mupirocin, rifamycin, thiamphenicol and tinidazole.

[00173] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of asthma and/or rhinitis and/or COPD; particular agents include but are not limited to: beta$_2$-adrenoceptor agonists (e.g. salbutamol, levalbuterol, terbutaline and bitolterol), epinephrine (inhaled or tablets), anticholinergics (e.g. ipratropium bromide), glucocorticoids (oral or inhaled) Long-acting β_2-agonists (e.g. salmeterol, formoterol, bambuterol, and sustained-release oral albuterol), combinations of inhaled steroids and long-acting bronchodilators (e.g. fluticasone/salmeterol, budesonide/formoterol), leukotriene antagonists and synthesis inhibitors (e.g. montelukast, zafirlukast and zileuton), inhibitors of mediator release (e.g. cromoglycate and ketotifen), biological regulators of IgE response (e.g. omalizumab), antihistamines (e.g. ceterizine, cinnarizine, fexofenadine), and vasoconstrictors (e.g. oxymethazoline, xylomethazoline, nafazoline and tramazoline).

[00174] Additionally, a compound of the invention may be administered in combination with emergency therapies for asthma and/or COPD, such therapies include oxygen or heliox administration, nebulized salbutamol or terbutaline (optionally combined with an anticholinergic (e.g. ipratropium), systemic steroids (oral or intravenous, e.g. prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone), intravenous salbutamol, non-specific beta-agonists, injected or inhaled (e.g. epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, e.g. glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bamiphylline), inhalation anesthetics that have a bronchodilatory effect (e.g. isoflurane, halothane, enflurane), ketamine, and intravenous magnesium sulfate.

[00175] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of inflammatory bowel disease (IBD); particular agents include but are not limited to: glucocorticoids (e.g. prednisone, budesonide) synthetic disease modifying, immunomodulatory agents (e.g. methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and ciclosporin) and biological disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

[00176] By co-administration is included any means of delivering two or more therapeutic- agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation this is not essential. The agents may be administered in different formulations and at different times.

GENERAL SYNTHETIC PROCEDURES

General

[00177] A compound of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[00178] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley-Blackwell; 4th Revised edition edition (2006), and references cited therein.

[00179] The following methods are presented with details as to the preparation of representative bicycloheteroaryls that have been listed hereinabove. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[00180] All reagents were of commercial grade and were used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Column chromatography was performed on silica standard (35-70 μm). Thin layer chromatography was carried out using pre-coated silica gel 60 F-254 plates (thickness 0.25 mm). ^{1}H NMR spectra were recorded on a Bruker Advance 400 NMR spectrometer (400 MHz) or a Bruker Advance 300 NMR spectrometer (300 MHz). Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or the appropriate residual solvent peak as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Electrospray MS spectra were obtained on a Waters platform LC/MS spectrometer. Analytic LCMS: Columns used, Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L or Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 30mm L. All the methods are using MeCN/H_2O gradients. MeCN and H_2O contain either 0.1% Formic Acid or NH_3 (10mM). Preparative LCMS: Column used, Waters XBridge Prep C18 5μm ODB 30mm ID x 100mm L. All the methods are using MeOH/H_2O gradients. MeOH and H_2O contain either 0.1% Formic Acid or 0.1% Diethylamine. Microwave heating was performed with a Biotage Initiator.

[00181] The following is a list of abbreviations used in the experimental section:

μL	microliter
ATP	Adenosine 5′-Triphosphate
Boc	tert-Butyloxy-carbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
br s	broad singlet
Cat.	Catalytic amount
CDI	1,1'-Carbonyldiimidazole
d	doublet
DCC	N,N'-Dicyclohexylcarbodiimide

DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	N,N-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMEM	Dulbecco's Modified Eagle Medium
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide

EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
EDTA 4 Na	Ethylenediaminetetraacetic Acid, tetrasodium Salt
EGTA	ethylene glycol tetraacetic acid
EtOAc	Ethyl acetate
FBS	Fetal bovine serum
FFAR2	free fatty acid receptor 2
g	gram
GDPDH	Guanosine diphosphate dehydrogenase
GTPγS	guanosine 5'-O-[gamma-thio]triphosphate
h	hour
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HOBt	1-Hydroxybenzotriazole
iPr_2O	Diisopropyl ether
KHMDS	Potassium hexamethyldisilazane
LCMS	Liquid Chromatography- Mass Spectrometry
LiHMDS	Lithium hexamethyldisilazane
m	multiplet
MeCN	Acetonitrile
mg	milligram
min	minute
mL	milliliter

MW	Molecular weight
NADP	Nicotinamide adenine dinucleotide phosphate
NEAA	Non-Essential Amino Acid
NMR	Nuclear Magnetic Resonnance
PBST	Phosphate buffered saline with Tween 3.2 mM Na_2HPO_4, 0.5 mM KH_2PO_4, 1.3 mM KCl, 135 mM NaCl, 0.05% Tween 20, pH 7.4
Pd/C	Palladium on Carbon 10%
ppm	part-per-million
q	quadruplet
rpm	revolutions per minute
RPMI medium	Roswell Park Memorial Institute medium
Rt	retention time
s	singlet
SM	Starting Material
spA	Scintillation proximity assay
t	triplet
TBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Synthetic Preparation of a compound of the invention

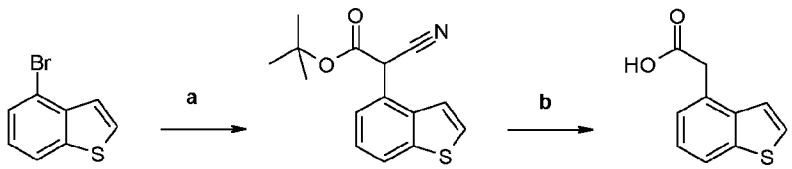
[00182] The compounds of the invention can be produced according to the following schemes.

General Synthetic Method

Intermediates

Synthesis of carboxylic acid

Illustrative synthesis of Intermediate 1: Benzo[b]thiophen-4-yl-acetic acid.



Step a: Benzo[b]thiophen-4-yl-cyano-acetic acid tert-butyl ester.

[00183] To a solution of 4-bromobenzothiophene (1 eq.) in DME were added tert-butyl cyanoacetate (1.1 eq.) and t-BuOK (2 eq.). The reaction was refluxed for 40 min. Thereto were added dichlorobis(triphenylphosphine)palladium(II) (0.02 eq.) and triphenylphosphine (0.06 eq.) . The resulting mixture was refluxed for 1.5h under argon and then cooled to 20°C. Aqueous HCl (6N) was added dropwise until pH=1 and the reaction mixture was partitioned between water and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/DCM: 9/1 to 1/1) to afford benzo[b]thiophen-4-yl-cyano-acetic acid tert-butyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.92 (1H, d), 7.59 (1H, d), 7.54 (1H, d), 7.49 (1H, d), 7.39 (1H, t), 5.04 (1H, s), 1.42 (9H, s).

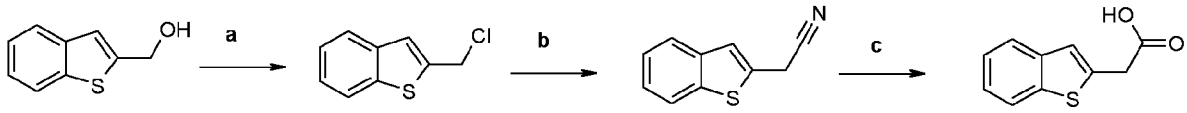
MW (calcd): 273.4; MW (obsd): 274.0 (M+1).

Step b: Benzo[b]thiophen-4-yl-acetic acid.

[00184] To a solution of benzo[b]thiophen-4-yl-cyano-acetic acid tert-butyl ester (1 eq.) in ethylene glycol were added an aqueous solution of 38 percent (w/w) potassium hydroxide and water. The reaction was heated at 95°C for 2h. The reaction mixture was partitioned between water and toluene, and the organic layer was discarded. The aqueous layer was acidified with aqueous HCl (6N) until pH =2 and extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the resulting residue was added a mixture of Et_2O/pentane and the precipitate was collected by filtration to provide benzo[b]thiophen-4-yl-acetic acid.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.82 (1H, d), 7.48 (1H, d), 7.42 (1H, d), 7.31 (1H, t), 7.26 (1H, d), 3.97 (2H, s).

Illustrative synthesis of Intermediate 2: Benzo[b]thiophen-2-yl-acetic acid.



Step a: 2-Chloromethyl-benzo[b]thiophene

[00185] A solution of benzo[b]thiophen-2-yl-methanol (1 eq.) in thionyl chloride was stirred at 20°C for 1h. The crude was concentrated under reduced pressure then partitioned between a saturated aqueous solution of $NaHCO_3$ and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-chloromethyl-benzo[b]thiophene, used as such without further purification.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.87-7.82 (1H, m), 7.80-7.75 (1H, m), 7.43-7.37 (2H, m), 7.34 (1H, s), 4.91 (2H, s)

Step b: Benzo[b]thiophen-2-yl-acetonitrile

[00186] To a solution of 2-chloromethyl-benzo[b]thiophene (1 eq.) in dioxane/water (2/1) was added KCN (1.5 eq.). The reaction was refluxed for 4h. The crude was partitioned between water and EtOAc. The organic layer was washed with water, then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 95/5 to 90/10) to afford benzo[b]thiophen-2-yl-acetonitrile.

^1H NMR δ (ppm) ($CDCl_3$): 7.86-7.76 (2H, m), 7.45-7.38 (2H, m), 7.37-7.34 (1H, m), 4.04 (2H, s)

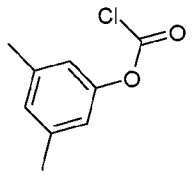
Step c: Benzo[b]thiophen-2-yl-acetic acid (Int 1)

[00187] To a solution of benzo[b]thiophen-2-yl-acetonitrile (1 eq.) in EtOH/water (1/1) wase added NaOH pellets (12 eq.). The reaction was heated at 80°C for 4h and then allowed to cooled down to 20°C, at which point concentrated HCl was added carefully until pH = 7 was reached.The reaction mixture was partially concentrated under reduced pressure then partitioned between water and EtOAc. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford benzo[b]thiophen-2-yl-acetic acid.

^1H NMR δ (ppm) ($CDCl_3$): 7.82 (1H, d), 7.75 (1H, d), 7.42-7.31 (2H, m), 7.24 (1H, s), 4.00 (2H, s).

Synthesis of chloroformate

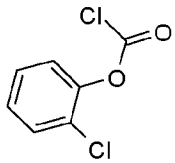
Illustrative synthesis of Intermediate 3: 3,5-dimethyl-phenyl-chloroformate



[00188] To a solution of triphosgene (0.5 eq.) in THF at 0°C was added a solution of 3,5-dimethyl-phenol (1 eq.) and DIPEA (1 eq.) in THF. The reaction was stirred for 15h at 20°C. The crude was partitioned between aqueous HCl (0.1N) and EtOAc. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-phenyl-chloroformate, used as such without further purification.

^1H NMR δ (ppm) ($CDCl_3$): 6.97 (1H, s), 6.86 (2H, s), 2.36 (6H, s).

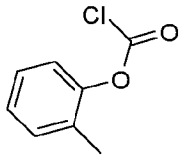
Illustrative synthesis of Intermediate 4: 2-chloro-phenyl-chloroformate



[00189] To a solution of triphosgene (0.5 eq.) in THF at 0°C was added a solution of 2-chloro-phenol (1 eq.) and DIPEA (1 eq.) in THF. The reaction was stirred for 15h at 20°C. The crude was partitioned between aqueous HCl (0.1N) and EtOAc. The aqueous layer was extracted three times with EtOAc. The

organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-chloro-phenyl-chloroformate, used as such without further purification.

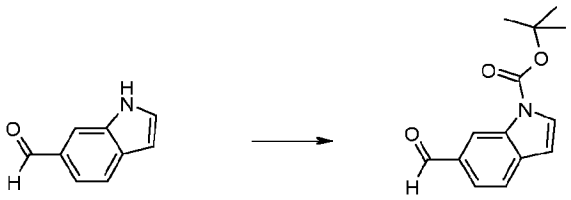
Illustrative synthesis of Intermediate 5: 2-methyl-phenyl-chloroformate



[00190] To a solution of 2-methyl-phenol (1 eq.) in DCM at 0°C were added DMAP (0.1 eq.), TEA (10 eq.) and triphosgene (2 eq.). The reaction was stirred for 30 min at 0°C. The reaction mixture was used as such in the next step without further treatment.

Synthesis of aldehydes

Illustrative synthesis of Intermediate 6: 6-Formyl-indole-1-carboxylic acid tert-butyl ester

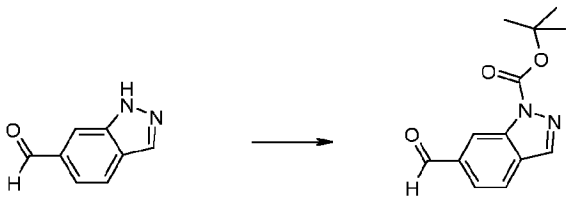


[00191] To a solution of tBuOK (1 eq.) in THF were added at 0°C under nitrogen a solution of 1H-Indole-6-carbaldehyde (1 eq.) in THF and a solution of Boc_2O (1.2 eq.) in THF. The reaction was stirred at 0°C for 1h, then at 20°C for 15h. The crude was partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 100/0 to 90/10) to afford 6-formyl-indole-1-carboxylic acid tert-butyl ester

^{1}H NMR δ (ppm) (DMSO, d_6): 10.08 (1H, s), 8.61 (1H, s), 7.95 (1H, d), 7.80 (2H, q), 6.86 (1H, m), 1.66 (9H, s).

MW (calcd): 245.3; MW (obsd): 189.9 (M-56)

Illustrative synthesis of Intermediate 7: 6-Formyl-indazole-1-carboxylic acid tert-butyl ester

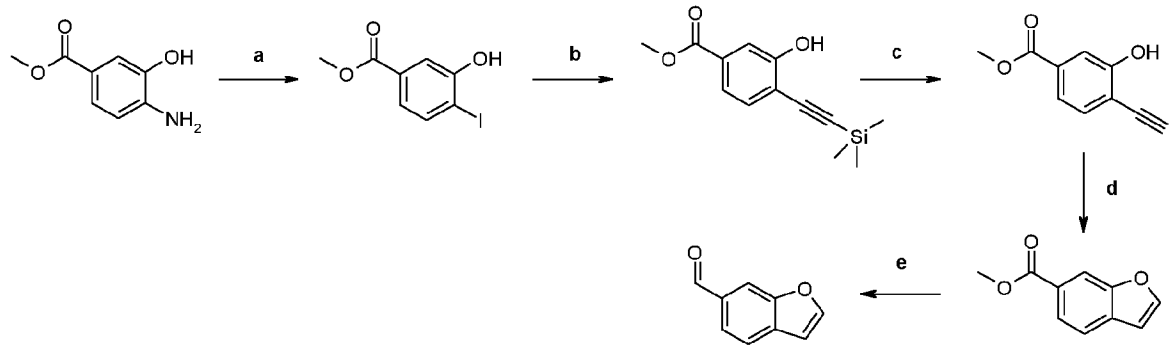


[00192] 6-Formyl-indazole-1-carboxylic acid tert-butyl ester was also prepared following the method described above.

^{1}H NMR δ (ppm) (DMSO, d_6): 10.20 (1H, s), 8.64 (1H, s), 8.57 (1H, d), 8.08 (1H, d), 7.87 (1H, dd), 1.68 (9H, s).

MW (calcd): 246.3; MW (obsd): 191.0 (M-56)

Illustrative synthesis of Intermediate 8: benzofuran-6-carboxaldehyde



Step a: methyl 3-hydroxy-4-iodobenzoate

[00193] A solution of methyl 4-amino-3-hydroxybenzoate (1 eq.) in THF was diluted with aqueous HCl 3N and cooled to 0°C. Sodium nitrite (1.1 eq.) in H_2O was added over 5min. The reaction mixture was stirred for 25 min at 0°C and then a solution of potassium iodide (4 eq.) in H_2O was added in one portion, and stirred for 15 min. The reaction mixture was partitioned between water and EtOAc, the organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM) to afford methyl 3-hydroxy-4-iodobenzoate.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.67 (1H, d), 7.33 (1H, d), 7.11 (1H, dd), 3.78 (3H, s).

MW (calcd): 278.1; MW (obsd): 276.8 (M-1).

Step b: methyl 3-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate

[00194] To a solution of methyl 3-hydroxy-4-iodobenzoate (1 eq.) in dry THF were added trimethylsilylacetylene (5 eq.), tetrakis(triphenylphosphine)palladium (0.03 eq.), copper iodide (0.02 eq.) and diisopropylamine (2.1 eq.) under argon. The reaction mixture was stirred at 60 °C for 15h, cooled to 20°C and the solvents removed under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 9/1) to afford methyl 3-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.64 (1H, s), 7.57 (1H, d), 7.43 (1H, d), 5.95 (1H, s), 3.95 (3H, s), 0.33 (9H, s).

MW (calcd): 248.4; MW (obsd): 249.1 (M+1).

Step c: 3-hydroxy-4-ethynylbenzoate

[00195] To a solution of methyl 3-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate (1 eq.) in dry THF was added 1M tetrabutylammonium fluoride (1.5 eq.) under argon. The reaction was stirred at 20°C for 30 min. The reaction mixture was quenched with aqueous HCl (1N), extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 1/1) to afford 3-hydroxy-4-ethynylbenzoate.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.66 (1H, d), 7.60 (1H, dd), 7.48 (1H, d), 5.93 (1H, s), 3.95 (3H, s), 3.63 (9H, s).

MW (calcd): 176.2; MW (obsd): 177.1 (M+1).

Step d: methyl benzofuran-6-carboxylate

[00196] To a solution of methyl 3-hydroxy-4-ethynylbenzoate (1 eq.) in dry toluene was added $PtCl_2$ (0.1 eq.) under argon. The reaction mixture was stirred at 80°C for 1.5 h, warmed to 20°C and the solvents removed under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 9/1) to afford methyl benzofuran-6-carboxylate.

^{1}H NMR δ (ppm) ($CDCl_3$): 8.21 (1H, s), 7.96 (1H, dd), 7.77 (1H, d), 7.64 (1H, d), 6.85-6.80 (1H, m), 3.95 (3H, s).

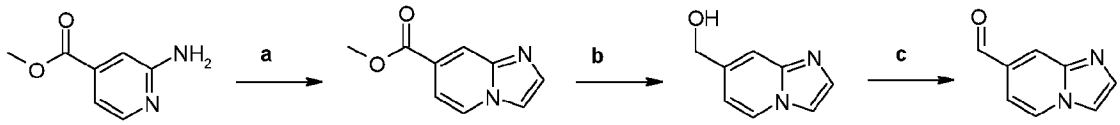
MW (calcd): 176.2; MW (obsd): 177.0 (M+1).

Step e: benzofuran-6-carboxaldehyde

[00197] To a solution of methyl benzofuran-6-carboxylate (1 eq.) in dry THF was added a solution of $LiAlH_4$ (1M in THF, 1.5 eq.) at 0°C under argon. The reaction mixture was stirred at 0 °C for 2.5 h. Water, aqueous NaOH (2N) and water were then added and the mixture was stirred at 20 °C for 30 min. The crude was passed through a pad of celite and solvent removed under reduced pressure. To a solution of the residue (1 eq.) in DCM was added MnO_2 (10 eq.). The dark suspension was stirred at 20°C for 15h, filtered through a pad of celite and the solvent removed under reduced pressure to afford benzofuran-6-carboxaldehyde which was used as such without further purification.

MW (calcd): 146.2; MW (obsd): 147.1 (M+1).

Illustrative synthesis of Intermediate 9: Imidazo[1,2-a]pyridine-7-carbaldehyde



Step a: imidazo[1,2-a]pyridine-7-carboxylic acid methyl ester

[00198] To a solution of 2-amino-isonicotinic acid methyl ester (1 eq.) and chloroacetaldehyde (45% w/w in water) (4.5 eq.) in ethanol was added $NaHCO_3$ (1.7 eq.). The reaction mixture was refluxed for 15h and the solvents removed under reduced pressure. The residue was partitioned between water and EtOAc, the organic layer was washed with a saturated aqueous solution of Na_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH: 100/0 to 98/2) to afford imidazo[1,2-a]pyridine-7-carboxylic acid methyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 8.36 (1H, s), 8.16 (1H, dd), 7.79 (1H, dd), 7.68 (1H, d), 7.39 (1H, dd), 3.96 (3H, s).

MW (calcd): 178.2; MW (obsd): 177.2 (M-1).

Step b: Imidazo[1,2-a]pyridin-7-yl-methanol

[00199] To a -78°C cooled solution of imidazo[1,2-a]pyridine-7-carboxylic acid methyl ester (1 eq.) in dry THF was slowly added a solution of $LiAlH_4$ in THF (1M in THF, 2 eq.). The reaction mixture was warmed to 0°C and stirred for 30 min. The reaction mixture was then poured onto a cooled aqueous solution of NaOH 2N, stirred for 5 min and filtered through a pad of celite. The filtrate was partitioned between water and EtOAc, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford imidazo[1,2-a]pyridin-7-yl-methanol which was used as such without further purification.

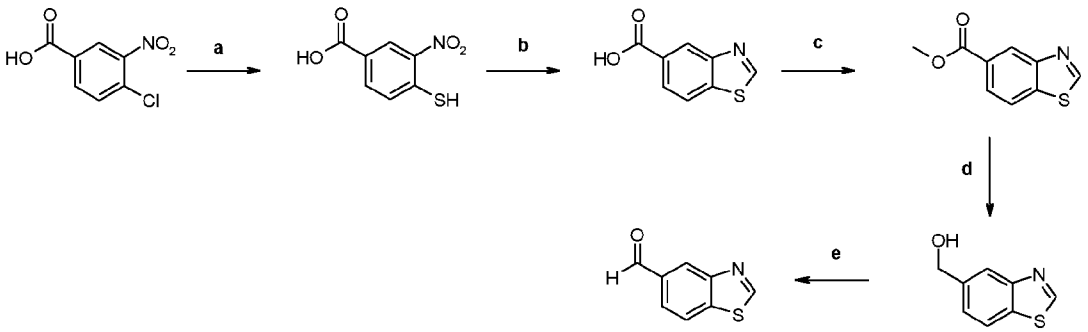
^{1}H NMR δ (ppm) (MeOD, d_4): 8.41 (1H, d), 7.82 (1H, s), 7.60-7.52 (2H, m), 6.92 (1H, d), 4.70 (2H, d).

Step c: Imidazo[1,2-a]pyridine-7-carbaldehyde

[00200] To a solution of imidazo[1,2-a]pyridin-7-yl-methanol (1 eq.) in chloroform was added MnO_2 (10 eq.). The dark suspension was heated at 60°C for 30 min, filtered through a pad of celite and the solvent removed under reduced pressure to afford imidazo[1,2-a]pyridine-7-carbaldehyde which was used as such without further purification.

^{1}H NMR δ (ppm) ($CDCl_3$): 10.03 (1H, s), 8.24 (1H, d), 8.16 (1H, s), 7.89 (1H, d), 7.79 (1H, d), 7.38 (1H, dd).

Illustrative synthesis of Intermediate 10: Benzothiazole-5-carbaldehyde



Step a: 4-mercapto-3-nitrobenzoic acid

[00201] To a suspension of 4-chloro-3-nitrobenzoic acid (1 eq.) in aqueous NaOH (0.15M) (1 eq.) was added Na_2S (4 eq.). The resulting mixture was refluxed for 24h, cooled to room temperature and aqueous HCl (2N) was added until pH=3. The resultant precipitate was collected by filtration to provide 4-mercapto-3-nitrobenzoic acid which was used as such without further purification.

Step b: benzothiazole-5-carboxylic acid

[00202] A mixture of 4-mercapto-3-nitrobenzoic acid (1 eq.) and zinc dust (0.35 eq) in formic acid was refluxed for 6 h. The mixture was allowed to cool to room temperature, filtered and concentrated under reduced pressure. The residue was diluted with water, adjusted to pH=6.5 with aqueous NaOH (2N) and extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH: 1/0 to 95/5) to afford benzothiazole-5-carboxylic acid.

^{1}H NMR δ (ppm) ($CDCl_3$): 9.51 (1H, s), 8.58 (1H, d), 8.30 (1H, d), 8.03 (1H, dd).

MW (calcd): 179.2; MW (obsd): 180.0 (M+1).

Step c: benzothiazole-5-carboxylic acid methyl ester

[00203] To a suspension of benzothiazole-5-carboxylic acid (1 eq.) in MeOH at 0°C was added dropwise thionyl chloride (2 eq.). The reaction was stirred at 60°C for 15h. The solvents were concentrated under reduced pressure to afford benzothiazole-5-carboxylic acid methyl ester.

^{1}H NMR δ (ppm) (1M in THF): 9.54 (1H, s), 8.60 (1H, d), 8.33 (1H, d), 8.04 (1H, dd), 3.91 (3H, s).

MW (calcd): 193.2; MW (obsd): 194.1 (M+1).

Step d: benzothiazol-5-yl-methanol

[00204] To a -78°C cooled solution of benzothiazole-5-carboxylic acid methyl ester (1 eq.) in dry THF under nitrogen was slowly added a solution of $LiAlH_4$ (1M in THF, 1.5 eq.). The reaction was stirred at -78°C for 2h, then warmed to 20°C. EtOAc was added to the reaction, then aqueous NaOH (2N) and finally water. The reaction mixture was stirred at 20°C for 30 min, then filtered through a pad of celite. The filtrate was concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 1/0 to 1/1) to afford benzothiazol-5-yl-methanol.

^{1}H NMR δ (ppm) ($CDCl_3$): 9.05 (1H, s), 8.17 (1H, s), 7.97 (1H, d), 7.52 (1H, d), 4.91 (2H, s).

MW (calcd): 165.2; MW (obsd): 166.2 (M+1).

Step e: benzothiazole-5-carbaldehyde

[00205] To a solution of benzothiazol-5-yl-methanol (1 eq.) in DCM was added MnO_2 (10 eq.). The dark suspension was stirred at 20°C for 15h, filtered through a pad of celite and the solvent removed under reduced pressure to afford benzothiazole-5-carbaldehyde which was used as such without further purification.

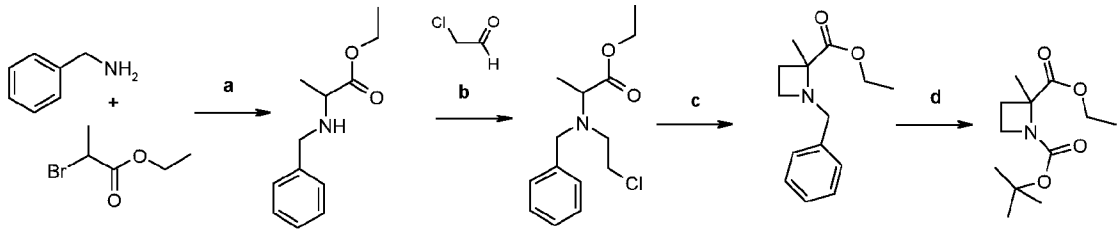
^{1}H NMR δ (ppm) ($CDCl_3$): 10.2 (1H, s), 9.13 (1H, s), 8.61 (1H, d), 8.12 (1H, d), 8.00 (1H, dd).

MW (calcd): 163.2; MW (obsd): 164.1 (M+1)

General Synthetic Methods

Method A: Azetidine formation

Illustrative synthesis of Intermediate 11: 2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester



Step a: 2-Benzylamino-propionic acid ethyl ester

[00206] To a solution of 2-bromo-propionic acid ethyl ester (1 eq.) in MeCN was added benzylamine (0.9 eq.) and potassium carbonate (1.5 eq.). The reaction was refluxed for 4 h then cooled to 20°C and diluted with EtOAc. The crude was filtered, the filtrate was concentrated under reduced pressure, then purified by chromatography on silica gel (elution with heptane/EtOAc : 7/3) to afford 2-benzylamino-propionic acid ethyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.29 (4H, m), 7.28-7.22 (1H, m), 4.20 (2H, q), 3.82 (1H, d), 3.69 (1H, d), 3.38 (1H, q), 1.33 (3H, d), 1.29 (3H, t)

MW (calcd): 207.2 ; MW (obsd) : 208.1 (M+1)

Step b: 2-[Benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester

(I) Drying of chloroacetaldehyde solution (solution I):

[00207] To a solution of chloroacetaldehyde (45% w/w in water) (3 eq.) in DCM under nitrogen was added $MgSO_4$ (4 eq.). The mixture was stirred for 15 min at 20°C under nitrogen. The solid was filtered, washed with dry DCM, and the resulting filtrate (solution I) was rapidly used in the following reaction.

(II) Reaction:

[00208] To a solution of 2-benzylamino-propionic acid ethyl ester (1 eq.) in dry DCM was added $MgSO_4$ (0.75 eq.). The reaction was cooled to 0°C then the above solution of chloroacetaldehyde in dry DCM (solution I) and acetic acid (1 eq.) were added. Sodium triacetoxyborohydride (1.5 eq.) was added portionwise. The reaction was stirred for 1h at 0°C. The crude was carefully quenched with a saturated aqueous solution of $NaHCO_3$. Then aqueous NaOH (2N) was added. The aqueous layer was extracted with DCM. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$, then dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc 98/2 to 95/5) to afford 2-[benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.29 (4H, m), 7.29-7.22 (1H, m), 4.24-4.14 (2H, m), 3.90 (1H, d), 3.77 (1H, d), 3.50 (1H, q), 3.43-3.36 (2H, m), 3.13-2.94 (2H, m), 1.34 (3H, d), 1.31 (3H, t)

MW (calcd): 269.8; MW (obsd): 270.1 (M+1, ^{35}Cl)

Step c: 1-Benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester

[00209] A solution of 2-[benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester (1 eq.) in dry THF was cooled to -78°C under nitrogen. KHMDS (15% w/w in toluene) (1.25 eq.) was slowly added so that

temperature was kept below -65°C. The reaction was stirred for 1h at -70°C. Then acetic acid (0.3 eq.) was added. The reaction was warmed to 20°C and stirred for 10 min, then quenched with a saturated aqueous solution of $NaHCO_3$ and partially concentrated under reduced pressure. The crude was extracted twice with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc 1/0 then 95/5) to afford 1-benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.34-7.19 (5H, m), 4.24-4.16 (2H, m), 3.79 (1H, d), 3.58 (1H, d), 3.30-3.22 (1H, m), 3.15-3.05 (1H, m), 2.63-2.54 (1H, m), 1.97-1.88 (1H, m), 1.49 (3H, s), 1.29 (3H, t)

MW (calcd): 233.3; MW (obsd): 234.1 (M+1)

Step d: 2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

[00210] To a solution of 1-benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester (1 eq.) in EtOH was added Boc_2O (1.2 eq.) and Pd/C (0.05 eq.). The flask was evacuated and backfilled with argon. Then the reaction was evacuated and backfilled with H_2 and stirred for 15h at 20°C under atmospheric pressure. The crude was filtered through a pad of celite and washed with EtOH and DCM. The filtrate was concentrated under reduced pressure to afford 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester.

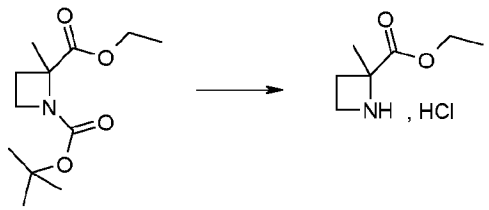
^{1}H NMR δ (ppm) ($CDCl_3$): 4.12-3.92 (2H, m), 3.86-3.71 (1H, m), 3.66-3.54 (1H, m), 2.17-2.00 (1H, m), 1.99-1.83 (1H, m), 1.33 (3H, s), 1.21 (9H, s), 1.11 (3H, t)

MW (calcd): 243.3; MW (obsd): 266^+ ($M+Na^+$)

Intermediate 12 and 200, listed in table I were also prepared following the same method.

Method B1: Boc deprotection

Illustrative synthesis of Intermediate 13: 2-Methyl-azetidine-2-carboxylic acid ethyl ester hydrochloride

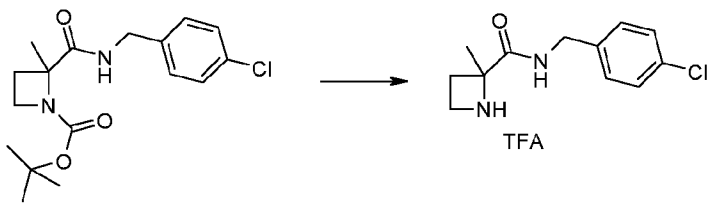


[00211] To a solution of Intermediate 11 (1 eq.) in dioxane under Argon was added a solution of HCl (4N in dioxane, 10 eq.). The reaction was stirred for 16h at 20°C, then concentrated under reduced pressure. The crude was triturated with a mixture of DCM/iPr_2O, and the resulting solid was filtered and dried to afford 2-methyl-azetidine-2-carboxylic acid ethyl ester hydrochloride.

^{1}H NMR δ (ppm) ($CDCl_3$): 9.48 (1H, br s), 4.35 (2H, q), 4.16-4.00 (2H, m), 2.82-2.70 (1H, m), 2.60-2.45 (1H, m), 1.95 (3H, s), 1.36 (3H, t)

Method B2: Boc deprotection

Illustrative synthesis of Intermediate 28: 2-Methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide, trifluoroacetic acid

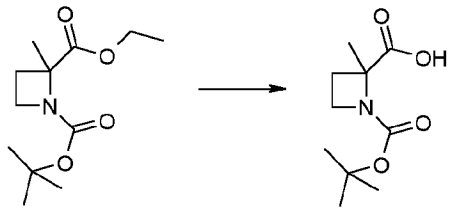


[00212] 2-(4-Chloro-benzylcarbamoyl)-2-methyl-azetidine-1-carboxylic acid tert-butyl ester, Intermediate 138 was dissolved in a solution of TFA (20% in DCM) and the reaction was stirred for 15h at 20°C. The solvents were removed under reduced pressure to afford the desired product which was used as such without further purification.

^{1}H NMR δ (ppm) (DMSO-d_6): 9.25 (1H, br s), 9.00 (1H, t), 7.41 (2H, d), 7.30 (2H, d), 4.35 (2H, d), 4.00-3.86 (1H, m), 3.70-3.59 (1H, m), 2.68-2.55 (1H, m), 2.46-2.35 (1H, m), 1.75 (3H, s)

Method C: Saponification

Illustrative synthesis of Intermediate 31: 2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester

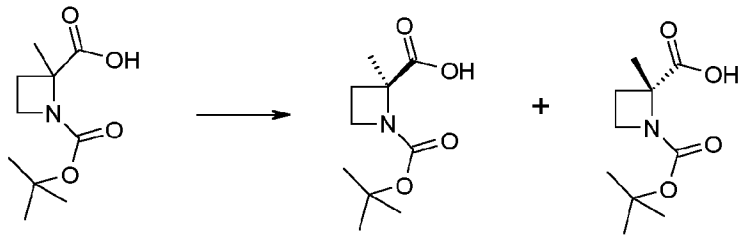


[00213] To a solution of 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester, Intermediate 11 (1 eq.) in EtOH was added an aqueous solution of 2N NaOH (2 eq.). The reaction was stirred at 20°C for 15h. The solvent was removed under reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was discarded and the aqueous layer was acidified by addition of a solution of citric acid 10% in water until pH=3 and thoroughly extracted by EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 3.93-3.81 (1H, m), 3.81-3.68 (1H, m), 2.85-2.71 (1H, m), 2.12-2.00 (1H, m), 1.72 (3H, s), 1.48 (9H, s)

Method D: Chiral separation

Illustrative synthesis of Intermediate 33: (R)-2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester



Intermediate 31

Intermediate 32
Configuration (S)
Rt = 6.42 min

Intermediate 33
Configuration (R)
Rt = 9.00 min

[00214] The chiral separation of racemic Intermediate 31 was performed by preparative chiral chromatography using the following conditions:

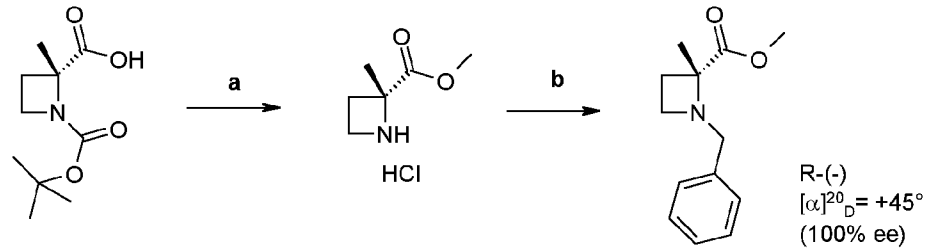
- column: Chiralpak AD-H, (20 x 250 mm), 5µm,
- mobile phase: Hexane : Ethanol : Formic acid (95:5 : 0.05),
- flow rate of 9.5 mL/min, at 20°C

thus affording Intermediates 32 and 33 in their enantiopure forms.

Determination of the absolute configuration of Intermediate 33:

[00215] The absolute configuration of Intermediate 33 was determined by converting it to Intermediate 34 (R)-1-benzyl-2-methyl-azetidine-2-carboxylic acid methyl ester for which $[\alpha]_D$ and absolute configuration are described in the literature (*J. Org. Chem* **2009**, 6077).

Synthesis of Intermediate 34 (R)-1-Benzyl-2-methyl-azetidine-2-carboxylic acid methyl ester



Intermediate 33 Intermediate 34

Step a: (R)-2-Methyl-azetidine-2-carboxylic acid methyl ester hydrochloride

[00216] After a chiral separation of the Intermediate 33 (1 eq.) (100% ee) in solution in MeOH was cooled at 0°C under nitrogen. Thionyl chloride (2.5 eq) was added dropwise, the reaction was stirred at 20°C for 15h. The solvents were concentrated under reduced pressure to afford (R)-2-methyl-azetidine-2-carboxylic acid methyl ester hydrochloride.

Step b: (R)-1-Benzyl-2-methyl-azetidine-2-carboxylic acid methyl ester

[00217] To a solution of (R)-2-methyl-azetidine-2-carboxylic acid methyl ester (1 eq.) in THF were added TEA (2 eq.) and benzyl bromide (1 eq.). The reaction was heated at 50°C for 15h. The solvent was concentrated under reduced pressure, the crude was purified by chromatography on silica gel (elution with heptane/EtOAc 1/0 to 1/1) to afford (R)-1-benzyl-2-methyl-azetidine-2-carboxylic acid methyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$):7.42-7.21 (5H, m), 3.86-3.74 (4H, m), 3.66-3.54 (1H, m), 3.34-3.07 (2H, m), 2.68-2.55 (1H, m), 2.02-1.91 (1H, m), 1.53 (3H, s)

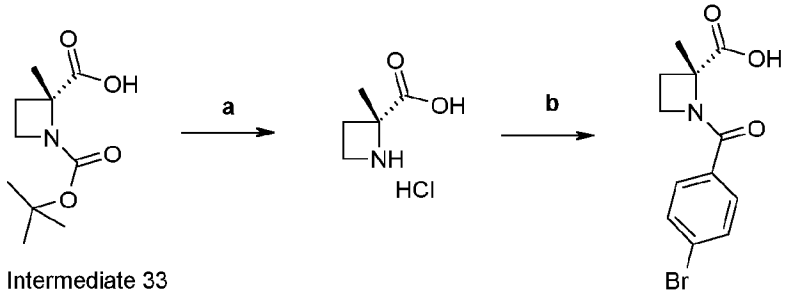
$[\alpha]^{20}_D$= +45 (c=1.55, $CHCl_3$)

Reported value for (R) enantiomer: $[\alpha]^{25}_D$= +36° (c=0.5, $CHCl_3$, 91% ee), described in the literature (*J. Org. Chem* **2009**, 6077)

[00218] Intermediate 34 corresponds to isomer (R). Therefore Intermediate 33 is undoubtedly (R)-2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester.

Intermediate 33 was also converted in Intermediate 35 (R)-1-(4-Bromo-benzoyl)-2-methyl-azetidine-2-carboxylic acid in order to determine the X-Ray structure.

Synthesis of Intermediate 35, (R)-1-(4-Bromo-benzoyl)-2-methyl-azetidine-2-carboxylic acid



Intermediate 33 Intermediate 35

Step a: (R)-2-Methyl-azetidine-2-carboxylic acid hydrochloride

[00219] After a chiral separation, Intermediate 33 (1 eq.) (100% ee) was solubilised in dioxane. A solution of HCl (4N) in dioxane was added and the reaction was stirred at 20°C for 15h. The solvent was removed under reduced pressure and the crude was crystallised in a mixture of DCM/iPr_2O/pentane to afford (R)-2-methyl-azetidine-2-carboxylic acid hydrochloride.

Step b: (R)-1-(4-Bromo-benzoyl)-2-methyl-azetidine-2-carboxylic acid

To a solution of (R)-2-methyl-azetidine-2-carboxylic acid methyl ester (1 eq.) in water were added aqueous NaOH (1M) (3 eq.) then 4-bromo-benzoyl-chloride (1 eq.) dropwise. The reaction was stirred for 4h at 20°C. The reaction was neutralised with acetic acid. The solvent was partially removed under reduced pressure and the crude was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH/AcOEt/AcOH/iPr2O: 95/5/98/2/300) to afford (R)-1-(4-bromo-benzoyl)-2-methyl-azetidine-2-carboxylic acid.

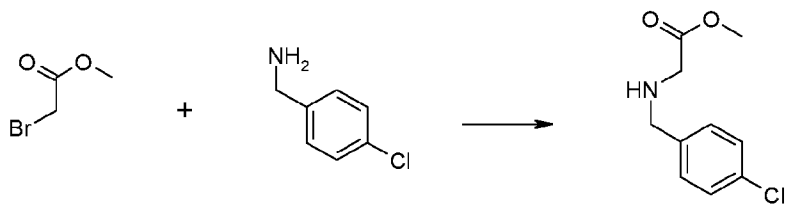
^{1}H NMR δ (ppm) ($CDCl_3$): 7.65 (2H, d), 7.59 (2H, d), 4.48-4.39 (1H, m), 4.28-4.19 (1H, m), 3.07-2.97 (1H, m), 2.34-2.24 (1H, m), 1.95 (3H, s)

[00220] The X-Ray structure of Intermediate 35 confirms (R) absolute configuration and consequently Intermediate 33 corresponds to isomer (R).

Method E: Synthesis of secondary amines

Method E1

Illustrative synthesis of Intermediate 36: (4-Chloro-benzylamino)-acetic acid methyl ester

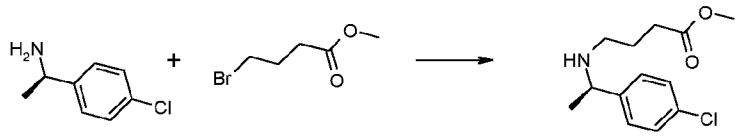


[00221] To a solution of 4-chloro-benzylamine (1 eq.) in MeCN was added bromo-acetic acid methyl ester (1 eq.), K_2CO_3 (1.5 eq.) and KI (0.1 eq.). The reaction was stirred for 15h at 20°C. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 1/0 to 8/2) to afford (4-chloro-benzylamino)-acetic acid methyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.35-7.28 (4H, m), 3.81 (2H, s), 3.77 (3H, s), 3.44 (2H, s), 2.00 (1H, s)

Method E2

Illustrative synthesis of Intermediate 44: 4-[(R)-1-(4-Chloro-phenyl)-ethylamino]-butyric acid methyl ester



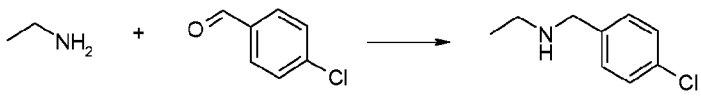
[00222] To a suspension of K_2CO_3 (1.5 eq.) and (R)-1-(4-chloro-phenyl)-ethylamine (0.9 eq.) in MeCN was added 4-bromo-butyric acid methyl ester (1 eq.) and KI (0.1 eq.). The reaction was stirred for 15h at 20°C, then heated to reflux until completion. The crude was partitioned between water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH : 99/1 to 90/10) to afford 4-[(R)-1-(4-chloro-phenyl)-ethylamino]-butyric acid methyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.35-7.24 (4H, m), 3.81-3.70 (1H, m), 3.68 (3H, s), 2.62-2.51 (1H, m), 2.47-2.31 (3H, m), 1.85-1.72 (2H, m), 1.39 (1H, br s), 1.33 (3H, d)

MW (calcd): 255.7; MW (obsd): 256.3 (M+1, ^{35}Cl)

Method E3

Illustrative synthesis of Intermediate 50: (4-Chloro-benzyl)-ethyl-amine



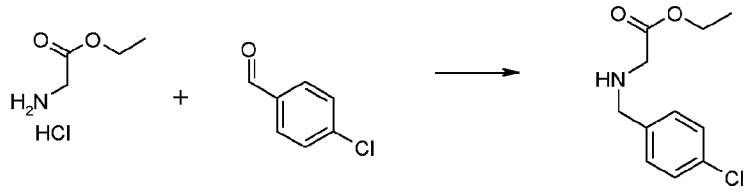
[00223] To a solution of 4-chlorobenzaldehyde (1 eq.) in MeOH was added ethylamine 70% in water (10 eq.). The reaction was stirred for 15h at 20°C under argon then $NaBH_4$ (2 eq.) was added. The reaction was stirred at 20°C for 5h. The reaction was quenched with water then acidified with aqueous HCl (2M). The aqueous layer was washed with EtOAc. The organic layer was discarded. Aqueous NaOH (2M) was then added to the aqueous layer until pH=10 and the crude was extracted twice with EtOAc. The organic layers

were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (4-chloro-benzyl)-ethyl-amine.

^1H NMR δ (ppm) ($CDCl_3$): 7.27-7.12 (4H, m), 3.69 (2H, s), 2.60 (2H, q), 1.64 (1H, br s), 1.06 (3H, t)

Method E4

Illustrative synthesis of Intermediate 56: (4-Chloro-benzylamino)-acetic acid ethyl ester



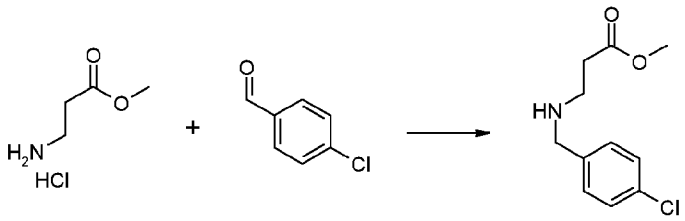
[00224] To a suspension of glycine ethyl ester hydrochloride (1.2 eq.) in DCE was added TEA (2 eq.) The reaction was stirred for 10 min at 20°C then 4-chlorobenzaldehyde (1 eq.), acetic acid (4 eq.) and sodium triacetoxyborohydride (2 eq.) were added. The reaction was stirred for 15h at 20°C. The crude was partitioned between DCM and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was then extracted twice with DCM. The organic layers were combined, washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to afford (4-chloro-benzylamino)-acetic acid ethyl ester.

^1H NMR δ (ppm) ($CDCl_3$): 7.25-7.16 (4H, m), 4.12 (2H, q), 3.71 (2H, s), 3.32 (2H, s), 1.79 (1H, br s), 1.20 (3H, t)

MW (calcd): 227.7; MW (obsd): 228.3 (M+1, ^{35}Cl)

Method E5

Illustrative synthesis of Intermediate 61: 3-(4-Chloro-benzylamino)-propionic acid methyl ester

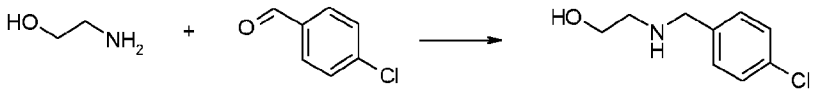


[00225] To a solution of 4-chlorobenzaldehyde (1 eq.) in MeOH were added $NaHCO_3$ (1.3 eq.) and β-alanine methyl ester hydrochloride (1.2 eq.). The reaction was stirred for 15h at 20°C under nitrogen, then cooled to 0°C. Sodium triacetoxyborohydride (1.5 eq.) was added portionwise. The reaction was then warmed to 20°C and stirred for 8h. The crude was concentrated under reduced pressure then partitioned between EtOAc and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/DCM/MeOH : 50/50/0, then 0/100/0, then 0/99/1) to afford 3-(4-chloro-benzylamino)-propionic acid methyl ester.

^1H NMR δ (ppm) ($CDCl_3$): 7.34-7.23 (4H, m), 3.77 (2H, s), 3.68 (3H, s), 2.87 (2H, t), 2.54 (2H, t), 1.90 (1H, br s).

Method E6

Illustrative synthesis of Intermediate 67: 2-(4-Chloro-benzylamino)-ethanol

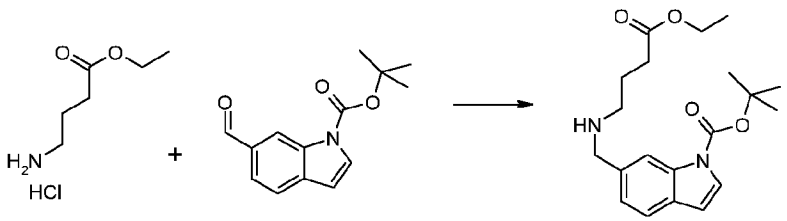


[00226] To a solution of ethanolamine (1.2 eq.) in either MeOH or THF were added $NaHCO_3$ (1.5 eq.) and 4-chlorobenzaldehyde (1 eq.). The reaction was refluxed for 4h, then cooled to 0°C. $NaBH_4$ (1.2 eq.) was added portionwise. The reaction was stirred for 1h at 0°C, then 15h at 20°C. The crude was concentrated under reduced pressure then partitioned between water and DCM. The aqueous layer was then extracted twice with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH : 1/0 to 95/5) to afford 2-(4-chloro-benzylamino)-ethanol.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.26 (4H, m), 3.82 (2H, s), 3.70 (2H, t), 2.83 (2H, t), 2.19 (2H, br s)

Method E7

Illustrative synthesis of Intermediate 71: 6-[(3-Ethoxycarbonyl-propylamino)-methyl]-indole-1-carboxylic acid tert-butyl ester



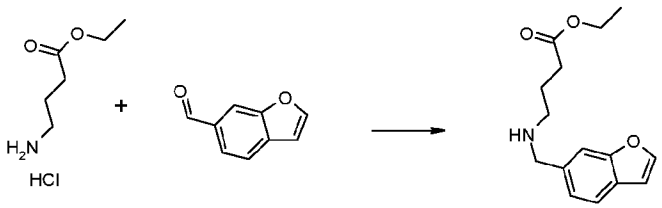
[00227] To a solution of 4-amino-butyric acid ethyl ester hydrochloride (1 eq.) in either MeOH or EtOH were added TEA (2.5 eq.), 6-formyl-indole-1-carboxylic acid tert-butyl ester (0.95 eq.) and $MgSO_4$ (1.5 eq.). The reaction was stirred at 20°C for 15h, then cooled to -15°C. $NaBH_4$ (2 to 6 eq.) was added portionwise. The reaction was stirred for 1h at -15°C, then 1h at 0°C. The reaction was quenched with the addition of cold water at 0°C. The crude was extracted three times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure at 20°C. The crude was purified by chromatography on silica gel (elution with DCM/MeOH : 1/0 to 99/1) to afford 6-[(3-ethoxycarbonyl-propylamino)-methyl]-indole-1-carboxylic acid tert-butyl ester.

^{1}H NMR δ (ppm) (DMSO-d_6): 8.06 (1H, s), 7.60 (1H, d), 7.52 (1H, d), 7.22-7.16 (1H, m), 6.68-6.64 (1H, m), 4.02 (2H, q), 3.77 (2H, s), 2.54-2.46 (2H, m), 2.37-2.30 (2H, t), 2.15 (1H, br s), 1.73-1.64 (2H, m), 1.63 (9H, s), 1.14 (3H, t).

MW (calcd): 360.5; MW (obsd): 361.1 (M+1)

Method E8

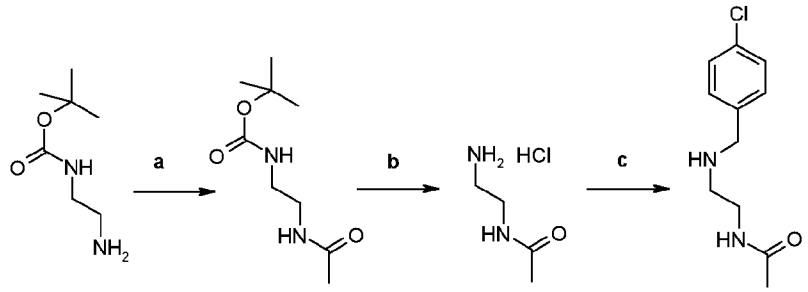
Illustrative synthesis of Intermediate 82: 4-[(Benzofuran-6-ylmethyl)-amino]-butyric acid ethyl ester



[00228] To a solution of 4-amino-butyric acid ethyl ester hydrochloride (1 eq.) in THF was added TEA (2.5 eq.). The mixture was stirred 5 min at 20°C, then benzofuran-6-carbaldehyde (0.95 eq.) and $MgSO_4$ (3 eq.) were added. The reaction was refluxed for 2h, then cooled to 20°C and filtered. The filtrate was added to a suspension of $NaBH_4$ (2 to 6 eq.) in MeOH at -15°C. The reaction was stirred for 2h at -15°C. The reaction was quenched with the addition of aqueous HCl 2N until pH=2. The aqueous layer was washed twice with EtOAc. The organic layers were discarded. Solid KOH was added to the aqueous layer. The crude was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure at 20°C. The crude was purified by chromatography on silica gel (elution with DCM/MeOH : 95/5) to afford 4-[(benzofuran-6-ylmethyl)-amino]-butyric acid ethyl ester.
^{1}H NMR δ (ppm) ($CDCl_3$): 7.65-7.63 (1H, m), 7.60-7.56 (1H, m), 7.54-7.51 (1H, m), 7.27-7.23 (1H, m), 6.79-6.76 (1H, m), 4.15 (2H, q), 3.95 (2H, s), 2.74 (2H, t), 2.42 (2H, t), 1.95-1.76 (3H, m), 1.27 (3H, t).
MW (calcd): 261.3; MW (obsd): 262.3 (M+1)

Method E9

Illustrative synthesis of Intermediate 84: N-[2-(4-Chloro-benzylamino)-ethyl]-acetamide



Step a: (2-Acetylamino-ethyl)-carbamic acid tert-butyl ester

[00229] To a solution of (2-amino-ethyl)-carbamic acid tert-butyl ester (1 eq.) in DCM was added TEA (3 eq.). The reaction was cooled to 0°C. Acetyl chloride (1 eq.) was filtered through a pad of alumina then added dropwise in solution in DCM to the reaction at 0°C. The reaction was stirred at 20°C for 4h. The crude was diluted with DCM, washed twice with water, then twice with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (2-acetylamino-ethyl)-carbamic acid tert-butyl ester. The compound was used as such without further purification.
^{1}H NMR δ (ppm) ($CDCl_3$): 6.32-6.03 (1H, m), 5.06-4.74 (1H, m), 3.35 (2H, t), 3.32-3.22 (2H, m), 1.99 (3H, s), 1.45 (9H, s)

Step b: N-(2-Amino-ethyl)-acetamide

[00230] To a solution of (2-acetylamino-ethyl)-carbamic acid tert-butyl ester (1 eq.) in DCM was added dropwise TFA (30 eq.) at 0°C. The reaction was stirred at 20°C for 15h, then concentrated under reduced pressure. A solution of HCl 2N in Et_2O was added. The crude was triturated with DCM. The resulting solid was filtered and dry to afford N-(2-amino-ethyl)-acetamide. The compound was used as such without further purification.

^{1}H NMR δ (ppm) (MeOD-d_4): 3.44 (2H, t), 3.05 (2H, t), 1.99 (3H, s)

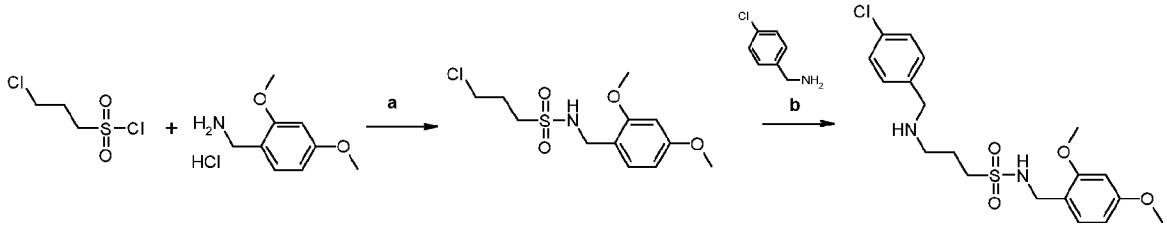
Step c: N-[2-(4-Chloro-benzylamino)-ethyl]-acetamide

[00231] To a solution of N-(2-amino-ethyl)-acetamide (1.2 eq.) in MeOH were added $NaHCO_3$ (1.5 eq.) and 4-chlorobenzaldehyde (1 eq.). The reaction was refluxed for 4h, then cooled to 0°C. $NaBH_4$ (1.2 eq.) was added portionwise. The reaction was stirred for 1h at 0°C, then 15h at 20°C. The crude was concentrated under reduced pressure then partitioned between water and DCM. The aqueous layer was then extracted twice with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 1/0 to 0/1) to afford N-[2-(4-chloro-benzylamino)-ethyl]-acetamide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.33-7.23 (4H, m), 6.10-6.00 (1H, m), 3.78 (2H, s), 3.39-3.33 (2H, m), 2.77 (2H, t), 1.99 (3H, s)

Method E10

Illustrative synthesis of Intermediate 86: 3-(4-Chloro-benzylamino)-propane-1-sulfonic acid 2,4-dimethoxy-benzylamide



Step a: 3-Chloro-propane-1-sulfonic acid 2,4-dimethoxy-benzylamide

[00232] To a solution of 2,4-dimethoxy-benzylamine hydrochloride (1 eq.) and TEA (2 eq.) in DCM was added dropwise at 0°C a solution of 3-chloro-propane-1-sulfonyl chloride (1 eq.) in DCM. The reaction was stirred at 20°C for 20h. The crude was diluted with DCM, washed twice with water, twice with aqueous HCl (0.1N) and twice with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 100/0 to 20/80) to afford 3-chloro-propane-1-sulfonic acid 2,4-dimethoxy-benzylamide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.16 (1H, d), 6.47-6.42 (2H, m), 4.87 (1H, t), 4.23 (2H, d), 3.85 (3H, s), 3.81 (3H, s), 3.52 (2H, t), 3.03-2.97 (2H, m), 2.19-2.10 (2H, m).

Step b: 3-(4-Chloro-benzylamino)-propane-1-sulfonic acid 2,4-dimethoxy-benzylamide

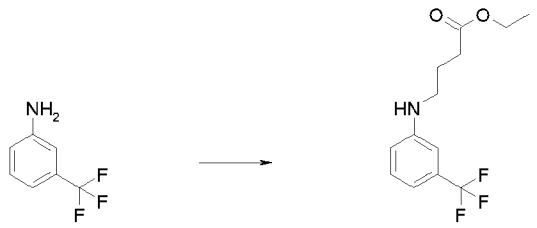
[00233] To a solution of the Intermediate obtained in step a (1 eq.) in THF were added a catalytic amount of sodium iodide and 4-chloro-benzylamine (5 eq.). The reaction was heated at 160°C under microwave irradiation for 2h. The solvent was concentrated under reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc/DCM/MeOH: 90/10/0/0 to 50/50/90/10) to afford 3-(4-chloro-benzylamino)-propane-1-sulfonic acid 2,4-dimethoxy-benzylamide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.30-7.26 (2H, m), 7.22-7.17 (2H, m), 7.16 (1H, d), 6.46-6.38 (2H, m), 4.21(2H, s), 3.81 (3H, s), 3.78 (3H, s), 3.66 (2H, s), 2.99-2.94 (2H, m), 2.58 (2H, t), 191-1.82 (2H, m).

MW (calcd): 412.9; MW (obsd): 413.4 (M+1, ^{35}Cl)

Method E11

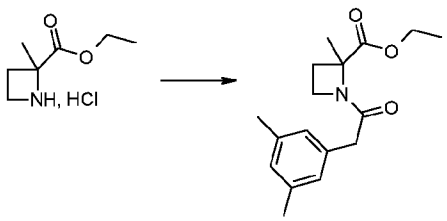
Illustrative synthesis of Intermediate 244: 4-(3-Trifluoromethyl-phenylamino)-butyric acid ethyl ester



[00234] To a solution of 3-trifluoromethyl-phenylamine (1 eq.) and ethyl 4-bromobutyrate (2 eq.) in DMF were added K_2CO_3 (3 eq.) and KI (cat.). The mixture was heated at 100°C for 16h, water and EtOAc were added, the organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 90/10 to 70/30) to afford 4-(3-trifluoromethyl-phenylamino)-butyric acid ethyl ester as a yellow oil.

Method F: Amide formation

Illustrative synthesis of Intermediate 94: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid ethyl ester.



[00235] To a solution of (3,5-dimethyl-phenyl)-acetic acid (1 eq.) in either DCM or THF was added HOBt (1.1 eq.), EDC.HCl (1.5 eq.). Then, 2-methyl-azetidine-2-carboxylic acid ethyl ester hydrochloride, Intermediate 13 (1 eq.) and TEA (4 eq.) were added. The reaction was stirred at 20°C for 15h. The crude

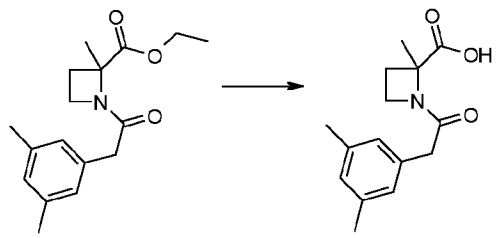
was concentrated under reduced pressure and partitioned between a saturated aqueous solution of $NaHCO_3$ and EtOAc. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with water then with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid ethyl ester.

^1H NMR δ (ppm) ($CDCl_3$): 6.93-6.84 (3H, m), 4.29-4.09 (3H, m), 4.07-3.88 (1H, m), 3.38 (2H, s), 2.53-2.25 (7H, m), 2.17-2.07 (1H, m), 1.80-1.66 (3H, m), 1.31-1.18 (3H, m)

MW (calcd): 289.4; MW (obsd): 290.0 (M+1)

Method G: Saponification

Illustrative synthesis of Intermediate 119: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid.



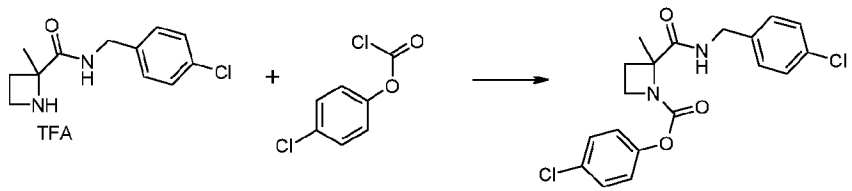
[00236] To a solution of 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid ethyl ester, Intermediate 94 (1 eq.) in either EtOH or MeOH was added aqueous NaOH (2N) (2 eq.). The reaction was stirred at 20°C for 6h. The solvent was removed under reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was discarded and the aqueous layer was neutralized by addition of aqueous HCl (2N) and thoroughly extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid.

^1H NMR δ (ppm) ($CDCl_3$): 6.94 (1H, s), 6.85 (2H, s), 4.10-3.89 (2H, m), 3.44 (2H, s), 2.95-2.84 (1H, m), 2.31 (6H, s), 2.17-2.06 (1H, m), 1.78 (3H, s)

MW (calcd): 261.3 ; MW (obsd): 262.0 (M+1)

Method H: Carbamate formation

Illustrative synthesis of compound 2: 2-(4-Chloro-benzylcarbamoyl)-2-methyl-azetidine-1-carboxylic acid 4-chloro-phenyl ester.



[00237] To a solution of 2-methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide, trifluoroacetic acid salt, Intermediate 28 (1 eq.) in THF were added TEA (2 eq.) and 4-chlorophenyl-chloroformate (2 eq.). The reaction was stirred at 20°C for 15h. The crude was concentrated under reduced pressure and partitioned

between a saturated aqueous solution of $NaHCO_3$ and EtOAc. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with water then with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/Et_2O: 98/2) to afford 2-(4-chloro-benzylcarbamoyl)-2-methyl-azetidine-1-carboxylic acid 4-chloro-phenyl ester.

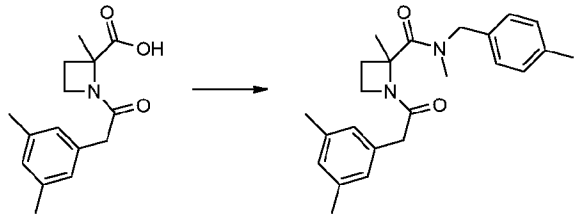
^{1}H NMR δ (ppm) (MeOD, d_4): 7.44-7.15 (7H, m), 7.02-6.94 (1H, m), 4.37-4.33 (2H, m), 4.29-3.94 (2H, m), 2.61-2.23 (2H, m), 1.88-1.75 (3H, m).

MW (calcd): 393; MW (obsd): 393.3 (M+1, ^{35}Cl).

Method I: Amide formation

Method I1

Illustrative synthesis of compound 6: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-methyl-benzyl)-amide



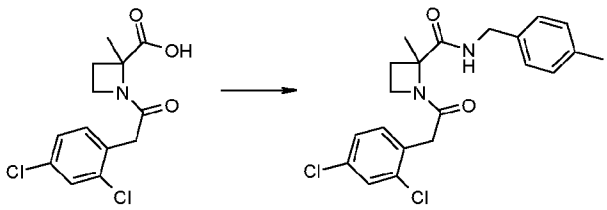
[00238] To a solution of Intermediate 119 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (1 eq.) in either DCM , THF or DMF was added HOBt (1.1 eq.), EDC.HCl (1.5 eq.), TEA (3 eq.) and methyl-(4-methyl benzyl)-amine (1.5 eq.). The reaction was stirred at 20°C for 15h, then the crude was concentrated under reduced pressure and partitioned between a saturated aqueous solution of $NaHCO_3$ and EtOAc. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with water then with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH: 100/0 to 99/1) to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-methyl-benzyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.23-7.04 (4H, m), 6.99-6.82 (3H, m), 4.81-4.21 (2H, m), 4.08-3.82 (2H, m), 3.81-3.15 (2H, m), 2.98-2.74 (3H, m), 2.64-2.44 (1H, m), 2.42-2.15 (10H, m), 1.96-1.74 (3H, m).

MW (calcd): 378.5 ; MW (obsd): 379.2 (M+1)

Method I2

Illustrative synthesis of compound 43: 1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-methyl-benzylamide



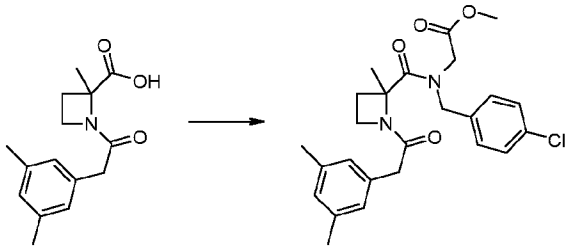
[00239] To a solution of 1-[2-(2,4-dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid, Intermediate 120 (1 eq.) in either THF or DMF was added TEA (4 eq.) and TBTU (2 eq.). The reaction was stirred at 20°C for 30 min, then 4-methyl-benzylamine (1.5 eq.) was added. The reaction was stirred at 20°C for 72h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The organic layer was washed twice with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by preparative LCMS to afford 1-[2-(2,4-dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-methyl-benzylamide.

^{1}H NMR δ (ppm) ($CDCl_3$): 8.59-8.50 (1H, m), 7.42 (1H, s), 7.22 (2H, s), 7.18-7.09 (4H, m), 4.44-4.39 (2H, m), 4.18-4.00 (2H, m), 3.56-3.50 (2H, m), 3.01-2.91 (1H, m), 2.36 (3H, s), 2.19-2.10 (1H, m), 1.81 (3H, s).

MW (calcd): 405.3; MW (obsd): 405.1 (M+1, ^{35}Cl)

Method I3

Illustrative synthesis of compound 48: ((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid methyl ester



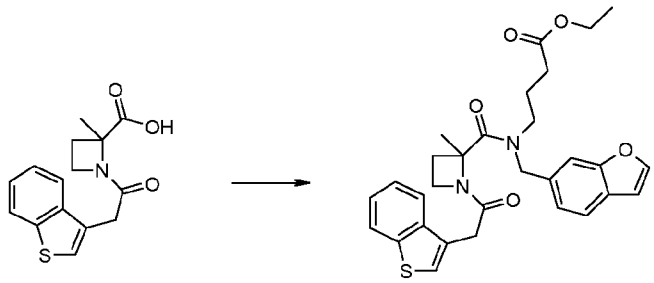
[00240] To a solution of 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid, Intermediate 119 (1 eq.) in DCM under nitrogen, was added DMF (0.01 eq.) then oxalyl chloride (2 eq.). The solution was stirred at 20°C for 30 min, then cooled to 0°C. A solution of (4-Chloro-benzylamino)-acetic acid methyl ester (1.5 eq.) and either TEA or DIPEA (2 to 7 eq.) in DCM was then added to the previous mixture. The solution was stirred at 0°C for 1 h then at 20°C until completion (1 h). The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted three times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 1/0 to 1/1) to afford ((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid methyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.42-7.23 (2H, m), 7.21-7.09 (2H, m), 6.99-6.72 (3H, m), 5.09-4.33(2H, m), 4.26-3.81 (3H, m), 3.79-3.60 (4H, m), 3.48-3.15 (m, 2H), 2.75-2.60 (1H, m), 2.35-2.18 (7H, m), 1.91-1.76 (3H, m).

MW (calcd): 457.0; MW (obsd): 457.2 (M+1, ^{35}Cl)

Method I4

Illustrative synthesis of Intermediate 164: 4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid ethyl ester



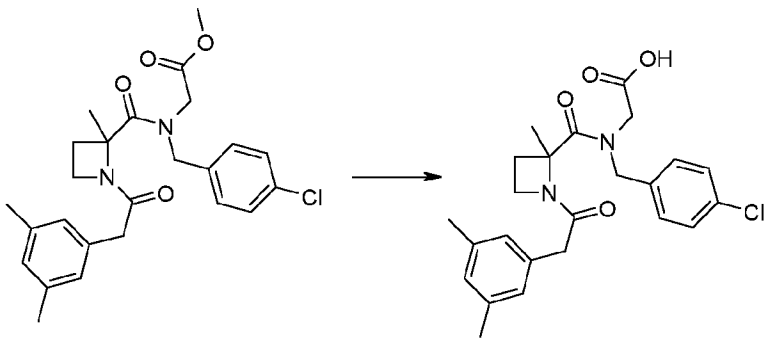
[00241] To a solution of 1-chloro-N,N,2-trimethylpropenylamine (2 eq.) in DCM under nitrogen was added 1-(2-benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid, Intermediate 121 (1 eq.). The solution was stirred at 20°C for 1h, then added to a solution of 4-[(Benzofuran-6-ylmethyl)-amino]-butyric acid ethyl ester, Intermediate 82 (1.2 eq.) in DCM at 0°C. TEA (2 eq.) was then added and the mixture was stirred at 0°C for 3h. The crude was diluted with DCM, washed twice with a saturated aqueous solution of $NaHCO_3$, twice with aqueous HCl (0.5N), twice with water, dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by chromatography on silica gel (elution with heptane/EtOAc 25/75 to 10/90) to afford 4-{[1-(2-benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid ethyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 8.02 (1H, s), 7.94-7.28 (7H, m), 7.18-6.96 (1H, m), 6.75 (1H, bs), 5.03-4.36 (2H, m), 4.15-4.01 (2H, m), 4.00-3.79 (2H, m), 3.78-2.96 (4H, m), 2.66-2.44 (1H, m), 2.40-2.12 (3H, m), 2.03-1.74 (5H, m), 1.28-1.16 (3H, m).

MW (calcd): 532.7; MW (obsd): 533.4 (M+1l)

Method J: Saponification

Illustrative synthesis of compound 49: ((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid



[00242] To a solution of ((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid methyl ester, compound 48 (1 eq.) in either EtOH or MeOH was added aqueous NaOH (2N) (2 eq.). The reaction was stirred at 20°C for 2h. The solvent was removed under

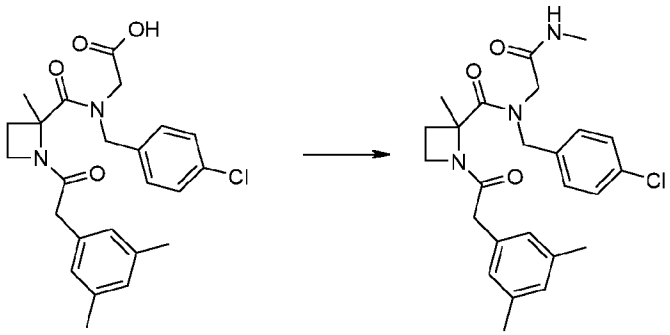
reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was discarded and the aqueous layer was acidified by addition of aqueous HCl (2N) and thoroughly extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to afford ((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.25 (2H, m), 7.21-7.10 (2H, m), 6.94-6.75 (3H, m), 5.16-4.60 (1H, m), 4.59-4.26 (1H, m), 4.25-3.64 (4H, m), 3.49-3.21 (2H, m), 2.70-2.59 (1H, m), 2.36-2.16 (7H, m), 1.91-1.76 (3H, m).

MW (calcd): 442.9; MW (obsd): 443.2 (M+1,^{35}Cl)

Method K: Amide formation

Illustrative synthesis of compound 53: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methylcarbamoylmethyl-amide



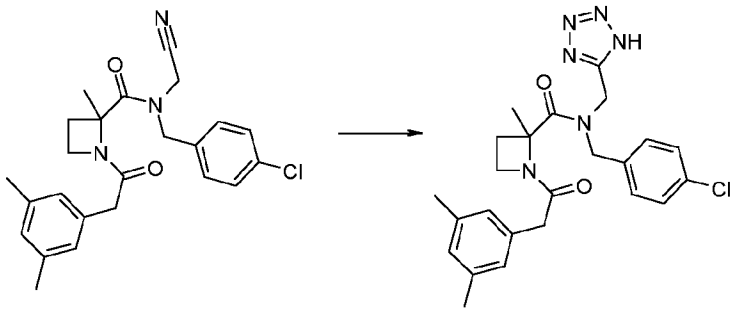
[00243] To a solution of ((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid, compound 49 (1 eq.) in DMF were added methylamine (33% w/w in EtOH) (1 eq.), TEA (1 eq.) and TBTU (1 eq.). The reaction was stirred at 20°C for 15h. The reaction was carried on with addition of methylamine (33% w/w in EtOH), TEA (1 eq.) and TBTU (1 eq.), then stirring at 20°C for 15h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The organic layer was washed twice with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by preparative LCMS to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methylcarbamoylmethyl-amide.

^{1}H NMR δ (ppm) (MeOD-d_4): 7.50-7.21 (4H, m), 7.01-6.85 (3H, m), 4.84-4.74 (1H, m), 4.68-4.44 (1H, m), 4.24-4.00 (2H, m), 3.95-3.71 (2H, m), 3.65-3.50 (1H, m), 3.42-3.34 (3H, m), 2.85-2.74 (3H, m), 2.32 (6H, s), 2.01-1.86 (3H, m).

MW (calcd): 456.0; MW (obsd): 456.4 (M+1,^{35}Cl)

Method L

Illustrative synthesis of compound 76: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(1H-tetrazol-5-ylmethyl)-amide



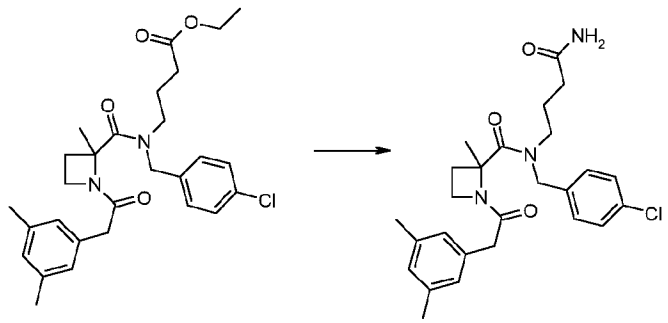
[00244] To a solution of 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyanomethyl-amide, Compound 68 (1 eq.) in toluene was added Bu_3SnN_3 (10 eq.). The reaction was refluxed for 6h and cooled to 20°C then HCl 2N in Et_2O was added. After 15h of stirring, the solid was filtered, dissolved in DCM and precipitated with iPr_2O. The solid was purified by chromatography on silica gel (elution with DCM/MeOH : 1/0 to 95/5) to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(1H-tetrazol-5-ylmethyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.35 (2H, d), 7.04 (2H, d), 6.78 (3H, d), 5.08 (1H, d), 4.61 (1H, d), 4.28 (1H, d), 4.21-3.91 (3H, m), 3.40-3.26 (2H, m), 2.74-2.55 (1H, m), 2.31-2.19 (1H, m), 2.15 (6H, s), 1.88 (3H, s).

MW (calcd): 467.0; MW (obsd): 467.3 (M+1,^{35}Cl)

Method M

Illustrative synthesis of compound 90: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide



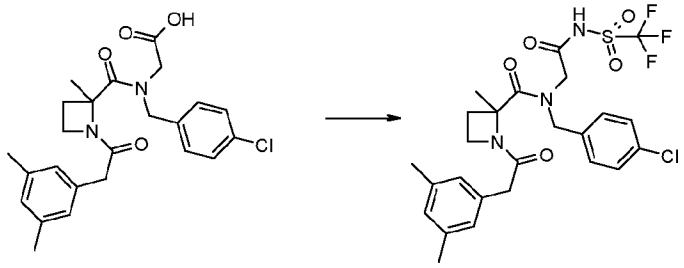
[00245] To a solution of 4-((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid ethyl ester, Intermediate 146 (1 eq.) in MeOH was added an aqueous solution of NH_3 (20% in water). The reaction was stirred at 60°C for 15h then cooled to 20°C. The solvents were evaporated under reduced pressure and the crude was purified by preparative LCMS to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.47-7.27 (2H, m), 7.24-6.98 (2H, m), 6.97-6.56 (3H, m), 5.61-5.20 (1H, m), 4.97-4.52(1H, m), 4.49-4.06 (1H, m), 4.04-3.52 (3H, m), 3.43-2.97 (2H, m), 2.62-2.43 (1H, m), 2.40-2.10 (7H, m), 2.09-1.73 (5H, m), 1.72-1.51 (2H, m).

MW (calcd): 470.0; MW (obsd): 470.1 (M+1,^{35}Cl)

Method N

Illustrative synthesis of compound 94: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-oxo-2-trifluoromethanesulfonylamino-ethyl)-amide



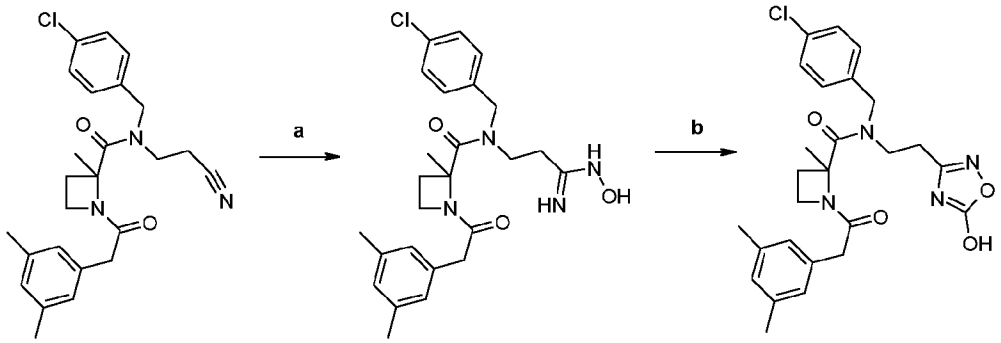
[00246] To a solution of compound 49 ((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid (1 eq.) in DMF was added EDC.HCl (1.3 eq.), DMAP (1.3 eq.) and trifluoromethanesulfonamide (1.3 eq.). The reaction was stirred for 15h at 20°C. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by preparative LCMS to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-oxo-2-trifluoromethanesulfonylamino-ethyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.32 (2H, d), 7.24-7.10 (3H, m), 6.91-6.89 (1H, m), 6.87-6.85 (2H, m), 4.50-4.22 (3H, m), 4.19-4.02 (2H, m), 3.47-3.25 (3H, m), 2.59-2.47 (1H, m), 2.37-2.21 (7H, m), 1.99 (3H, s)

MW (calcd): 574.0; MW (obsd): 573.7 (M+1,^{35}Cl)

Method O

Illustrative synthesis of compound 107: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-amide



Step a:

[00247] To a solution of Compound 77 (1 eq.) in EtOH was added a solution of hydroxylamine 50% in water (2 eq.). The reaction was refluxed for 15h. The crude was concentrated under reduced pressure and used as such without further purification.

MW (calcd): 471.0; MW (obsd): 471.0 (M+1,^{35}Cl)

Step b:

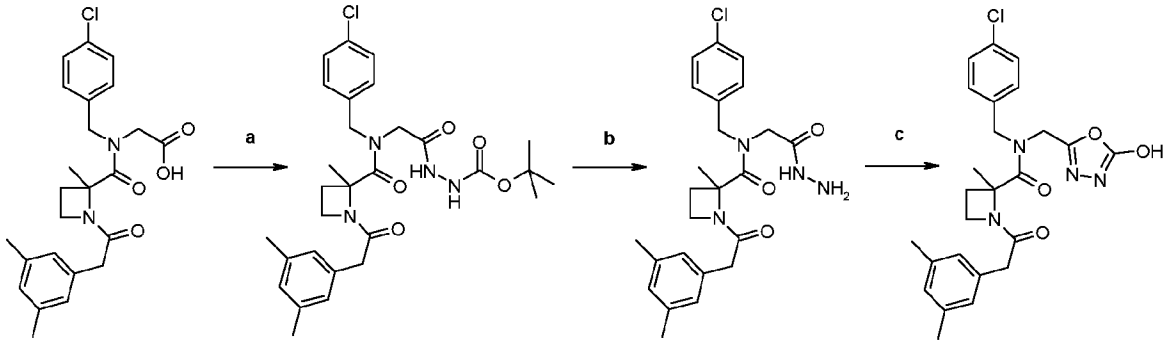
[00248] To a solution of 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(N-hydroxycarbamimidoyl)-ethyl]-amide (1 eq.) in dioxane was added triphosgene (1.7 eq.) under nitrogen. The reaction was stirred at 20°C for 15h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The layers were separated, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc/DCM/MeOH : 50/50/0/0 to 50/50/90/10) to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.35 (2H, d), 7.21-6.98- (2H, m), 6.97-6.80 (3H, m), 4.72-4.51 (1H, m), 4.37-3.90 (4H, m), 3.36 (2H, bs), 3.07-2.86 (1H, m), 2.74-2.40 (3H, m), 2.35-2.10 (7H, m), 1.82 (3H, bs)

MW (calcd): 497.0; MW (obsd): 497.1 (M+1,^{35}Cl)

Method P

Illustrative synthesis of compound 111: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,3,4]oxadiazol-2-ylmethyl)-amide



Step a:N'-[2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetyl]-hydrazinecarboxylic acid tert-butyl ester.

[00249] N'-[2-((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetyl]-hydrazinecarboxylic acid tert-butyl ester was prepared via method I1, using Compound 49 and Boc-hydrazine.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.27 (2H, m), 7.22-7.05 (2H, m), 6.97-6.80 (3H, m), 4.92-4.33 (2H, m), 4.22-3.81 (2H, m), 3.78-3.21 (3H, m), 3.01-2.83 (1H, m), 2.83-2.53 (1H, m), 2.38-2.22 (6H, m), 2.22-2.07 (1H, m), 1.96-1.79 (3H, m), 1.55-1.32 (9H, m).

MW (calcd): 557.1; MW (obsd): 557.1 (M+1,^{35}Cl)

Step b: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-hydrazinocarbonylmethyl-amide.

[00250] 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-hydrazinocarbonylmethyl-amide was prepared via method B2. The crude was concentrated under reduced pressure then partitioned between EtOAc and a saturated aqueous solution of $NaHCO_3$. The layers were

separated, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc/DCM/MeOH : 50/50/95/5 to 0/0/98/2).

^{1}H NMR δ (ppm) ($CDCl_3$): 8.40-8.11 (1H, m), 7.48-7.27 (3H, m), 7.24-7.12 (1H, m), 7.10-6.95 (2H, m), 6.95-6.80 (3H, m), 4.77 (1H, d), 4.36 (1H, d), 4.24 (1H, d), 4.12-3.83 (2H, m), 3.73 (1H, d), 3.53-3.25 (2H, m), 2.68-2.46 (1H, m), 2.36-2.22 (6H, m), 2.22-2.10 (1H, m), 1.91-1.79 (3H, m)

MW (calcd): 457.0; MW (obsd): 457.1 (M+1,^{35}Cl)

Step c: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,3,4]oxadiazol-2-ylmethyl)-amide.

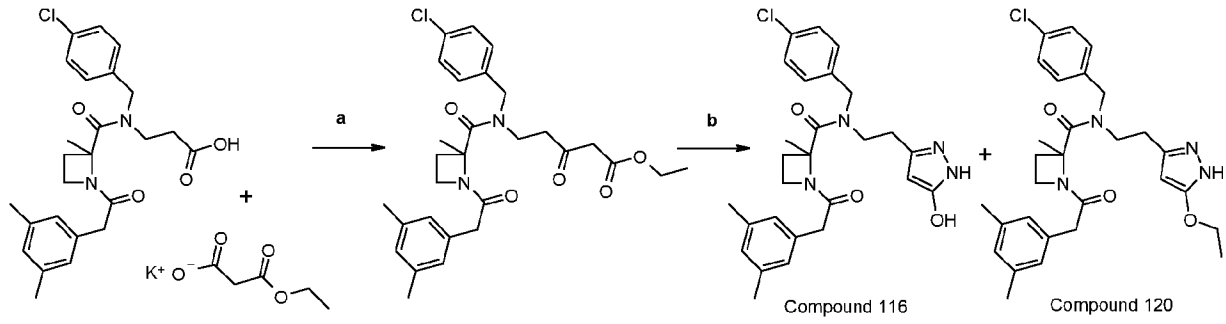
[00251] To a solution of the Intermediate obtained in step b above (1 eq.) in dioxane was added triphosgene (1.5 eq.) under nitrogen. The reaction was stirred at 20°C for 15h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The layers were separated, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with Hept/EtOAc/DCM/MeOH : 50/50/0/0 to 50/50/95/5) to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,3,4]oxadiazol-2-ylmethyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 9.51-9.32 (1H, m), 7.44-7.29 (2H, m), 7.23-7.11 (2H, m), 6.97-6.75 (3H, m), 4.87 (1H, d), 4.65-4.32 (2H, m), 4.21-3.69 (3H, m), 3.45-3.21 (2H, m), 2.75-2.56 (1H, m), 2.36-2.21 (7H, m), 1.89 (3H, bs)

MW (calcd): 483.0; MW (obsd): 483.1 (M+1,^{35}Cl)

Method Q

Illustrative synthesis of compound 116 : 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-1H-pyrazol-3-yl)-ethyl]-amide and compound 120 : 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-ethoxy-1H-pyrazol-3-yl)-ethyl]-amide.



Step a: 5-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-3-oxo-pentanoic acid ethyl ester

[00252] To a solution of CDI (4 eq) in THF was added 3-((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid, compound 65 (1 eq.), the mixture was stirred for 4h at 20°C, then $MgCl_2$ (4 eq.) and ethyl potassium malonate (5 eq.) were added. The reaction was stirred for 15h at 20°C. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with Hept/EtOAc/DCM/MeOH: 50/50/95/5 then 50/50/90/10) to afford 5-((4-chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-3-oxo-pentanoic acid ethyl ester.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.30 (2H, m), 7.25-7.05 (2H, m), 7.04-6.75 (3H, m), 5.09-4.36 (2H, m),4.21 (2H, q), 4.07-3.85 (2H, m), 3.85-3.16 (6H, m), 3.05-2.73 (2H, m), 2.62-2.49 (1H, m), 2.37-2.18 (7H, m), 1.84 (3H, d), 1.30 (3H, t)

MW (calcd): 527.1; MW (obsd): 527.1 (M+1,^{35}Cl)

Step b: Compound 116 and 120.

[00253] To a solution of the Intermediate obtained in step a above (1 eq.) in EtOH were added few drops of concentrated. HCl and hydrazine hydrate (4 eq.). The reaction was stirred at 20°C for 2h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The layers were separated, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with Hept/EtOAc/DCM/MeOH: 50/50/95/5 then 50/50/90/10, then DCM/MeOH : 98/2) to afford two compounds: Compound 116 and Compound 120.

[00254] Compound 116: 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-1H-pyrazol-3-ylmethyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.07 (2H, m), 7.03-6.91 (2H, m), 6.92-6.80 (3H, m), 5.49-5.33 (1H, m), 4.72-4.56 (1H, m), 4.11-3.72 (4H, m), 3.41-3.09 (3H, m), 3.02-2.74 (2H, m), 2.47-2.35 (1H, m), 2.28 (6H, s), 2.17-2.05 (1H, m), 1.83 (3H, s)

MW (calcd): 494.2; MW (obsd): 495.1 (M+1,^{35}Cl)

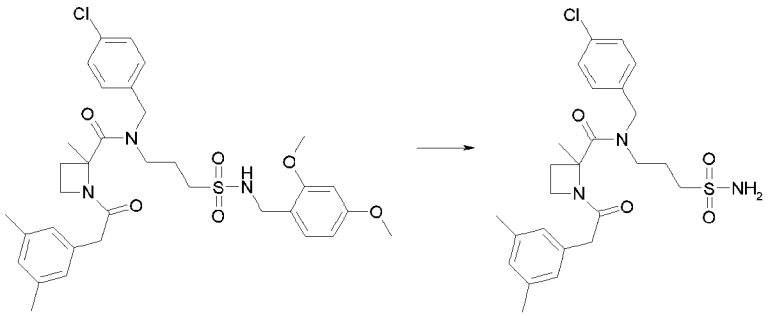
[00255] Compound 120 : 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-ethoxy-1H-pyrazol-3-ylmethyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.44-7.11 (3H, m), 7.03-6.85 (4H, m), 5.60-5.40 (1H, m), 4.74 (1H, m), 4.28-3.75 (6H, m), 3.58-2.77 (6H, m), 2.35-2.09 (7H, m), 1.91-1.74 (3H, m), 1.41 (3H, t)

MW (calcd): 522.2 ; MW (obsd) : 523.4 (M+1,^{35}Cl)

Method R

Illustrative synthesis of compound 171: 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide



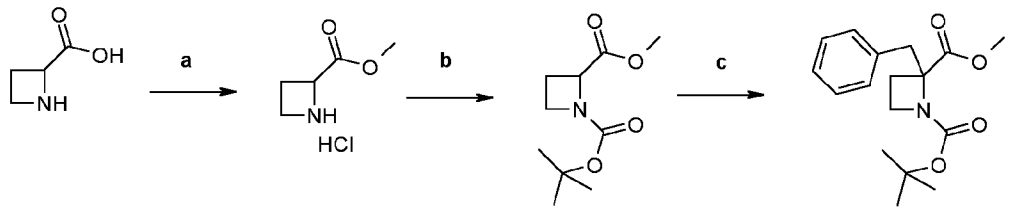
[00256] 1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2,4-dimethoxy-benzylsulfamoyl)-propyl]-amide, compound 168 was dissolved in TFA and stirred at 20°C for 15h. The crude was concentrated under reduced pressure then partitioned between water and EtOAc. The organic layer was washed twice with water, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc/DCM/MeOH : 1/0/0/0 then 0/1/0/0 then 50/50/95/5 then 50/50/90/10) to afford 1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide.

^{1}H NMR δ (ppm) ($CDCl_3$): 7.43-7.29 (2H, m), 7.22-6.99 (2H, m), 6.96-6.79 (3H, m), 5.30-5.01 (2H, m), 4.75 (1H, d), 4.59-4.14 (1H, m), 4.06-3.80 (2H, m), 3.79-3.58 (1H, m), 3.34-3.01 (5H, m), 2.61-2.43 (1H, m), 2.33-2.24 (6H, m), 2.24-2.12 (1H, m), 2.13-2.03 (2H, m), 1.84 (3H, bs)

MW (calcd): 506.1; MW (obsd): 506.5 (M+1,^{35}Cl)

Method S

Illustrative synthesis of Intermediate 188: 2-Benzyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



Step a: Azetidine-2-carboxylic acid methyl ester hydrochloride

[00257] To a solution of azetidine-2-carboxylic acid (1 eq.) in MeOH at 0°C was added dropwise thionyl chloride (2.5 eq.). The reaction was stirred at 20°C for 15h. The crude was concentrated under reduced pressure and used as such without further purification.

^{1}H NMR δ (ppm) ($CDCl_3$): 5.18 (1H, br s), 4.53-4.05 (2H, m), 3.92 (3H, br s), 3.09-2.56 (2H, m), 2.39-2.05 (1H, m)

Step b: Azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

[00258] To a solution of azetidine-2-carboxylic acid methyl ester hydrochloride (1 eq.) in MeOH were added TEA (2.5 eq.) and Boc_2O (1.1 eq.). The reaction was stirred at 20°C for 15h. The solvent was

concentrated under reduced pressure. The crude was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was used as such without further purification.

^1H NMR δ (ppm) ($CDCl_3$): 4.71-4.60 (1H, m), 4.14-3.86 (2H, m), 3.81 (3H, s), 2.62-2.46 (1H, m), 2.29-2.13 (1H, m), 1.46 (9H, s)

Step c: 2-Benzyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

[00259] To a solution of azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (1 eq.) in dry THF under Argon at -78°C was added a solution of LiHMDS 1M in hexane (1.3 eq.). The mixture was stirred at -78°C for 1h, then benzyl bromide (1.3 eq.) was added. The reaction was stirred at -78°C for 30 min, then at 0°C for 2h, then at 20°C for 1h. The crude was diluted with EtOAc, carefully hydrolyzed with a saturated aqueous solution of NH_4Cl. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 98/2 to 80/20) to afford 2-benzyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester.

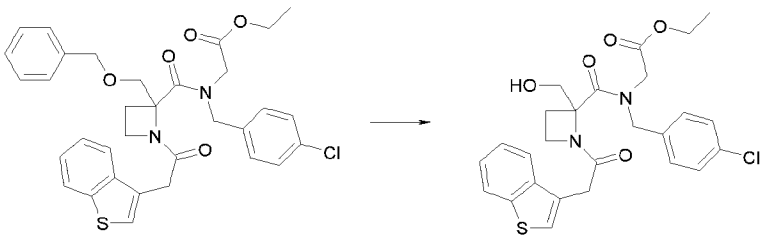
^1H NMR δ (ppm) ($CDCl_3$): 7.40-7.23 (5H, m), 3.85 (3H, s), 3.84-3.51 (1H, m), 3.42-3.33 (1H, m), 3.14-3.04 (1H, m), 2.18-2.09 (2H, m), 1.59 (2H, s), 1.50 (9H, s)

MW (calcd): 305.4; MW (obsd): 328.3 (M+23)

[00260] Intermediate 189, listed in table I was also prepared following the same method, using Chloromethoxymethyl-benzene as the electrophile.

Method T

Illustrative synthesis of Intermediate 191: [[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-hydroxymethyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid ethyl ester

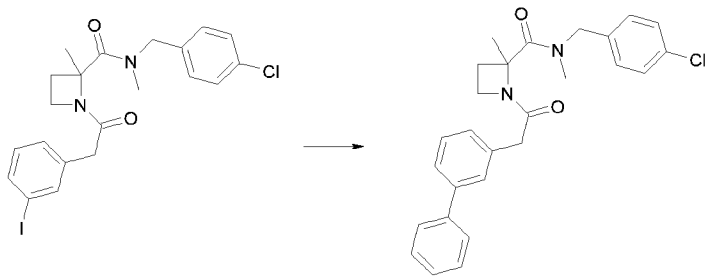


[00261] To a solution of [[1-(2-benzo[b]thiophen-3-yl-acetyl)-2-benzyloxymethyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid ethyl ester, Intermediate 163 (1 eq.) in DCM at 0°C was added BBr_3. The reaction was stirred at 0°C for 2h. The crude was diluted with DCM and poured into a saturated aqueous solution of $NaHCO_3$. The layers were separated, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with DCM/MeOH : 100/0 to 95/5) to afford [[1-(2-benzo[b]thiophen-3-yl-acetyl)-2-hydroxymethyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid ethyl ester.

MW (calcd): 515.0; MW (obsd): 514.8 (M+1, ^{35}Cl)

Method U

Illustrative synthesis of Compound 27: 1-(2-Biphenyl-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide



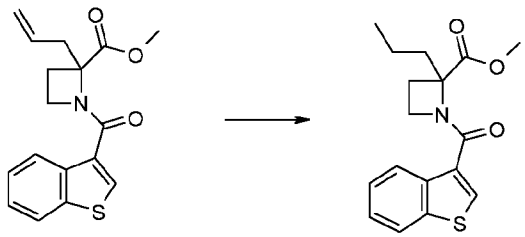
[00262] To a solution of phenyl boronic acid (1.5 eq.) in Dioxane/H_2O (9/1) were added Na_2CO_3 (4 eq.) and 1-[2-(3-iodo-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide, compound 8 (1 eq.). The flask was evacuated and backfilled with argon. Then $Pd(PPh_3)_4$ was added and the reaction was heated at 90°C until completion. The crude was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was was purified by chromatography on silica gel (elution with Hpetane/EtOAc: 100/0 to 20/80) to afford 1-(2-biphenyl-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide.

^1H NMR δ (ppm) (MeOD-d_4): 7.85-7.73 (3H, m), 7.72-7.36 (10H, m), 4.80-4.60 (2H, m), 4.40-4.20 (1H, m), 4.13-3.62 (3H, m), 3.14-2.99 (3H, m), 2.84-2.49 (2H, m), 2.17-2.00 (3H, m)

MW (calcd): 447.0; MW (obsd): 447.2 (M+1, ^{35}Cl)

Method V

Illustrative synthesis of Intermediate 192: 1-(Benzo[b]thiophene-3-carbonyl)-2-propyl-azetidine-2-carboxylic acid methyl ester



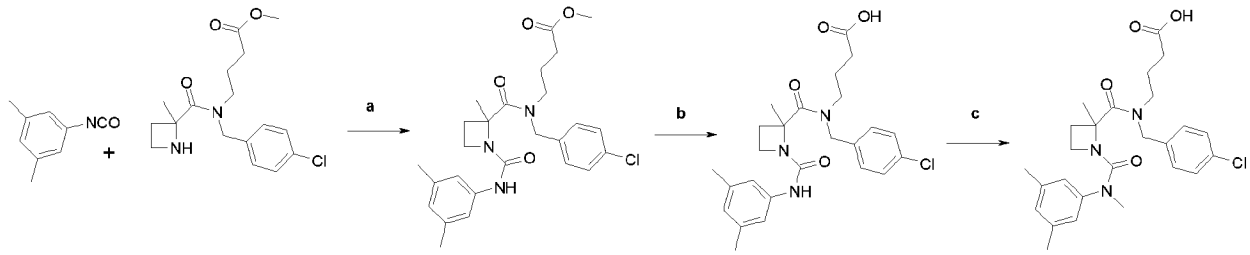
[00263] To a solution of 2-allyl-1-(benzo[b]thiophene-3-carbonyl)-azetidine-2-carboxylic acid methyl ester Intermediate 197 (1 eq.) in MeOH was added Pd/C (0.2 eq.), the flask was evacuated and backfilled with H_2. The reaction was stirred for 15h at 20°C under atmospheric pressure. The crude was filtered through a pad of celite and washed with EtOH and EtOAc. The filtrate was concentrated under reduced pressure to afford 1-(benzo[b]thiophene-3-carbonyl)-2-propyl-azetidine-2-carboxylic acid methyl ester.

^1H NMR δ (ppm) ($CDCl_3$): 8.37-8.24 (1H, m), 7.89 (1H, d), 7.73 (1H, s), 7.53-7.37 (2H, m), 4.35-4.08 (2H, m), 3.87 (3H, s), 2.48-2.29 (3H, m), 2.16-1.97 (1H, m), 1.75-1.50 (2H, m), 1.15-0.98 (3H, m)

MW (calcd): 317.4; MW (obsd): 318.0 (M+1)

Method W

Illustrative synthesis of compound 201: 4-((4-Chloro-benzyl)-{1-[(3,5-dimethyl-phenyl)-methyl-carbamoyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid



Step a: 4-{(4-Chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid methyl ester

[00264] To a solution of 4-[(4-chloro-benzyl)-(2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester hydrochloride, Intermediate 23 (1 eq.) and TEA (5 eq.) in THF under nitrogen was added 3,5-dimethyl-phenyl-isocyanate (1.5 eq.). The reaction was stirred for 15h at 20°C. The crude was partitioned between a saturated aqueous solution of $NaHCO_3$ and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 75/25 to 40/60) to afford 4-{(4-chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid methyl ester.
MW (calcd): 486.0; MW (obsd): 486.4 (M+1, ^{35}Cl)

Step b: Compound 200, 4-{(4-Chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid

[00265] Compound 200, 4-{(4-chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid was prepared via method J.
^1H NMR δ (ppm) ($CDCl_3$): 9.82-9.74 (1H, m), 7.44-7.40 (1H, m), 7.39-7.34 (1H, m), 7.26-7.21 (1H, m), 7.20-7.15 (2H, m), 7.13-7.11 (1H, m), 6.68 (1H, s), 4.79-4.62 (1H, m), 4.51-4.36 (1H, m), 4.19-3.97 (1H, m), 3.72-3.47 (2H, m), 3.36-3.10 (2H, m), 2.80-2.65 (1H, m), 2.48-2.35 (2H, m), 2.32 (3H, s), -2.30 (3H, s), 1.99-1.91 (2H, m), 1.82-1.71 (3H, m)
MW (calcd): 472.0; MW (obsd): 472.4 (M+1, ^{35}Cl)

Step c: Compound 201, 4-((4-Chloro-benzyl)-{1-[(3,5-dimethyl-phenyl)-methyl-carbamoyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid

[00266] To a solution of 4-{(4-chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid, compound 200 (1 eq.) in DMF was added NaH (3 eq.). The reaction was stirred for 1h at 20°C, then MeI (2.5 eq.) was added. The reaction was stirred for 15h at 20°C. The crude was partitioned between aqueous HCl (0.1N) and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by preparative

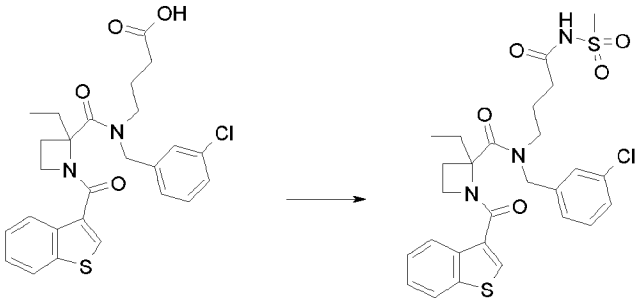
LCMS to afford 4-((4-chloro-benzyl)-{1-[(3,5-dimethyl-phenyl)-methyl-carbamoyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid.

^{1}H NMR δ (ppm) (MeOD, d_4): 7.52-7.31 (4H, m), 7.07-6.91 (2H, m), 6.72-6.63 (1H, m), 4.87-4.61 (2H, m), 3.50-3.41 (1H, m), 3.23-3.10 (3H, m), 3.01-2.74 (2H, m), 2.44-2.23 (9H, m), 1.99-1.82 (5H, m), 1.39-1.10 (2H, m)

MW (calcd): 486.0; MW (obsd): 486.4 (M+1, ^{35}Cl)

Method X

Illustrative synthesis of compound 228 : 1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide

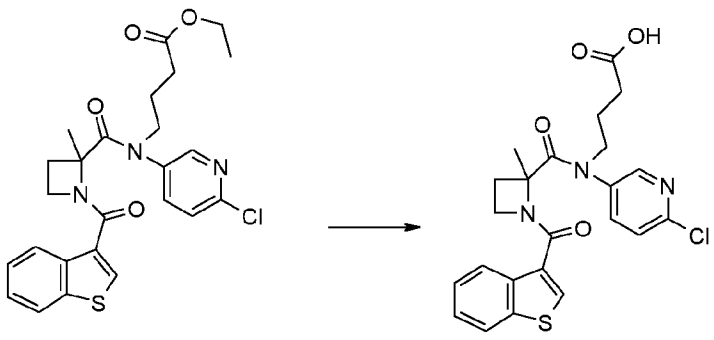


[00267] To a solution of compound 195 in THF is added CDI (2 eq.), The mixture is heated at 40°C for 2.5 h, 1,8-Diazabicyclo[5.4.0]undec-7-ene (2 eq.) and methanesulfonamide (2 eq.) are added and the mixture is stirred at 20°C for 1h30. The mixture is hydrolysed by addition of aqueous HCl 0.1N and diluted in DCM. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residu was coevaporated with Et_2O to afford 1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide as a white solid.

MW (calcd): 576.2; MW (obsd): 576.1 (M+1, ^{35}Cl)

Method Y

Illustrative synthesis of compound 249 : 4-(1-(benzo[b]thiophene-3-carbonyl)-N-(6-chloropyridin-3-yl)-2-methylazetidine-2-carboxamido)butanoic acid

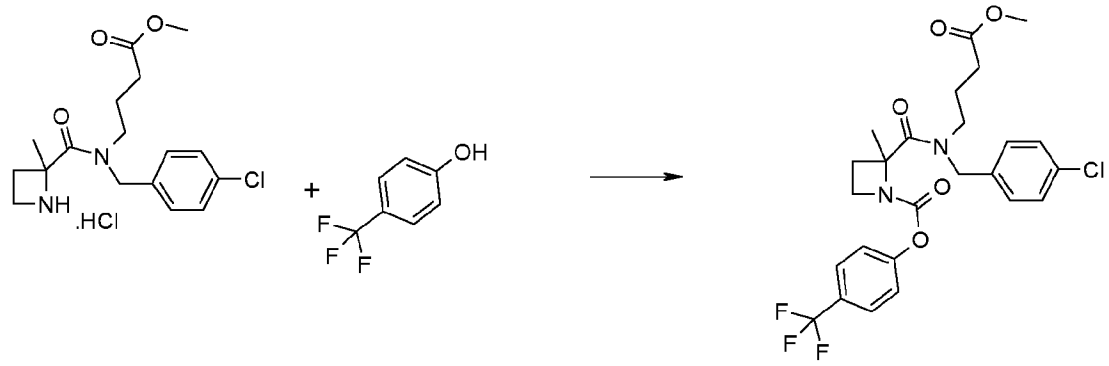


To a solution of Intermediate 239 in THF/water (1/1) is added LiOH monohydrate (1 eq.), The mixture is stirred at 20°C for 16h. The pH is adjusted to pH=7-8 by addition of aqueous HCl 0.1N and the mixture is concentrated. The crude is purified by preparative LCMS to afford 4-(1-(benzo[b]thiophene-3-carbonyl)-N-(6-chloropyridin-3-yl)-2-methylazetidine-2-carboxamido)butanoic acid.

MW (calcd): 472.0 ; MW (obsd): 472.0 (M+1, ^{35}Cl)

Method Z

Illustrative synthesis of Intermediate 251 : 2-[(4-Chloro-benzyl)-(3-methoxycarbonyl-propyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 4-trifluoromethyl-phenyl ester

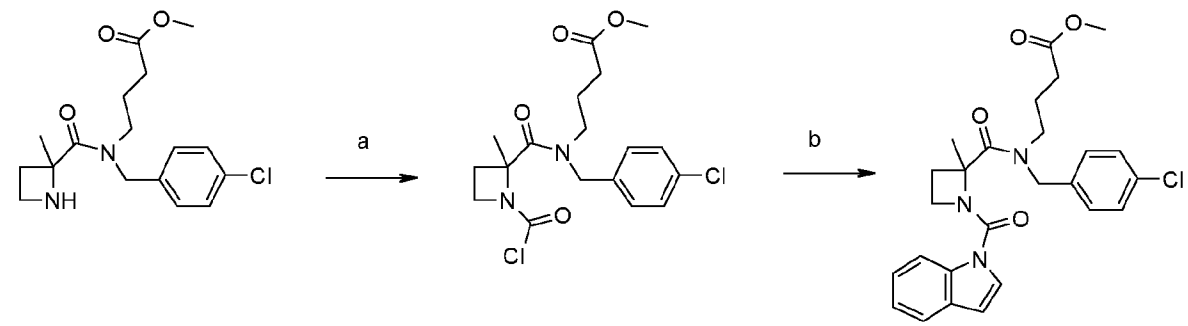


To a solution of triphosgene (0.7 eq.) in anhydrous DCM is added a solution of 4-trifluoromethyl phenol (2 eq.) and DIPEA (2 eq.) in DCM. After stirring for 1h at 20°C, Intermediate 23 and DIPEA (2eq.) are added. The mixture is stirred at 20°C for 16h, diluted with DCM, washed with aqueous HCl (0.1N), a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude is purified by chromatography on silica gel (elution with heptane/EtOAc: 90/10 to 60/40) to afford 2-[(4-Chloro-benzyl)-(3-methoxycarbonyl-propyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 4-trifluoromethyl-phenyl ester.

MW (calcd): 526.9 ; MW (obsd): 527.1 (M+1, ^{35}Cl)

Method AA

Illustrative synthesis of Intermediate 275: 4-{(4-Chloro-benzyl)-[1-(indole-1-carbonyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid methyl ester



Step a: 4-[(4-Chloro-benzyl)-(1-chlorocarbonyl-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester

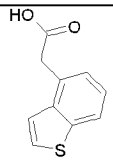
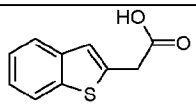
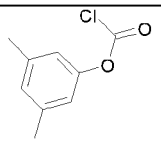
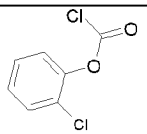
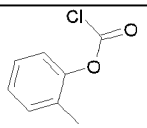
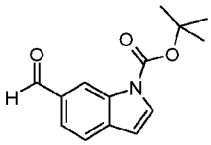
A solution of Intermediate 23 and DIPEA (3 eq.) in DCM is added at 0°C to a solution of triphosgene (1 eq.) in DCM and the mixture is stirred at 0°C for 1h, diluted with DCM, washed with aqueous HCl (0.1N) dired over Na_2SO_4 and concentrated to afford 4-[(4-Chloro-benzyl)-(1-chlorocarbonyl-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester.

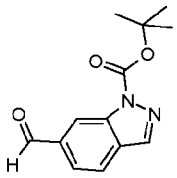
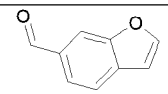
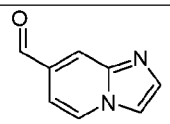
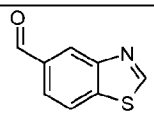
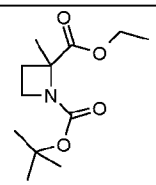
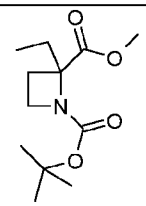
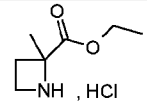
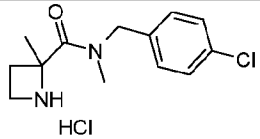
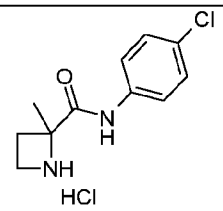
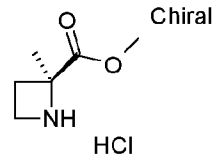
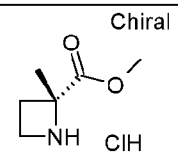
Step b: 4-{(4-Chloro-benzyl)-[1-(indole-1-carbonyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid methyl ester

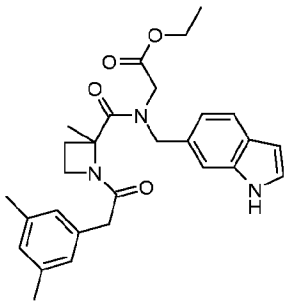
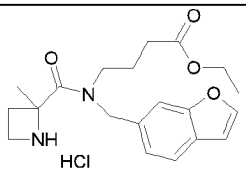
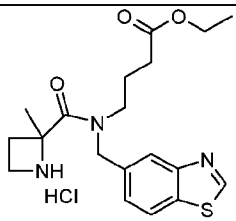
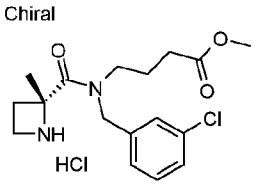
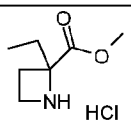
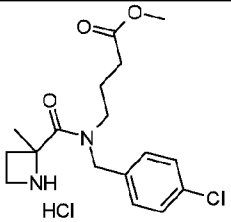
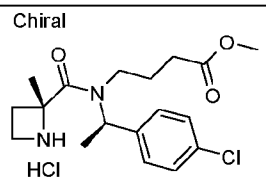
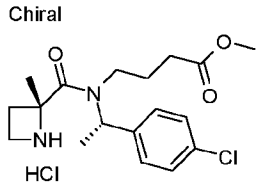
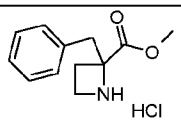
To a solution of indole (1 eq.) in THF is added NaH (1.5 eq., 60% in oil) and the mixture is stirred at 20°C for 1h. A solution of 4-[(4-Chloro-benzyl)-(1-chlorocarbonyl-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester in THF in added dropwise and the mixture is stirred at 20°C for 16h. The mixture was concentrated and the residue dissolved in EtOAc, washed with aqueous HCl (0.1N), a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue is used as such in next step.

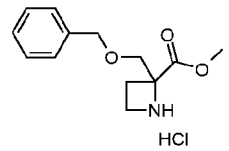
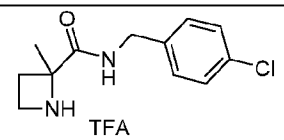
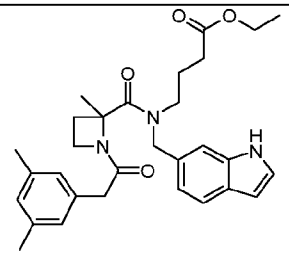
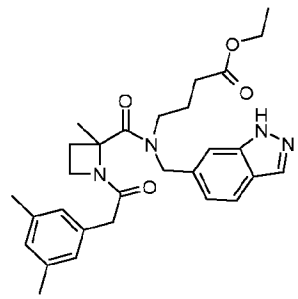
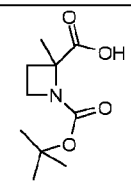
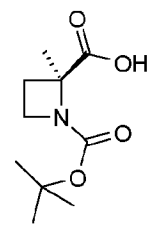
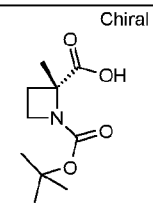
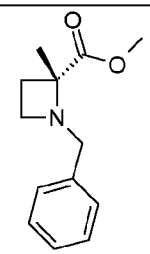
[00268] Table Ia: Synthesis of intermediates for the preparation of the compounds of the invention

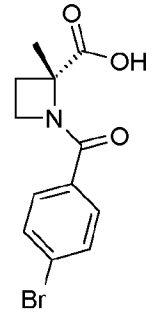
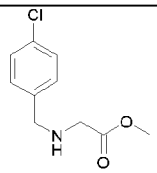
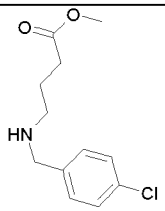
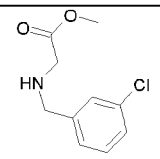
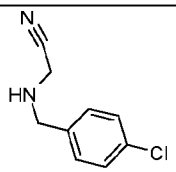
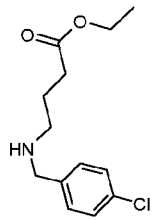
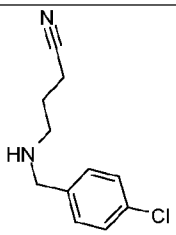
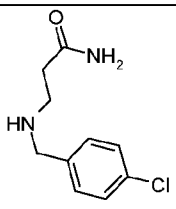
SM= Starting Material Mtd= Method MS Mes'd= Mesured mass

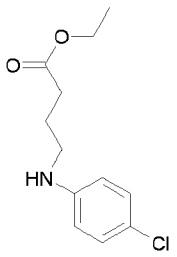
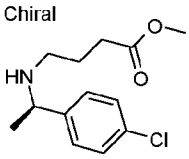
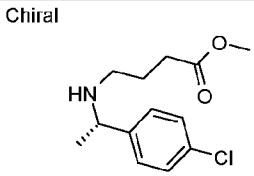
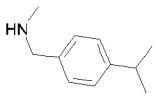
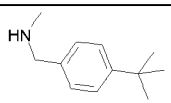
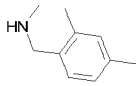
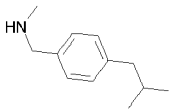
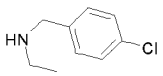
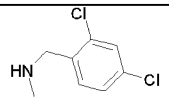
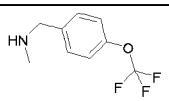
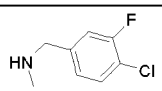
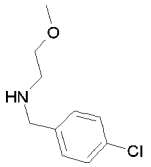
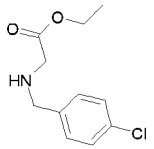
Int	Structure	SM	Mtd	MW	MS Mes'd
1		-	Acid	192.2	NMR
2		-	Acid		NMR
3		-	Chlorof ormate	184.6	NMR
4		-	Chlorof ormate	191.0	N/A
5		-	Chlorof ormate	170.6	N/A
6		1H-Indole-6-carbaldehyde	Ald	245.3	246.1 (M+1)

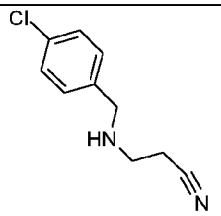
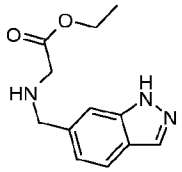
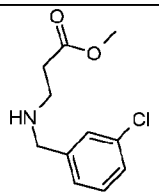
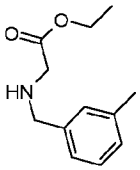
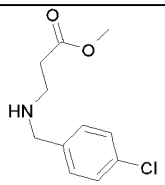
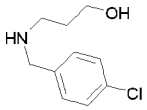
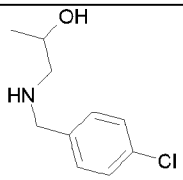
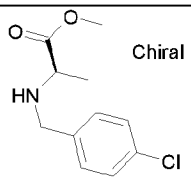
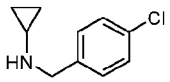
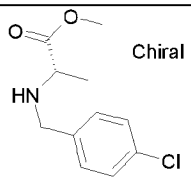
Int	Structure	SM	Mtd	MW	MS Mes'd
7		1H-Indazole-6-carbaldehyde	Ald	246.3	191.0 (M-55)
8		Benzofuran-6-carboxylic acid methyl ester	Ald	146.1	147.1 (M+1)
9		-	Ald	146.1	NMR
10		-	Ald	163.2	164.1 (M+1)
11		Benzylamine, 2-bromo-propionic acid ethyl ester, chloroacetaldehyde and Boc_2O	A	243.3	266.2 (M+23)
12		Benzylamine, 2-bromo-butyric acid methyl ester, chloroacetaldehyde and Boc_2O	A	243.3	NMR
13		Int 11	B1	143.2	NMR
14		Int 139	B1	252.7	NMR
15		Int 140	B1	224.7	NMR
16		Int 142	B1	129.2	N/A
17		Int 143	B1	129.2	NMR

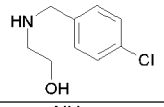
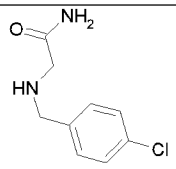
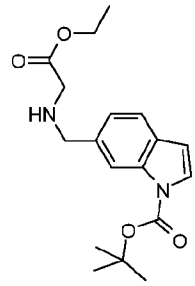
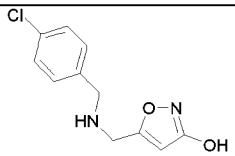
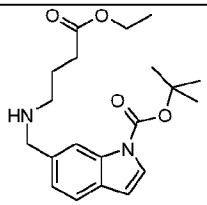
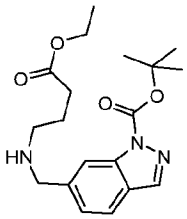
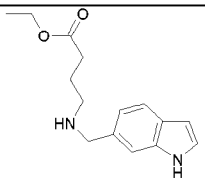
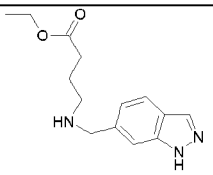
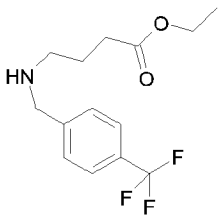
Int	Structure	SM	Mtd	MW	MS Mes'd
18		Int 147	B1	475.6	476.1 (M+1)
19		Int 165	B1	358.4	359.4 (M+1)
20		Int 169	B1	375.5	376.4 (M+1)
21		Int 175	B1	338.89	339.3 (M+1, ^{35}Cl)
22		Int 12	B1	143.2	NMR
23		Int 181	B1	338.8	N/A
24		Int 182	B1	352.9	353.3 (M+1, ^{35}Cl)
25		Int 183	B1	352.9	353.3 (M+1, ^{35}Cl)
26		Int 188	B1	205.3	206.2 (M+1)

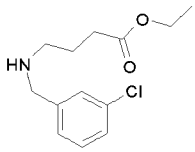
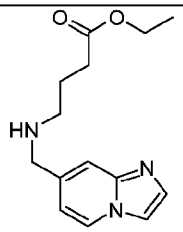
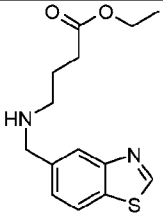
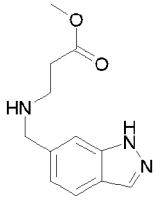
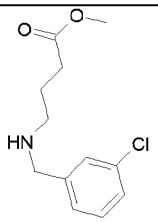
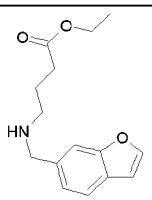
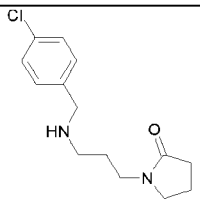
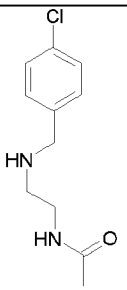
Int	Structure	SM	Mtd	MW	MS Mes'd
27		Int 189	B1	235.3	NMR
28		Int 138	B2	238.7	NMR
29		Int 149	B2	503.6	504.2 (M+1)
30		Int 151	B2	504.6	505.1 (M+1)
31		Int 11	C	215.2	N/A
32		Int 31	D	215.2	N/A
33		Int 31	D	215.2	N/A
34		Int 33	D	219.3	NMR

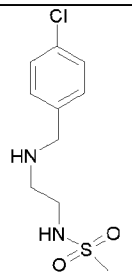
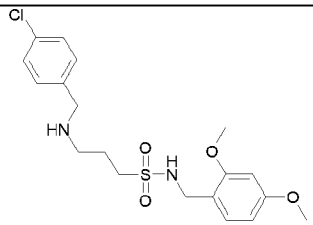
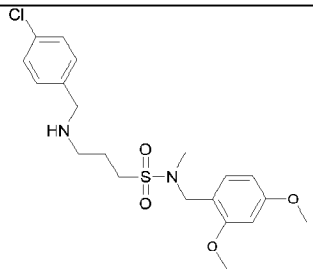
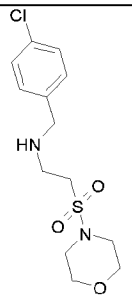
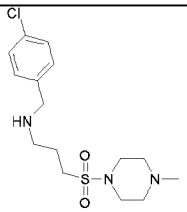
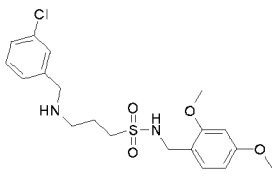
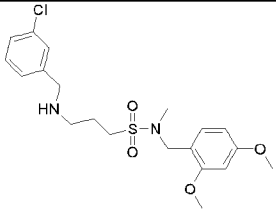
Int	Structure	SM	Mtd	MW	MS Mes'd
35		Int 33	D	298.1	NMR
36		4-chlorobenzylamine and bromo-acetic acid methyl ester	E1	213.7	NMR
37		4-Bromo-butyric acid methyl ester and 4-chlorobenzylamine	E1	241.7	242.3 (M+1, ^{35}Cl)
38		Bromo-acetic acid methyl ester and 3-chlorobenzylamine	E1	213.6	NMR
39		Bromo-acetonitrile and 4-chloro-benzylamine	E1	180.6	NMR
40		4-Bromo-butyric acid ethyl ester and 4-chloro-benzylamine	E1	255.7	NMR
41		4-Bromo-butyronitrile and 4-chloro-benzylamine	E1	208.7	209.0 (M+1, ^{35}Cl)
42		3-Bromo-propionamide and 4-chloro-benzylamine	E1	212.7	213.1 (M+1, ^{35}Cl)

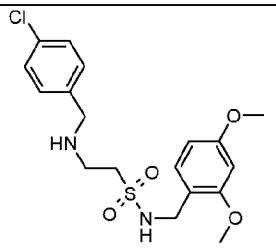
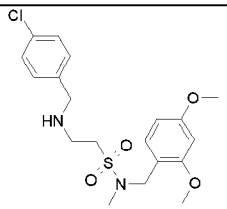
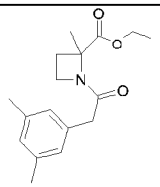
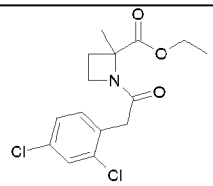
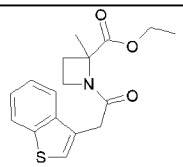
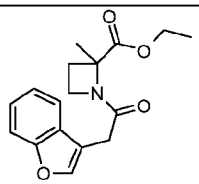
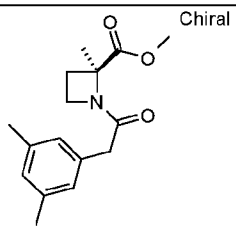
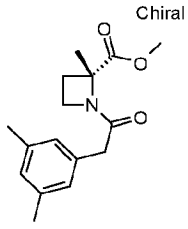
Int	Structure	SM	Mtd	MW	MS Mes'd
43		4-Bromo-butyric acid ethyl ester (4 eq.), K_2CO_3 (3 eq.) and 4-chloro-aniline	E2	241.7	242.3 (M+1, ^{35}Cl)
44		(R)-1-(4-Chloro-phenyl)-ethylamine and 4-bromo-butyric acid methyl ester	E2	255.7	256.3 (M+1, ^{35}Cl)
45		(S)-1-(4-Chloro-phenyl)-ethylamine and 4-bromo-butyric acid methyl ester	E2	255.7	256.3 (M+1, ^{35}Cl)
46		Methylamine and 4-Isopropyl-benzaldehyde	E3		N/A
47		Methylamine and 4-tert-butyl-benzaldehyde	E3		N/A
48		Methylamine and 2,4-dimethyl-benzaldehyde	E3		N/A
49		Methylamine and 4-iso-butyl-benzaldehyde	E3		N/A
50		Ethylamine (70% in H_2O) and 4-chloro-benzaldehyde	E3		NMR
51		Methylamine and 2,4-dichloro-benzaldehyde	E3		N/A
52		Methylamine and 4-trifluoromethoxy-benzaldehyde	E3		N/A
54		Methylamine and 4-chloro-3-fluoro-benzaldehyde	E3		N/A
55		2-methoxyethylamine and 4-chlorobenzaldehyde	E4	199.9	NMR
56		Glycine ethyl ester hydrochloride and 4-chlorobenzaldehyde	E4	227.7	228.3 (M+1, ^{35}Cl)

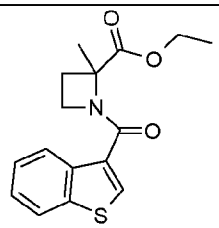
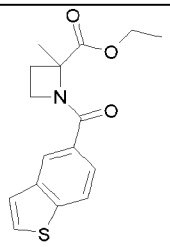
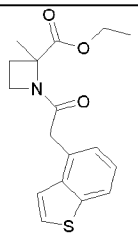
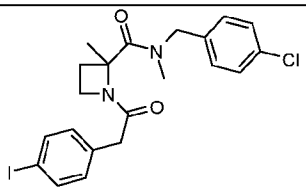
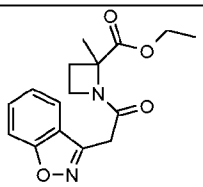
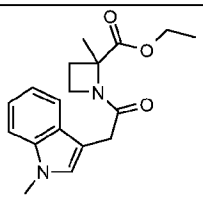
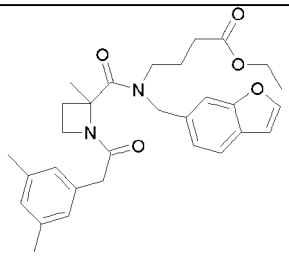
Int	Structure	SM	Mtd	MW	MS Mes'd
57		3-Amino-propionitrile and 4-chloro-benzaldehyde	E4	194.7	195.1 (M+1, ^{35}Cl)
58		Glycine ethyl ester hydrochloride and 1H-Indazole-6-carbaldehyde	E4	233.3	234.1 (M+1)
59		□-alanine methyl ester hydrochloride and 3-chlorobenzaldehyde	E4	227.7	NMR
60		Glycine ethyl ester hydrochloride and 3-methylbenzaldehyde	E4	207.3	208.5 (M+1)
61		□-alanine methyl ester hydrochloride and 4-chlorobenzaldehyde	E5	227.7	NMR
62		3-aminopropan-1-ol and 4-chloro-benzaldehyde	E5	199.7	N/A
63		1-Amino-propan-2-ol and 4-chloro-benzaldehyde	E5	199.7	200.1 (M+1, ^{35}Cl)
64		D-alanine methyl ester hydrochloride and 4-chloro-benzaldehyde	E5	227.7	NMR
65		Cyclopropylamine and 4-chlorobenzaldehyde	E6	181.7	N/A
66		L-alanine methyl ester hydrochloride and 4-chloro-benzaldehyde	E5	227.7	N/A

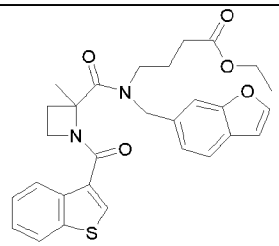
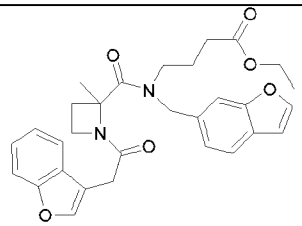
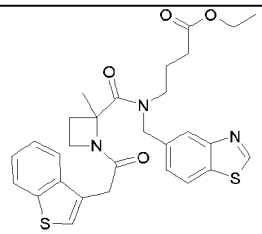
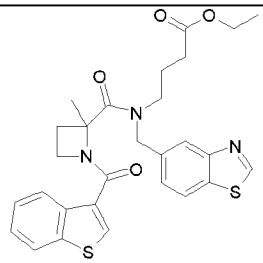
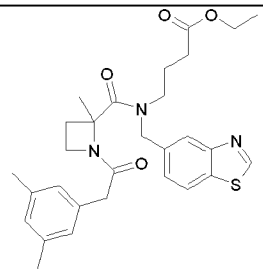
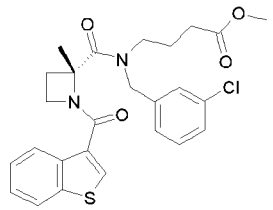
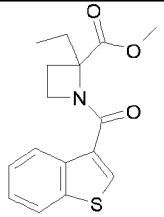
Int	Structure	SM	Mtd	MW	MS Mes'd
67		Ethanolamine and 4-chlorobenzaldehyde	E6	185.7	NMR
68		2-Amino-acetamide and 4-chloro-benzaldehyde	E6	198.6	199.1 (M+1, ^{35}Cl)
69		Int 6 and glycine ethyl ester hydrochloride	E6	332.4	NMR
70		Muscimol and 4-chloro-benzaldehyde	E6	238.7	239.0 (M+1, ^{35}Cl)
71		Int 6 and 4-amino-butyric acid ethyl ester hydrochloride	E7	360.5	361.1 (M+1)
72		Int 7 and 4-amino-butyric acid ethyl ester hydrochloride	E7	361.4	362.1 (M+1)
73		4-amino-butyric acid ethyl ester hydrochloride and 1H-Indole-6-carbaldehyde	E7	260.3	261.3 (M+1)
74		4-amino-butyric acid ethyl ester hydrochloride and 1H-Indazole-6-carbaldehyde	E7	261.3	262.3 (M+1)
75		4-amino-butyric acid ethyl ester hydrochloride and 4-trifluoromethyl-benzaldehyde	E7	289.3	290.3 (M+1)

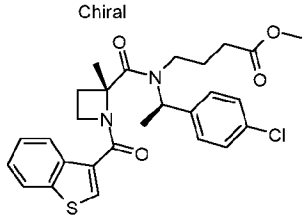
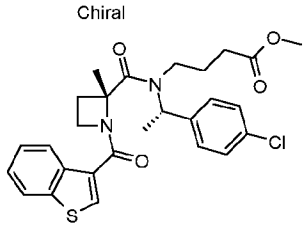
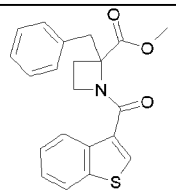
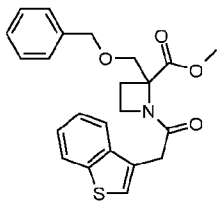
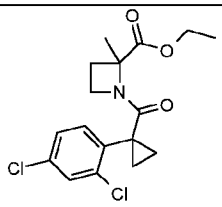
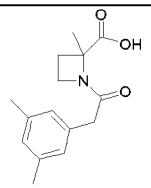
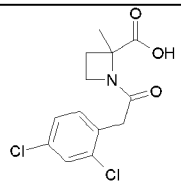
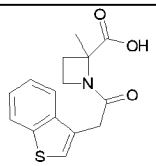
Int	Structure	SM	Mtd	MW	MS Mes'd
76		4-amino-butyric acid ethyl ester hydrochloride and 3-chloro-benzaldehyde	E7	255.7	256.2 (M+1, ^{35}Cl)
77		4-amino-butyric acid ethyl ester hydrochloride and int 9	E7	261.3	262.4 (M+1)
78		Int 10 and 4-amino-butyric acid ethyl ester hydrochloride	E7	278.4	279.3 (M+1)
79		□-alanine methyl ester hydrochloride and 1H-Indazole-6-carbaldehyde	E7	233.3	234.3 (M+1)
80		4-amino-butyric acid ethyl ester hydrochloride and 3-chloro-benzaldehyde	E7	241.7	242.2 (M+1, ^{35}Cl)
82		4-amino-butyric acid ethyl ester hydrochloride and int 8	E8	261.3	262.3 (M+1)
83		1-(3-Amino-propyl)-pyrrolidin-2-one and 4-chloro-benzaldehyde	E8	266.8	267.3 (M+1, ^{35}Cl)
84		(2-amino-ethyl)-carbamic acid tert-butyl ester, acetyl chloride and 4-chloro-benzaldehyde	E9	226.7	NMR

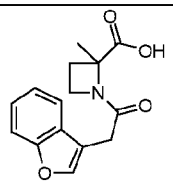
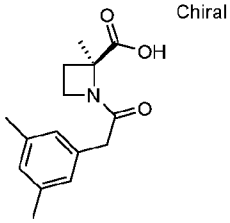
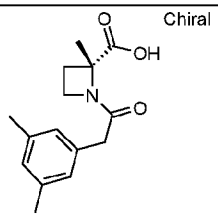
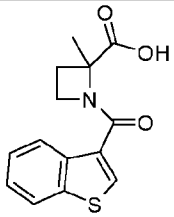
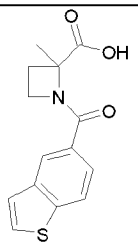
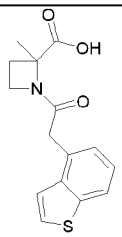
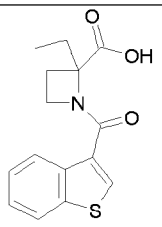
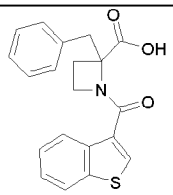
Int	Structure	SM	Mtd	MW	MS Mes'd
85		(2-amino-ethyl)-carbamic acid tert-butyl ester, methane sulfonyl chloride and 4-chloro-benzaldehyde	E9	262.8	263.0 (M+1, ^{35}Cl)
86		3-Chloro-propanesulfonyl chloride, 2,4-Dimethoxy-benzylamine and 4-chlorobenzylamine	E10	412.9	413.4 (M+1, ^{35}Cl)
87		3-Chloro-propanesulfonyl chloride, (2,4-Dimethoxy-benzyl)-methyl-amine and 4-chlorobenzylamine	E10	427.0	427.4 (M+1, ^{35}Cl)
88		2-Chloro-ethanesulfonyl chloride, morpholine and 4-chlorobenzylamine	E10	318.8	319.3 (M+1, ^{35}Cl)
89		3-Chloro-propanesulfonyl chloride, 1-methyl-piperazine and 4-chlorobenzylamine	E10	345.9	346.4 (M+1, ^{35}Cl)
90		3-Chloro-propanesulfonyl chloride, 2,4-Dimethoxy-benzylamine and 3-chlorobenzylamine	E10	412.9	413.4 (M+1, ^{35}Cl)
91		3-Chloro-propanesulfonyl chloride, (2,4-Dimethoxy-benzyl)-methyl-amine and 3-chlorobenzylamine	E10	427.0	427.4 (M+1, ^{35}Cl)

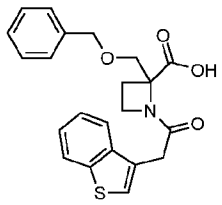
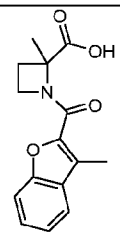
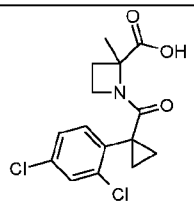
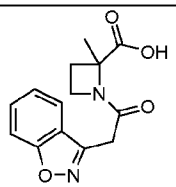
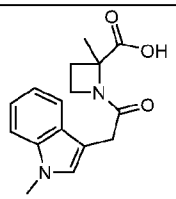
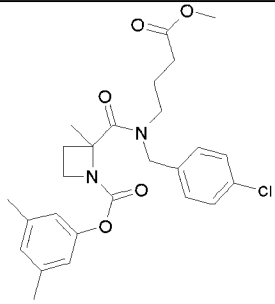
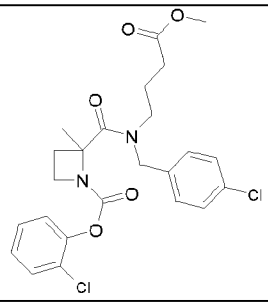
Int	Structure	SM	Mtd	MW	MS Mes'd
92		2-Chloro-ethanesulfonyl chloride, 2,4-Dimethoxy-benzylamine and 4-chlorobenzylamine	E10	398.9	399.3 (M+1, ^{35}Cl)
93		2-Chloro-ethanesulfonyl chloride, (2,4-Dimethoxy-benzyl)-methyl-amine and 4-chlorobenzylamine	E10	412.9	413.4 (M+1, ^{35}Cl)
94		Int 13 and (3,5-Dimethyl-phenyl)-acetic acid	F	289.4	290.0 (M+1)
95		Int 13 and (2,4-dichloro-phenyl)-acetic acid	F	330.2	330.0 (M+1, ^{35}Cl)
96		Int 13 and Benzo[b]thiophen-3-yl-acetic acid	F	317.4	318.0 (M+1)
97		Int 13 and Benzofuran-3-yl-acetic acid	F	301.3	302.0 (M+1)
98		Int 16 and (3,5-Dimethyl-phenyl)-acetic acid	F	275.3	276.0 (M+1)
99		Int 17 and (3,5-Dimethyl-phenyl)-acetic acid	F	275.3	276.1 (M+1)

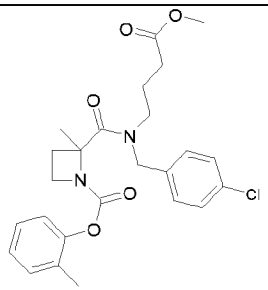
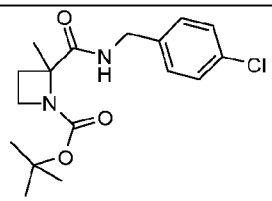
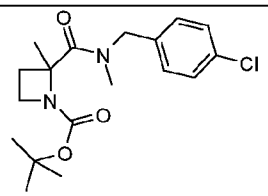
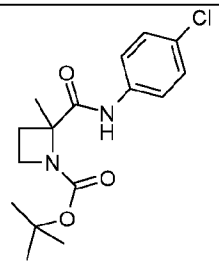
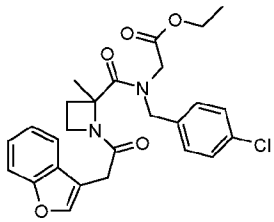
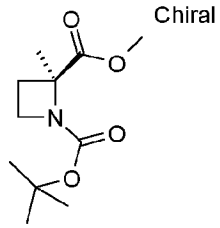
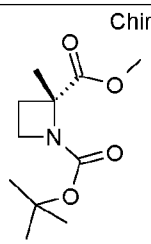
Int	Structure	SM	Mtd	MW	MS Mes'd
100		Int 13 and Benzo[b]thiophene-3-carboxylic acid	F	303.4	304.0 (M+1)
101		Int 13 and Benzo[b]thiophene-5-carboxylic acid	F	303.4	304.2 (M+1)
102		Int 13 and int 1	F	317.4	318.2 (M+1)
103		Int 14 and (4-iodo-phenyl)-acetic acid	F	496.8	497.3 (M+1)
104		Int 13 and Benzo[d]isoxazol-3-yl-acetic acid	F	302.3	303.5 (M+1)
105		Int 13 and (1-Methyl-1H-indol-3-yl)-acetic acid	F	314.4	314.9 (M+1)
106		Int 19 and (3,5-Dimethyl-phenyl)-acetic acid	F	504.6	505.5 (M+1)

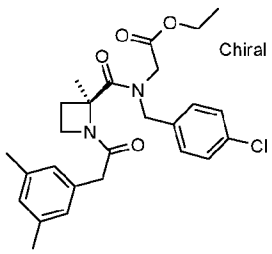
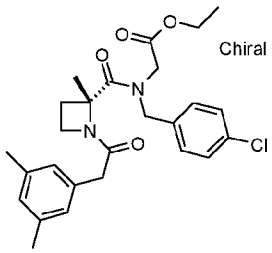
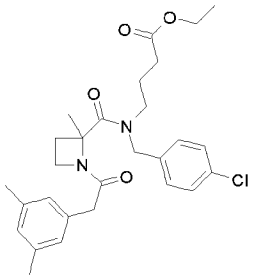
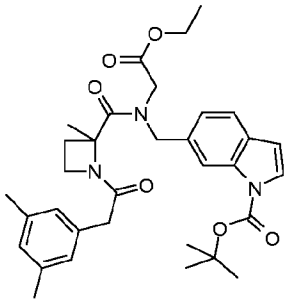
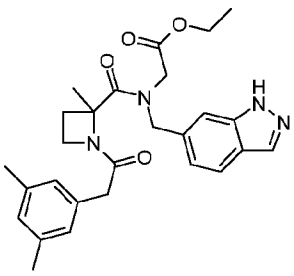
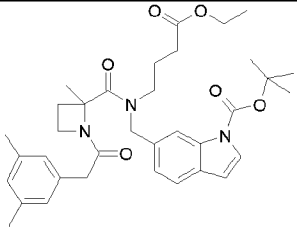
Int	Structure	SM	Mtd	MW	MS Mes'd
107		Int 19 and Benzo[b]thiophene-3-carboxylic acid	F	518.6	519.4 (M+1)
108		Int 19 and Benzofuran-3-acetic acid	F	516.6	517.5 (M+1)
109		Int 20 and Benzo[b]thiophene-3-acetic acid	F	549.7	550.4 (M+1)
110		Int 20 and Benzo[b]thiophene-3-carboxylic acid	F	535.7	536.5 (M+1)
111		Int 20 and (3,5-Dimethyl-phenyl)-acetic acid	F	521.7	522.5 (M+1)
112	Chiral 	Int 21 and Benzo[b]thiophene-3-carboxylic acid	F	499.0	499.3 (M+1, ^{35}Cl)
113		Int 22 and Benzo[b]thiophene-3-carboxylic acid	F	303.4	304.3 (M+1)

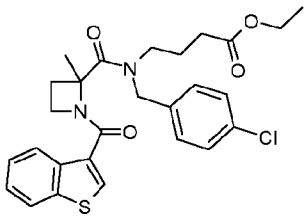
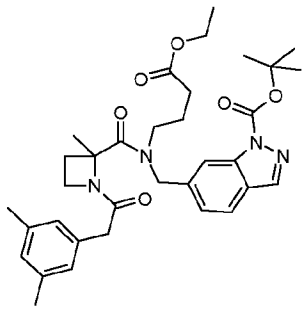
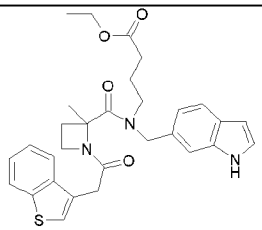
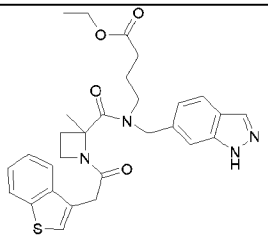
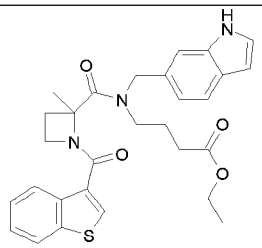
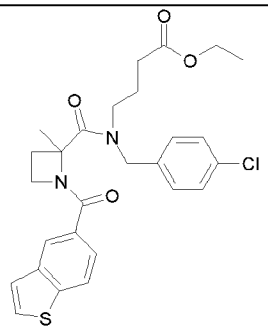
Int	Structure	SM	Mtd	MW	MS Mes'd
114	Chiral 	Int 24 and Benzo[b]thiophene-3-carboxylic acid	F	513.1	513.4 (M+1, ^{35}Cl)
115	Chiral 	Int 25 and Benzo[b]thiophene-3-carboxylic acid	F	513.1	NMR
116		Int 26 and Benzo[b]thiophene-3-carboxylic acid	F	365.4	366.2 (M+1)
117		Int 27 and Benzo[b]thiophene-3-acetic acid	F	409.5	410.4 (M+1)
118		Int 13 and 1-(2,4-Dichloro-phenyl)cyclopropane carboxylic acid	F	356.2	356.0 (M+1, ^{35}Cl)
119		Int 94	G	261.3	262.0 (M+1)
120		Int 95	G	302.2	302.0 (M+1, ^{35}Cl)
121		Int 96	G	289.3	NMR

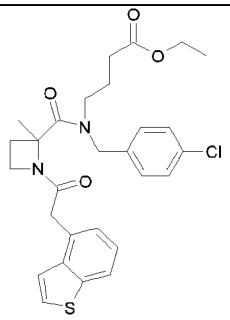
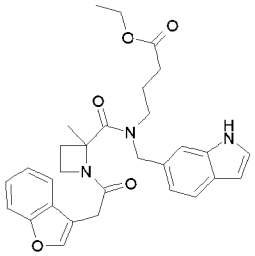
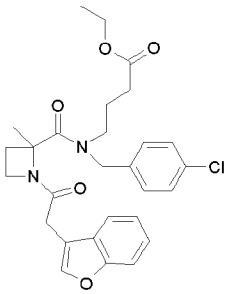
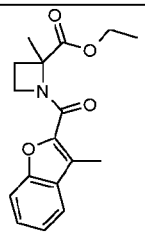
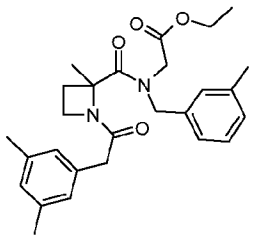
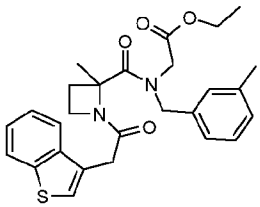
Int	Structure	SM	Mtd	MW	MS Mes'd
122		Int 97	G	273.3	274.1 (M+1)
123		Int 98	G	261.3	262.0
124		Int 99	G	261.3	N/A
125		Int 100	G	275.3	NMR
126		Int 101	G	275.3	276.2 (M+1)
127		Int 102	G	289.4	290.2 (M+1)
128		Int 113	G	289.4	290.3 (M+1)
129		Int 116	G	351.4	352.2 (M+1)

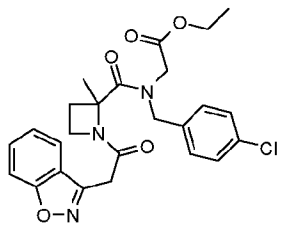
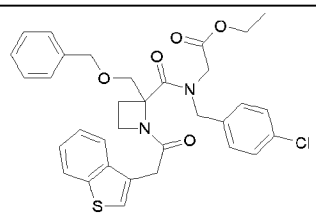
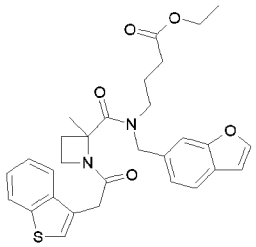
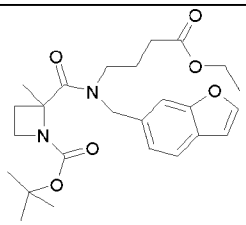
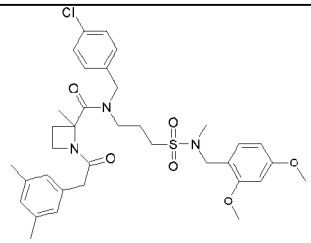
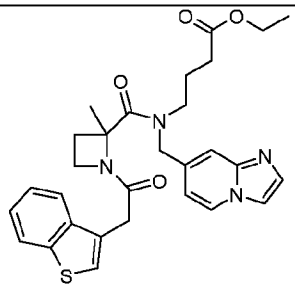
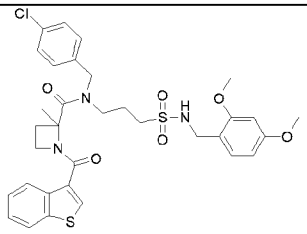
Int	Structure	SM	Mtd	MW	MS Mes'd
130		Int 117	G	395.5	396.2 (M+1)
131		Int 159	G	273.3	296.1 (M+23)
132		Int 118	G	328.2	327.9 (M+1, ^{35}Cl)
133		Int 104	G	274.3	275.1 (M+1)
134		Int 105	G	286.3	287.1 (M+1)
135		Int 3 and int 23	H	487.0	487.7 (M+1, ^{35}Cl)
136		Int 4 and int 23	H	507.4	507.3 (M+1, ^{35}Cl)

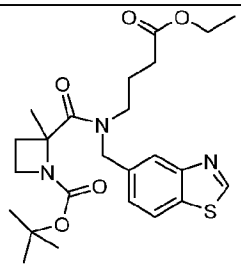
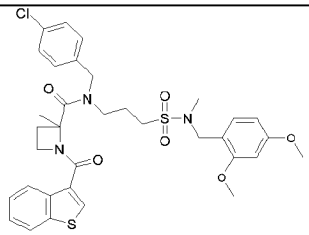
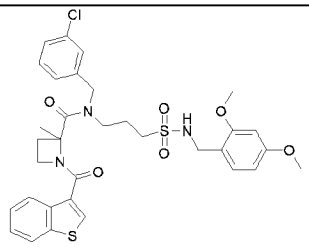
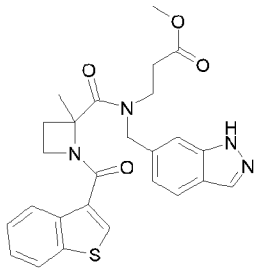
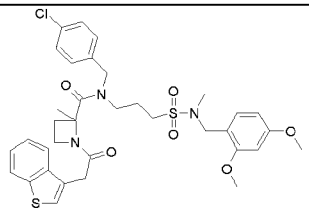
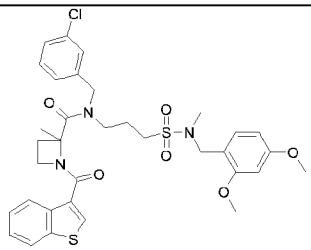
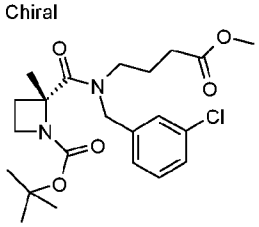
Int	Structure	SM	Mtd	MW	MS Mes'd
137		Int 5 and int 23	H	473.0	473.1 (M+1, ^{35}Cl)
138		Int 31 and 4-chloro-benzylamine	I1	338.8	NMR
139		Int 31 and (4-Chloro-benzyl)-methyl-amine	I1	352.8	NMR
140		Int 31 and 4-chloro-aniline	I1	324.8	N/A
141		Int 56 and int 122	I3	483.0	483.0 (M+1, ^{35}Cl)
142		Int 32 and MeOH	I3	229.3	N/A
143		Int 33 and MeOH	I3	229.3	NMR

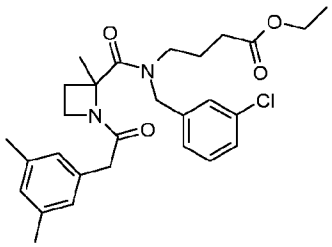
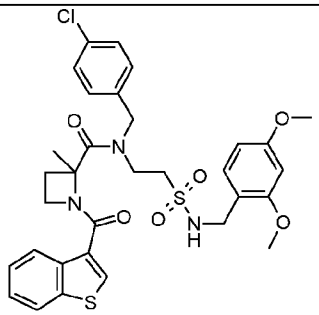
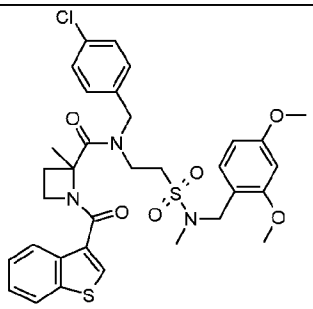
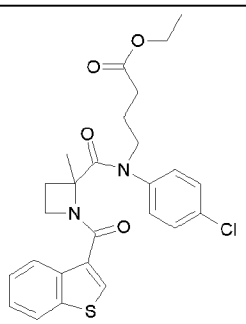
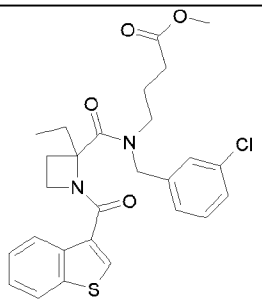
Int	Structure	SM	Mtd	MW	MS Mes'd
144		Int 56 and 123	I3	471.0	470.9 (M+1, ^{35}Cl)
145		Int 56 and int 124	I3	471.0	470.9 (M+1, ^{35}Cl)
146		Int 40 and int 119	I3	499.1	498.6 (M+1, ^{35}Cl)
147		Int 69 and Int 119	I3	575.7	576.2 (M+1)
148		Int 58 and Int 119	I3	476.6	477.1 (M+1)
149		Int 71 and int 119	I3	603.8	604.2 (M+1)

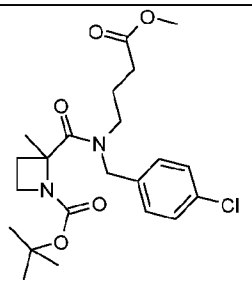
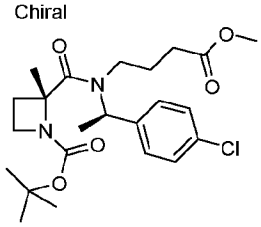
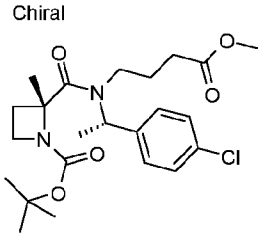
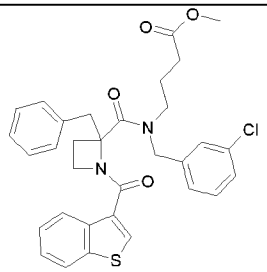
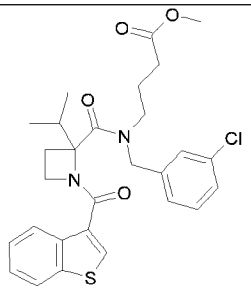
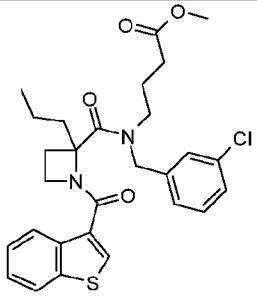
Int	Structure	SM	Mtd	MW	MS Mes'd
150		Int 40 and int 125	I3	513.1	513.0 (M+1, ^{35}Cl)
151		Int 72 and int 119	I3	604.7	605.1 (M+1)
152		Int 73 and int 121	I3	531.7	532.4 (M+1)
153		Int 74 and int 121	I3	532.7	533.4 (M+1)
154		Int 73 and int 125	I3	517.6	518.4 (M+1)
155		Int 40 and int 126	I3	513.1	513.3 (M+1, ^{35}Cl)

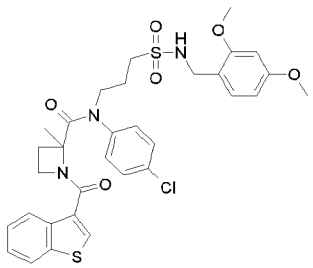
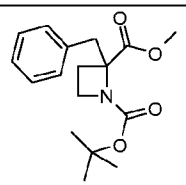
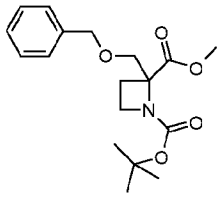
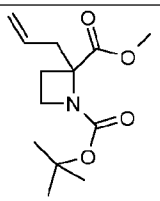
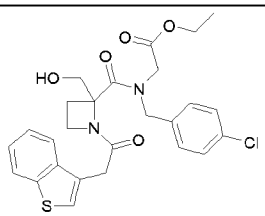
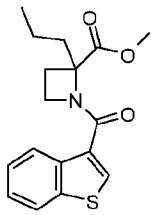
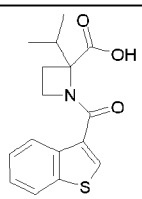
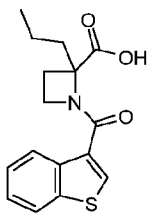
Int	Structure	SM	Mtd	MW	MS Mes'd
156		Int 40 and int 127	I3	527.1	527.3 (M+1, ^{35}Cl)
157		Int 73 and int 122	I3	515.6	516.5 (M+1)
158		Int 40 and int 122	F	511.0	511.1 (M+1, ^{35}Cl)
159		Int 13 and 3-Methylbenzofuran-2-carboxylic acid	I3	301.3	324.1 (M+23)
160		Int 60 and int 119	I3	450.6	451.1 (M+1)
161		Int 60 and int 121	I3	478.6	479.3 (M+1)

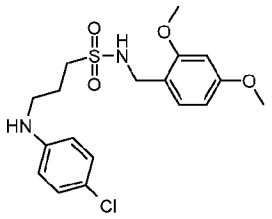
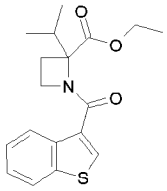
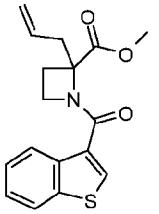
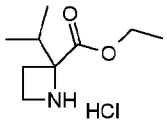
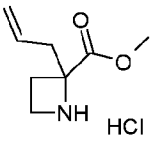
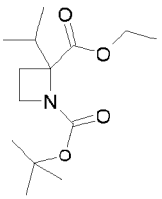
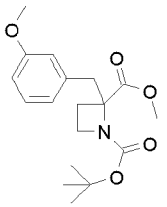
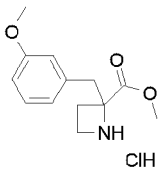
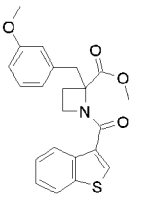
Int	Structure	SM	Mtd	MW	MS Mes'd
162		Int 133 and int 56	I3	484.0	483.9 (M+1, ^{35}Cl)
163		Int 56 and int 130	I3	605.2	605.3 (M+1, ^{35}Cl)
164		Int 82 and int 121	I4	532.7	533.4 (M+1)
165		Int 31 and int 82	I4	458.6	459.4 (M+1)
166		Int 87 and int 119	I4	670.3	670.6 (M+1, ^{35}Cl)
167		Int 77 and int 121	I4	532.7	533.5 (M+1)
168		Int 86 and int 125	I4	670.2	670.5 (M+1, ^{35}Cl)

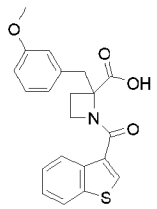
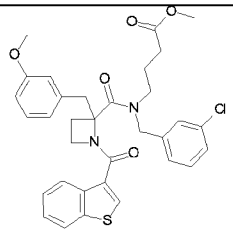
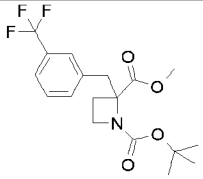
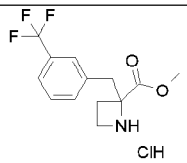
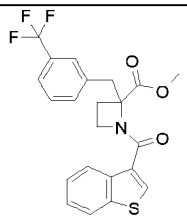
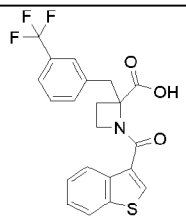
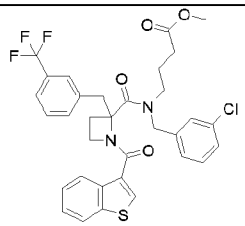
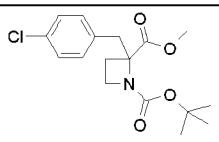
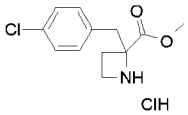
Int	Structure	SM	Mtd	MW	MS Mes'd
169		Int 31 and int 78	I4	475.6	476.5 (M+1)
170		Int 87 and int 125	I4	684.3	684.5 (M+1, ^{35}Cl)
171		Int 90 and int 125	I4	670.2	670.5 (M+1, ^{35}Cl)
172		Int 79 and int 125	I4	490.6	491.5 (M+1)
173		Int 87 and int 121	I4	698.3	698.6 (M+1, ^{35}Cl)
174		Int 91 and int 125	I4	683.3	684.6 (M+1, ^{35}Cl)
175	Chiral 	Int 33 and int 80	I4	439.0	439.4 (M+1, ^{35}Cl)

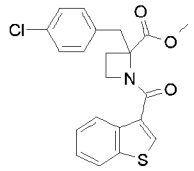
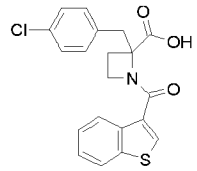
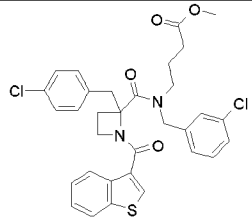
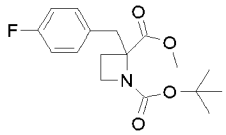
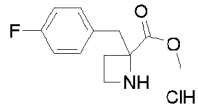
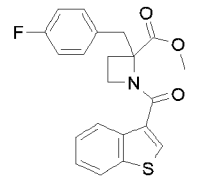
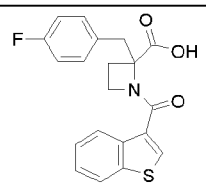
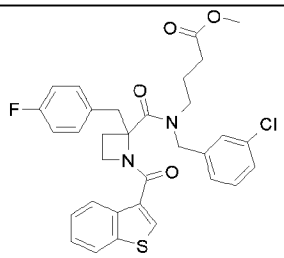
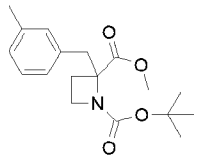
Int	Structure	SM	Mtd	MW	MS Mes'd
176		Int 76 and int 119	I4	499.0	499.5 (M+1, ^{35}Cl)
177		Int 92 and int 125	I4	656.3	656.5 (M+1, ^{35}Cl)
178		Int 93 and int 125	I4	670.2	670.4 (M+1, ^{35}Cl)
179		Int 43 and int 125	I4	499.0	499.3 (M+1, ^{35}Cl)
180		Int 80 and int 128	I4	513.1	513.4 (M+1, ^{35}Cl)

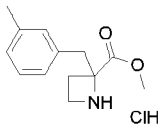
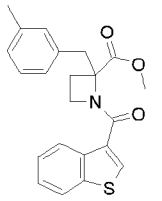
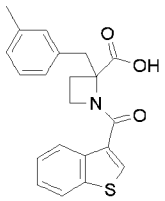
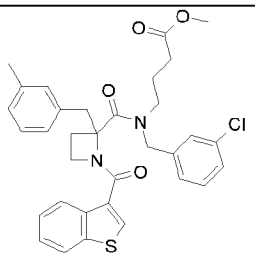
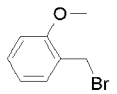
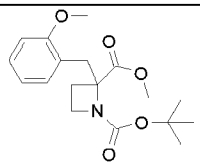
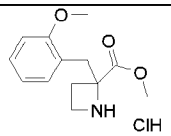
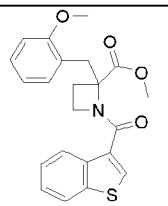
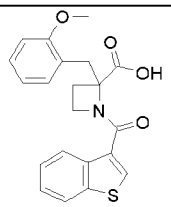
Int	Structure	SM	Mtd	MW	MS Mes'd
181		Int 31 and int 37	I4	439.0	439.4 (M+1, ^{35}Cl)
182	Chiral 	Int 33 and int 44	I4	453.0	453.5 (M+1, ^{35}Cl)
183	Chiral 	Int 33 and int 45	I4	453.0	453.5 (M+1, ^{35}Cl)
184		Int 80 and int 129	I4	575.1	575.4 (M+1, ^{35}Cl)
185		Int 80 and int 193	I4	527.1	527.4 (M+1, ^{35}Cl)
186		Int 80 and int 194	I4	527.1	527.4 (M+1, ^{35}Cl)

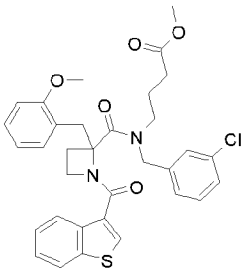
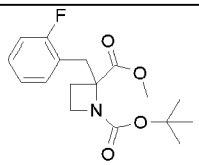
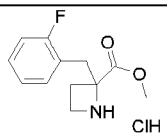
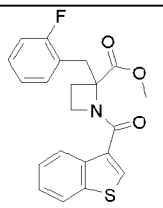
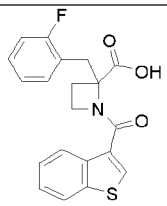
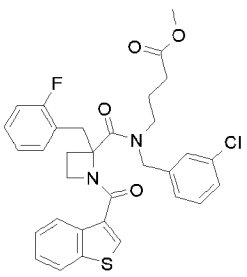
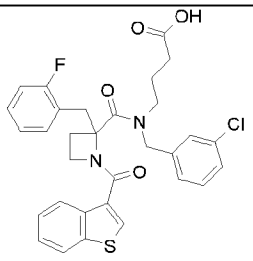
Int	Structure	SM	Mtd	MW	MS Mes'd
187		Int 195 and int 125	I4	656.2	656.1 (M+1, ^{35}Cl)
188		Benzyl bromide	S	305.4	328.3 (M+23)
189		Chloromethoxymethyl-benzene	S	335.4	358.2 (M+23)
190		Allyl bromide	S	255.3	278.3 (M+23)
191		Int 163	T	515.0	514.8 (M+1, ^{35}Cl)
192		Int 197	V	317.4	318.0 (M+1)
193		Int 196	G	303.4	304.3 (M+1)
194		Int 192	G	303.4	304.0 (M+1)

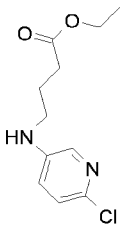
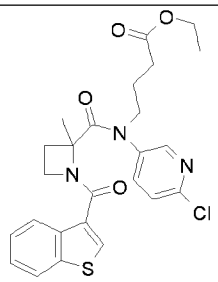
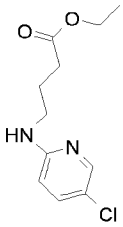
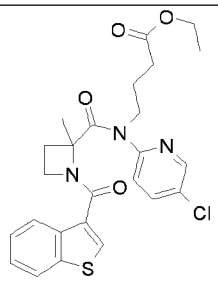
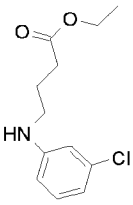
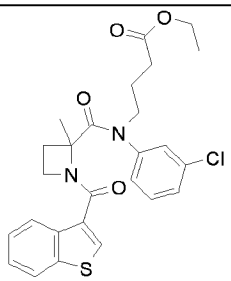
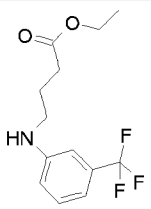
Int	Structure	SM	Mtd	MW	MS Mes'd
195		3-Chloro-propanesulfonyl chloride, 2,4-Dimethoxy-benzylamine and 4-chloroaniline	E10	398.9	399.2 (M+1, ^{35}Cl)
196		Int 198 and Benzo[b]thiophene-3-carboxylic acid	F	331.4	332.3 (M+1)
197		Int 199 and Benzo[b]thiophene-3-carboxylic acid	F	315.4	316.2 (M+1)
198		Int 200	B1	171.2	N/A
199		Int 190	B1	155.2	N/A
200		Benzylamine, 2-Bromo-3-methyl-butyric acid ethyl ester, chloroacetaldehyde and Boc_2O	A	271.6	N/A
201		3-Methoxy benzyl bromide	S	335.4	NMR
202		Int 201	B1	235.3	N/A
203		Int 202 and 3-thiophene carboxylic acid	I1	396.5	396.1 (M+1)

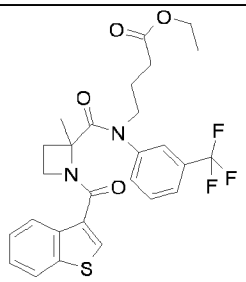
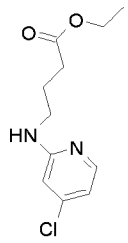
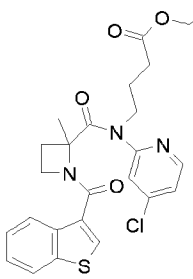
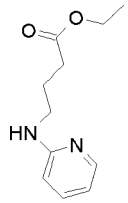
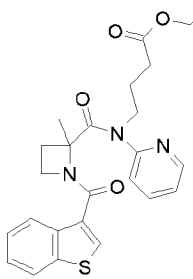
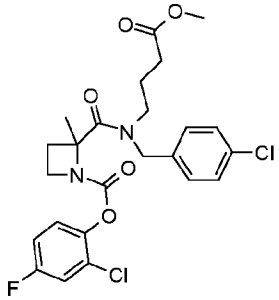
Int	Structure	SM	Mtd	MW	MS Mes'd
204		Int 203	J	381.5	382.1 (M+1)
205		Int 204 and Int 80	I4	605.2	N/A
206		3-Trifluoromethyl benzyl bromide	S	373.4	NMR
207		Int 206	B1	273.3	N/A
208		Int 207 and 3-thiophene carboxylic acid	I1	433.5	434.1 (M+1)
209		Int 208	J	419.4	420.1 (M+1)
210		Int 209 and Int 80	I4	643.1	N/A
211		4-Chlorobenzyl bromide	S	339.8	NMR
212		Int 211	B1	239.7	N/A

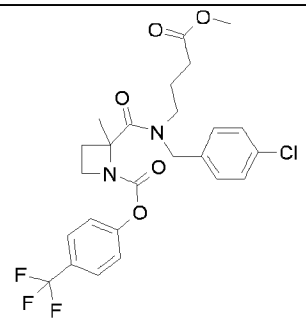
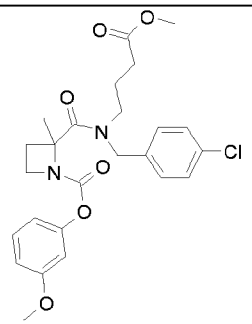
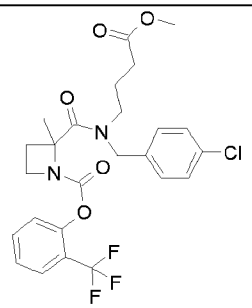
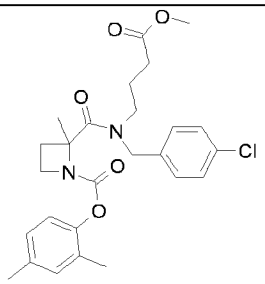
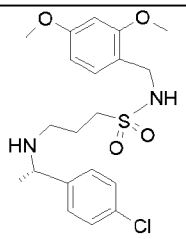
Int	Structure	SM	Mtd	MW	MS Mes'd
213		Int 212 and 3-thiophene carboxylic acid	F	399.9	400.0 (M+1, ^{35}Cl)
214		Int 213	G	385.9	386.0 (M+1, ^{35}Cl)
215		Int 214 and Int 80	I4	609.6	609.0 (M+1, ^{35}Cl)
216		4-Fluorobenzyl bromide	S	323.4	NMR
217		Int 216	B1	223.3	N/A
218		Int 217 and 3-thiophene carboxylic acid	F	383.4	384.0 (M+1)
219		Int 218	G	369.4	370.0 (M+1)
220		Int 219 and Int 80	I4	593.1	N/A
221		3-Methylbenzyl bromide	S	319.4	NMR

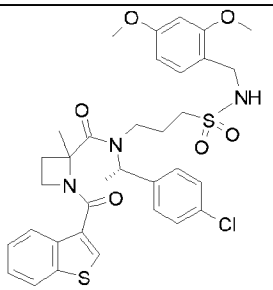
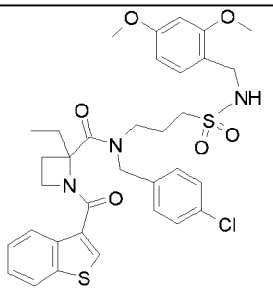
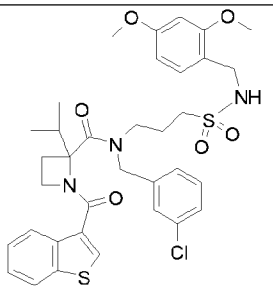
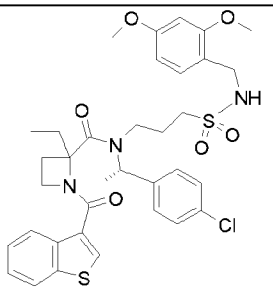
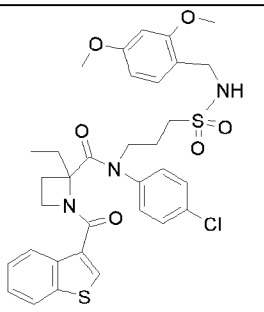
Int	Structure	SM	Mtd	MW	MS Mes'd
222		Int 220	B1	219.3	N/A
223		Int 221 and 3-thiophene carboxylic acid	F	379.5	380.5 (M+1)
224		Int 223	G	365.5	366.1 (M+1)
225		Int 224 and Int 80	I4	589.2	N/A
226		2-Methoxylbenzyl alcohol	Patent Schering corp. US5892 039 (1999)	201.1	NMR
227		Int 226	S	335.4	NMR
228		Int 227	B1	239.7	N/A
229		Int 228 and 3-thiophene carboxylic acid	F	395.5	396.1 (M+1)
230		Int 229	G	381.5	382.1 (M+1)

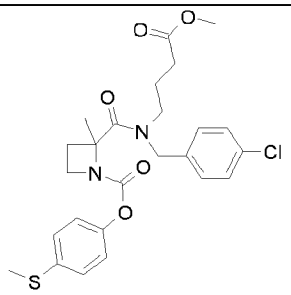
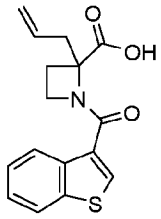
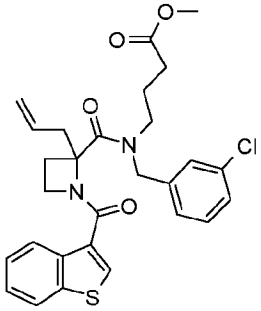
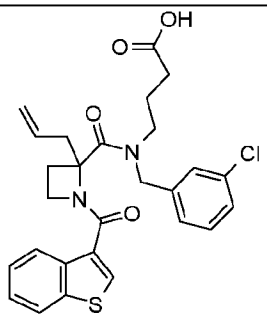
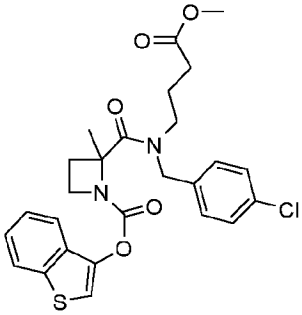
Int	Structure	SM	Mtd	MW	MS Mes'd
231		Int 230	I4	605.2	605.1 (M+1, ^{35}Cl)
232		2-Fluorobenzyl bromide	S	323.4	NMR
233		Int 232	B1	223.3	N/A
234		Int 233 and 3-thiophene carboxylic acid	F	383.4	384.1 (M+1)
235		Int 234	G	369.4	N/A
236		Int 235	I4	593.1	N/A
237		Int 236	J	579.1	579.1 (M+1, ^{35}Cl)

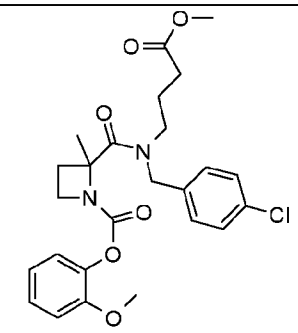
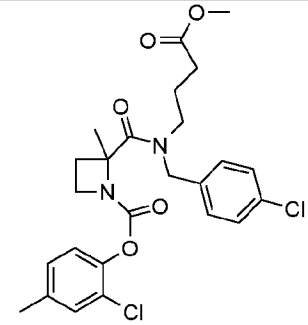
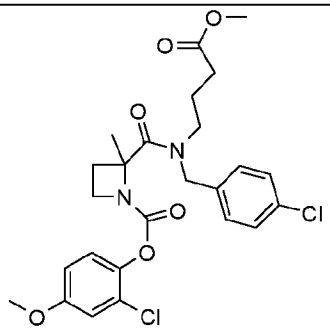
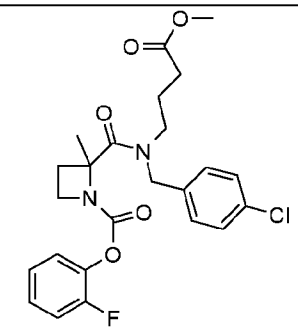
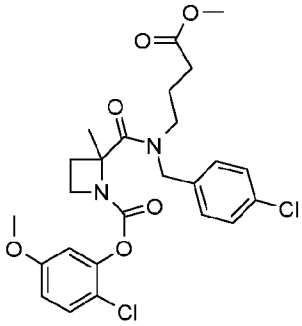
Int	Structure	SM	Mtd	MW	MS Mes'd
238		5-amino-2-chloropyridine and ethyl 4-bromobutyrate	E11	242.7	N/A
239		Int 238 and Int 125	I4	500.0	500.1 (M+1, ^{35}Cl)
240		2-amino-5-chloropyridine and ethyl 4-bromobutyrate	E11	242.7	N/A
241		Int 240 and Int 125	I4	500.0	500.1 (M+1, ^{35}Cl)
242		3-chloroaniline and ethyl 4-bromobutyrate	E2	241.7	242.0 (M+1, ^{35}Cl)
243		Int 242 and Int 125	I4	499.0	499.1 (M+1, ^{35}Cl)
244		3-trifluoromethylaniline and ethyl 4-bromobutyrate	E11	275.3	N/A

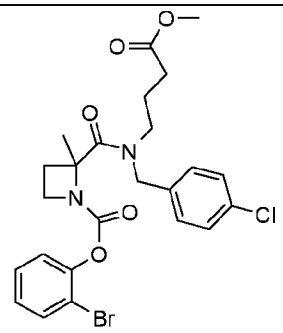
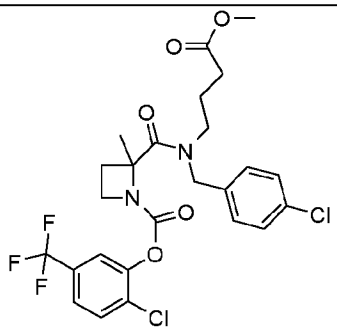
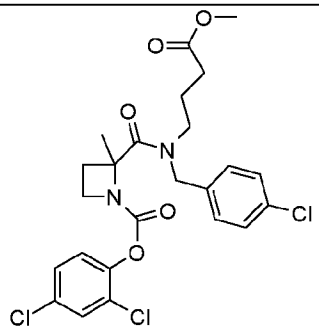
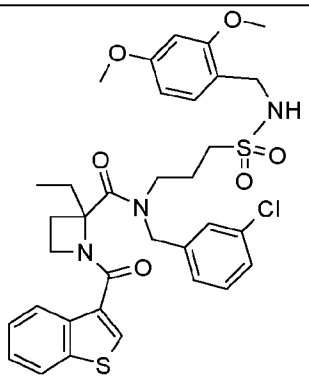
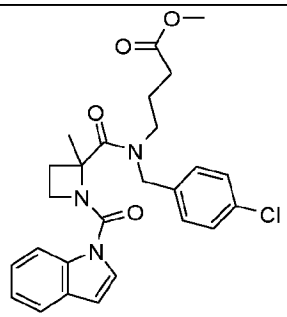
Int	Structure	SM	Mtd	MW	MS Mes'd
245		Int 244 and Int 125	I4	532.6	N/A
246		4-chloro-2-aminopyridine and ethyl 4-bromobutyrate	E11 (μW heating)	242.7	NMR
247		Int 246 and Int 125	I4	500.0	500.4 (M+1, ^{35}Cl)
248		4-aminopyridine and ethyl 4-bromobutyrate	E11	208.3	209.4 (M+1)
249		Int 248 and Int 125	I4	465.6	466.1 (M+1, ^{35}Cl)
250		Int 23 and 2-chloro-4-fluoro-phenol	Z	511.4	511.1 (M+1, ^{35}Cl)

Int	Structure	SM	Mtd	MW	MS Mes'd
251		Int 23 and 4-trifluoromethyl-phenol	Z	526.9	527.1 (M+1, ^{35}Cl)
252		Int 23 and 3-methoxy-phenol	Z	489.0	489.2 (M+1, ^{35}Cl)
253		Int 23 and 2-trifluoromethyl-phenol	Z (with DMAP and TEA instead of DIPEA)	526.9	527.1 (M+1, ^{35}Cl)
254		Int 23 and 2,4-dimethyl-phenol	Z (with DMAP and TEA instead of DIPEA)	487.0	487.2 (M+1, ^{35}Cl)
255		3-Chloro-propanesulfonyl chloride, 2,4-Dimethoxy-benzylamine and (S)-1-(4-chloro-phenyl)-ethylamine	E10	427.0	NMR

Int	Structure	SM	Mtd	MW	MS Mes'd
256		Int 125 and Int 255	I4	684.3	684.2 (M+1, ^{35}Cl)
257		Int 128 and Int 86	I4	684.3	684.2 (M+1, ^{35}Cl)
258		Int 193 and Int 90	I4	698.3	698.2 (M+1, ^{35}Cl)
259		Int 128 and Int 255	I4	698.3	698.2 (M+1, ^{35}Cl)
260		Int 128 and Int 195	I4	670.2	670.2 (M+1, ^{35}Cl)

Int	Structure	SM	Mtd	MW	MS Mes'd
261		Int 23 and 4-methylsulfanyl-phenol	Z	505.0	505.1 (M+1, ^{35}Cl)
262		Int 197	G	301.4	302.0 (M+1)
263		Int 262 and Int 80	I4	525.1	525.1 (M+1, ^{35}Cl)
264		Int 263	J	511.0	511.1 (M+1, ^{35}Cl)
265		Int 23 and benzo[b]thiophen-3-ol	Z	515.0	515.1 (M+1, ^{35}Cl)

Int	Structure	SM	Mtd	MW	MS Mes'd
266		Int 23 and 2-methoxy-phenol	Z	489.0	489.1 (M+1, ^{35}Cl)
267		Int 23 and 2-chloro-4-methyl-phenol	Z	507.4	507.1 (M+1, ^{35}Cl)
268		Int 23 and 2-chloro-4-methoxy-phenol	Z	523.4	523.1 (M+1, ^{35}Cl)
269		Int 23 and 2-fluoro-phenol	Z	476.9	477.1 (M+1, ^{35}Cl)
270		Int 23 and 2-chloro-5-methoxy-phenol	Z	523.4	523.1 (M+1, ^{35}Cl)

Int	Structure	SM	Mtd	MW	MS Mes'd
271		Int 23 and 2-bromo-phenol	Z	537.8	539.0 (M+1)
272		Int 23 and 2-chloro-5-trifluoromethyl-phenol	Z	561.4	561.1 (M+1, ^{35}Cl)
273		Int 23 and 2,4-dichloro-phenol	Z	527.8	529.0 (M+1)
274		Int 128 and Int 90	I4	684.3	684.4 (M+1, ^{35}Cl)
275		Int 23 and indole	AA	482.0	NA

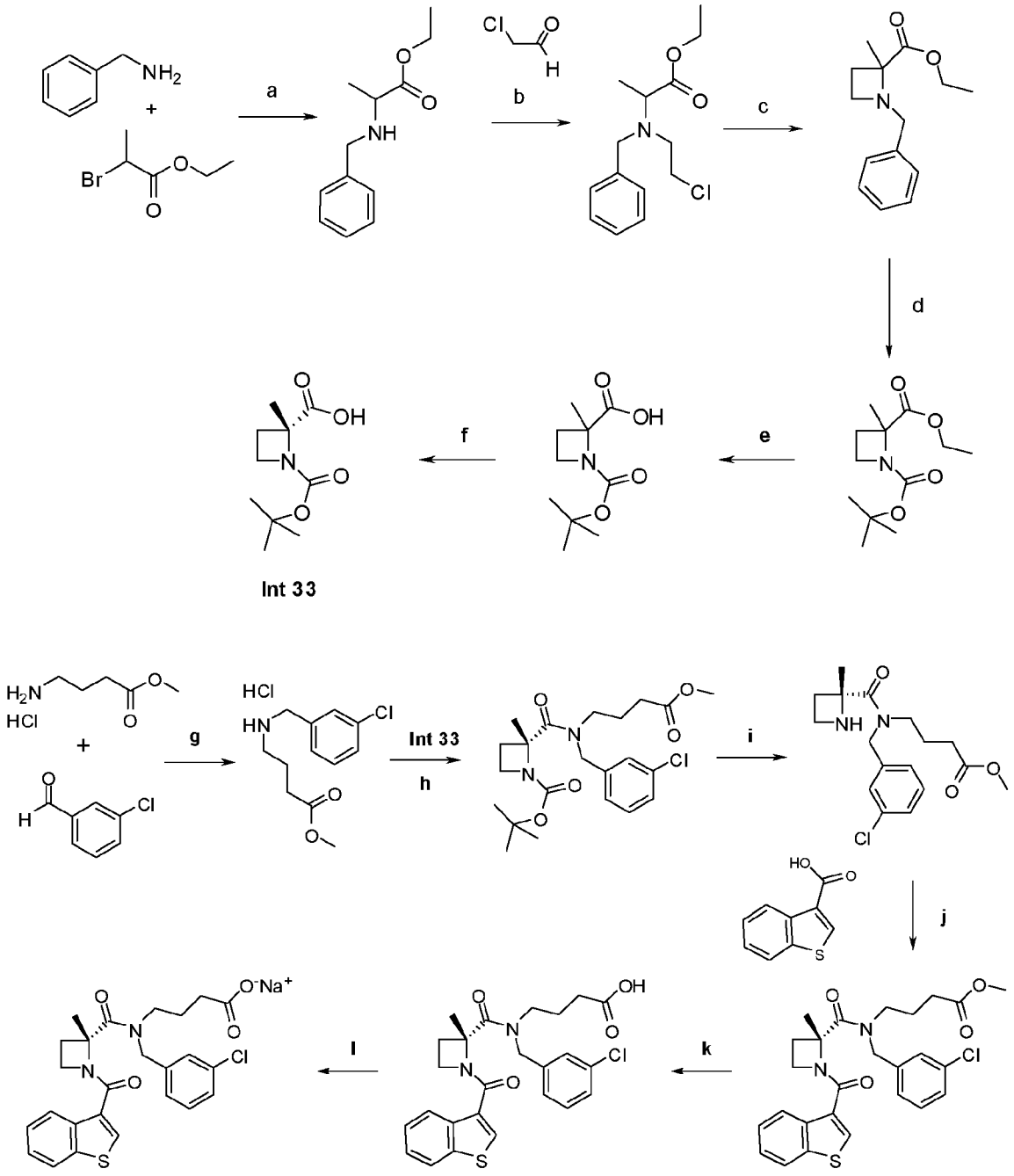
[00269] **Table Ib: NMR Data of the Intermediates of the Invention**

Int	NMR data
1	^{1}H NMR δ (ppm) ($CDCl_3$): 7.82 (1H, d), 7.48 (1H, d), 7.42 (1H, d), 7.31 (1H, t), 7.26 (1H, d), 3.97 (2H, s)
2	^{1}H NMR δ (ppm) ($CDCl_3$): 7.82 (1H, d), 7.75 (1H, d), 7.42-7.31 (2H, m), 7.24 (1H, s), 4.00 (2H, s)
3	^{1}H NMR δ (ppm) ($CDCl_3$): 6.97 (1H, s), 6.86 (2H, s)
9	^{1}H NMR δ (ppm) ($CDCl_3$): 10.03 (1H, s), 8.24 (1H, d), 8.16 (1H, s), 7.89 (1H, d), 7.79 (1H, d), 7.38 (1H, dd)
12	^{1}H NMR δ (ppm) ($CDCl_3$): 4.05-3.94 (1H, m), 3.80 (3H, s), 3.79-3.71 (1H, m), 2.31-2.14 (2H, m), 2.10-1.88 (2H, m), 1.52-1.37 (9H, m), 1.06 (3H, t)
13	^{1}H NMR δ (ppm) ($CDCl_3$): 9.48 (1H, br s), 4.35 (2H, q), 4.16-4.00 (2H, m), 2.82-2.70 (1H, m), 2.60-2.45 (1H, m), 1.95 (3H, s), 1.36 (3H, t)
14	^{1}H NMR δ (ppm) (MeOD, d_4):7.46-7.40 (2H, m), 7.38-7.32 (2H, m), 4.78-4.58 (2H, m), 4.21-4.07 (1H, m), 3.87-3.77 (1H, m), 3.11-2.98 (1H, m), 2.93 (3H, s), 2.76-2.65 (1H, m), 1.97 (3H, s)
15	^{1}H NMR δ (ppm) (MeOD, d_4): 7.74 (2H, d), 7.40 (2H, d), 4.21-4.10 (1H, m), 4.00-3.90 (1H, m), 3.00-2.90 (1H, m), 2.82-2.72 (1H, m), 2.03 (3H, s)
17	^{1}H NMR δ (ppm) ($CDCl_3$): 9.53 (1H, br s), 4.20-4.03 (2H, m), 3.94 (3H, s), 2.90-2.79 (1H, m), 2.63-2.50 (1H, m), 2.00 (3H, s)
22	^{1}H NMR δ (ppm) ($CDCl_3$): 9.60 (1H, br s), 4.18-4.00 (2H, m), 3.94 (3H, s), 2.84-2.70 (1H, m), 2.63-2.40 (2H, m), 2.32-2.17 (1H, m), 1.14-0.99 (3H, m)
27	^{1}H NMR δ (ppm) ($CDCl_3$): 9.79 (1H, br s), 7.48-7.30 (5H, m), 4.75 (2H, s), 4.18 (1H, d), 4.15-4.04 (2H, m), 4.00 (1H, d), 3.90 (3H, s), 2.72-2.56 (2H, m)
28	^{1}H NMR δ (ppm) (DMSO, d_6): 9.25 (1H, br s), 9.00 (1H, t), 7.41 (2H, d), 7.30 (2H, d), 4.35 (2H, d), 4.00-3.86 (1H, m), 3.70-3.59 (1H, m), 2.68-2.55 (1H, m), 2.46-2.35 (1H, m), 1.75 (3H, s)
31	^{1}H NMR δ (ppm) ($CDCl_3$): 3.93-3.81 (1H, m), 3.81-3.68 (1H, m), 2.85-2.71 (1H, m), 2.12-2.00 (1H, m), 1.72 (3H, s), 1.48 (9H, s)
34	^{1}H NMR δ (ppm) ($CDCl_3$):7.42-7.21 (5H, m), 3.86-3.74 (4H, m), 3.66-3.54 (1H, m), 3.34-3.07 (2H, m), 2.68-2.55 (1H, m), 2.02-1.91 (1H, m), 1.53 (3H, s)
35	^{1}H NMR δ (ppm) ($CDCl_3$): 7.65 (2H, d), 7.59 (2H, d), 4.48-4.39 (1H, m), 4.28-4.19 (1H, m), 3.07-2.97 (1H, m), 2.34-2.24 (1H, m), 1.95 (3H, s)
36	^{1}H NMR δ (ppm) ($CDCl_3$): 7.35-7.28 (4H, m), 3.81 (2H, s), 3.77 (3H, s), 3.44 (2H, s), 2.00 (1H, s)
38	^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.35 (1H, m), 7.32-7.21 (3H, m), 3.82 (2H, s), 3.77 (3H, s), 3.45 (2H, s), 2.02 (1H, s)
39	^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.31 (4H, m), 3.94 (2H, s), 3.59 (2H, s), 1.68 (1H, s)
40	^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.26 (4H, m), 4.15 (2H, q), 3.79 (2H, s), 2.68 (2H, t), 2.40 (2H, t), 1.86 (2H, tt), 1.78 (1H, br s), 1.27 (3H, t)
50	^{1}H NMR δ (ppm) ($CDCl_3$): 7.27-7.12 (4H, m), 3.69 (2H, s), 2.60 (2H, q), 1.64 (1H, br s), 1.06 (3H, t)
55	^{1}H NMR δ (ppm) ($CDCl_3$): 7.36-7.27 (4H, m), 3.82 (2H, s), 3.54 (2H, t), 3.39 (3H, s), 2.84 (2H, t), 1.94 (1H, br s)
59	^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.35 (1H, m), 7.29-7.21 (3H, m), 3.82 (2H, s), 3.72 (3H, s), 2.92 (2H, t), 2.58 (2H, t), 2.30 (1H, s)
61	^{1}H NMR δ (ppm) ($CDCl_3$): 7.34-7.23 (4H, m), 3.77 (2H, s), 3.68 (3H, s), 2.87 (2H, t), 2.54 (2H, t), 1.90 (1H, br s)
62	^{1}H NMR δ (ppm) ($CDCl_3$): 7.28-7.13 (4H, m), 3.73 (2H, t), 3.70 (2H, s), 3.04 (2H, br s), 2.81 (2H, t), 1.66 (2H, tt)
64	^{1}H NMR δ (ppm) ($CDCl_3$): 7.34-7.27 (4H, m), 3.82 (1H, d), 3.77 (3H, s), 3.67 (1H, d), 3.41 (1H, q), 2.25 (1H, br s), 1.26 (3H, d)

	Int	NMR data
	67	^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.26 (4H, m), 3.82 (2H, s), 3.70 (2H, t), 2.83 (2H, t), 2.19 (2H, br s)
	69	^{1}H NMR δ (ppm) (MeOD, d_4): 8.28 (1H, s), 7.71 (1H, d), 7.62 (1H, d), 7.40-7.35 (1H, m), 6.68 (1H, d), 4.27-4.20 (1H, m), 4.17-4.08 (2H, m), 4.00-3.92 (1H, m), 3.57-3.42 (2H, m), 1.75 (9H, s), 1.23 (3H, t)
	84	^{1}H NMR δ (ppm) ($CDCl_3$): 7.33-7.23 (4H, m), 6.10-6.00 (1H, m), 3.78 (2H, s), 3.39-3.33 (2H, m), 2.77 (2H, t), 1.99 (3H, s)
	115	^{1}H NMR δ (ppm) ($CDCl_3$): 8.31-8.21 (1H, m), 7.89 (1H, d), 7.72 (1H, br s), 7.51-7.39 (2H, m), 7.39-7.33 (2H, m), 7.29-7.18 (2H, m), 4.28-4.17 (1H, m), 4.09-3.94 (1H, m), 3.67 (3H, s), 3.59-3.44 (1H, m), 2.86-2.70 (1H, m), 2.44-2.04 (5H, m), 2.03-1.74 (2H, m), 1.70 (3H, d), 1.69 (3H, s)
	121	^{1}H NMR δ (ppm) ($CDCl_3$): 87.92 (1H, d), 7.78 (1H, d), 7.50-7.40 (2H, m), 7.35 (1H, s), 4.05-3.93 (2H, m), 3.79 (2H, s), 2.96-2.76 (1H, m), 2.19-2.08 (1H, m), 1.80 (3H, s)
	125	^{1}H NMR δ (ppm) ($CDCl_3$): 8.41 (1H, d), 7.92 (1H, d), 7.87 (1H, s), 7.57-7.44 (2H, m), 4.49-4.39 (1H, m), 4.31-4.21 (1H, m), 3.10-3.00 (1H, m), 2.36-2.25 (1H, m), 2.01 (3H, s)
	138	^{1}H NMR δ (ppm) ($CDCl_3$): 8.33 (1H, br s), 7.37-7.20 (4H, m),
	139	^{1}H NMR δ (ppm) ($CDCl_3$): 7.39-7.31 (2H, m), 7.26-7.15 (2H, m), 4.77-4.44 (2H, m), 3.94-3.74 (2H, m), 2.94 (3H, s), 2.55-2.39 (1H, m), 2.31-2.18 (1H, m), 1.82 (3H, s), 1.48 (9H, s)
	201	^{1}H NMR δ (ppm) ($CDCl_3$): 7.22 (1 H, d), 6.91 - 6.67 (3 H, m), 3.87 - 3.75 (7 H, m), 3.49 (0.3 H, d), 3.32 (0.7 H, d), 3.26 - 3.11 (1 H, m), 3.04 (1 H, d), 2.18 - 2.05 (2 H, m), 1.47 (9 H, s)
	206	^{1}H NMR δ (ppm) ($CDCl_3$): 7.58 - 7.49 (2 H, m), 7.44 (2 H, d), 3.91 - 3.75 (4 H, m), 3.58 (0.4 H, d), 3.39 (0.6 H, d), 3.25 - 3.04 (2 H, m), 2.20 - 2.05 (2 H, m), 1.45 (9 H, s)
GG136-004-A01	211	^{1}H NMR δ (ppm) ($CDCl_3$): 7.33 (2 H, d), 7.16 - 7.26 (2 H, m), 3.94 - 3.84 (3.7 H, m), 3.83 - 3.75 (0.3 H, m), 3.52 (0.3 H, d), 3.33 (0.7 H, d), 3.27- 3.18 (0.7 H, m), 3.17- 3.12 (0.3 H, m), 3.08 (1 H, d), 2.18 - 2.06 (2 H, m), 1.52 - 1.47 (9 H, m)
	216	^{1}H NMR δ (ppm) ($CDCl_3$): 7.25 - 7.14 (2 H, m), 7.02 (2 H, t), 3.90 - 3.65 (4 H, m), 3.30 (1 H, d), 3.24 - 3.10 (1 H, m), 3.10 - 2.96 (1 H, m), 2.16 - 1.95 (2 H, m), 1.52 - 1.39 (9 H, m)
	221	^{1}H NMR δ (ppm) ($CDCl_3$): 7.20 (1 H, t), 7.11 - 7.00 (3 H, m), 3.87 - 3.68 (4 H, m), 3.49 (0.3 H, d), 3.31 (0.7 H, d), 3.22 – 3.06 (1 H, m), 3.02 (1 H, d), 2.34 (3 H, s), 2.19-2.01 (2 H, m), 1.47 (9 H, s)
GG136-045-A01	226	^{1}H NMR δ (ppm) ($CDCl_3$): 7.36 - 7.26 (2 H, m), 6.95 - 6.85 (2 H, m), 4.57 (2 H, s), 3.90 (3 H, s)
GG136-046-A01	227	^{1}H NMR δ (ppm) ($CDCl_3$): 7.31 - 7.11 (2 H, m), 6.96 - 6.80 (2 H, m), 3.87 - 3.70 (7 H, m), 3.60 - 3.45 (1 H, d), 3.27 - 2.96 (2 H, m), 2.08 (2 H, t), 1.47 (9 H, s)
	232	^{1}H NMR δ (ppm) ($CDCl_3$): 7.33 - 7.17 (2 H, m), 7.17 - 6.98 (2 H, m), 3.94 - 3.69 (4 H, m), 3.53 - 3.28 (1 H, m), 3.28 - 3.08 (2 H, m), 2.25 - 2.06 (2 H, m), 1.46 (9 H, s)
	246	^{1}H NMR δ (ppm) ($CDCl_3$): 7.98 (1 H, d), 6.59 (1 H, dd), 6.41 (1 H, d), 4.84 (1 H, br. s.), 4.17 (2 H, q), 3.41 - 3.29 (2 H, m), 2.45 (2 H, t), 1.98 (2 H, quin), 1.29 (3 H, t)
	255	^{1}H NMR δ (ppm) ($CDCl_3$): 7.36 - 7.27 (3 H, m), 7.27 - 7.14(3 H, m), 6.50 (1 H, d), 6.46 (1 H, dd), 5.13 (1 H, br. s.), 4.24 (2 H, d), 3.83 (3 H, s), 3.87 (3 H, s), 3.68 (1 H, q), 3.07 - 2.92 (1 H, m), 2.92 - 2.77 (1 H, m), 2.52 (1 H, dt), 2.34 (1 H, dt), 1.78 (2 H, quin), 1.30 (3 H, d)

Synthesis of representative Compounds of the Invention.

Compound 191: 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid



Step a: 2-Benzylamino-propionic acid ethyl ester

[00270] To a solution of 2-bromo-propionic acid ethyl ester (17.90 mL, 1 eq.) in 250 mL of MeCN were added benzylamine (13.45 mL, 0.9 eq.) and potassium carbonate (28.60 g, 1.5 eq.). The reaction was refluxed for 2h then cooled to 20°C. The crude was filtered, washed with EtOAc. The filtrate was concentrated under reduced pressure, then purified by chromatography on silica gel (elution with heptane/EtOAc : 9/1 to 7/3) to afford 2-benzylamino-propionic acid ethyl ester (24.74 g, yield = 97%).

^{1}H NMR δ (ppm) ($CDCl_3$): 7.37-7.29 (4H, m), 7.28-7.22 (1H, m), 4.20 (2H, q), 3.82 (1H, d), 3.69 (1H, d), 3.38 (1H, q), 1.33 (3H, d), 1.29 (3H, t)
MW (calcd): 207.2; MW (obsd): 208.1 (M+1)

Step b: 2-[Benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester

(I) Drying of chloroacetaldehyde solution (solution I):

[00271] To a solution of chloroacetaldehyde (45% w/w in water, 56 mL, 3 eq.) in 75 mL of dry DCM under nitrogen was added $MgSO_4$ (55 g, 3.8 eq.). The mixture was stirred for 1h at 20°C. The solid was filtered, washed twice with 110 mL of dry DCM, and the resulting filtrate (solution I) was rapidly used in the following reaction.

(II) Reaction:

[00272] To a solution of 2-benzylamino-propionic acid ethyl ester (24.72 g, 1 eq.) in 114 mL of dry DCM under nitrogen was added $MgSO_4$ (10.80 g, 0.75 eq.). The reaction was cooled to 0°C then acetic acid (6.82 mL, 1 eq) and the above solution of chloroacetaldehyde in dry DCM (solution I) were added. Sodium triacetoxyborohydride (38 g, 1.5 eq.) was added portionwise. The reaction was stirred for 2h at 0°C. The crude was carefully quenched with 160 mL of a saturated aqueous solution of $NaHCO_3$. Then 75 mL of an aqueous solution of NaOH (2N) was added. The aqueous layer was extracted twice with 120 mL of DCM. The combined organic layers were washed twice with 120 mL of a saturated aqueous solution of $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 100/0 to 93/7) to afford 2-[benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester (27.40 g, yield = 85%).
^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.29 (4H, m), 7.29-7.22 (1H, m), 4.24-4.14 (2H, m), 3.90 (1H, d), 3.77 (1H, d), 3.50 (1H, q), 3.43-3.36 (2H, m), 3.13-2.94 (2H, m), 1.34 (3H, d), 1.31 (3H, t)
MW (calcd): 269.8; MW (obsd): 270.1 (M+1, ^{35}Cl)

Step c: 1-Benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester

[00273] A solution of 2-[benzyl-(2-chloro-ethyl)-amino]-propionic acid ethyl ester (27.4 g, 1 eq.) in 253 mL of dry THF was cooled to -78°C under argon. KHMDS (15% w/w in toluene, 170.40 g, 1.25 eq.) was slowly added so that temperature was kept below -76°C. The reaction was stirred for 1h at -76°C, then warmed to 20°C and stirred for 1h. Acetic acid (1.74 mL, 0.3 eq.) was added and the reaction was stirred at 20°C for 10 min. The reaction was quenched with 50 mL of a saturated aqueous solution of $NaHCO_3$ and partially concentrated under reduced pressure. The crude was extracted three times with DCM. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc 100/0 to 90/10) to afford 1-benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester (18.75 g, yield = 79%).
^{1}H NMR δ (ppm) ($CDCl_3$): 7.34-7.19 (5H, m), 4.24-4.16 (2H, m), 3.79 (1H, d), 3.58 (1H, d), 3.30-3.22 (1H, m), 3.15-3.05 (1H, m), 2.63-2.54 (1H, m), 1.97-1.88 (1H, m), 1.49 (3H, s), 1.29 (3H, t)

MW (calcd): 233.3; MW (obsd): 234.1 (M+1)

Step d: Intermediate 11 2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

[00274] To a solution of 1-benzyl-2-methyl-azetidine-2-carboxylic acid ethyl ester (69.27 g, 1 eq.) in 1500 mL of EtOH were added Boc_2O (74.93 g, 1.15 eq.) and Pd/C (7.29 g, 0.02 eq.). The flask was evacuated and backfilled with argon. Then the reaction was backfilled with H_2 and stirred for 24h at 20°C under atmospheric pressure. The crude was filtered through a pad of celite and washed with EtOH. The filtrate was concentrated under reduced pressure and purified by chromatography on silica gel (elution with heptane/EtOAc 100/0 to 80/20) to afford 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (57 g, yield = 79%).

^{1}H NMR δ (ppm) ($CDCl_3$): 4.12-3.92 (2H, m), 3.86-3.71 (1H, m), 3.66-3.54 (1H, m), 2.17-2.00 (1H, m), 1.99-1.83 (1H, m), 1.33 (3H, s), 1.21 (9H, s), 1.11 (3H, t)

MW (calcd): 243.3; MW (obsd): 266 ($M+Na^+$)

Step e: Intermediate 31 2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester

[00275] To a solution of 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (63 g, 1 eq.) in 260 mL of EtOH was added 260 mL of an aqueous solution of NaOH 2N (2 eq.). The reaction was stirred at 20°C for 15h. The solvent was removed under reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was discarded and the aqueous layer was acidified by addition of a solution of citric acid 10% in water until pH=5 and thoroughly extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester (50 g, yield = 89%).

^{1}H NMR δ (ppm) ($CDCl_3$): 3.93-3.81 (1H, m), 3.81-3.68 (1H, m), 2.85-2.71 (1H, m), 2.12-2.00 (1H, m), 1.72 (3H, s), 1.48 (9H, s)

Step f: Intermediate 33 (R)-2-Methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester

[00276] The chiral separation of racemic Intermediate 31, 2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester was performed by preparative chiral chromatography using a column Chiralpak AD-H, (20 x 250 mm), 5 µ, a mobile phase: hexane : ethanol : Formic acid (95 : 5 : 0.05), a flow rate of 9.5 mL/min, at 20°C. Retention time of isomer (R): 9.00 min.

ee = 100%

Step g: Intermediate 80 4-(3-Chloro-benzylamino)-butyric acid methyl ester hydrochloride

[00277] To a solution of 4-amino-butyric acid methyl ester hydrochloride (30 g, 1 eq.) in 360 mL of THF were added TEA (67.7 mL, 2.5 eq.), then 3-chlorobenzaldehyde (19 mL, 0.9 eq.) and $MgSO_4$ (35 g, 1.5 eq.). The reaction was stirred at 20°C for 15h under nitrogen. 360 mL of MeOH was added then the reaction was cooled to-20°C. $NaBH_4$ (14.75 g, 2 eq.) was added portionwise. The reaction was stirred for 1h at 0°C. The crude was partially concentrated under reduced pressure at 20°C, filtered and washed with DCM. The

filtrate was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure at 20°C. The residue, in solution in 1600 mL of Et_2O, was treated with 87 mL of HCl 2N in Et_2O. A solid was formed, filtrated, washed with Et_2O, then pentane and dried to afford 4-(3-chloro-benzylamino)-butyric acid methyl ester hydrochloride (32 g, yield = 65%).

^1H NMR δ (ppm) ($CDCl_3$): 7.66-7.58 (2H, m), .7.43-7.36 (2H, m), 4.16-4.09 (2H, m), 3.67 (3H, s), 3.00-2.90 (2H, m), 2.54-2.46 (2H, m), 2.27-2.16 (2H, m)

MW (calcd): 241.7; MW (obsd): 242.3 (M+1,^{35}Cl)

Step h: Intermediate 175 (R)-2-[(3-Chloro-benzyl)-(3-methoxycarbonyl-propyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid tert-butyl ester

[00278] To a solution of (R)-2-methyl-azetidine-1,2-dicarboxylic acid 1-tert-butyl ester, Intermediate 33 (13 g, 1 eq.) in 300 mL of dry DCM under nitrogen was added dropwise a solution of 1-chloro-N,N,2-trimethylpropenylamine (16 mL, 2 eq.) in 50 mL of DCM. The solution was stirred at 20°C for 30 min, then cooled to -5°C. A solution of 4-(3-chloro-benzylamino)-butyric acid methyl ester hydrochloride, Intermediate 80 (18.5 g, 1.1 eq.) and TEA (25 mL, 3 eq.) in 200 mL of DCM was added slowly to the previous mixture. The reaction was stirred at 20°C for 2.5h. The mixture was added to 500 mL of a saturated aqueous solution of $NaHCO_3$. The crude was extracted three times with DCM. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc: 90/10 to 50/50) to afford (R)-2-[(3-chloro-benzyl)-(3-methoxycarbonyl-propyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid tert-butyl ester (27 g, yield = quantitative).

^1H NMR δ (ppm) ($CDCl_3$): 7.35-7.04 (4H, m), 5.13-4.29 (2H, m), 3.96-3.74 (1H, m), 3.68 (3H, s), 3.13-2.90 (4H, m), 2.65-2.40 (1H, m), 2.39-2.15 (2H, m), 2.00-1.65 (5H, m), 1.58-1.30 (9H, m)

MW (calcd): 439.0; MW (obsd): 439.4 (M+1, ^{35}Cl)

Step i: Intermediate 21 4-[(3-Chloro-benzyl)-((R)-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester hydrochloride

[00279] To a solution of (R)-2-[(3-chloro-benzyl)-(3-methoxycarbonyl-propyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid tert-butyl ester, Intermediate 175 (17.6 g, 1 eq.) in 200 mL of dioxane under nitrogen was added a solution of HCl (4N) in dioxane (50 mL, 5 eq.). The reaction was stirred for 16h at 20°C, then concentrated under reduced pressure. The crude was solubilised in DCM, poured into Et_2O and the resulting solid was filtered, washed with Et_2O and pentane and dried to afford 4-[(3-chloro-benzyl)-((R)-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester hydrochloride(12.5 g, yield = 81%).

^1H NMR δ (ppm) ($CDCl_3$): 8.82 (1H, br s), 7.41-7.26 (2H, m), 7.25-7.11 (2H, m), 4.83-4.53 (1H, m), 4.47-4.31 (1H, m), 4.31-3.95 (2H, m), 3.72-3.64 (3H, m), 3.51-3.26 (1H, m), 3.17-3.07 (1H, m), 3.02-2.86 (1H, m), 2.78-2.52 (1H, m), 2.40-2.30 (2H, m), 2.16-2.01 (3H, m), 1.97-1.83 (2H, m)

MW (calcd): 338.8; MW (obsd): 339.3 (M+1, ^{35}Cl)

Step j: Intermediate 112 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid methyl ester

[00280] To a suspension of benzo[b]thiophene-3-carboxylic acid (7.12 g, 1.2 eq.) in 210 mL of DCM and 210 mL of THF were added HOBt (5.4 g, 1.2 eq.) EDC.HCl (9.6 g, 1.5 eq.) and TEA (18.5 mL, 4 eq.). The reaction was stirred at 20°C for 15h, then a solution of 4-[(3-chloro-benzyl)-((R)-2-methyl-azetidine-2-carbonyl)-amino]-butyric acid methyl ester hydrochloride obtained in step i above (12.5 g, 1 eq.) in 105 mL of DCM and 105 mL of THF was added. The reaction was stirred at 20°C for 4.5h. The crude was diluted with DCM. A saturated aqueous solution of $NaHCO_3$ was added. The aqueous layer was extracted three times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (elution with heptane/EtOAc : 90/10 to 50/50) to afford 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid methyl ester (14.53 g, yield = 87%).

^{1}H NMR δ (ppm) ($CDCl_3$): 8.37-8.07 (1H, m), 7.92-7.77 (1H, m), 7.51-7.36 (2H, m), 7.34-6.67 (5H, m), 5.49-4.72 (1H, m), 4.57-4.33 (1H, m), 4.05-3.76 (2H, m), 3.69 (3H, s), 3.29-2.66 (2H, m), 2.50-2.19 (3H, m), 2.15-1.83 (5H, m), 1.74-1.57 (1H, m)

MW (calcd): 499.0; MW (obsd):499.3 (M+1, ^{35}Cl)

Step k: Compound 191 *4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid*

[00281] To a solution of 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid methyl ester, Intermediate 112 (25 g, 1 eq.) in 750 mL of MeOH was added aqueous NaOH (2N) (75 mL, 3 eq.). The reaction was stirred at 20°C for 15h. The solvent was removed under reduced pressure and the crude was partitioned between water and EtOAc. The organic layer was discarded. The aqueous layer was acidified by addition of HCl (2N) until pH=2 and thoroughly extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid (23.7 g, yield = 97%).

$[\alpha]^{20}_D$= +176 (c=1.01, $CHCl_3$); ee > 99.0%

^{1}H NMR δ (ppm) (DMSO, d_6) at 80°C: 8.14-8.08 (1H, m), 7.99-7.93 (1H, m), 7.90 (1H, s), 7.44-7.31 (3H, m), 7.30-7.25 (2H, m), 7.22-7.16 (1H, m), 4.73-4.54 (2H, m), 4.11-3.98 (2H, m), 3.44-3.34 (1H, m), 3.26-3.15 (1H, m), 2.58-2.51 (1H, m), 2.41-2.32 (1H, m), 2.18 (2H, t), 1.85-1.76 (5H, m)

MW (calcd): 485.0; MW (obsd):485.4 (M+1, ^{35}Cl)

Step l: 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid, sodium salt

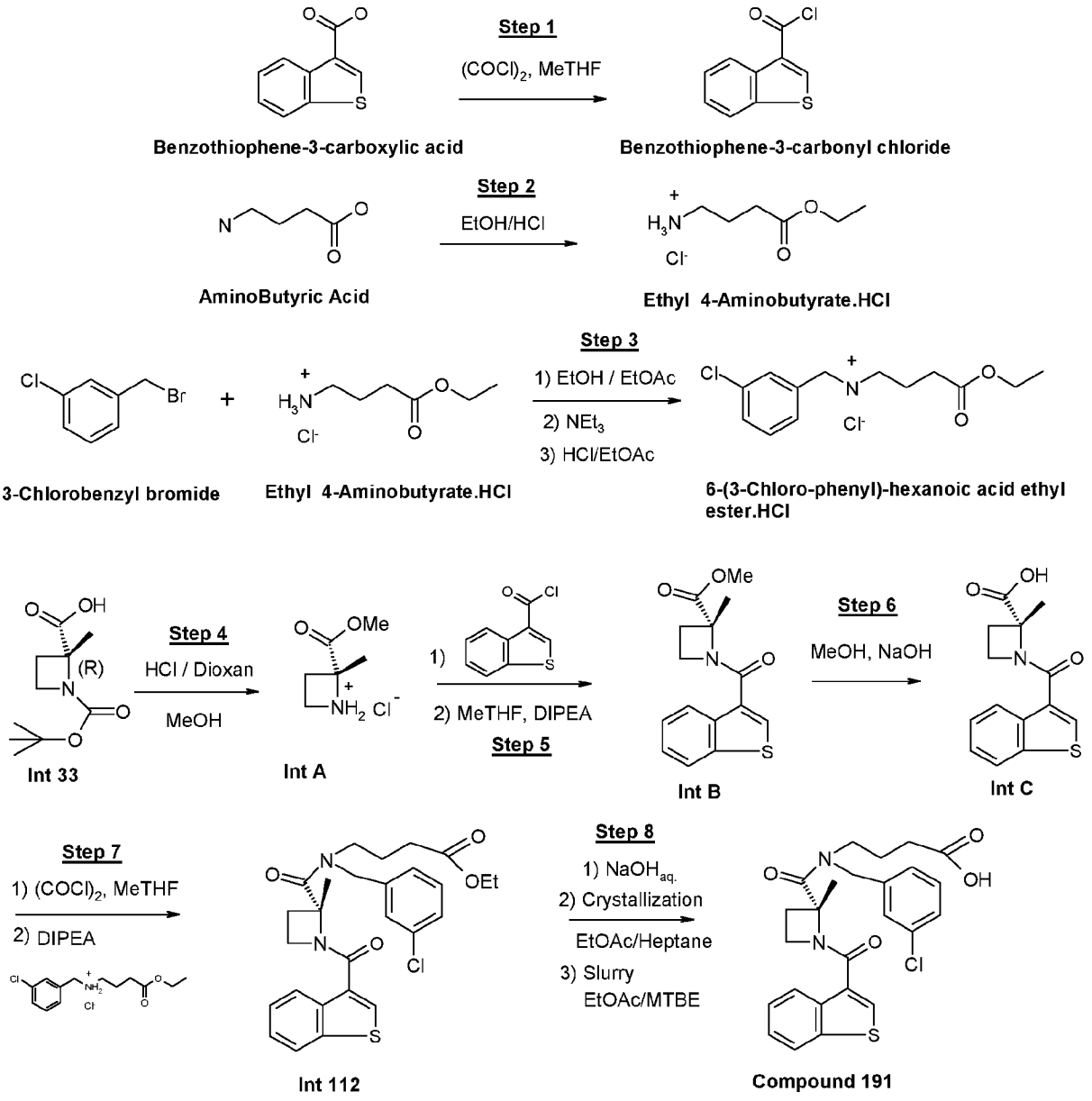
[00282] To a solution of 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid (51.00 g, 1 eq.) in 1000 mL of EtOH was added aqueous NaOH (1N) (105.15 mL, 1 eq.). The reaction was stirred at 20°C for 15 min under nitrogen. The solvent was removed

under reduced pressure. The crude was solubilised in 200 mL of DCM, poured dropwise into 4000 mL of Et_2O. The resulting solid was filtered, washed with pentane and dried to afford 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid, sodium salt (49.3 g, yield = 92%).

^{1}H NMR δ (ppm) ($CDCl_3$): 8.14-8.06 (1H, m), 7.82-7.72 (1H, m), 7.40-7.27 (3H, m), 7.23-7.08 (3H, m), 7.05-6.96 (1H, m), 4.82-4.64 (1H, m), 4.33-4.22 (1H, m), 4.06-3.94 (1H, m), 3.80-3.25 (3H, m), 3.10-2.53 (2H, m), 2.21-1.47 (7H, m)

MW (calcd): 485.0; MW (obsd):485.4 ($M+1$, ^{35}Cl)

Alternative route to 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid



Step 1: Synthesis of the benzo[b]thiophene-3-carbonyl chloride

[00283] To benzothiophene carboxylic acid (7g) in MeTHF (6.5 Vols, 45.5 mL) is added a catalytic amount of DMF (0.01 eq.). Then, oxalyl chloride (1.1 eq.) is charged slowly to control the gaz release. After 16 h of stirring at 20°C, the end of the reaction is controlled by HPLC. MeTHF (6.5 Vols) is next added and the reaction mixture is concentrated to 5 volumes to remove the excess of oxalyl chloride. The resulting benzo[b]thiophene-3-carbonyl chloride is stored in a MeTHF solution.

Step 2: Synthesis of the Ethyl 4-amino butyrate hydrochloride

[00284] Aminobutyric acid (103.6 g, 5.5 eq.) is dissolved in ethanol (1.5 Vols, 156 mL) at 15°C. A solution of hydrochloric acid in ethanol 2.5N (2.2 eq., 890 mL) is slowly added over 30 min. After 16 h, the reaction is complete (TLC), and the ethyl 4-aminobutyrate solution in ethanol is concentrated to 2 residual volumes.

Step 3: Synthesis of ethyl 4-(3-chlorobenzylamino) butyrate hydrochloride

[00285] To the solution of ethyl 4-aminobutyrate in ethanol obtained in step 2 above, is added ethyl acetate (12 Vols, 450 mL), then the reaction mixture is cooled to 0-5°C. The triethylamine (5.7 eq.) is charged, followed by the addition of the 3-chlorobenzyl bromide (1 eq., 37.6 g) over 30 min. The reaction is ended after 5 h (HPLC monitoring), and quenched by the addition of water (3 Vols). The organic phase is separated, and the aqueous phase is extracted twice with ethyl acetate (3 Vols). The organic phases are combined and washed several times by water (7 Vols) to eliminate the triethylamine, and finally washed with a brine solution (7 Vols). A solution of HCl in EtOAc at 1.1N is added (1.2 eq.) to precipitate ethyl 4-(3-chlorobenzylamino) butyrate hydrochloride. After 1 h stirring at 5°C, the resulting white powder is filtered, rinsed twice with ethyl acetate (2 Vols), and dried at 40°C under reduced pressure for 16 h.

Step 4: Synthesis of Int A: (R)-Methyl-2-methyl-azetidine-2-carboxylate hydrochloride salt

[00286] Int 33 (7 g) is dissolved in methanol (4 Vols, 28 mL) and a solution of HCl/dioxan at 4N (5 eq., 40.6 mL) is added. The reaction mixture is stirred for 16 h at 30°C. Once the reaction is complete, a solvent exchange from methanol to MeTHF-dioxan is performed to finally store the suspension of Int A in 5 volumes of MeTHF-dioxan.

Step 5: Synthesis of Int B: (R)-methyl 1-(benzo[b]thiophene-2-carbonyl)-2-methyl azetidine-2-carboxylate

[00287] To Int A (5.4 g) in MeTHF/dioxan suspension is added DIPEA (5 eq.). After 1 h stirring at 20°C, the pH is adjusted at 10 (pH $\geq$ 9 targeted), and the reaction is cooled down to 5°C. Then, the solution of benzothiophene 3-carbonyl chloride (Step 1) in MeTHF (1.05 eq.) is charged over 30 min. The reaction mixture is next warmed up to 20°C and left stirring 16 h to complete the reaction. After a quench with water (7 Vols), washed twice with 7 HCl 1N (7 Vols), and water (7 Vols) to obtain Int B in MeTHF.

Step 6: Synthesis of Int C: (R)-methyl 1-(benzo[b]thiophene-2-carbonyl)-2-methyl azetidine-2-carboxylic acid.

[00288] A solvent exchange from the MeTHF to methanol (7 Vols, 49 mL) is performed on the Int B solution obtained in Step 5 above. Then, an aqueous solution of NaOH 2N (2.5 eq.) is added. After 1 h stirring at 20°C, the completion of the reaction is obtained. The methanol is then removed by distillation (0.2 % w/w), dichloromethane (3 Vols, 21 mL) is added followed by the acidification of the aqueous layer with an aqueous solution of HCl at 2N (to pH= 1). Int 4 is then extracted with dichloromethane (7 Vols, 49 mL). Finally, the organic solution is concentrated to 1.5 volumes (10 mL).

[00289] The precipitated residual benzothiophene carboxylic acid is separated by filtration, rinced with dichloromethane (0.5 Vols). Int C is obtained in solution in 2 volumes of dichloromethane.

[00290] Diisopropylether (7 Vols, 49 mL) is then added, the resulting mixture is heated to 40°C for 2 h and cooled down to 20°C in 1 h. The reaction mixture is maintained for 16 h at 20°C, then heptane (5 Vols, 35 mL) is added, cooled down to 5°C. After 2 h at that temperature, Int C has precipitated, is filtered, rinsed twice with diisopropylether (2 Vols, 14 mL) and dried for 16 h at 40°C under reduced pressure.

Step 7: Synthesis of Int 112: Ethyl 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyrate

[00291] Int C (31 g) is dissolved in MeTHF (25 Vols, 775 mL) and a catalytic amount of DMF (0.01 eq.) is charged. The resulting mixture is cooled down to 10°C and oxalyl chloride (1.1 eq.) is added slowly. After 30 min, DIPEA (9 eq.) is added to reach a pH $\geq$ 9 (10). Int 5 (1.3 eq.) is added over 30 min. After 16 h of stirring at 20°C, the reaction mixture is quenched with water (7 Vols, 217 mL), washed twice with HCl 2N (7 Vols, 217 mL) and water (7 Vols, 217 mL). The resulting Int 112 is stored in MeTHF (10 Vols, 310 mL).

Step 8: Synthesis of Compound 191: Ethyl 4-[[(R)-1-(benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid

[00292] A solvent exchange from MeTHF to ethanol (7 Vols, 217 mL) of Int 112 solution (31 g) obtained in Step 7 above is performed. Then, an aqueous solution of NaOH 1N (2.5 eq.) is added. After 15 h stirring at 20°C, a full conversion is obtained. The reaction mixture is then acidified with HCl 2N (10 Vols) to pH=1 and is extracted with dichloromethane (15 Vols).

[00293] A solvent exchange from dichloromethane to ethyl acetate (7 Vols) is performed. The resulting ethyl acetate solution is heated to 50°C, and heptane (4.5 Vols) is slowly added. A temperature drop ramp to 10°C is performed over 1 h, and heptane (5 Vols) is added. The resulting suspension is then re-heated to 70°C for 5 h. Finally, the suspension is cooled down to 10°C over 2 h and maintained for 16 h at this temperature before filtration. The wet cake is washed twice by MTBE (2 Vols).

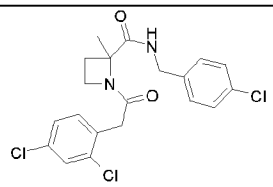
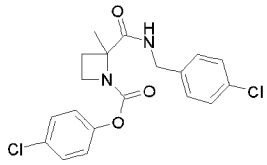
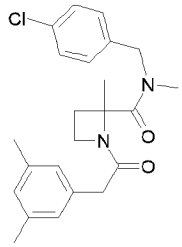
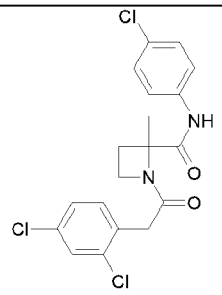
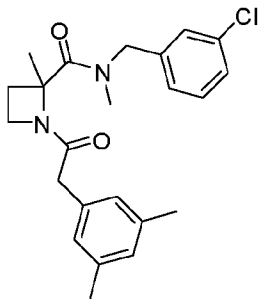
[00294] The wet cake is charged in the reactor and slurried at 50°C for 5 h in a mixture EtOAc/MTBE (4 Vols). The slurry is then cooled down to 0°C over 2 h, and maintained at 0°C for 16 h before filtration.

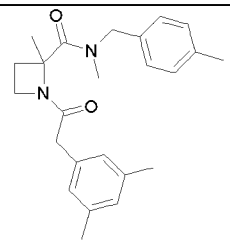
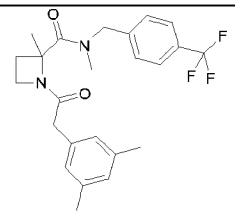
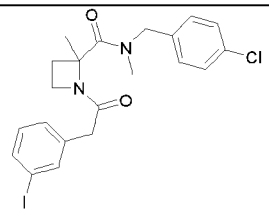
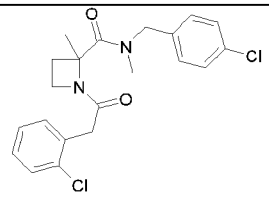
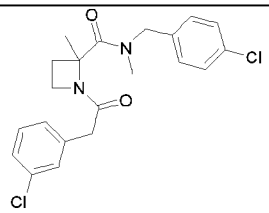
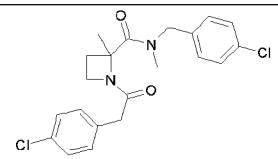
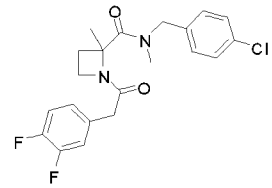
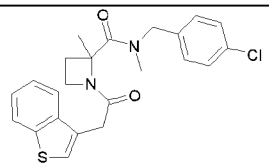
The wet cake is rinsed twice by MTBE (2 Vols) and dried at 40°C for 16 h under reduced pressure to obtain 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid (Compound 191) at 99.7% purity by HPLC.

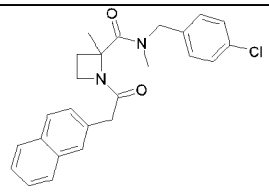
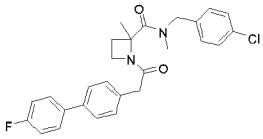
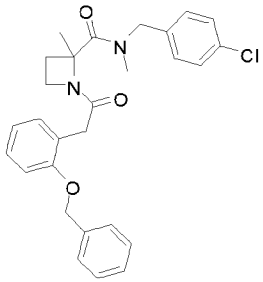
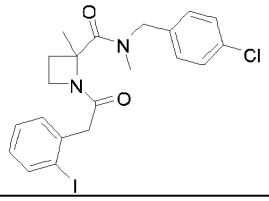
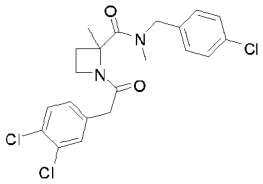
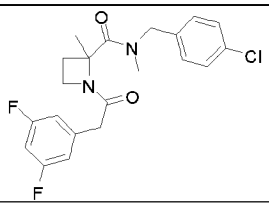
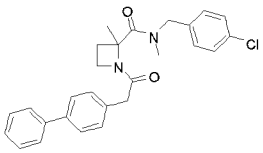
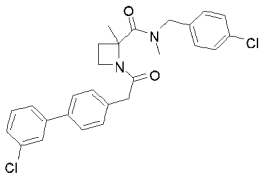
[00295] Compounds of the Invention that have been or can be prepared according to the synthetic method described herein are listed in Table IIa below. The NMR spectral data of said compounds of the invention are given in Table IIb.

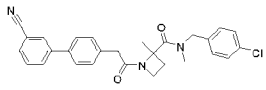
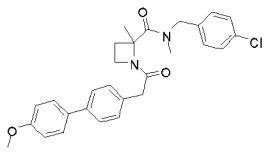
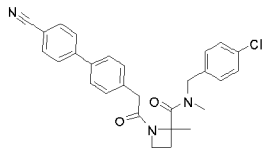
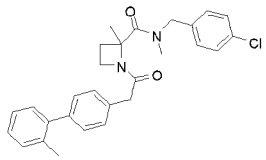
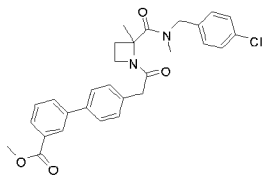
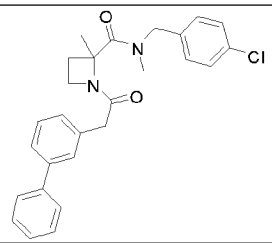
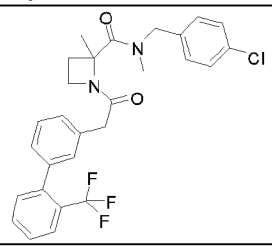
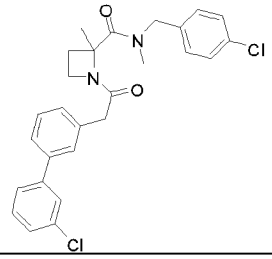
[00296] Table IIa: Mass spectral data of the Compounds of the Invention

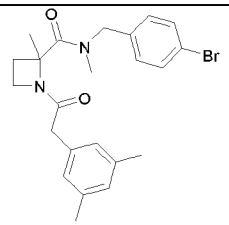
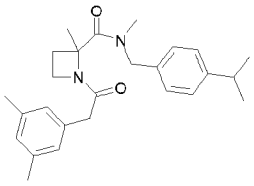
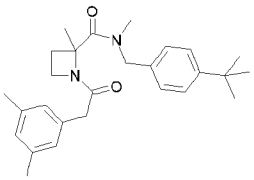
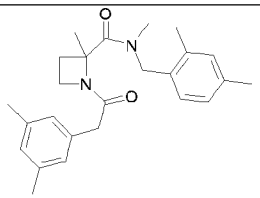
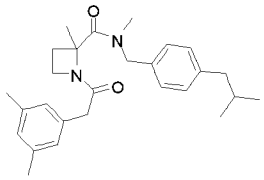
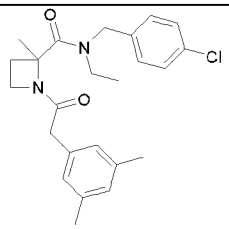
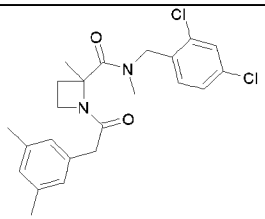
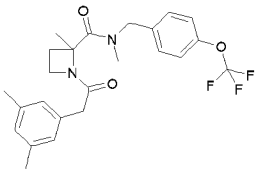
Mtd= Preparation Method SM= Starting Material Ms'd= Measured mass

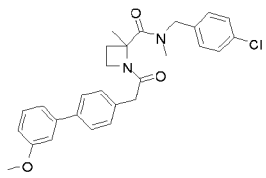
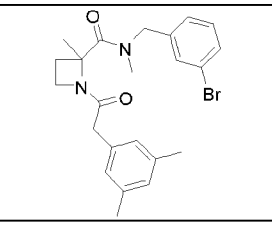
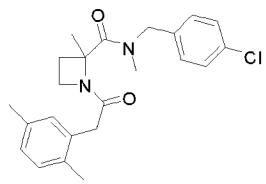
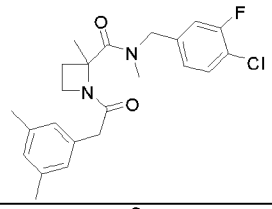
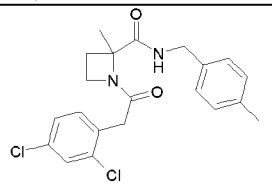
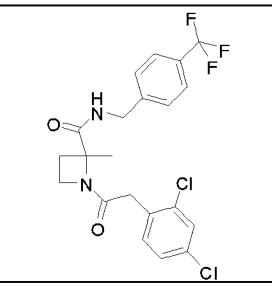
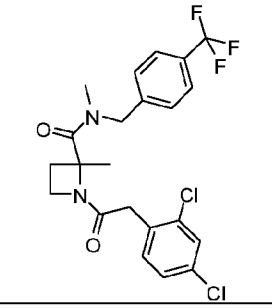
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
1		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide	F	Int 28 and (2,4-Dichloro-phenyl)-acetic acid	424.1	425.3 (M+1, ^{35}Cl)
2		2-(4-Chloro-benzylcarbamoyl)-2-methyl-azetidine-1-carboxylic acid 4-chloro-phenyl ester	H	Int 28 and 4-chlorophenyl-chloroformate	392.1	393.3 (M+1, ^{35}Cl)
3		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3,5-Dimethyl-phenyl)-acetic acid	398.2	399.4 (M+1, ^{35}Cl)
4		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-phenyl)-amide	F	Int 15 and (2,4-Dichloro-phenyl)-acetic acid	410.0	411.2 (M+1, ^{35}Cl)
5		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-methyl-amide	I1	Int 119 and Methyl-(3-chlorobenzyl)-amine	398.2	399.2 (M+1, ^{35}Cl)

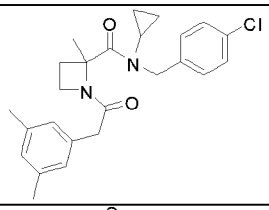
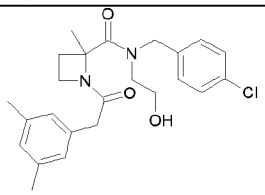
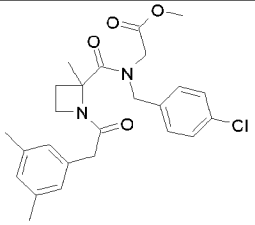
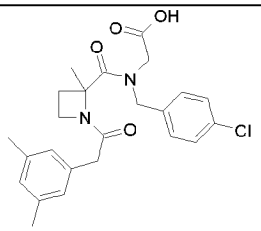
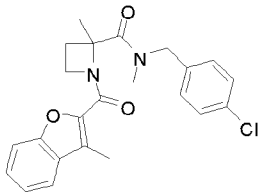
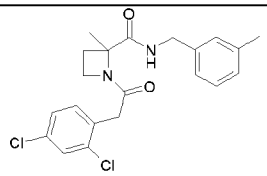
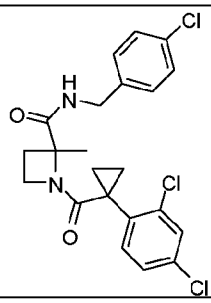
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
6		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-methyl-benzyl)-amide	I1	Int 119 and Methyl-(4-methyl-benzyl)-amine	378.2	379.4 (M+1)
7		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethyl-benzyl)-amide	I1	Int 119 and Methyl-(4-methyl-benzyl)-amine	432.2	433.4 (M+1)
8		1-[2-(3-Iodo-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3-Iodo-phenyl)-acetic acid	496.0	497.2 (M+1, ^{35}Cl)
9		1-[2-(2-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (2-Chloro-phenyl)-acetic acid	404.1	405.3 (M+1, ^{35}Cl)
10		1-[2-(3-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3-Chloro-phenyl)-acetic acid	404.1	405.3 (M+1, ^{35}Cl)
11		1-[2-(4-Chloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (4-Chloro-phenyl)-acetic acid	404.1	405.4 (M+1, ^{35}Cl)
12		1-[2-(3,4-Difluoro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3,4-Difluoro-phenyl)-acetic acid	406.1	407.3 (M+1, ^{35}Cl)
13		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and Benzo[b]thiophen-3-yl-acetic acid	426.1	427.3 (M+1, ^{35}Cl)

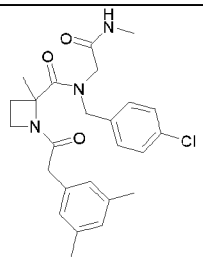
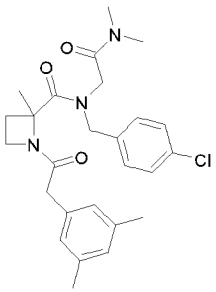
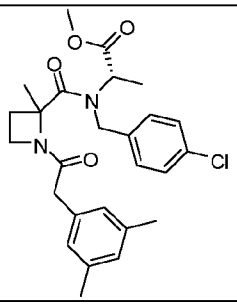
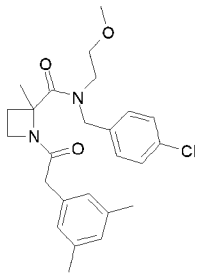
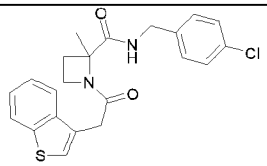
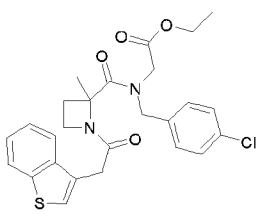
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
14		2-Methyl-1-(2-naphthalen-2-yl-acetyl)-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and Naphthalen-2-yl-acetic acid	420.2	421.3 (M+1, ^{35}Cl)
15		1-[2-(4'-Fluoro-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (4'-Fluoro-biphenyl-4-yl)-acetic acid	464.2	465.4 (M+1, ^{35}Cl)
16		1-[2-(2-Benzyloxy-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (2-Benzyloxy-phenyl)-acetic acid	476.2	477.4 (M+1, ^{35}Cl)
17		1-[2-(2-Iodo-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (2-Iodo-phenyl)-acetic acid	496.0	497.3 (M+1, ^{35}Cl)
18		1-[2-(3,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3,4-Dichloro-phenyl)-acetic acid	438.1	439.3 (M+1, ^{35}Cl)
19		1-[2-(3,5-Difluoro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (3,5-Difluoro-phenyl)-acetic acid	406.1	407.3 (M+1, ^{35}Cl)
20		1-(2-Biphenyl-4-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and phenyl boronic acid	446.2	447.4 (M+1, ^{35}Cl)
21		1-[2-(3'-Chloro-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 3-chloro-phenyl boronic acid	480.1	481.2 (M+1, ^{35}Cl)

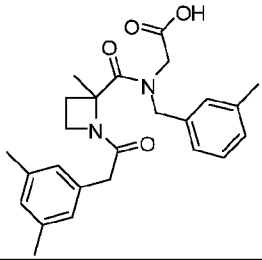
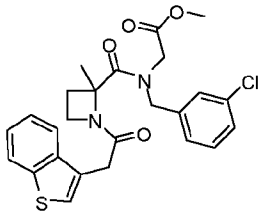
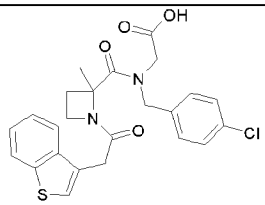
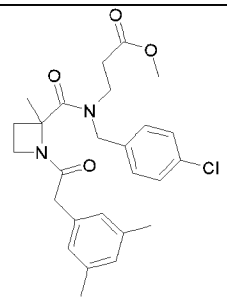
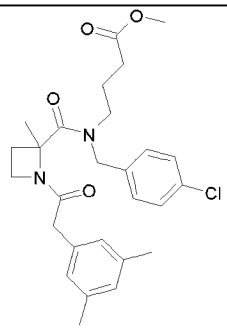
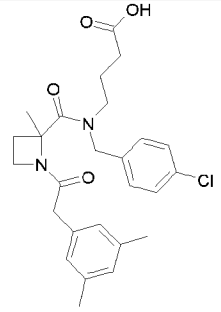
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
22		1-[2-(3'-Cyano-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 3-cyano-phenyl boronic acid	471.2	472.2 (M+1, ^{35}Cl)
23		1-[2-(4'-Methoxy-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 4-methoxy-phenyl boronic acid	476.2	477.2 (M+1, ^{35}Cl)
24		1-[2-(4'-Cyano-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 4-cyano-phenyl boronic acid	471.2	472.2 (M+1, ^{35}Cl)
25		2-Methyl-1-[2-(2'-methyl-biphenyl-4-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 2-methyl-phenyl boronic acid	460.2	461.3 (M+1, ^{35}Cl)
26		methyl 4'-(2-(2-((4-chlorobenzyl)(methyl)carbamoyl)-2-methylazetidin-1-yl)-2-oxoethyl)biphenyl-3-carboxylate	U	Int 103 and 3-methoxycarbonyl-phenyl boronic acid	504.2	505.2 (M+1, ^{35}Cl)
27		1-(2-Biphenyl-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Cpd 8 and phenyl boronic acid	446.2	447.2 (M+1, ^{35}Cl)
28		2-Methyl-1-[2-(2'-trifluoromethyl-biphenyl-3-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Cpd 8 and 2-trifluoromethyl-phenyl boronic acid	514.2	515.1 (M+1, ^{35}Cl)
29		1-[2-(3'-Chloro-biphenyl-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Cpd 8 and 3-chloro-phenyl boronic acid	480.1	481 (M+1, ^{35}Cl)

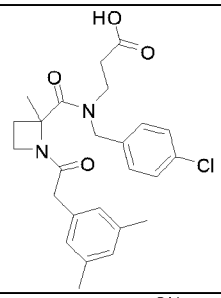
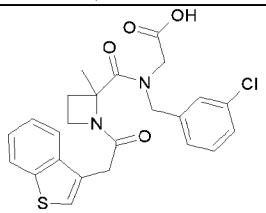
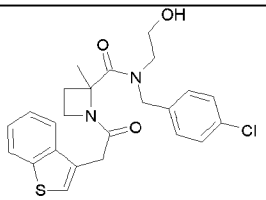
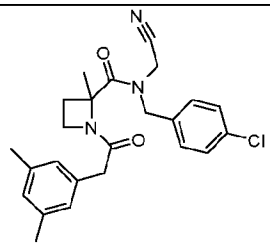
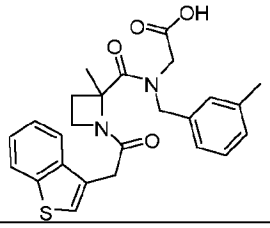
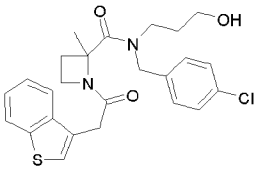
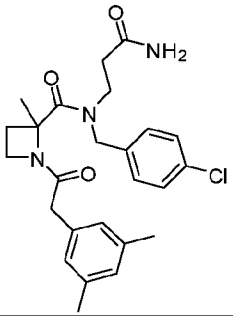
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
30		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-bromo-benzyl)-methyl-amide	I1	Int 119 and Methyl-(4-bromo-benzyl)-amine	442.1	443.3 (M+1, ^{79}Br)
31		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-isopropyl-benzyl)-methyl-amide	I1	Int 46 and int 119	406.3	407.5 (M+1)
32		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-tert-butyl-benzyl)-methyl-amide	I1	Int 47 and int 119	420.3	421.5 (M+1)
33		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2,4-dimethyl-benzyl)-methyl-amide	I1	Int 48 and int 119	392.2	393.5 (M+1)
34		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-isobutyl-benzyl)-methyl-amide	I1	Int 49 and int 119	420.3	421.4 (M+1)
35		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-ethyl-amide	I1	Int 50 and int 119	412.2	413.4 (M+1, ^{35}Cl)
36		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2,4-dichloro-benzyl)-methyl-amide	I1	Int 51 and int 119	432.1	433.4 (M+1, ^{35}Cl)
37		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethoxy-benzyl)-amide	I1	Int 52 and int 119	448.2	449.4 (M+1)

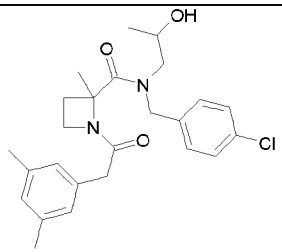
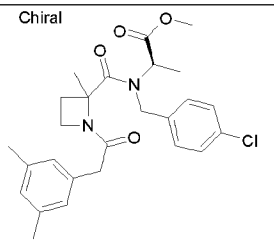
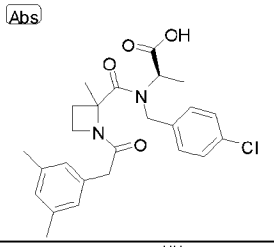
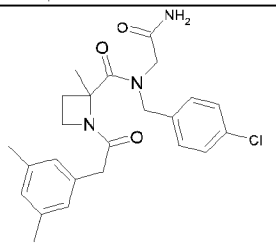
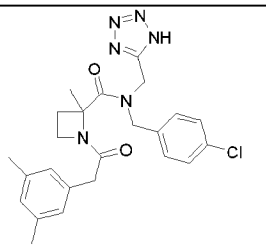
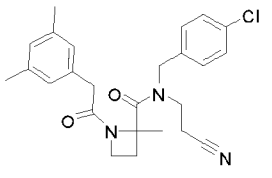
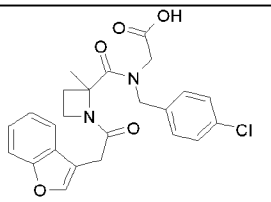
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
38		1-[2-(3'-Methoxy-biphenyl-4-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	U	Int 103 and 3-methoxy-phenyl boronic acid	477.0	477.2 (M+1, ^{35}Cl)
39		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-bromo-benzyl)-methyl-amide	I1	Int 119 and Methyl-(3-bromo-benzyl)-amine	442.1	443.3 (M+1, ^{79}Br)
41		1-[2-(2,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (2,5-Dimethyl-phenyl)-acetic acid	398.2	399.3 (M+1, ^{35}Cl)
42		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-3-fluoro-benzyl)-methyl-amide	I1	Int 54 and int 119	416.2	417.3 (M+1, ^{35}Cl)
43		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-methyl-benzylamide	I2	Int 120 and 4-methyl-benzylamine	404.1	405.3 (M+1, ^{35}Cl)
44		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 4-trifluoromethyl-benzylamide	I1	Int 120 and 4-trifluoromethyl-benzylamine	458.1	459.1 (M+1, ^{35}Cl)
45		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid methyl-(4-trifluoromethyl-benzyl)-amide	I1	Int 120 and Methyl-(4-trifluoromethyl-benzyl)-amine	472.1	473.1 (M+1, ^{35}Cl)

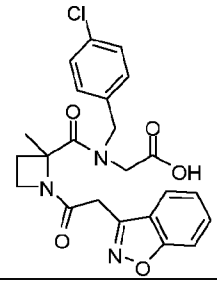
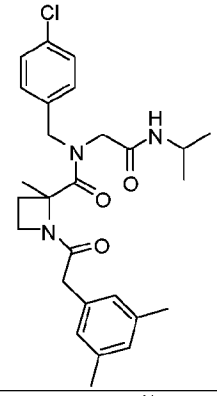
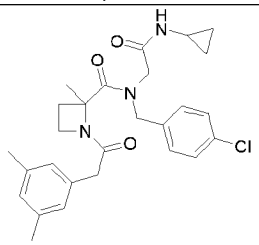
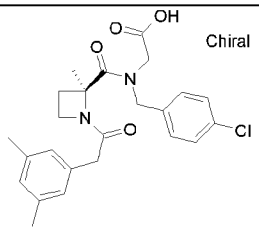
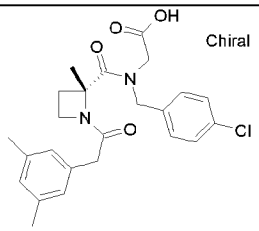
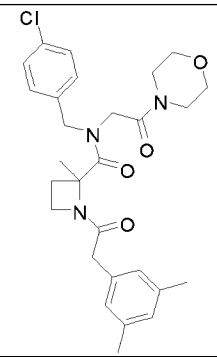
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
46		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyclopropyl-amide	I3	Int 65 and int 119	424.2	425.2 (M+1, ^{35}Cl)
47		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-ethyl)-amide	I3	Int 67 and int 119	428.2	429.4 (M+1, ^{35}Cl)
48		((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid methyl ester	I3	Int 36 and int 119	456.2	457.4 (M+1, ^{35}Cl)
49		((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid	J	Cpd 48	442.2	443.4 (M+1, ^{35}Cl)
50		N-(4-chlorobenzyl)-N,2-dimethyl-1-(3-methylbenzofuran-2-carbonyl)azetidine-2-carboxamide	I3	Int 131 and Methyl-(4-chloro-benzyl)-amine	410.1	411.1 (M+1, ^{35}Cl)
51		1-[2-(2,4-Dichloro-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid 3-methyl-benzylamide	I1	Int 120 and 3-methyl-benzylamine	404.1	405.3 (M+1, ^{35}Cl)
52		N-(4-chlorobenzyl)-1-(1-(2,4-dichlorophenyl)cyclopropanecarbonyl)-2-methylazetidine-2-carboxamide	I1	Int 132 and 4-chloro-benzylamine	450.1	450.8 (M+1, ^{35}Cl)

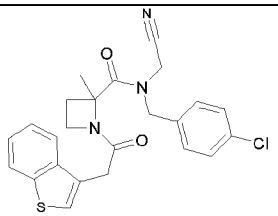
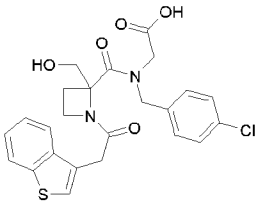
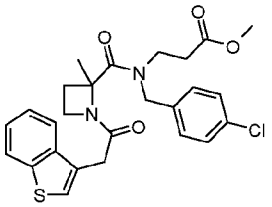
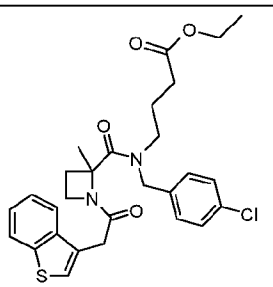
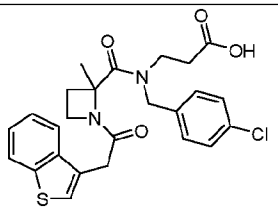
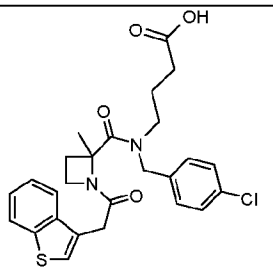
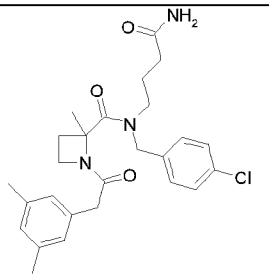
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
53		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methylcarbamoylmethyl-amide	K	Cpd 49 and methylamine	455.2	456.4 (M+1, ^{35}Cl)
54		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-dimethylcarbamoylmethyl-amide	K	Cpd 49 and dimethylamine	469.2	470.4 (M+1, ^{35}Cl)
55		(S)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester	I3	Int 66 and int 119	470.2	471.5 (M+1, ^{35}Cl)
56		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methoxy-ethyl)-amide	I3, 15h	Int 55 and int 119	442.2	443.4 (M+1, ^{35}Cl)
57		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid 4-chloro-benzylamide	I3, 15h	Int 121 and 4-chloro-benzylamine	412.1	413.3 (M+1, ^{35}Cl)
58		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid ethyl ester	I3, 15h	Int 56 and int 121	498.1	499.4 (M+1, ^{35}Cl)

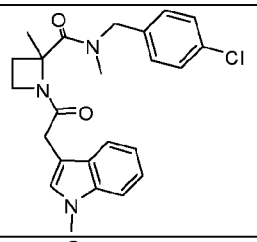
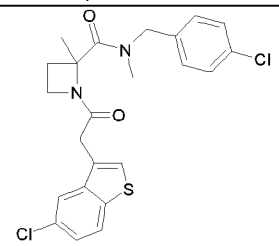
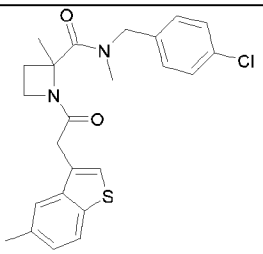
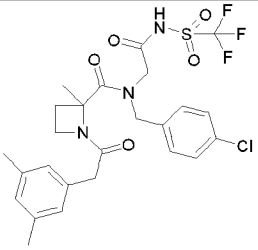
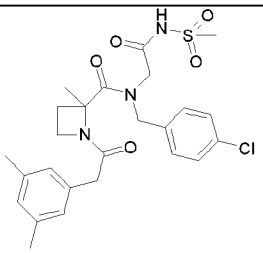
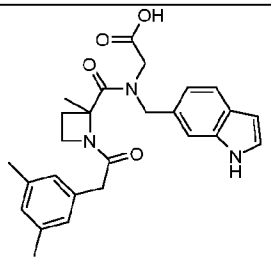
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
59		[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(3-methyl-benzyl)-amino]-acetic acid	J	Int 160	422.2	423.3 (M+1)
60		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-acetic acid methyl ester	I3	Int 38 and int 121	484.1	485.3 (M+1, ^{35}Cl)
61		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid	J	Cpd 58	470.1	471.3 (M+1, ^{35}Cl)
62		3-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester	I3, 15h	Int 61 and int 119	#N/A	471.4 (M+1, ^{35}Cl)
63		4-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid methyl ester	I3, 15h	Int 37 and int 119	484.2	485.5 (M+1, ^{35}Cl)
64		4-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid	J	Cpd 63	470.2	471.4 (M+1, ^{35}Cl)

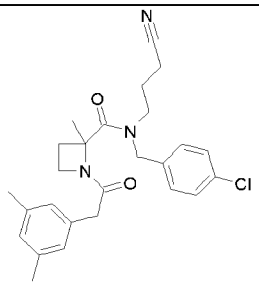
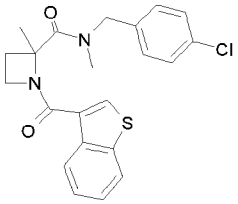
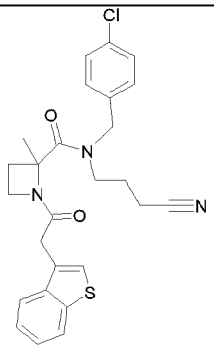
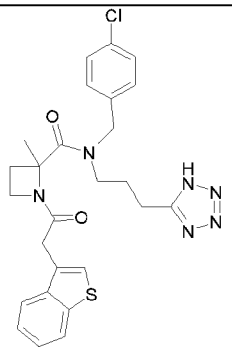
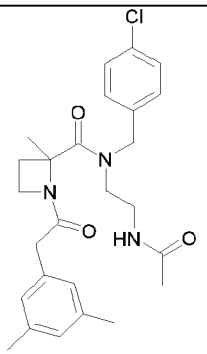
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
65		3-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid	J	Cpd 62	456.2	457.3 (M+1, ^{35}Cl)
66		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-acetic acid	J	Cpd 60	470.1	471.3 (M+1, ^{35}Cl)
67		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-ethyl)-amide	I3, 15h	Int 67 and int 121	456.1	457.3 (M+1, ^{35}Cl)
68		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyanomethyl-amide	I3	Int 39 and int 119	423.2	424.4 (M+1, ^{35}Cl)
69		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-methyl-benzyl)-amino]-acetic acid	J	Int 161	450.2	451.2 (M+1)
70		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-hydroxy-propyl)-amide	I3, 15h	Int 62 and int 121	470.1	471.3 (M+1, ^{35}Cl)
71		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-carbamoyl-ethyl)-(4-chloro-benzyl)-amide	I3	Int 42 and int 119	455.2	456.3 (M+1, ^{35}Cl)

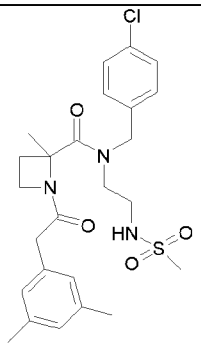
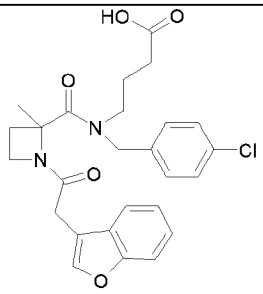
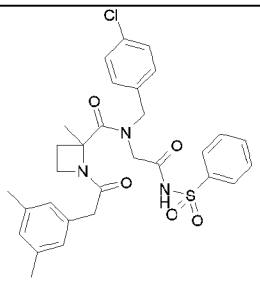
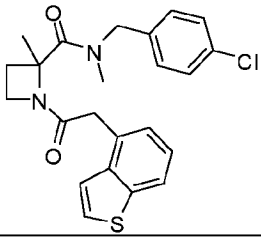
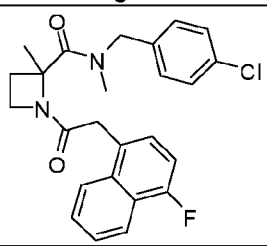
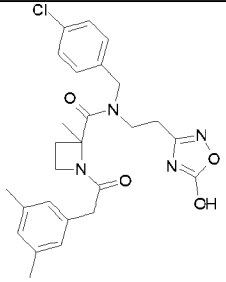
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
72		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-hydroxy-propyl)-amide	I3, 15h	Int 63 and int 119	442.2	465.3 (M+23, ^{35}Cl)
73		(R)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid methyl ester	I3, 15h	Int 64 and int 119	470.2	471.3 (M+1, ^{35}Cl)
74		(R)-2-((4-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-propionic acid	J	Cpd 73	456.2	457.3 (M+1, ^{35}Cl)
75		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid carbamoylmethyl-(4-chloro-benzyl)-amide	I3, 2.5h	Int 68 and int 119	441.2	442.3 (M+1, ^{35}Cl)
76		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(1H-tetrazol-5-ylmethyl)-amide	L	Cpd 68	466.2	467.3 (M+1, ^{35}Cl)
77		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-cyano-ethyl)-amide	I3	Int 57 and int 119	437.2	438.1 (M+1, ^{35}Cl)
78		[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid	J	Int 141	454.1	454.9 (M+1, ^{35}Cl)

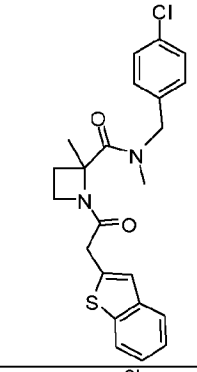
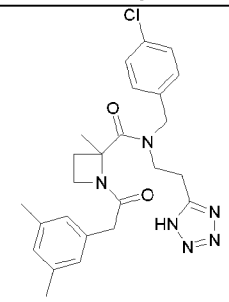
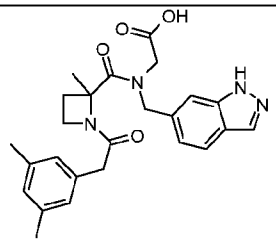
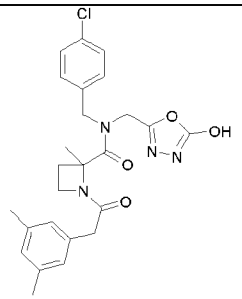
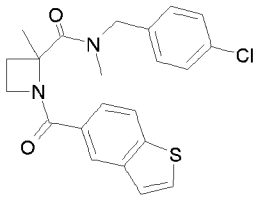
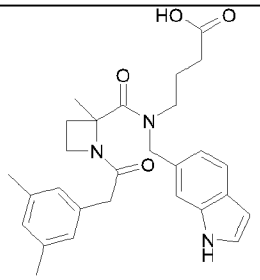
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
79		[[1-(2-Benzo[d]isoxazol-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid	J	Int 162	455.1	455.9 (M+1, ^{35}Cl)
80		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(isopropylcarbamoyl-methyl)-amide	K	Cpd 49 and isopropylamine	483.2	484.0 (M+1, ^{35}Cl)
81		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyclopropylcarbamoylmethyl-amide	K	Cpd 49 and cyclopropyl amine	481.2	482.0 (M+1, ^{35}Cl)
81a		((4-Chloro-benzyl)-{(S)-1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid	J	Int 144	442.2	443.0 (M+1, ^{35}Cl)
82		((4-Chloro-benzyl)-{(R)-1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-acetic acid	J	Int 145	442.2	442.9 (M+1, ^{35}Cl)
83		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-morpholin-4-yl-2-oxo-ethyl)-amide	K	Cpd 49 and morpholine	511.2	512.0 (M+1, ^{35}Cl)

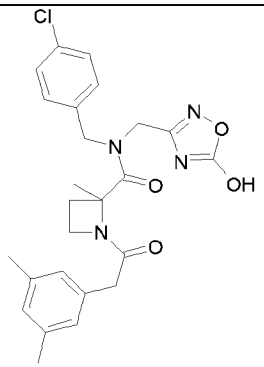
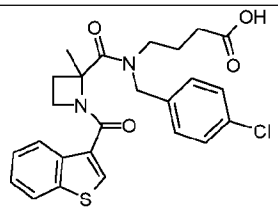
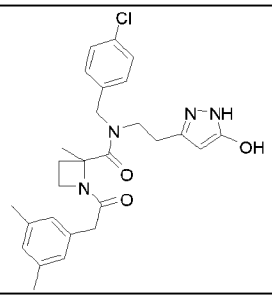
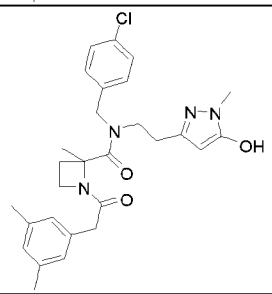
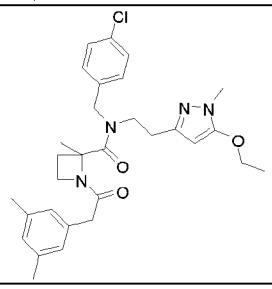
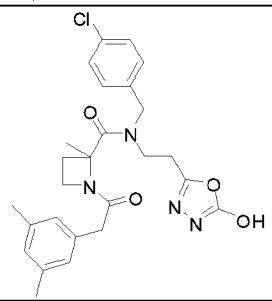
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
84		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-cyanomethyl-amide	I3, 15h	Int 39 and int 121	451.1	451.9 (M+1, ^{35}Cl)
85		[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-hydroxymethyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-acetic acid	J	Int 191	486.1	486.7 (M+1, ^{35}Cl)
86		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester	I3	Int 61 and int 121	498.1	498.7 (M+1, ^{35}Cl)
87		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid ethyl ester	I3, 15h	Int 40 and int 121	526.2	526.7 (M+1, ^{35}Cl)
88		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid	J	Cpd 86	484.1	484.7 (M+1, ^{35}Cl)
89		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid	J	Cpd 87	498.1	498.7 (M+1, ^{35}Cl)
90		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide	M	Int 146	469.2	470.1 (M+1, ^{35}Cl)

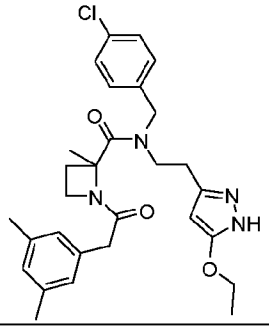
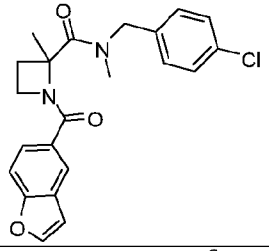
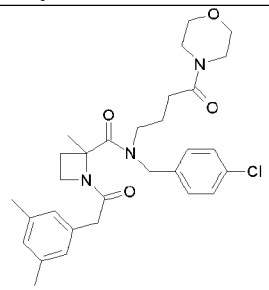
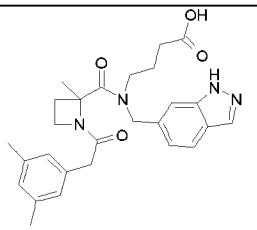
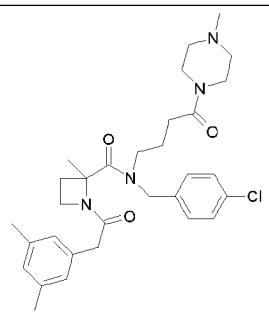
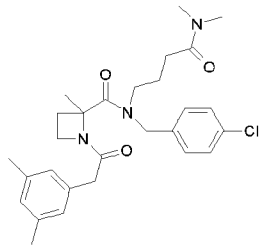
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
91		2-Methyl-1-[2-(1-methyl-1H-indol-3-yl)-acetyl]-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	I1	Int 134 and Methyl-(4-chloro-benzyl)-amine	423.2	424.1 (M+1, ^{35}Cl)
92		1-[2-(5-Chloro-benzo[b]thiophen-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (5-Chloro-benzo[b]thiophen-3-yl)-acetic acid	460.1	NMR
93		1-[2-(5-Methyl-benzo[b]thiophen-3-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (5-Methyl-benzo[b]thiophen-3-yl)-acetic acid	440.1	NMR
94		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-oxo-2-trifluoromethanesulfonylamino-ethyl)-amide	N	Cpd 49 and Trifluoro-methanesulfonamide	573.1	573.7 (M+1, ^{35}Cl)
95		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methanesulfonylamino-2-oxo-ethyl)-amide	N	Cpd 49 and methanesulfonamide	519.2	520.1 (M+1, ^{35}Cl)
96		[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indol-6-ylmethyl)-amino]-acetic acid	J	Int 18	447.2	448.2 (M+1, ^{35}Cl)

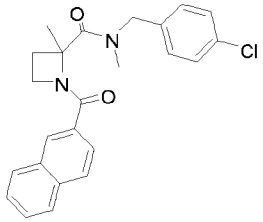
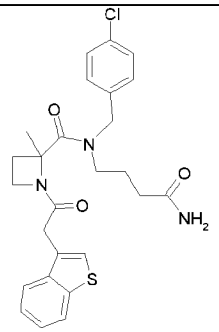
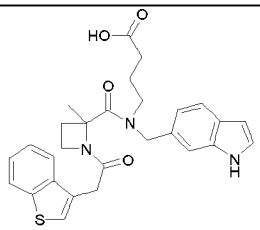
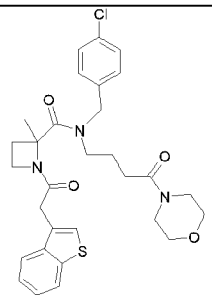
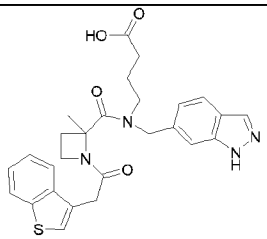
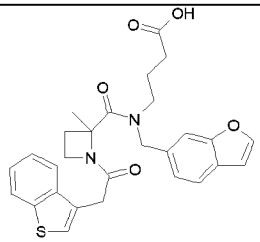
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
97		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-cyano-propyl)-amide	I3	Int 41 and int 119	451.2	452.1 (M+1, ^{35}Cl)
98		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and Benzo[b]thiophene-3-carboxylic acid	412.1	413.0 (M+1, ^{35}Cl)
99		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-cyano-propyl)-amide	I3	Int 41 and int 121	479.1	480.0 (M+1, ^{35}Cl)
100		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(1H-tetrazol-5-yl)-propyl]-amide	L	Cpd 99	522.2	523.1 (M+1, ^{35}Cl)
101		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-acetylamino-ethyl)-(4-chloro-benzyl)-amide	I4	Int 84 and int 119	469.2	470.1 (M+1, ^{35}Cl)

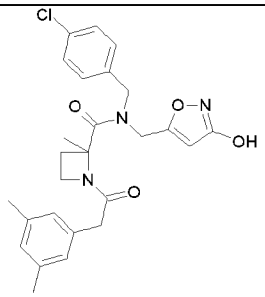
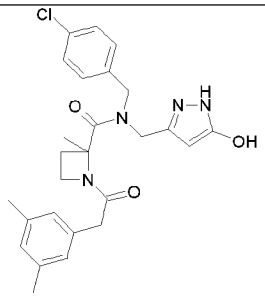
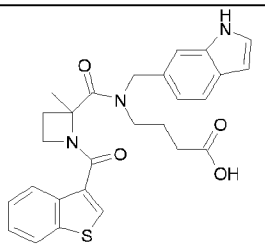
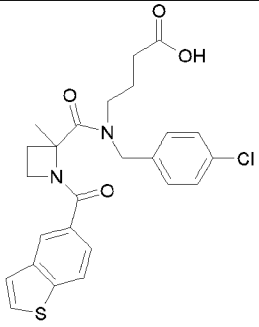
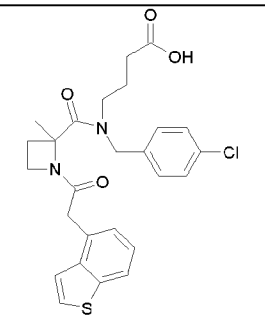
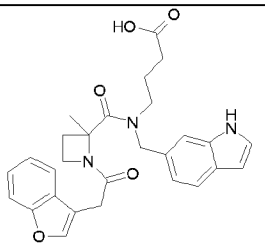
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
102		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methanesulfonylamino-ethyl)-amide	I4	Int 85 and int 119	505.2	506.1 (M+1, ^{35}Cl)
103		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid	J	Int 158	482.2	483.0 (M+1, ^{35}Cl)
104		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (2-benzenesulfonylamino-2-oxo-ethyl)-(4-chloro-benzyl)-amide	N	Cpd 49 and phenylsulfonamide	581.2	582.0 (M+1, ^{35}Cl)
105		1-(2-Benzo[b]thiophen-4-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 1 and int 14	426.1	427.0 (M+1, ^{35}Cl)
106		1-[2-(4-Fluoro-naphthalen-1-yl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and (4-Fluoro-naphtalen-1-yl)-acetic acid	438.2	439.0 (M+1, ^{35}Cl)
107		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-amide	O	Cpd 77	496.2	497.1 (M+1, ^{35}Cl)

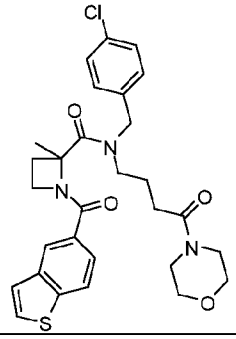
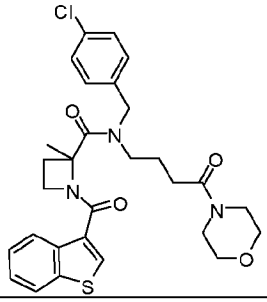
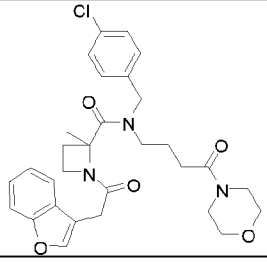
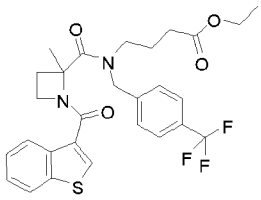
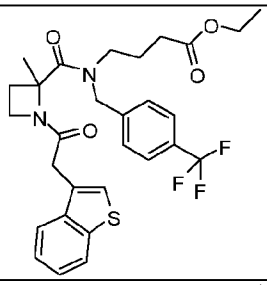
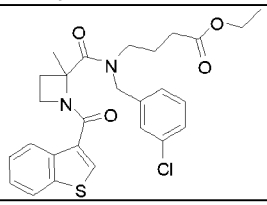
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
108		1-(2-Benzo[b]thiophen-2-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 2 and int 14	426.1	427.0 (M+1, ^{35}Cl)
109		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(1H-tetrazol-5-yl)-ethyl]-amide	L	Cpd 77	480.2	481.0 (M+1, ^{35}Cl)
110		[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indazol-6-ylmethyl)-amino]-acetic acid	J	Int 148	448.2	449.1 (M+1)
111		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,3,4]oxadiazol-2-ylmethyl)-amide	P	Cpd 49	482.2	483.1 (M+1, ^{35}Cl)
112		1-(Benzo[b]thiophene-5-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-methyl-amide	F	Int 14 and Benzo[b]thiophene-5-carboxylic acid	412.1	413.0 (M+1, ^{35}Cl)
113		4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indol-6-ylmethyl)-amino]-butyric acid	J	Int 29	475.2	477.2 (M+1)

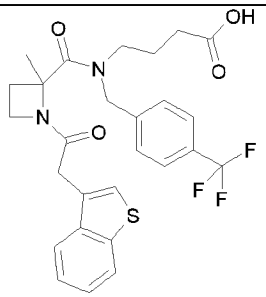
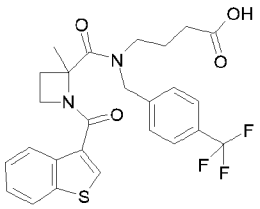
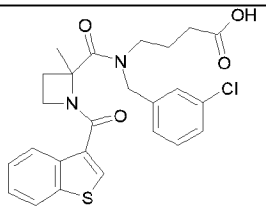
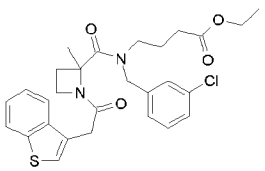
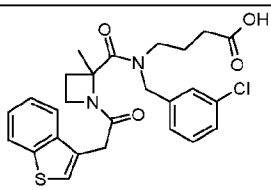
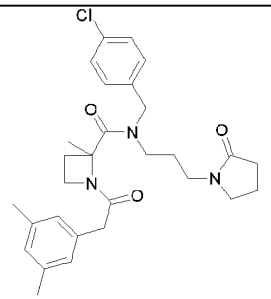
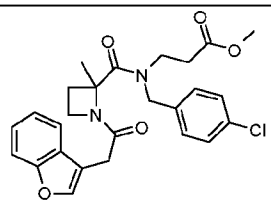
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
114		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethyl)-amide	O	Cpd 68	482.2	483.1 (M+1, ^{35}Cl)
115		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid	J	Int 150	484.1	485.0 (M+1, ^{35}Cl)
116		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-1H-pyrazol-3-yl)-ethyl]-amide	Q	Cpd 65 with hydrazine	494.2	495.1 (M+1, ^{35}Cl)
117		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-1-methyl-1H-pyrazol-3-yl)-ethyl]-amide	Q	Cpd 65 with methylhydrazine	508.2	509.0 (M+1, ^{35}Cl)
118		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-ethoxy-1-methyl-1H-pyrazol-3-yl)-ethyl]-amide	Q	Cpd 65 with methylhydrazine	536.3	537.1 (M+1, ^{35}Cl)
119		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-hydroxy-[1,3,4]oxadiazol-2-yl)-ethyl]-amide	P	Cpd 65	496.2	497.4 (M+1, ^{35}Cl)

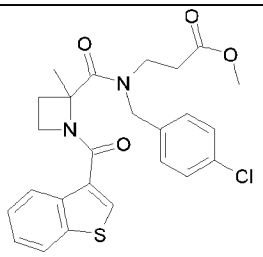
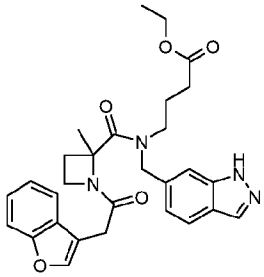
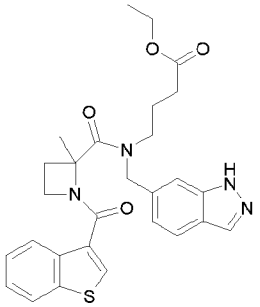
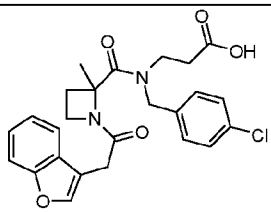
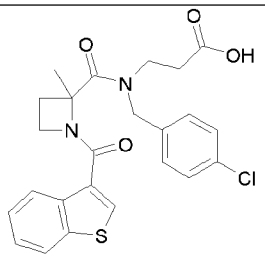
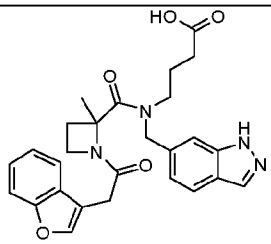
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
120		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(5-ethoxy-1H-pyrazol-3-yl)-ethyl]-amide	Q	Cpd 65 with hydrazine	522.2	523.4 (M+1, ^{35}Cl)
121		1-(benzofuran-5-carbonyl)-N-(4-chlorobenzyl)-N,2-dimethylazetidine-2-carboxamide	F	Int 14 and benzofuran-5-carboxylic acid	396.1	397.4 (M+1, ^{35}Cl)
122		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide	I1	Cpd 64 and morpholine	539.3	540.4 (M+1, ^{35}Cl)
123		4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(1H-indazol-6-ylmethyl)-amino]-butyric acid	J	Int 30	476.2	477.1 (M+1)
124		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[4-(4-methyl-piperazin-1-yl)-4-oxo-butyl]-amide	I1	Cpd 64 and 1-methyl-piperazine	552.3	553.4 (M+1, ^{35}Cl)
125		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-dimethylcarbamoyl-propyl)-amide	I1	Cpd 64 and 9 eq of dimethyl-amine (1N in THF)	497.2	498.4 (M+1, ^{35}Cl)

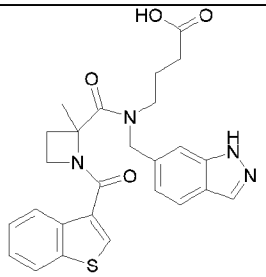
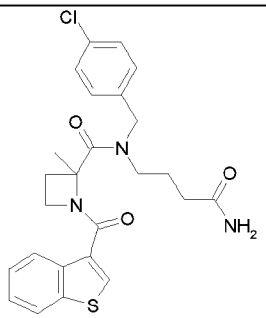
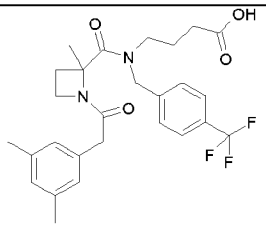
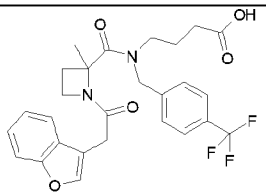
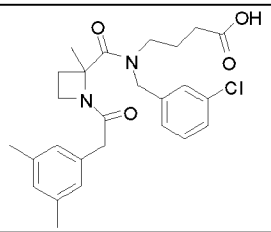
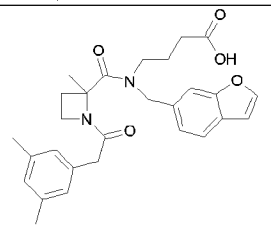
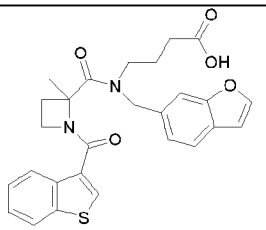
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
126		1-(2-naphthoyl)-N-(4-chlorobenzyl)-N,2-dimethylazetidine-2-carboxamide	F	Int 14 and naphthalene-2-carboxylic acid	406.1	407.3 (M+1, ^{35}Cl)
127		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide	M	Cpd 87	497.2	498.3 (M+1, ^{35}Cl)
128		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid	J	Int 152	503.2	504.3 (M+1)
129		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide	I1	Cpd 89 and morpholine	567.2	568.4 (M+1, ^{35}Cl)
130		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid	J	Int 153	504.2	505.4 (M+1)
131		4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid	J	Int 164	504.2	505.3 (M+1)

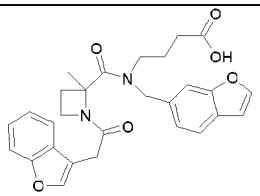
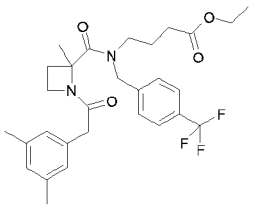
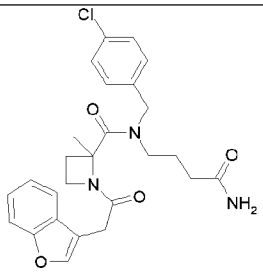
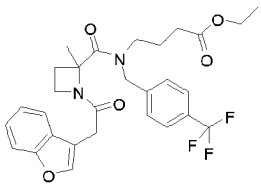
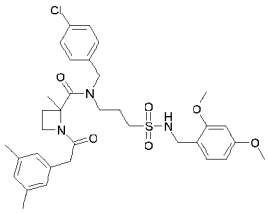
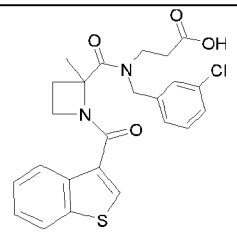
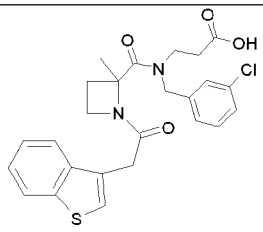
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
132		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-hydroxy-isoxazol-5-ylmethyl)-amide	I4	Int 70 and int 119	481.2	482.3 (M+1, ^{35}Cl)
133		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(5-hydroxy-1H-pyrazol-3-ylmethyl)-amide	Q	Cpd 49 with hydrazine	480.2	481.3 (M+1, ^{35}Cl)
134		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid	J	Int 154	489.2	490.3 (M+1)
135		4-[[1-(Benzo[b]thiophene-5-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid	J	Int 155	484.1	485.3 (M+1, ^{35}Cl)
136		4-[[1-(2-Benzo[b]thiophen-4-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-butyric acid	J	Int 156	498.1	499.3 (M+1, ^{35}Cl)
137		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indol-6-ylmethyl)-amino]-butyric acid	J	Int 157	487.2	488.4 (M+1)

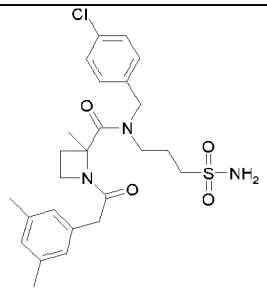
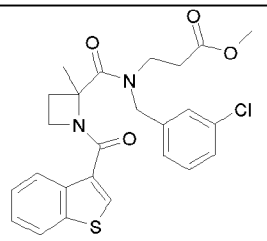
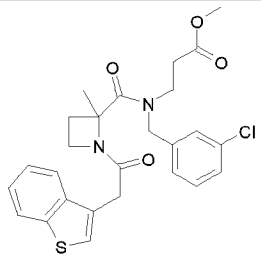
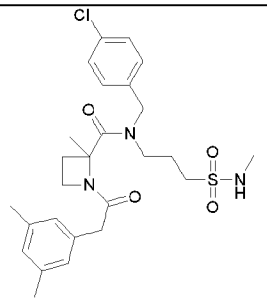
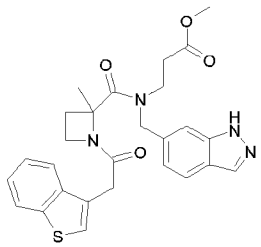
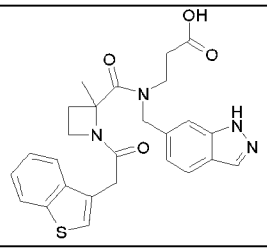
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
138		1-(benzo[b]thiophene-5-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-morpholino-4-oxobutyl)azetidine-2-carboxamide	I4	Cpd 135 and morpholine	553.2	554.4 (M+1, ^{35}Cl)
139		1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-morpholino-4-oxobutyl)azetidine-2-carboxamide	I4	Cpd 115 and morpholine	553.2	554.3 (M+1, ^{35}Cl)
140		1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(4-morpholin-4-yl-4-oxo-butyl)-amide	I4	Cpd 103 and morpholine	551.2	552.4 (M+1, ^{35}Cl)
141		ethyl 4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(4-(trifluoromethyl)benzyl) azetidine-2-carboxamido)butanoate	I4	Int 75 and int 125	546.2	547.4 (M+1)
142		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester	I4	Int 75 and int 121	560.2	561.4 (M+1)
143		ethyl 4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoate	I4	Int 76 and int 125	512.2	513.3 (M+1, ^{35}Cl)

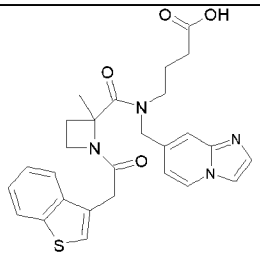
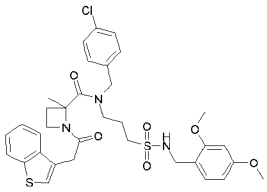
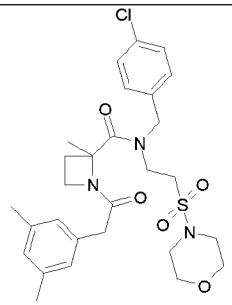
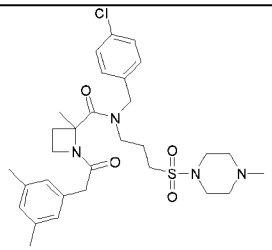
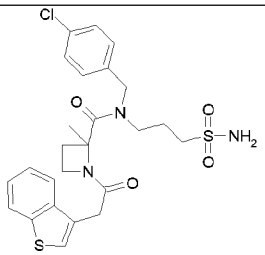
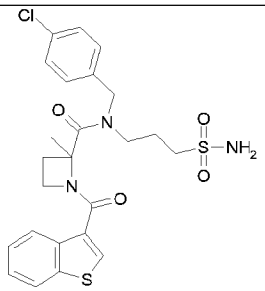
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
144		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid	J	Cpd 142	532.2	533.3 (M+1)
145		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid	J	Cpd 141	518.1	519.3 (M+1)
146		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Cpd 143	484.1	485.3 (M+1)
147		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid ethyl ester	I4	Int 76 and int 121	526.2	527.3 (M+1, ^{35}Cl)
148		4-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Cpd 147	498.1	499.3 (M+1, ^{35}Cl)
149		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide	I4	Int 83 and int 119	509.2	510.4 (M+1, ^{35}Cl)
150		3-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester	I4	Int 61 and int 122	482.2	483.3 (M+1, ^{35}Cl)

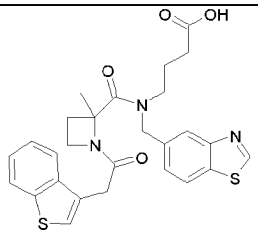
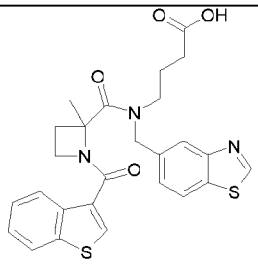
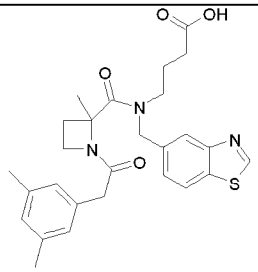
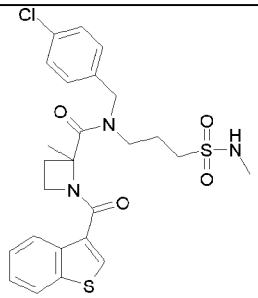
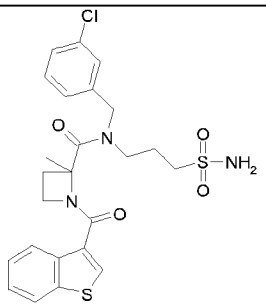
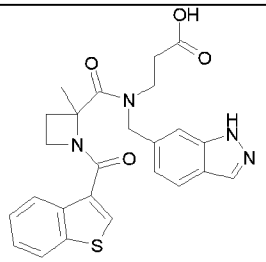
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
151		3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid methyl ester	I4	Int 61 and int 125	484.1	485.3 (M+1, ^{35}Cl)
152		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid ethyl ester	I4	Int 74 and int 122	516.2	517.4 (M+1)
153		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid ethyl ester	I4	Int 74 and int 125	518.2	519.4 (M+1)
154		3-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid	J	Cpd 150	468.1	469.3 (M+1, ^{35}Cl)
155		3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-benzyl)-amino]-propionic acid	J	Cpd 151	470.1	471.3 (M+1, ^{35}Cl)
156		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid	J	Cpd 152	488.2	489.4 (M+1)

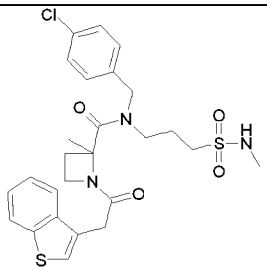
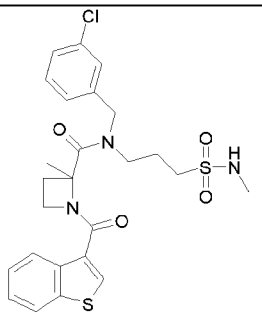
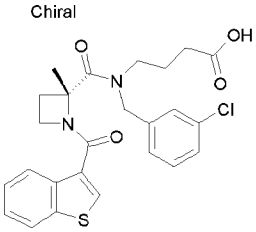
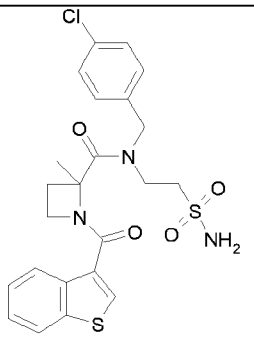
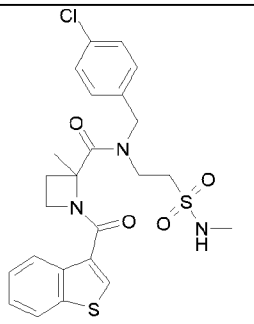
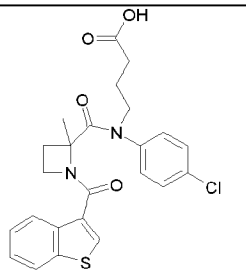
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
157		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-butyric acid	J	Cpd 153	490.2	491.4 (M+1)
158		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide	M	Int 150	483.1	484.4 (M+1, ^{35}Cl)
159		4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(4-trifluoromethyl-benzyl)-amino]-butyric acid	J	Cpd 165	504.2	505.5 (M+1)
160		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid	J	Cpd 167	516.2	517.4 (M+1)
161		4-((3-Chloro-benzyl)-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid	J	Int 176	470.2	
162		4-(Benzofuran-6-ylmethyl-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid	J	Int 106	476.2	477.5 (M+1)
163		4-{[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid	J	Int 107	490.2	491.4 (M+1)

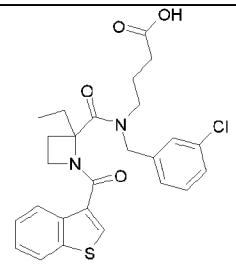
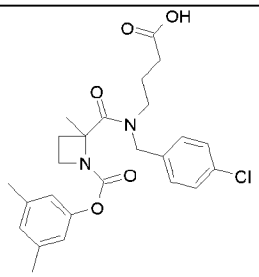
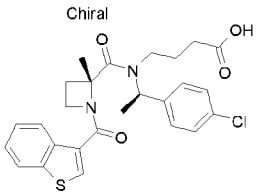
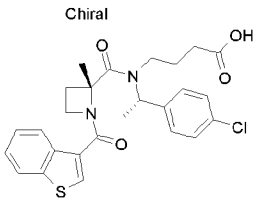
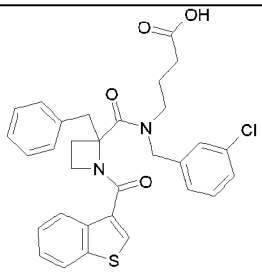
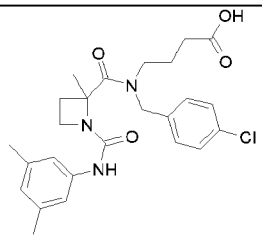
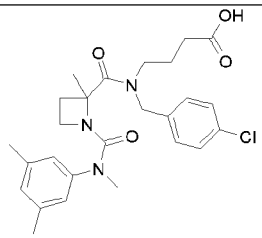
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
164		4-{[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzofuran-6-ylmethyl-amino}-butyric acid	J	Int 108	488.2	489.4 (M+1)
165		4-[{1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester	I4	Int 75 and int 119	532.3	533.5 (M+1)
166		1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (3-carbamoyl-propyl)-(4-chloro-benzyl)-amide	M	Int 158	481.2	482.4 (M+1, ^{35}Cl)
167		4-[[1-(2-Benzofuran-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(4-trifluoromethyl-benzyl)-amino]-butyric acid ethyl ester	I4	Int 75 and int 122	544.2	545.5 (M+1)
168		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2,4-dimethoxy-benzylsulfamoyl)-propyl]-amide	I4	Int 86 and int 119	655.2	565.6 (M+1, ^{35}Cl)
169		3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid	J	Cpd 172	470.1	471.4 (M+1, ^{35}Cl)
170		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid	J	Cpd 173	484.1	485.4 (M+1, ^{35}Cl)

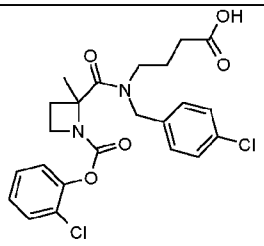
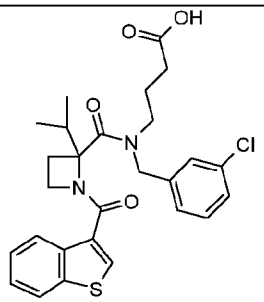
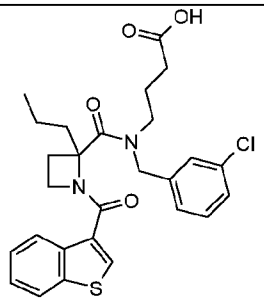
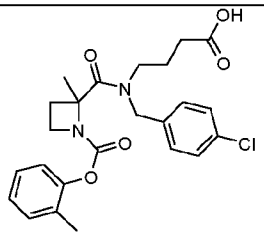
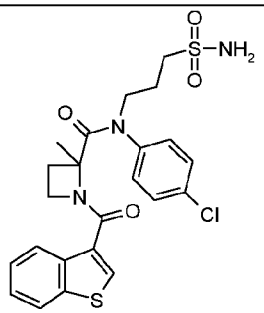
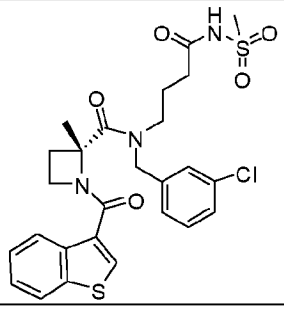
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
171		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide	R	Cpd 168	505.2	506.5 (M+1, ^{35}Cl)
172		3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid methyl ester	I4	Int 59 and int 125	484.1	485.4 (M+1, ^{35}Cl)
173		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-propionic acid methyl ester	I4	Int 59 and int 121	498.1	499.4 (M+1, ^{35}Cl)
174		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide	R	Int 166	519.2	520.5 (M+1, ^{35}Cl)
175		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid methyl ester	I4	Int 79 and int 121	504.2	505.5 (M+1)
176		3-[[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid	J	Cpd 175	490.2	491.4 (M+1)

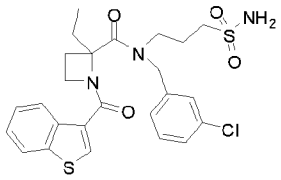
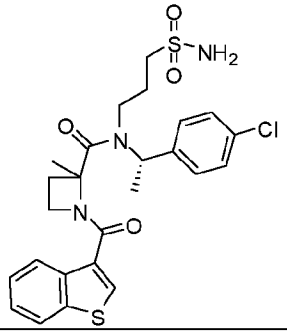
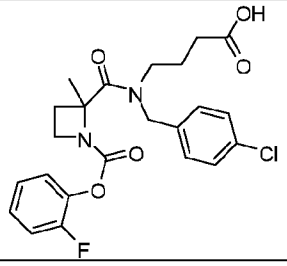
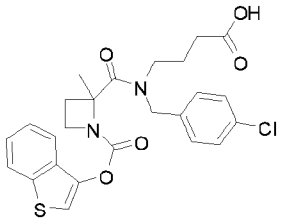
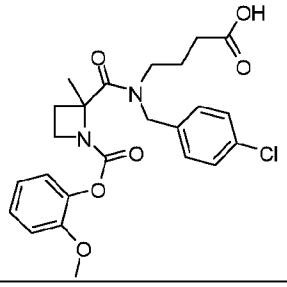
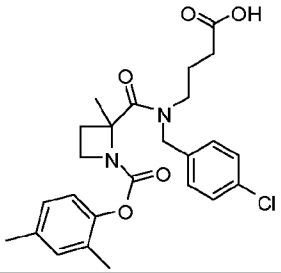
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
177		4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-imidazo[1,2-a]pyridin-7-ylmethyl-amino}-butyric acid	J	Int 167	504.2	505.5 (M+1)
178		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(2,4-dimethoxy-benzylsulfamoyl)-propyl]-amide	I4	Int 86 and int 121	683.2	684.6 (M+1, ^{35}Cl)
179		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[2-(morpholine-4-sulfonyl)-ethyl]-amide	I4	Int 88 and int 119	561.2	562.6 (M+1, ^{35}Cl)
180		1-[2-(3,5-Dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-[3-(4-methyl-piperazine-1-sulfonyl)-propyl]-amide	I4	Int 89 and int 119	588.3	589.6 (M+1, ^{35}Cl)
181		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide	R	Cpd 178	533.1	534.4 (M+1, ^{35}Cl)
182		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-sulfamoyl-propyl)-amide	R	Int 168	519.1	520.4 (M+1, ^{35}Cl)

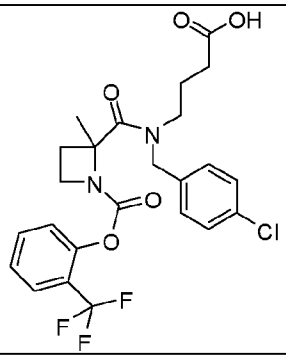
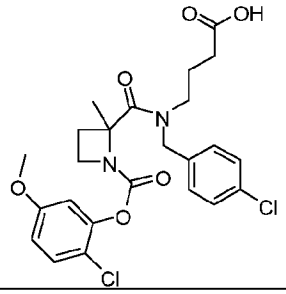
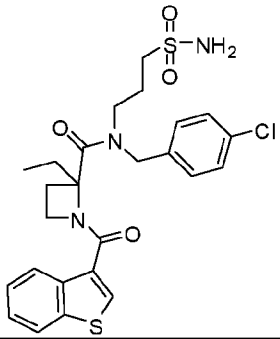
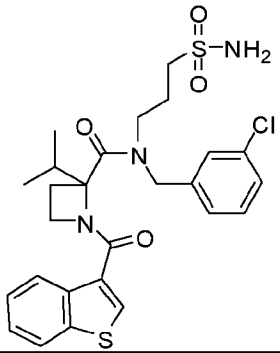
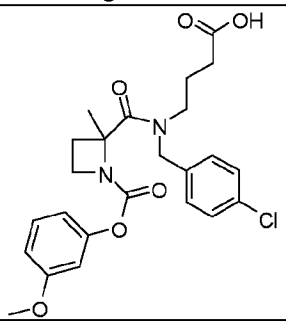
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
183		4-{[1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carbonyl]-benzothiazol-5-ylmethyl-amino}-butyric acid	J	Int 109	521.1	522.4 (M+1)
184		4-{[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-benzothiazol-5-ylmethyl-amino}-butyric acid	J	Int 110	507.1	508.4 (M+1)
185		4-(Benzothiazol-5-ylmethyl-{1-[2-(3,5-dimethyl-phenyl)-acetyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid	J	Int 111	493.2	494.4 (M+1)
186		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide	R	Int 170	533.1	534.4 (M+1, ^{35}Cl)
187		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-(3-sulfamoyl-propyl)-amide	R	Int 171	519.1	520.3 (M+1, ^{35}Cl)
188		3-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(1H-indazol-6-ylmethyl)-amino]-propionic acid	J	Int 172	476.2	477.4 (M+1)

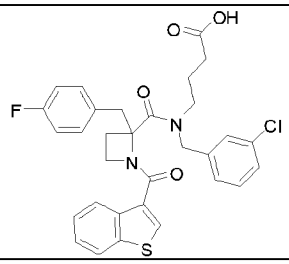
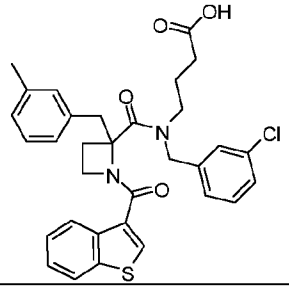
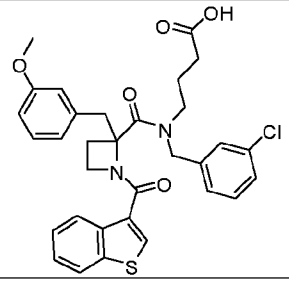
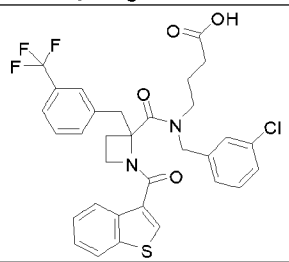
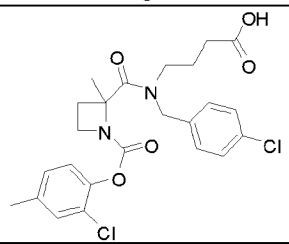
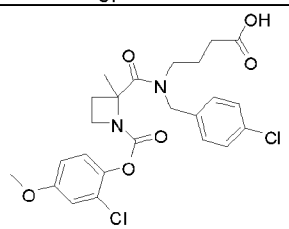
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
189		1-(2-Benzo[b]thiophen-3-yl-acetyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide	R	Int 173	547.1	548.5 (M+1, ^{35}Cl)
190		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (3-chloro-benzyl)-(3-methylsulfamoyl-propyl)-amide	R	Int 174	533.1	534.4 (M+1, ^{35}Cl)
191		4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Int 112	484.1	485.4 (M+1, ^{35}Cl)
192		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-sulfamoyl-ethyl)-amide	R	Int 177	505.1	506.3 (M+1, ^{35}Cl)
193		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-benzyl)-(2-methylsulfamoyl-ethyl)-amide	R	Int 178	519.1	520.4 (M+1, ^{35}Cl)
194		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(4-chloro-phenyl)-amino]-butyric acid	J	Int 179	470.1	471.4 (M+1, ^{35}Cl)

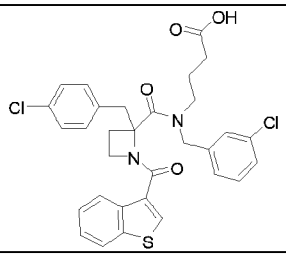
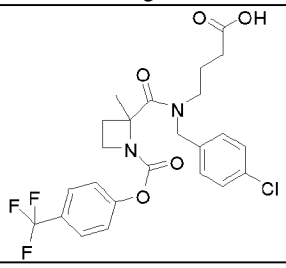
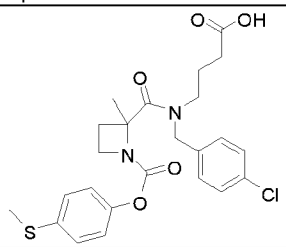
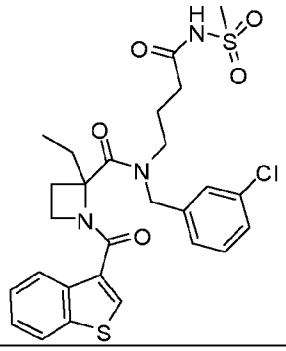
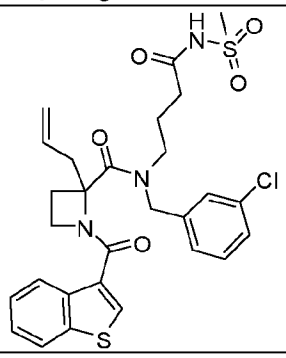
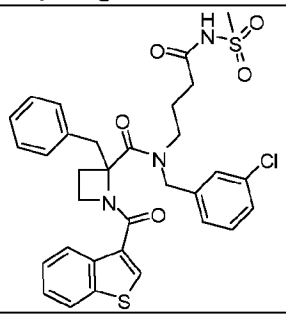
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
195		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-ethyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Int 180	498.1	499.4 (M+1, ^{35}Cl)
196		2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 3,5-dimethyl-phenyl ester	J	Int 135	472.2	473.5 (M+1, ^{35}Cl)
197		4-{[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-[(R)-1-(4-chloro-phenyl)-ethyl]-amino}-butyric acid	J	Int 114	498.1	499.3 (M+1, ^{35}Cl)
198		4-{[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-[(S)-1-(4-chloro-phenyl)-ethyl]-amino}-butyric acid	J	Int 115	498.1	499.3 (M+1, ^{35}Cl)
199		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-benzyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Int 184	560.2	561.4 (M+1, ^{35}Cl)
200		4-{(4-Chloro-benzyl)-[1-(3,5-dimethyl-phenylcarbamoyl)-2-methyl-azetidine-2-carbonyl]-amino}-butyric acid	W	Int 23	472.0	472.4 (M+1, ^{35}Cl)
201		4-((4-Chloro-benzyl)-{1-[(3,5-dimethyl-phenyl)-methyl-carbamoyl]-2-methyl-azetidine-2-carbonyl}-amino)-butyric acid	W	Cpd 200	486.0	486.4 (M+1, ^{35}Cl)

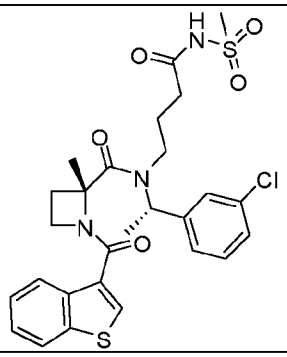
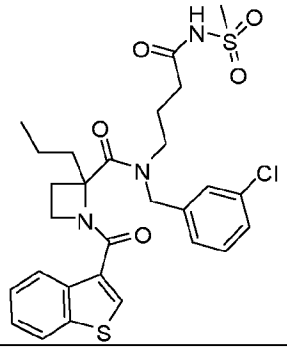
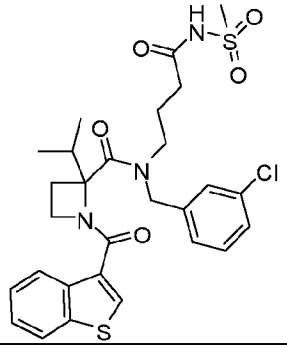
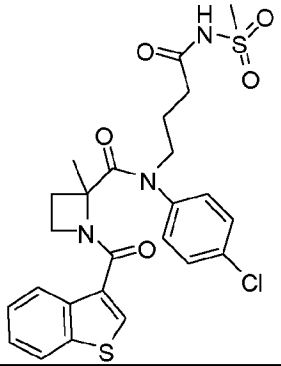
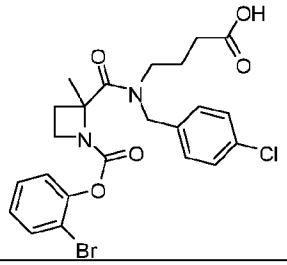
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
202		2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid 2-chloro-phenyl ester	J	Int 136	479.4	479.3 (M+1, ^{35}Cl)
203		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-isopropyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Int 185	513.1	513.2 (M+1, ^{35}Cl)
204		4-[[1-(Benzo[b]thiophene-3-carbonyl)-2-propyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid	J	Int 186	513.1	513.1 (M+1, ^{35}Cl)
205		2-[(3-Carboxy-propyl)-(4-chloro-benzyl)-carbamoyl]-2-methyl-azetidine-1-carboxylic acid o-tolyl ester	J	Int 137	458.9	459.1 (M+1, ^{35}Cl)
206		1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carboxylic acid (4-chloro-phenyl)-(3-sulfamoyl-propyl)-amide	R	Int 187	506.0	506.0 (M+1, ^{35}Cl)
207		(R)-1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	I4	Cpd 191 and methanesulfonamide	561.1	562.1 (M+1, ^{35}Cl)

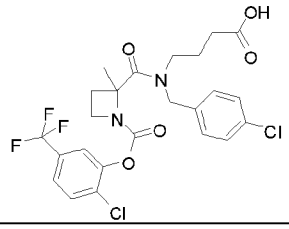
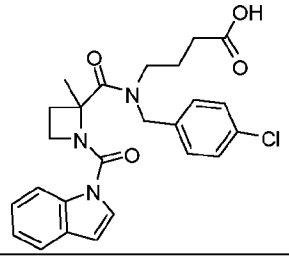
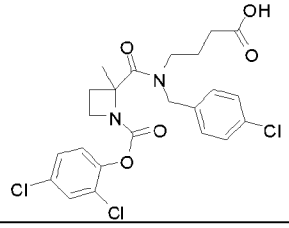
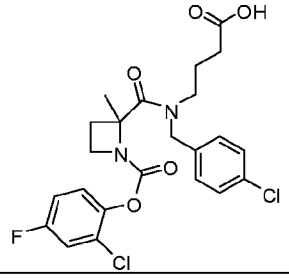
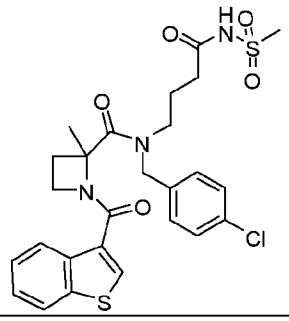
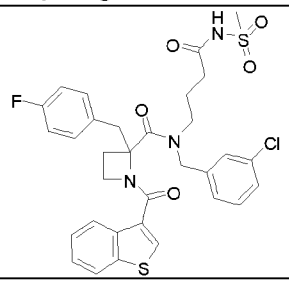
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
208		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 274	533.1	534.1 (M+1, ^{35}Cl)
209		1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-methyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 256	533.1	534.1 (M+1, ^{35}Cl)
210		4-(N-(4-chlorobenzyl)-1-((2-fluorophenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 269	462.1	463.1 (M+1, ^{35}Cl)
211		4-(1-((benzo[b]thiophen-3-yloxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 265	500.1	501.1 (M+1, ^{35}Cl)
212		4-(N-(4-chlorobenzyl)-1-((2-methoxyphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 266	474.2	475.1 (M+1, ^{35}Cl)
213		4-(N-(4-chlorobenzyl)-1-((2,4-dimethylphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 254	472.2	473.2 (M+1, ^{35}Cl)

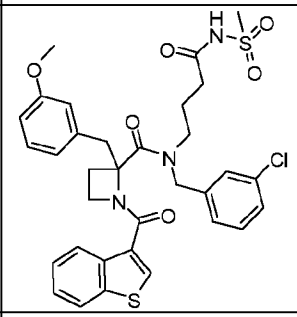
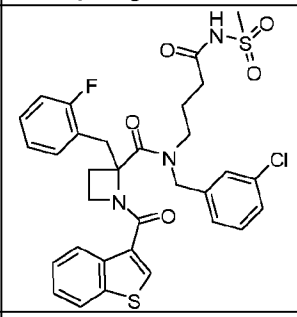
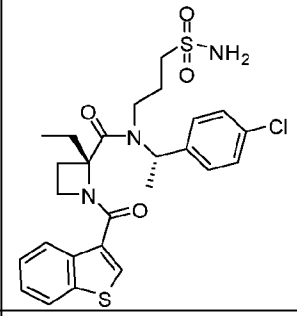
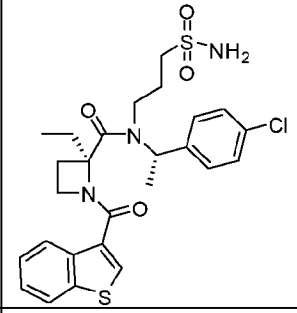
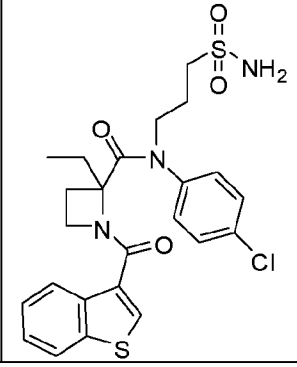
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
214		4-(N-(4-chlorobenzyl)-2-methyl-1-((2-(trifluoromethyl)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid	J	Int 253	512.1	513.1 (M+1, ^{35}Cl)
215		4-(1-((2-chloro-5-methoxyphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 270	508.1	509.1 (M+1, ^{35}Cl)
216		1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 257	533.1	534.1 (M+1, ^{35}Cl)
217		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-isopropyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 258	547.1	548.1 (M+1, ^{35}Cl)
218		4-(N-(4-chlorobenzyl)-1-((3-methoxyphenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 252	474.2	475.1 (M+1, ^{35}Cl)

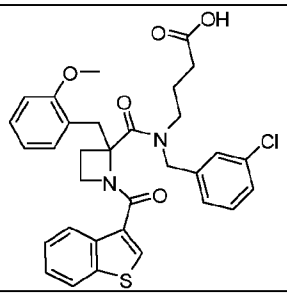
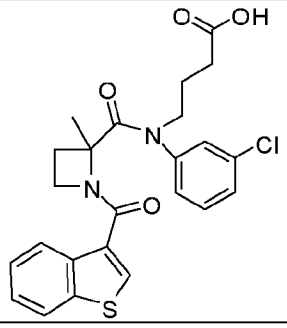
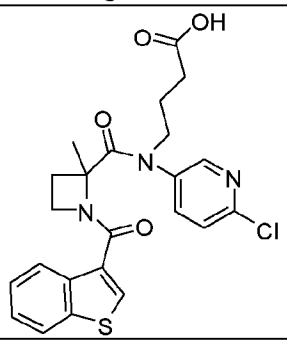
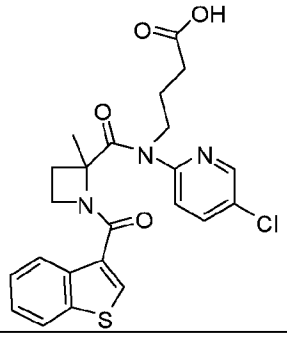
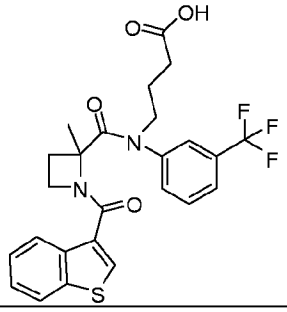
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
219		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-fluorobenzyl)azetidine-2-carboxamido)butanoic acid	J	Int 220	578.1	579.1 (M+1, ^{35}Cl)
220		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methylbenzyl)azetidine-2-carboxamido)butanoic acid	J	Int 225	574.2	575.1 (M+1, ^{35}Cl)
221		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methoxybenzyl)azetidine-2-carboxamido)butanoic acid	J	Int 205	590.2	591.1 (M+1, ^{35}Cl)
222		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-(trifluoromethyl)benzyl)azetidine-2-carboxamido)butanoic acid	J	Int 210	628.1	629.1 (M+1, ^{35}Cl)
223		4-(1-((2-chloro-4-methylphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 267	492.1	493.1 (M+1, ^{35}Cl)
224		4-(1-((2-chloro-4-methoxyphenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 268	508.1	509.1 (M+1, ^{35}Cl)

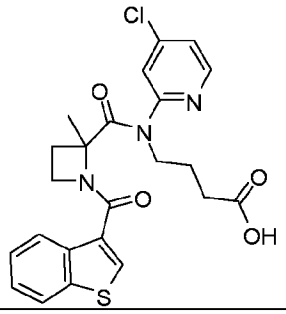
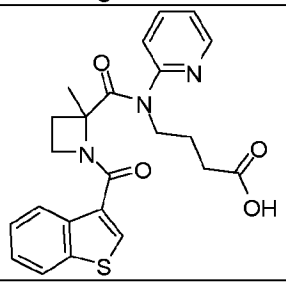
Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
225		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-chlorobenzyl)azetidine-2-carboxamido)butanoic acid	J	Int 215	594.1	595.1 (M+1, ^{35}Cl)
226		4-(N-(4-chlorobenzyl)-2-methyl-1-((4-(trifluoromethyl)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid	J	Int 251	512.1	513.1 (M+1, ^{35}Cl)
227		4-(N-(4-chlorobenzyl)-2-methyl-1-((4-(methylthio)phenoxy)carbonyl)azetidine-2-carboxamido)butanoic acid	J	Int 261	490.1	491.1 (M+1, ^{35}Cl)
228		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-ethyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 195	575.1	576.1 (M+1, ^{35}Cl)
229		2-allyl-1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Int 264	587.1	588.1 (M+1, ^{35}Cl)
230		1-(benzo[b]thiophene-3-carbonyl)-2-benzyl-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 199	637.1	638.1 (M+1, ^{35}Cl)

Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
231		(R)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 198	575.1	576.0 (M+1, ^{35}Cl)
232		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)-2-propylazetidine-2-carboxamide	X	Cpd 204	589.1	590.1 (M+1, ^{35}Cl)
233		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-isopropyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 203	589.1	590.1 (M+1, ^{35}Cl)
234		1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorophenyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 194	547.1	548.0 (M+1, ^{35}Cl)
235		4-(1-((2-bromophenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 271	522.1	523.0 (M+1)

Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
236		4-(1-((2-chloro-5-(trifluoromethyl)phenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 272	546.1	547.0 (M+1, ^{35}Cl)
237		4-(N-(4-chlorobenzyl)-1-(1H-indole-1-carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 275	467.2	468.1 (M+1, ^{35}Cl)
238		4-(N-(4-chlorobenzyl)-1-((2,4-dichlorophenoxy)carbonyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 273	512.1	513.0 (M+1, ^{35}Cl)
239		4-(1-((2-chloro-4-fluorophenoxy)carbonyl)-N-(4-chlorobenzyl)-2-methylazetidine-2-carboxamido)butanoic acid	J (dioxane instead of MeOH)	Int 250	496.1	497.0 (M+1, ^{35}Cl)
240		1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorobenzyl)-2-methyl-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 115	561.1	562.0 (M+1, ^{35}Cl)
241		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(4-fluorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 219	655.1	656.1 (M+1, ^{35}Cl)

Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
242		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(3-methoxybenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Cpd 221	667.2	668.2 (M+1, ^{35}Cl)
243		1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(2-fluorobenzyl)-N-(4-(methylsulfonamido)-4-oxobutyl)azetidine-2-carboxamide	X	Int 236	655.1	656.2 (M+1, ^{35}Cl)
244		(R)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 259	547.1	548.1 (M+1, ^{35}Cl)
245		(S)-1-(benzo[b]thiophene-3-carbonyl)-N-((S)-1-(4-chlorophenyl)ethyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 259	547.1	548.1 (M+1, ^{35}Cl)
246		1-(benzo[b]thiophene-3-carbonyl)-N-(4-chlorophenyl)-2-ethyl-N-(3-sulfamoylpropyl)azetidine-2-carboxamide	R	Int 260	519.1	520.0 (M+1, ^{35}Cl)

Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
247		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorobenzyl)-2-(2-methoxybenzyl)azetidine-2-carboxamido)butanoic acid	J	Int 231	590.2	591.1 (M+1, ^{35}Cl)
248		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(3-chlorophenyl)-2-methylazetidine-2-carboxamido)butanoic acid	J	Int 243	470.1	471.0 (M+1, ^{35}Cl)
249		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(6-chloropyridin-3-yl)-2-methylazetidine-2-carboxamido)butanoic acid	Y	Int 239	471.1	472.0 (M+1, ^{35}Cl)
250		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(5-chloropyridin-2-yl)-2-methylazetidine-2-carboxamido)butanoic acid	Y	Int 241	471.1	472.0 (M+1, ^{35}Cl)
251		4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(3-(trifluoromethyl)phenyl)azetidine-2-carboxamido)butanoic acid	Y	Int 245	504.1	505.1 (M+1, ^{35}Cl)

Cpd #	Structures	Name	Mtd	SM	Exact mass	MS Ms'd
252		4-(1-(benzo[b]thiophene-3-carbonyl)-N-(4-chloropyridin-2-yl)-2-methylazetidine-2-carboxamido)butanoic acid	Y	Int 247	471.1	472.0 (M+1, ^{35}Cl)
253		4-(1-(benzo[b]thiophene-3-carbonyl)-2-methyl-N-(pyridin-2-yl)azetidine-2-carboxamido)butanoic acid	Y	Int 249	437.1	438.1 (M+1)

[00297] Table IIb: NMR Data of the Compounds of the Invention

Cpd	NMR data (δ)
1	^{1}H NMR δ (ppm) ($CDCl_3$): 8.66 (1H, br s), 7.44 (1H, s), 7.30-7.15 (6H, m), 4.41 (2H, d), 4.20-4.02 (2H, m), 3.59-3.48 (2H, m), 3.01-2.90 (1H, m), 2.19-2.10 (1H, m), 1.81 (3H, s)
2	^{1}H NMR δ (ppm) (MeOD, d_4): 7.44-7.15 (7H, m), 7.02-6.94 (1H, m), 4.37-4.33 (2H, m), 4.29-3.94 (2H, m), 2.61-2.23 (2H, m), 1.88-1.75 (3H, m)
3	^{1}H NMR δ (ppm) (MeOD, d_4): 7.49-7.25 (4H, m), 7.02-6.89 (3H, m), 4.75-4.49 (2H, m), 4.22-4.05 (1H, m), 3.95-3.81 (1H, m), 3.51-3.35 (2H, m), 3.00-2.88 (3H, m), 2.70-2.36 (2H, m), 2.35-2.30 (6H, m), 2.00-1.87 (3H, m)
4	^{1}H NMR δ (ppm) ($CDCl_3$): 10.57 (1H, br s), 7.54 (2H, d), 7.47 (1H, s), 7.35-7.25 (4H, m), 4.25-4.05 (2H, m), 3.59 (2H, dd), 3.09-2.98 (1H, m), 2.25-2.13 (1H, m), 1.87 (3H, s)
5	^{1}H NMR δ (ppm) ($CDCl_3$): 7.38-7.07 (4H, m), 7.05-6.81 (3H, m), 4.68-4.52 (1H, m), 4.10-3.85 (2H, m), 3.86-3.47 (1H, m), 3.04-2.96 (2H, m), 2.96-2.84 (4H, m), 2.64-2.50 (1H, m), 2.31 (6H, s), 1.98-1.72 (3H, m)
6	^{1}H NMR δ (ppm) ($CDCl_3$): 7.23-7.04 (4H, m), 6.99-6.82 (3H, m), 4.81-4.21 (2H, m), 4.08-3.82 (2H, m), 3.81-3.15 (2H, m), 2.98-2.74 (3H, m), 2.64-2.44 (1H, m), 2.42-2.15 (10H, m), 1.96-1.74 (3H, m)
7	^{1}H NMR δ (ppm) ($CDCl_3$): 7.70-7.58 (2H, m), 7.45-7.32 (2H, m), 6.98 (1H, s), 6.95-6.81 (2H, m), 4.74-4.60 (1H, m), 4.09-3.85 (2H, m), 3.84-3.47 (1H, m), 3.02-2.87 (4H, m), 2.63-2.50 (1H, m), 2.38-2.26 (8H, m), 1.98-1.86 (3H)
8	^{1}H NMR δ (ppm) (MeOD, d_4): 7.85-7.60 (2H, m), 7.52-7.25 (5H, m), 7.18-7.06 (1H, m), 4.74-4.50 (2H, m), 4.26-4.07 (1H, m), 3.97-3.80 (2H, m), 3.62-3.45 (1H, m), 2.94 (3H, d), 2.72-2.38 (2H, m), 1.95 (3H, d)
9	^{1}H NMR δ (ppm) (MeOD, d_4): 7.53-7.37 (4H, m), 7.37-7.25 (4H, m), 4.72-4.54 (2H, m), 4.34-4.11 (1H, m), 4.06-3.83 (2H, m), 3.79-3.55 (1H, m), 2.97 (3H, s), 2.73-2.43 (2H, m), 1.97 (3H, d)
10	^{1}H NMR δ (ppm) (MeOD, d_4): 7.52-7.23 (8H, m), 4.74-4.51 (2H, m), 4.26-4.08 (1H, m), 3.98-3.48 (3H, m), 2.95 (3H, d), 2.72-2.40 (2H, m), 1.97 (3H, d)
11	^{1}H NMR δ (ppm) (MeOD, d_4): 7.51-7.25 (8H, m), 4.74-4.53 (2H, m), 4.26-4.07 (1H, m), 3.96-3.46 (3H, m), 2.95 (3H, d), 2.72-2.40 (2H, m), 1.96 (3H, d)
12	^{1}H NMR δ (ppm) (MeOD, d_4): 7.51-7.08 (7H, m), 4.75-4.53 (2H, m), 4.28-4.08 (1H, m), 3.98-3.47 (3H, m), 2.96 (3H, d), 2.73-2.42 (2H, m), 1.97 (3H, d)

Cpd	NMR data (δ)
13	^{1}H NMR δ (ppm) (MeOD, d_4): 8.05-7.85 (2H, m), 7.63-7.22 (7H, m), 4.73-4.53 (2H, m), 4.27-3.84 (3H, m), 3.84-3.69 (1H, m), 2.93 (3H, d), 2.75-2.39 (2H, m), 1.95 (3H, d)
14	^{1}H NMR δ (ppm) (MeOD, d_4): 7.94-7.79 (4H, m), 7.60-7.23 (7H, m), 4.76-4.49 (2H, m), 4.30-3.65 (4H, m), 2.94 (3H, d), 2.75-2.37 (2H, m), 1.98 (3H, d)
15	^{1}H NMR δ (ppm) (MeOD, d_4): 7.71-7.64 (2H, m), 7.62-7.56 (2H, m), 7.50-7.27 (6H, m), 7.25-7.17 (2H, m), 4.73-4.53 (2H, m), 4.29-4.09 (1H, m), 3.99-3.52 (3H, m), 2.96 (3H, d), 2.74-2.39 (2H, m), 1.98 (3H, d)
16	^{1}H NMR δ (ppm) (MeOD, d_4): 7.58-7.18 (11H, m), 7.10-6.91 (2H, m), 5.11 (2H, d), 4.68-4.47 (2H, m), 4.10-3.38 (4H, m), 2.88 (3H, d), 2.63-2.04 (2H, m), 1.69 (3H, d)
17	^{1}H NMR δ (ppm) (MeOD, d_4): 7.90 (2H, d), 7.52-7.26 (6H, m), 7.08-6.98 (1H, m), 4.78-4.55 (2H, m), 4.39-4.03 (1H, m), 3.99-3.80 (1H, m), 3.76-3.60 (1H, m), 3.44-3.35 (1H, m), 2.97 (3H, s), 2.73-2.42 (2H, m), 1.97 (3H, s)
18	^{1}H NMR δ (ppm) (MeOD, d_4): 7.65-7.22 (7H, m), 4.74-4.51 (2H, m), 4.29-4.08 (1H, m), 4.00-3.47 (3H, m), 2.95 (3H, d), 2.73-2.42 (2H, m), 1.96 (3H, d)
19	^{1}H NMR δ (ppm) (MeOD, d_4): 7.58-7.32 (4H, m), 7.17-7.01 (2H, m), 6.99-6.88 (1H, m), 4.82-4.57 (2H, m), 4.35-4.15 (1H, m), 4.10-3.57 (3H, m), 3.02 (3H, d), 2.80-2.48 (2H, m), 2.03 (3H, d)
20	^{1}H NMR δ (ppm) (MeOD, d_4): 7.88-7.68 (4H, m), 7.68-7.36 (9H, m), 4.89-4.61 (2H, m), 4.42-4.19 (1H, m), 4.13-3.63 (3H, m), 3.06 (3H, d), 2.87-2.49 (2H, m), 2.08 (3H, d)
21	^{1}H NMR δ (ppm) (MeOD, d_4): 7.87-7.66 (4H, m), 7.66-7.35 (8H, m), 4.86-4.62 (2H, m), 4.40-4.19 (1H, m), 4.11-3.62 (3H, m), 3.06 (3H, d), 2.84-2.49 (2H, m), 2.08 (3H, d)
22	^{1}H NMR δ (ppm) (MeOD, d_4): 8.16-8.03 (2H, m), 7.88-7.66 (4H, m), 7.66-7.32 (6H, m), 4.84-4.60 (2H, m), 4.40-4.19 (1H, m), 4.10-3.61 (3H, m), 3.03 (3H, d), 2.83-2.47 (2H, m), 2.06 (3H, d)
23	^{1}H NMR δ (ppm) (MeOD, d_4): 7.76-7.63 (4H, m), 7.59-7.36 (6H, m), 7.15 (2H, d), 4.86-4.63 (2H, m), 4.37-4.19 (1H, m), 3.99 (3H, s), 4.08-3.60 (3H, m), 3.06 (3H, d), 2.83-2.48 (2H, m), 2.08 (3H, d)
24	^{1}H NMR δ (ppm) (MeOD, d_4): 8.06-7.85 (4H, m), 7.85-7.73 (2H, m), 7.73-7.34 (6H, m), 4.88-4.60 (2H, m), 4.41-4.20 (1H, m), 4.13-3.61 (3H, m), 3.05 (3H, d), 2.83-2.48 (2H, m), 2.07 (3H, d)
25	^{1}H NMR δ (ppm) (MeOD, d_4): 7.63-7.28 (12H, m), 4.87-4.64 (2H, m), 4.42-4.22 (1H, m), 4.11-3.63 (3H, m), 3.07 (3H, d), 2.85-2.50 (2H, m), 2.40 (3H, d), 2.09 (3H, d)
26	^{1}H NMR δ (ppm) (MeOD, d_4): 8.38 (1H, s), 8.16-8.09 (1H, m), 7.98 (1H, d), 7.77-7.65 (3H, m), 7.63-7.33 (6H, m), 4.84-4.60 (2H, m), 4.36-4.18 (1H, m), 4.07 (3H, s), 4.06-3.59 (3H, m), 3.03 (3H, d), 2.81-2.47 (2H, m), 2.05 (3H, d)
27	^{1}H NMR δ (ppm) (MeOD-d_4): 7.85-7.73 (3H, m), 7.72-7.36 (10H, m), 4.80-4.60 (2H, m), 4.40-4.20 (1H, m), 4.13-3.62 (3H, m), 3.14-2.99 (3H, m), 2.84-2.49 (2H, m), 2.17-2.00 (3H, m)
28	^{1}H NMR δ (ppm) (MeOD, d_4): 7.92 (1H, d), 7.78 (1H, dd), 7.69 (1H, dd), 7.61-7.31 (9H, m), 4.86-4.60 (2H, m), 4.35-4.16 (1H, m), 4.09-3.62 (3H, m), 3.05 (3H, d), 2.81-2.47 (2H, m), 2.05 (3H, d)
29	^{1}H NMR δ (ppm) (MeOD, d_4): 7.87-7.61 (4H, m), 7.61-7.35 (8H, m), 4.85-4.58 (2H, m), 4.39-4.16 (1H, m), 4.14-3.62 (3H, m), 3.05 (3H, d), 2.82-2.48 (2H, m), 2.08 (3H, d)
30	^{1}H NMR δ (ppm) ($CDCl_3$): 7.59-7.45 (2H, m), 7.24-7.05 (2H, m), 7.04-6.80 (3H, m), 4.85-4.34 (2H, m), 4.10-3.86 (2H, m), 3.85-3.18 (2H, m), 2.88 (3H, s), 2.62-2.47 (1H, m), 2.39-2.19 (7H, s), 1.90 (3H, s)
31	^{1}H NMR δ (ppm) ($CDCl_3$): 7.49-7.11 (4H, m), 7.11-6.85 (3H, m), 4.85-4.27 (2H, m), 4.15-3.22 (4H, m), 3.12-2.80 (4H, m), 2.66-2.50 (1H, m), 2.48-2.21 (7H, m), 1.92 (3H, s), 1.28 (6H, d)
32	^{1}H NMR δ (ppm) ($CDCl_3$): 7.48-7.35 (2H, m), 7.26-7.10 (2H, m), 7.06-6.86 (3H, m), 4.85-4.27 (2H, m), 4.15-3.22 (4H, m), 2.90 (3H, s), 2.66-2.52 (1H, m), 2.38-2.24 (7H, m), 1.91 (3H, d), 1.35 (9H, s)
33	^{1}H NMR δ (ppm) ($CDCl_3$): 7.13-6.74 (6H, m), 5.05-4.18 (2H, m), 4.15-3.76 (3H, m), 3.61-3.38 (1H, m), 3.08-2.75 (3H, m), 2.67-2.52 (1H, m), 2.43-2.17 (13H, m), 2.00-1.77 (3H, m)

Cpd	NMR data (δ)
34	^{1}H NMR δ (ppm) ($CDCl_3$): 7.25-7.06 (4H, m), 7.06-6.84 (3H, m), 4.82-4.28 (2H, m), 4.11-3.38 (4H, m), 3.00-2.79 (3H, m), 2.65-2.45 (3H, m), 2.39-2.23 (7H, m), 1.99-1.82 (4H, m), 0.93 (6H, d)
35	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.28 (2H, m), 7.28-7.06 (2H, m), 7.06-6.70 (3H, m), 5.04-4.23 (2H, m), 4.13-3.00 (6H, m), 2.70-2.44 (1H, m), 2.41-2.21 (7H, m), 2.01-1.79 (3H, m), 1.32-1.08 (3H, m)
36	^{1}H NMR δ (ppm) (MeOD-d_4): 7.62-7.51 (1H, m), 7.46-7.25 (2H, m), 7.02-6.88 (3H, m), 4.90-4.60 (2H, m), 4.27-3.41 (4H, m), 2.99 (3H, d), 2.79-2.36 (2H, m), 2.32 (6H, s), 2.04-1.80 (3H, m)
37	^{1}H NMR δ (ppm) (MeOD-d_4): 7.51-7.28 (4H, m), 7.02-6.89 (3H, m), 4.80-4.55 (2H, m), 4.24-3.83 (2H, m), 3.83-3.43 (2H, m), 2.98 (3H, d), 2.72-2.36 (2H, m), 2.33 (3H, s), 2.32 (3H, s), 1.96 (3H, d)
38	^{1}H NMR δ (ppm) (MeOD-d_4): 7.69-7.57 (2H, m), 7.52-7.16 (9H, m), 7.01-6.93 (1H, m), 4.75-4.51 (2H, m), 4.28-3.50 (4H, m), 3.90 (3H, s), 2.95 (3H, d), 2.73-2.37 (2H, m), 1.97 (3H, d)
39	^{1}H NMR δ (ppm) ($CDCl_3$): 7.52-7.33 (2H, m), 7.30-7.09 (2H, m), 7.04-6.79 (3H, m), 4.80-4.23 (2H, m), 4.07-3.16 (4H, m), 2.86 (3H, s), 2.60-2.45 (1H, m), 2.37-2.21 (7H, m), 1.87 (3H, d)
41	^{1}H NMR δ (ppm) (MeOD-d_4): 7.40 (2H, d), 7.37-7.27 (2H, m), 7.08 (2H, d), 7.00 (1H, dd), 4.72-4.53 (2H, m), 4.21-3.82 (2H, m), 3.67-3.43 (2H, m), 2.95 (3H, d), 2.72-2.37 (2H, m), 2.31 (6H, d), 1.95 (3H, d)
42	^{1}H NMR δ (ppm) (MeOD-d_4): 7.59-7.45 (1H, m), 7.29-7.08 (2H, m), 7.02-6.88 (3H), 4.76-4.51 (2H, m), 4.25-3.82 (2H, m), 3.80-3.40 (2H, m), 2.96 (3H, d), 2.71-2.35 (2H, m), 2.32 (6H, m), 1.94 (3H, d)
43	^{1}H NMR δ (ppm) ($CDCl_3$): 8.59-8.50 (1H, m), 7.42 (1H, s), 7.22 (2H, s), 7.18-7.09 (4H, m), 4.44-4.39 (2H, m), 4.18-4.00 (2H, m), 3.56-3.50 (2H, m), 3.01-2.91 (1H, m), 2.36 (3H, s), 2.19-2.10 (1H, m), 1.81 (3H, s)
44	^{1}H NMR δ (ppm) ($CDCl_3$): 8.77 (1H, br s), 7.58 (2H, d), 7.43 (1H, s), 7.37 (2H, d), 7.25 (2H, d), 4.50 (2H, d), 4.21-4.06 (2H, m), 3.55 (2H, d), 3.02-2.93 (1H, m), 2.20-2.12 (1H, m), 1.82 (3H, s)
45	^{1}H NMR δ (ppm) ($CDCl_3$): 7.70-7.58 (2H, m), 7.49-7.33 (4H, m), 7.24 (1H, d), 4.89-4.44 (2H, m), 4.22-4.06 (1H, m), 4.04-3.73 (2H, m), 3.70-3.46 (1H, m), 2.93 (3H, s), 2.68-2.32 (2H, m), 1.95 (3H, s)
46	^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.30 (2H, m), 7.24-7.14 (2H, m), 6.98-6.87 (3H, m), 4.74-4.42 (2H, m), 4.10-3.86 (2H, m), 3.79-3.30 (2H, m), 2.79-2.48 (2H, m), 2.37-2.20 (7H, m), 1.98 (3H, s), 0.93-0.58 (4H, m)
47	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.28-7.03 (2H, m), 7.02-6.78 (3H, m), 5.04-4.24 (2H, m), 4.07-3.58 (5H, m), 3.54-3.06 (3H, m), 2.68-2.55 (1H, m), 2.38-2.23 (7H, m), 1.90 (3H, s)
48	^{1}H NMR δ (ppm) ($CDCl_3$): 7.42-7.23 (2H, m), 7.21-7.09 (2H, m), 6.99-6.72 (3H, m), 5.09-4.33(2H, m), 4.26-3.81 (3H, m), 3.79-3.60 (4H, m), 3.48-3.15 (m, 2H), 2.75-2.60 (1H, m), 2.35-2.18 (7H, m), 1.91-1.76 (3H, m).
49	^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.25 (2H, m), 7.21-7.10 (2H, m), 6.94-6.75 (3H, m), 5.16-4.60 (1H, m), 4.59-4.26 (1H, m), 4.25-3.64 (4H, m), 3.49-3.21 (2H, m), 2.70-2.59 (1H, m), 2.36-2.16 (7H, m), 1.91-1.76 (3H, m)
50	^{1}H NMR δ (ppm) ($CDCl_3$): 7.64 (1H, d), 7.50-7.38 (2H, m), 7.38-7.05 (5H, m), 4.90-4.00 (4H, m), 3.22-3.05 (1H, m), 2.98 (2H, s), 2.75-2.59 (4H, m), 2.47-2.29 (1H, m), 2.15-1.93 (3H, m)
51	^{1}H NMR δ (ppm) ($CDCl_3$): 8.56 (1H, br s), 7.42 (1H, s), 7.24-7.18 (3H, m), 7.10-7.04 (3H, m), 4.42 (2H, d), 4.18-4.02 (2H, m), 3.54 (2H, d), 3.01-2.92 (1H, m), 2.34 (3H, s), 2.19-2.11 (1H, m), 1.82 (3H, s)

Cpd	NMR data (δ)
52	^{1}H NMR δ (ppm) ($CDCl_3$): 8.66 (1H, br s), 7.44 (1H, s), 7.35-7.31 (2H, m), 7.28 (1H, s), 7.27-7.22 (3H, m), 4.51-4.35 (2H, m), 3.42-3.32 (1H, m), 3.19-3.09 (1H, m), 2.72-2.62 (1H, m), 1.94-1.84 (1H, m), 1.77 (3H, s), 1.77-1.70 (1H, m), 1.70-1.62 (1H, m), 1.22-1.14 (1H, m), 1.04-0.96 (1H, m)
53	^{1}H NMR δ (ppm) (MeOD-d_4): 7.50-7.21 (4H, m), 7.01-6.85 (3H, m), 4.84-4.74 (1H, m), 4.68-4.44 (1H, m), 4.24-4.00 (2H, m), 3.95-3.71 (2H, m), 3.65-3.50 (1H, m), 3.42-3.34 (3H, m), 2.85-2.74 (3H, m), 2.32 (6H, s), 2.01-1.86 (3H, m)
54	^{1}H NMR δ (ppm) (MeOD, d_4): 7.50-7.28 (4H, m), 7.00-6.85 (3H, m), 4.82-4.52 (2H, m), 4.43-4.08 (2H, m), 4.05-3.79 (2H, m), 3.78-3.52 (1H, m), 3.47-3.40 (1H, m), 3.07-2.96 (6H, m), 2.88-2.40 (2H, m), 2.35-2.29 (6H, m), 2.00-1.84 (3H, m)
55	^{1}H NMR δ (ppm) (MeOD, d_4): 7.60-7.24 (4H, m), 7.01-6.75 (3H, m), 4.90-4.50 (2H, m), 4.18-3.40 (7H, m), 3.35-3.15 (1H, m), 2.76-2.37 (2H, m), 2.33 (3H, s), 2.31 (3H, s), 2.04-1.80 (3H, m), 1.58-1.31 (3H, m)
56	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.28 (2H, m), 7.27-7.06 (2H, m), 7.04-6.76 (3H, m), 4.99-4.47 (2H, m), 4.16-3.09 (11H, m), 2.73-2.50 (1H, m), 2.38-2.21 (7H, m), 1.98-1.82 (3H, m)
57	^{1}H NMR δ (ppm) ($CDCl_3$): 8.74 (1H, br s), 7.91 (1H, d), 7.74 (1H, d), 7.45-7.35 (2H, m), 7.27-7.21 (3H, m), 7.15 (2H, d), 4.39 (2H, ddd), 4.10-3.94 (2H, m), 3.71 (2H, s), 2.96-2.86 (1H, m), 2.15-2.06 (1H, m), 1.81 (3H, s)
58	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.71 (2H, m), 7.46-7.27 (5H, m), 7.25-7.10 (2H, m), 5.04-3.53 (10H, m), 2.79-2.62 (1H, m), 2.42-2.22 (1H, m), 1.91 (3H, d), 1.38-1.22 (3H, m)
59	^{1}H NMR δ (ppm) (MeOD, d_4): 7.39-7.25 (1H, m), 7.25-7.06 (3H, m), 7.00-6.86 (3H, m), 4.87-4.51 (2H, m), 4.41-3.67 (5H, m), 3.62-3.41 (1H, m), 2.85-2.43 (2H, m), 2.45-2.37 (3H, m), 2.33 (3H, s), 2.31 (3H, s), 2.00-1.86 (3H, m)
60	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.69 (2H, m), 7.47-7.27 (5H, m), 7.27-7.07 (2H, m), 5.11-4.28 (3H, m), 4.12-3.89 (3H, m), 3.89-3.49 (5H, m), 2.78-2.65 (1H, m), 2.42-2.26 (1H, m), 1.98-1.75 (3H, m)
61	^{1}H NMR δ (ppm) ($CDCl_3$): 7.91-7.69 (2H, m), 7.48-7.29 (5H, m), 7.17 (2H, d), 4.71-4.33 (3H, m), 4.22-3.92 (3H, m), 3.86-3.61 (2H, m), 2.79-2.17 (2H, m), 2.01-1.69 (3H, m)
62	^{1}H NMR δ (ppm) ($CDCl_3$): 7.62-7.31 (2H, m), 7.26-7.06 (2H, m), 7.04-6.72 (3H, m), 4.99-4.35 (2H, m), 4.17-3.73 (3H, m), 3.72-3.61 (3H, m), 3.59-2.96 (3H, m), 2.73-2.47 (3H, m), 2.44-2.20 (7H, m), 1.95-1.77 (3H, m)
63	^{1}H NMR δ (ppm) ($CDCl_3$): 7.70-7.30 (2H, m), 7.27-7.04 (2H, m), 7.03-6.72 (3H, m), 5.00-4.28 (2H, m), 4.19-3.83 (2H, m), 3.83-3.33 (5H, m), 3.32-2.95 (2H, m), 2.79-2.16 (10H, m), 2.09-1.78 (5H, m)
64	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.30 (2H, m), 7.27-7.03 (2H, m), 7.03-6.74 (3H, m), 4.98-4.27 (2H, m), 4.11-2.95 (8H, m), 2.64-2.50 (1H, m), 2.44-2.22 (7H, m), 2.00-1.78 (5H, m)
65	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.31 (2H, m), 7.25-7.06 (2H, m), 7.01-6.75 (3H, m), 4.91-4.36 (2H, m), 4.01-3.18 (6H, m), 2.77-2.49 (3H, m), 2.37-2.22 (7H, m), 1.93-1.77 (3H, m)
66	^{1}H NMR δ (ppm) ($CDCl_3$): 7.92-7.70 (2H, m), 7.46-7.19 (6H, m), 7.12 (1H, s), 4.80-3.54 (8H, m), 2.78-2.59 (1H, m), 2.42-2.24 (1H, m), 1.98-1.70 (3H, m)
67	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.73 (2H, m), 7.47-7.26 (5H, m), 7.26-6.98 (2H, m), 4.85-4.23 (2H, m), 4.17-3.51 (6H, m), 3.59-3.05 (2H, m), 2.80-2.52 (1H, m), 2.37-2.22 (1H, m), 1.87 (3H, d), 1.96 (1H, br s)
68	^{1}H NMR δ (ppm) ($CDCl_3$): 7.49-7.33 (2H, m), 7.27-7.15 (2H, m), 7.02-6.80 (3H, m), 5.03-4.42 (3H, m), 4.18-3.87 (3H, m), 3.83-3.32 (2H, m), 2.80-2.67 (1H, m), 2.44-2.25 (7H, m), 1.92 (3H, d)
69	^{1}H NMR δ (ppm) ($CDCl_3$): 7.92-7.72 (2H, m),7.49-7.22 (4H, m), 7.21-7.09 (1H, m), 7.03 (2H, s), 4.73-4.32 (2H, m), 4.32-4.12 (1H, m), 4.12-3.84 (3H, m), 3.84-3.58 (2H, m), 2.81-2.60 (1H, m), 2.43-2.24 (4H, m), 2.02-1.69 (3H, m)
70	^{1}H NMR δ (ppm) ($CDCl_3$): 7.96-7.87 (2H, m), 7.48-7.26 (5H, m), 7.26-7.00 (2H, m), 4.94-3.77 (5H, m), 3.71-3.43 (4H, m), 3.36-3.01 (1H, m), 2.66-2.27 (2H, m), 2.01-1.66 (5H, m)
71	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.27-7.04 (2H, m), 7.00-6.74 (3H, m), 4.86-4.35 (2H, m), 4.09-3.85 (2H, m), 3.84-3.66 (1H, m), 3.59-3.23 (3H, m), 2.72-2.49 (3H, m), 2.50-2.17 (9H, m), 1.86 (3H, s)

Cpd	NMR data (δ)
72	^{1}H NMR δ (ppm) ($CDCl_3$): 7.44-7.31 (2H, m), 7.28-7.04 (2H, m), 7.02-6.76 (3H, m), 5.04-4.27 (2H, m), 4.14-3.70 (4H, m), 3.62-3.10 (3H, m), 2.93-2.81 (1H, m), 2.69-2.53 (1H, m), 2.34-2.26 (7H, m), 1.92-1.84 (3H, m), 1.23-1.08 (3H, m)
73	^{1}H NMR δ (ppm) ($CDCl_3$): 7.47-7.31 (2H, m), 7.26-7.06 (2H, m), 7.04-6.72 (3H, m), 5.01-4.35 (2H, m), 4.05-3.60 (6H, m), 3.59-3.10 (3H, m), 2.77-2.48 (3H, m), 2.42-2.18 (7H, m), 1.98-1.80 (3H, m)
74	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.26-7.06 (2H, m), 7.01-6.75 (3H, m), 4.90-4.75 (1H, m), 4.56-4.36 (1H, m), 4.04-3.85 (2H, m), 3.85-3.37 (3H, m), 3.36-3.17 (1H, m), 2.78-2.48 (3H, m), 2.38-2.19 (7H, m), 1.95-1.78 (3H, m)
75	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.31 (2H, m), 7.26-6.93 (3H, m), 6.89 (2H, s), 4.94-4.44 (2H, m), 4.32-3.86 (3H, m), 3.86-3.28 (3H, m), 2.73-2.52 (1H, m), 2.33 (6H, s), 2.25-2.12 (1H, m), 1.87 (3H, s)
76	^{1}H NMR δ (ppm) ($CDCl_3$): 7.35 (2H, d), 7.04 (2H, d), 6.78 (3H, d), 5.08 (1H, d), 4.61 (1H, d), 4.28 (1H, d), 4.21-3.91 (3H, m), 3.40-3.26 (2H, m), 2.74-2.55 (1H, m), 2.31-2.19 (1H, m), 2.15 (6H, s), 1.88 (3H, s)
77	^{1}H NMR δ (ppm) ($CDCl_3$): 7.47-7.32 (2H, m), 7.21-7.10 (2H, m), 7.02-6.78 (3H, m), 4.95-4.47 (2H, m), 4.09-3.88 (2H, m), 3.87-3.40 (2H, m), 3.39-3.22 (2H, m), 2.89-2.55 (1H, m), 2.41-2.25 (7H, m), 1.94-1.82 (5H, m)
78	^{1}H NMR δ (ppm) (MeOD, d_4): 7.83-7.62 (2H, m), 7.54-7.45 (2H, m), 7.44-7.24 (5H, m), 4.84-4.49 (2H, m), 4.31-4.01 (2H, m), 4.00-3.84 (2H, m), 3.77-3.46 (2H, m), 2.85-2.38 (2H, m), 2.07-1.87 (3H, m)
79	^{1}H NMR δ (ppm) (MeOD, d_4): 8.12-7.87 (1H, m), 7.70-7.62 (2H, m), 7.48 (1H, d), 7.45-7.34 (3H, m), 7.34-7.27 (1H, m), 4.84-4.46 (2H, m), 4.41-4.30 (1H, m), 4.30-3.87 (5H, m), 2.89-2.49 (2H, m), 2.11-1.88 (3H, m)
80	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.30 (2H, m), 7.25-6.84 (5H, m), 4.85 (1H, d), 4.68-4.18 (2H, m), 4.18-4.03 (2H, m), 4.03-3.67 (2H, m), 3.42-3.24 (2H, m), 2.73-2.49 (1H, m), 2.32 (6H, s), 2.25-2.10 (1H, m), 1.87 (3H, s), 1.18 (6H, d)
81	^{1}H NMR δ (ppm) ($CDCl_3$): 7.47-7.30 (2H, m), 7.27-6.82 (5H, m), 4.86-4.37 (2H, m), 4.21-3.85 (3H, m), 3.83-3.27 (3H, m), 2.84-2.69 (1H, m),2.62-2.46 (1H, m), 2.22-2.08 (1H, m), 2.33 (6H, s), 1.85 (3H, s), 0.78 (2H, d), 0.70-0.47 (2H, m)
81a	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.31 (2H, m), 7.19 (2H, d), 6.99-6.80 (3H, m), 4.82-4.37 (2H, m), 4.25-3.88 (3H, m), 3.87-3.26 (3H, m), 2.79-2.61 (1H, m), 2.42-2.21 (7H, m), 1.96-1.78 (3H, m)
82	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.32 (2H, m), 7.25-7.16 (2H, m), 6.97-6.81 (3H, m), 4.91-4.30 (2H, m), 4.10-3.71 (4H, m), 3.52-3.27 (2H, m), 2.76-2.64 (1H, m), 2.37-2.23 (7H, m), 1.94-1.83 (3H, m)
83	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.20 (2H, d), 7.03-6.82 (3H, m), 5.36-4.72 (1H, m), 4.64-3.84 (5H, m), 3.77-3.48 (7H, m), 3.45-3.28 (3H, m), 2.88-2.74 (1H, m), 2.40-2.23 (7H, m), 1.97-1.82 (3H, m)
84	^{1}H NMR δ (ppm) ($CDCl_3$): 7.94-7.73 (2H, m), 7.48-7.32 (5H, m), 7.26-7.11 (2H, m), 4.94-4.41 (3H, m), 4.30-3.87 (3H, m), 3.85-3.64 (2H, m), 2.75-2.60 (1H, m), 2.45-2.33 (1H, m), 1.92 (3H, d)
85	^{1}H NMR δ (ppm) ($CDCl_3$): 7.99-7.59 (2H, m), 7.53-7.31 (5H, m), 7.28-7.11 (2H, m), 4.72-4.35 (2H, m), 4.35-3.76 (6H, m), 3.76-3.56 (2H, m), 2.58-2.35 (2H, m)
86	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.71 (2H, m), 7.46-7.30 (5H, m), 7.22-7.04 (2H, m), 4.82-4.34 (2H, m), 4.15-3.81 (3H, m), 3.75-3.30 (6H, m), 2.71-2.50 (3H, m), 2.35-2.23 (1H, m), 1.96-1.76 (3H, m)
87	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.70 (2H, m), 7.46-7.29 (5H, m), 7.27-7.00 (2H, m), 4.85-4.23 (2H, m), 4.12 (2H, q), 4.09-3.80 (3H, m), 3.79-2.96 (3H, m), 2.63-2.47 (1H, m), 2.42-2.13 (3H, m), 2.03-1.75 (5H, m), 1.25 (3H, t)
88	^{1}H NMR δ (ppm) ($CDCl_3$): 8.25-7.80 (2H, m), 7.80-7.00 (7H, m), 6.40-5.60 (1H, m), 5.09-4.32 (2H, m), 4.30-3.31 (5H, m), 3.05-2.41 (3H, m), 2.39-2.11 (1H, m), 2.11-1.50 (3H, m)

Cpd	NMR data (δ)
89	^{1}H NMR δ (ppm) (MeOD, d_4): 7.89-7.63 (2H, m), 7.48-7.03 (7H, m), 4.67-3.86 (3H, m), 3.86-3.25 (3H, m), 3.20-2.92 (2H, m), 2.57-2.23 (2H, m), 2.12-1.93 (2H, m), 1.90-1.65 (5H, m)
90	^{1}H NMR δ (ppm) ($CDCl_3$): 7.47-7.27 (2H, m), 7.24-6.98 (2H, m), 6.97-6.56 (3H, m), 5.61-5.20 (1H, m), 4.97-4.52(1H, m), 4.49-4.06 (1H, m), 4.04-3.52 (3H, m), 3.43-2.97 (2H, m), 2.62-2.43 (1H, m), 2.40-2.10 (7H, m), 2.09-1.73 (5H, m), 1.72-1.51 (2H, m)
91	^{1}H NMR δ (ppm) ($CDCl_3$): 7.71-7.54 (1H, m), 7.40-7.09 (8H, m), 4.83-4.28 (2H, m), 4.12-3.84 (2H, m), 3.78 (3H, s), 3.67-3.50 (2H, m), 2.88 (3H, s), 2.61-2.22 (2H, m), 1.90 (3H, d)
92	^{1}H NMR δ (ppm) ($CDCl_3$): 7.97-7.73 (2H, m), 7.66-7.47 (1H, m), 7.44-7.12 (5H, m), 4.77-4.37 (2H, m), 4.18-3.54 (4H, m), 2.89 (3H, d), 2.67-2.28 (2H, m), 1.92 (3H, d)
93	^{1}H NMR δ (ppm) ($CDCl_3$): 7.81-7.56 (2H, m), 7.51-7.12 (6H, m), 4.80-4.32 (2H, m), 4.10-3.55 (4H, m), 2.88 (3H, d), 2.68-2.22 (5H, m), 1.90 (3H, d)
94	^{1}H NMR δ (ppm) ($CDCl_3$): 7.32 (2H, d), 7.24-7.10 (3H, m), 6.91-6.89 (1H, m), 6.87-6.85 (2H, m), 4.50-4.22 (3H, m), 4.19-4.02 (2H, m), 3.47-3.25 (3H, m), 2.59-2.47 (1H, m), 2.37-2.21 (7H, m), 1.99 (3H, s)
95	^{1}H NMR δ (ppm) ($CDCl_3$): 7.35 (2H, d), 7.16 (2H, d), 6.96-6.87 (3H, m), 4.60-4.36 (2H, m), 4.19-3.95 (3H, m), 3.78-3.57 (1H, m), 3.46-3.32 (2H, m), 3.10 (3H, s), 2.64-2.52 (1H, m), 2.36-2.26 (7H, m), 1.99 (3H, s)
96	^{1}H NMR δ (ppm) (MeOD, d_4): 7.50-7.35 (2H, m), 7.22-7.08 (2H, m), 6.85-6.67 (4H, m), 6.37-6.28 (1H, m), 4.71-4.41 (2H, m), 4.03-3.54 (4H, m), 3.50-3.27 (2H, m), 2.79-2.23 (2H, m), 2.16 (3H, s), 2.12 (3H, s), 1.91-1.71 (3H, m)
97	^{1}H NMR δ (ppm) ($CDCl_3$): 7.49-7.31 (2H, m), 7.26-7.03 (2H, m), 7.02-6.74 (3H, m), 5.01-4.25 (2H, m), 4.21-3.64 (3H, m), 3.63-3.05 (3H, m), 2.71-2.56 (1H, m), 2.50-2.13 (9H, m), 2.01-2.69 (5H, m)
98	^{1}H NMR δ (ppm) ($CDCl_3$): 8.23 (1H, br s), 7.87 (1H, d), 7.50-7.38 (2H, m), 7.34 (2H, d), 7.32-7.09 (3H, m), 5.39-3.95 (4H, m), 3.01 (3H, s), 2.87-2.58 (1H, m), 2.48-2.35 (1H, m), 2.21-1.58 (3H, m)
99	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.74 (2H, m), 7.47-7.27 (5H, m), 7.22-6.95 (2H, m), 4.76 (1H, d), 4.53-3.80 (4H, m), 3.74-3.01 (3H, m), 2.68-2.52 (1H, m), 2.46-2.21 (3H, m), 2.00-1.80 (5H, m)
100	^{1}H NMR δ (ppm) ($CDCl_3$): 7.95-7.74 (2H, m), 7.47-4.31 (5H, m), 7.21-6.94 (2H, m), 4.73-4.58 (1H, m), 4.32-3.99 (3H, m), 3.69 (2H, s), 3.48-3.10 (2H, m), 2.99-2.79 (2H, m), 2.61-2.22 (2H, m), 2.04-1.79 (5H, m)
101	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.28-7.01 (2H, m), 7.01-6.81 (3H, m), 4.90-4.18 (2H, m), 4.13-3.70 (3H, m), 3.69-3.03 (5H, m), 2.62-2.46 (1H, m), 2.37-2.17 (7H, m), 2.03-1.72 (7H, m)
102	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.27-7.11 (1H, m), 7.10-6.85 (4H, m), 5.25-4.70 (1H, m), 4.64-4.21 (2H, m), 4.16-3.63 (3H, m), 3.50-3.21 (4H, m), 3.03-2.89 (4H, m), 2.77-2.49 (1H, m), 2.33 (6H, s), 1.86 (3H, s)
103	^{1}H NMR δ (ppm) ($CDCl_3$): 7.78-7.62 (2H, m), 7.48 (1H, t), 7.43-7.01 (6H, m), 4.84-4.50 (1H, m), 4.49-4.24 (1H, m), 4.08-3.87 (2H, m), 3.79-2.97 (4H, m), 2.64-2.16 (4H, m), 1.98-1.80 (5H, m)
104	^{1}H NMR δ (ppm) ($CDCl_3$): 8.06 (2H, d), 7.68-7.39 (3H, m), 7.36-7.17 (2H, m), 7.15-7.75 (5H, m), 4.72-7.16 (2H, m), 4.12-3.23 (5H, m), 2.71-2.51 (1H, m), 2.38-2.09 (7H, m), 1.94-1.66 (4H, m)
105	^{1}H NMR δ (ppm) ($CDCl_3$): 7.85-7.77 (1H, m), 7.70-7.45 (2H, m), 7.41-7.28 (4H, m), 7.28-7.06 (2H, m), 4.75-3.69 (6H, m), 2.86 (3H, d), 2.67-2.20 (2H, m), 1.91 (3H, d)
106	^{1}H NMR δ (ppm) ($CDCl_3$): 8.27-7.96 (2H, m), 7.66-7.52 (2H, m), 7.47-7.28 (3H, m), 7.28-7.05 (3H, m), 4.75-3.76 (6H, m), 2.87 (3H, d), 2.69-2.25 (2H, m), 1.92 (3H, d)
107	^{1}H NMR δ (ppm) ($CDCl_3$): 7.35 (2H, d), 7.21-6.98- (2H, m), 6.97-6.80 (3H, m), 4.72-4.51 (1H, m), 4.37-3.90 (4H, m), 3.36 (2H, bs), 3.07-2.86 (1H, m), 2.74-2.40 (3H, m), 2.35-2.10 (7H, m), 1.82 (3H, br s)
108	^{1}H NMR δ (ppm) ($CDCl_3$): 7.80 (1H, d), 7.72 (1H, d), 7.44-7.09 (7H, m), 4.77-3.56 (6H, m), 2.89 (3H, s), 2.65-2.26 (2H, m), 1.93 (3H, d)

Cpd	NMR data (δ)
109	^{1}H NMR δ (ppm) ($CDCl_3$): 7.33 (2H, d), 7.18-6.83 (5H, m), 4.53-4.35 (1H, m), 4.03-3.74 (3H, m), 3.50-3.37 (4H, m), 3.33-3.20 (2H, m), 2.51-2.38 (1H, m), 2.35-2.28 (6H, m), 2.18-2.06 (1H, m), 1.80-1.66 (3H, m)
110	^{1}H NMR δ (ppm) ($CDCl_3$): 8.11-7.95 (1H, m), 7.80-7.43 (2H, m), 7.12-6.67 (4H, m), 4.94-4.54 (2H, m), 4.24-3.69 (4H, m), 3.56-3.13 (2H, m), 2.82-2.68 (1H, m), 2.39-2.14 (7H, m), 2.00-1.83 (3H, m)
111	^{1}H NMR δ (ppm) ($CDCl_3$): 9.51-9.32 (1H, m), 7.44-7.29 (2H, m), 7.23-7.11 (2H, m), 6.97-6.75 (3H, m), 4.87 (1H, d), 4.65-4.32 (2H, m), 4.21-3.69 (3H, m), 3.45-3.21 (2H, m), 2.75-2.56 (1H, m), 2.36-2.21 (7H, m), 1.89 (3H, br s)
112	^{1}H NMR δ (ppm) ($CDCl_3$): 8.26-7.76 (2H, m), 7.53 (1H, d), 7.40-7.02 (6H, m), 4.86-3.61 (4H, m), 3.06 (3H, s), 2.91-2.57 (1H, m), 2.47-2.33 (1H, m), 2.05 (3H, s)
113	^{1}H NMR δ (ppm) (MeOD, d_4): 7.67-7.53 (1H, m), 7.43-7.24 (2H, m), 7.05-6.83 (4H, m), 6.49 (1H, br s), 5.03-4.55 (2H, m), 4.24-4.00 (1H, m), 3.95-3.05 (6H, m), 2.80-4.47 (1H, m), 2.44-2.21 (8H, m), 2.03-1.86 (5H, m)
114	^{1}H NMR δ (ppm) ($CDCl_3$): 7.40 (2H, d), 7.10 (2H, d), 6.91-6.78 (3H, m), 4.82-4.53 (2H, m), 4.37-3.70 (4H, m), 3.35 (2H, s), 2.68-2.55 (1H, m), 2.37-2.17 (7H, m), 1.90 (3H, s)
115	^{1}H NMR δ (ppm) ($CDCl_3$): 8.33-8.03 (1H, m), 7.90-7.81 (1H, m), 7.49-7.37 (2H, m), 7.33 (2H, d), 7.27-7.07 (2H, m), 6.83 (1H, br s), 5.33-4.73 (1H, m), 4.55-4.34 (1H, m), 4.30-3.72 (3H, m), 3.25-3.01 (1H, m), 2.89-2.67 (1H, m), 2.54-2.23 (3H, m), 2.18-1.83 (5H, m)
116	^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.07 (2H, m), 7.03-6.91 (2H, m), 6.92-6.80 (3H, m), 5.49-5.33 (1H, m), 4.72-4.56 (1H, m), 4.11-3.72 (4H, m), 3.41-3.09 (3H, m), 3.02-2.74 (2H, m), 2.47-2.35 (1H, m), 2.28 (6H, s), 2.17-2.05 (1H, m), 1.83 (3H, s)
117	^{1}H NMR δ (ppm) ($CDCl_3$): 7.46-7.26 (2H, m), 7.24-7.04 (2H, m), 7.00-6.72 (3H, m), 5.02-4.89 (1H, m), 4.57-4.29 (1H, m), 4.01-3.81 (2H, m), 3.80-3.33 (3H, m), 3.33-3.08 (5H, m), 2.97-2.48 (3H, m), 2.35-2.25 (7H, m), 1.95-177 (3H, m)
118	^{1}H NMR δ (ppm) ($CDCl_3$): 7.42-7.28 (2H, m), 7.28-7.03 (2H, m), 7.01-6.74 (3H, m), 5.34 (1H, d), 4.89-4.23 (2H, m), 4.12-3.66 (5H, m), 3.59 (3H, d), 3.53-3.11 (3H, m), 2.89-2.72 (2H, m), 2.64-2.42 (1H, m), 2.34-2.20 (7H, m), 1.96-1.73 (3H, m), 1.42 (3H, t)
119	^{1}H NMR δ (ppm) ($CDCl_3$): 9.91 (1H, d), 7.45-7.32 (2H, m), 7.21-7.08 (2H, m), 6.98-6.75 (3H, m), 4.87-4.27 (2H, m), 4.06-3.73 (3H, m), 3.56-3.18 (3H, m), 2.87-2.77 (2H, m), 2.66-2.55 (1H, m), 2.35-2.46 (7H, m), 1.93-1.80 (3H, m)
120	^{1}H NMR δ (ppm) ($CDCl_3$): 7.44-7.11 (3H, m), 7.03-6.85 (4H, m), 5.60-5.40 (1H, m), 4.74 (1H, m), 4.28-3.75 (6H, m), 3.58-2.77 (6H, m), 2.35-2.09 (7H, m), 1.91-1.74 (3H, m), 1.41 (3H, t)
121	^{1}H NMR δ (ppm) ($CDCl_3$): 8.06-7.40 (3H, m), 7.38-7.30 (2H, m), 7.28-6.93 (3H, m), 6.80 (1H, s), 5.52-3.58 (4H, m), 3.07 (3H, s), 2.92-2.30 (2H, m), 2.04 (3H, s)
122	^{1}H NMR δ (ppm) (MeOD, d_4): 7.52-7.20 (4H, m), 7.02-6.83 (3H), 4.86-4.49 (2H, m), 4.22-3.73 (2H, m), 3.73-3.43 (10H, m), 3.35-3.12 (2H, m), 2.69-2.27 (10H, m), 2.06-1.81 (5H, m)
123	^{1}H NMR δ (ppm) ($CDCl_3$): 8.14-7.96 (1H, m), 7.84-7.39 (2H, m), 7.22-6.67 (4H, m), 5.11-4.49 (2H, m), 4.21-3.79 (2H, m), 3.79-3.27 (3H, m), 3.27-3.05 (2H, m), 2.74-2.46 (1H, m), 2.44-2.14 (8H, m), 2.04-1.79 (5H, m)
124	^{1}H NMR δ (ppm) (MeOD, d_4): 7.52-7.19 (4H, m), 7.03-6.83 (3H), 4.85-4.49 (2H, m), 4.23-3.69 (2H, m), 3.69-3.12 (7H, m), 2.69-2.26 (18H, m), 2.05-1.80 (5H, m)
125	^{1}H NMR δ (ppm) ($CDCl_3$): 7.44-7.04 (4H, m), 7.02-6.74 (3H, m), 4.92-4.32 (2H, m), 4.16-3.73 (2H, m), 3.73-3.04 (4H, m), 3.03-2.88 (6H, m), 2.62-2.45 (1H, m), 2.44-2.20 (9H, m), 2.04-1.76 (5H, m)
126	^{1}H NMR δ (ppm) ($CDCl_3$): 8.31-7.65 (4H, m), 7.63-7.50 (2H, m), 7.44-7.08 (5H, m), 5.56-3.63 (4H, m), 3.07 (3H, s), 2.93-2.34 (2H, m), 2.08 (3H, s)
127	^{1}H NMR δ (ppm) ($CDCl_3$): 7.93-7.75 (2H, m), 7.47-7.27 (5H, m), 7.27-6.97 (2H, m), 6.29 (1H, d), 5.48 (1H, d), 4.80-4.16 (2H, m), 4.16-3.79 (3H, m), 3.79-3.50 (2H, m), 3.28-3.04 (1H, m), 2.66-2.45 (1H, m), 2.42-2.12 (3H, m), 2.12-1.74 (5H, m)

Cpd	NMR data (δ)
128	^{1}H NMR δ (ppm) (MeOD, d_4): 8.07-7.77 (2H, m), 7.67-7.22 (6H, m), 7.08-6.87 (1H, m), 6.49 (1H, s), 5.02-4.53 (2H, m), 4.27-3.43 (5H, m), 3.33-3.10 (1H, m), 2.85-2.23 (4H, m), 2.03-1.85 (5H, m)
129	^{1}H NMR δ (ppm) ($CDCl_3$): 7.96-7.72 (2H, m), 7.52-7.31 (5H, m), 7.27-6.99 (2H, m), 4.87-4.22 (2H, m), 4.19-3.81 (3H, m), 3.80-3.01 (12H, m), 2.66-2.18 (3H, m), 2.03-1.75 (5H, m)
130	^{1}H NMR δ (ppm) (MeOD, d_4): 8.14-7.75 (4H, m), 7.65-7.34 (4H, m), 7.23-7.00 (1H, m), 5.03-4.59 (2H, m), 4.30-3.41 (5H, m), 3.31-3.11 (1H, m), 2.81-2.15 (4H, m), 2.04-1.84 (5H, m)
131	^{1}H NMR δ (ppm) (MeOD, d_4): 8.07-7.35 (8H, m), 7.32-7.08 (1H, m), 6.95-6.84 (1H, m), 4.90-4.54 (1H, m), 4.27-3.59 (5H, m), 3.48-3.10 (2H, m), 2.81-2.22 (4H, m), 2.03-1.85 (5H, m)
132	^{1}H NMR δ (ppm) ($CDCl_3$): 7.49-7.32 (2H, m), 7.24-7.09 (2H, m), 7.01-6.78 (3H, m), 5.92 (1H, br s), 5.05-4.23 (3H, m), 4.22-3.86 (3H, m), 3.86-3.21 (2H, m), 2.74-2.50 (1H, m), 2.40-2.24 (7H, m), 1.91 (3H, s)
133	^{1}H NMR δ (ppm) ($CDCl_3$): 7.43-7.29 (2H, m), 7.19-7.02 (2H, m), 6.97-6.90 (1H, m), 6.89-6.77 (3H, m), 5.57-5.35 (1H, m), 4.67 (2H, d), 4.49-4.13 (1H, m), 4.08-3.68 (3H, m), 3.52-3.14 (2H, m), 2.58-2.45 (1H, m), 2.34-2.14 (7H, m), 1.85 (3H, br s)
134	^{1}H NMR δ (ppm) (MeOD, d_4): 8.17-7.88 (2H, m), 7.66-7.23 (6H, m), 7.12-6.89 (1H, m), 6.50 (1H, s), 5.11-4.60 (2H, m), 4.39-3.70 (3H, m), 3.33-3.18 (1H, m), 2.86-2.27 (4H, m), 2.22-1.82 (5H, m)
135	^{1}H NMR δ (ppm) (MeOD, d_4): 8.26-7.59 (3H, m), 7.59-7.19 (6H, m), 5.20-4.55 (2H, m), 4.48-4.16 (1H, m), 3.99-3.71 (1H, m), 3.62-3.09 (2H, m), 2.87-2.65 (1H, m), 2.59-2.27 (3H, m), 2.06-1.92 (5H, m)
136	^{1}H NMR δ (ppm) (MeOD, d_4): 7.91-7.81 (1H, m), 7.78-7.50 (2H, m), 7.50-7.15 (6H, m), 4.81-3.72 (6H, m), 3.62-3.07 (2H, m), 2.74-2.19 (4H, m), 2.05-1.79 (5H, m)
137	^{1}H NMR δ (ppm) (MeOD, d_4): 7.85-7.54 (3H, m), 7.50 (1H, d), 7.44-7.21 (4H, m), 7.07-6.87 (1H, m), 6.49 (1H, br s), 5.04-4.55 (2H, m), 4.32-3.87 (2H, m), 3.80-3.41 (3H, m), 3.34-3.11 (1H, m), 2.84-2.19 (4H, m), 2.07-1.85 (5H, m)
138	^{1}H NMR δ (ppm) ($CDCl_3$): 8.17-6.97 (9H, m), 5.44-4.29 (2H, m), 4.08-2.72 (13H, m), 2.51-2.29 (2H, m), 2.18-1.91 (6H, m)
139	^{1}H NMR δ (ppm) ($CDCl_3$): 8.41-7.68 (2H, m), 7.53-6.72 (7H, m), 5.10 (1H, d), 4.46 (1H, d), 4.36-3.78 (3H, m), 3.77-3.34 (7H, m), 3.31-2.66 (3H, m), 2.51-1.85 (8H, m)
140	^{1}H NMR δ (ppm) ($CDCl_3$): 7.80-7.53 (2H, m), 7.53-7.45 (1H, m), 7.44-7.02 (6H, m), 4.90-3.84 (4H, m), 3.75-3.20 (11H, m), 3.18-3.01 (1H, m), 2.66-2.20 (4H, m), 2.04-1.79 (5H, m)
141	^{1}H NMR δ (ppm) ($CDCl_3$): 8.26-7.62 (2H, m), 7.50 (2H, d), 7.41-7.14 (4H, m), 6.50 (1H, br s), 5.47-4.31 (2H, m), 4.14-3.57 (4H, m), 3.21-2.55 (2H, m), 2.44-2.08 (3H, m), 2.07-1.43 (6H, m), 1.25-1.02 (3H, m)
142	^{1}H NMR δ (ppm) ($CDCl_3$): 8.30-7.95 (1H, m), 7.86-7.64 (1H, m), 7.50 (2H, d), 7.40-7.12 (4H, m), 6.43 (1H, br s), 5.49-4.30 (2H, m), 4.22-3.41 (5H, m), 3.20-2.52 (2H, m), 2.40-2.08 (3H, m), 2.05-1.65 (5H, m), 1.50 (2H, s), 1.24-1.02 (3H, m)
143	^{1}H NMR δ (ppm) ($CDCl_3$): 8.36-7.78 (2H, m), 7.50-7.35 (2H, m), 7.33-6.63 (5H, m), 5.48-4.75 (1H, m), 4.58-4.34 (1H, m), 4.31-3.72 (5H, m), 3.28-2.64 (2H, m), 2.49-2.19 (3H, m), 2.19-1.81 (4H, m), 1.65 (1H, s), 1.34-1.17 (3H, m)
144	^{1}H NMR δ (ppm) ($CDCl_3$): 7.97-7.55 (4H, m), 7.52-7.14 (5H, m), 4.95-4.28 (2H, m), 4.12-2.99 (6H, m), 2.64-2.48 (1H, m), 2.45-2.16 (3H, m), 2.02-1.73 (5H, m)
145	^{1}H NMR δ (ppm) ($CDCl_3$): 8.35-8.06 (1H, m), 7.95-7.75 (1H, m), 7.62 (2H, d), 7.49-7.30 (4H, m), 6.58 (1H, br s), 5.46 (1H, br s), 4.65-4.43 (1H, m), 4.12-3.69 (3H, m), 3.30-2.67 (2H, m), 2.55-2.25 (3H, m), 2.16-1.89 (5H, m)
146	^{1}H NMR δ (ppm) ($CDCl_3$): 8.34-8.08 (1H, m), 7.84 (1H, d), 7.50-7.36 (2H, m), 7.34-7.16 (3H, m), 7.08 (1H, br s), 6.83 (1H, br s), 5.34 (1H, br s), 4.60-4.34 (1H, m), 4.30-3.77 (3H, m), 3.31-2.69 (2H, m), 2.53-2.25 (3H, m), 2.17-1.87 (5H, m)
147	^{1}H NMR δ (ppm) ($CDCl_3$): 7.97-7.67 (2H, m), 7.56-7.33 (3H, m), 7.33-6.98 (4H, m), 4.91-4.27 (2H, m), 4.13 (2H, q), 4.06-3.83 (3H, m), 3.81-2.97 (3H, m), 2.64-2.49 (1H, m), 2.43-2.23 (3H, m), 2.04-1.61 (5H, m), 1.26 (3H, t)

Cpd	NMR data (δ)
148	^{1}H NMR δ (ppm) ($CDCl_3$): 7.94-7.68 (2H, m), 7.45-7.32 (3H, m), 7.32-6.96 (4H, m), 4.87-4.23 (2H, m), 4.19-3.82 (3H, m), 3.80-3.43 (2H, m), 3.37-3.01 (1H, m), 2.63-2.48 (1H, m), 2.45-2.17 (3H, m), 2.00-1.74 (5H, m)
149	^{1}H NMR δ (ppm) ($CDCl_3$): 7.43-7.31 (2H, m), 7.24-7.05 (2H, m), 7.02-6.94 (1H, m), 6.89 (1H, s), 6.80 (1H, br s), 4.94-4.28 (2H, m), 4.00-3.72 (2H, m), 3.62-2.94 (8H, m), 2.66-2.43 (1H, m), 2.42-2.20 (9H, m), 2.07-1.96 (2H, m), 1.93-1.68 (5H, m)
150	^{1}H NMR δ (ppm) ($CDCl_3$): 7.80-7.46 (3H, m), 7.45-7.04 (6H, m), 4.88-4.34 (2H, m), 4.25-3.75 (3H, m), 3.74-3.26 (6H, m), 2.75-2.25 (4H, m), 1.98-1.81 (3H, m)
151	^{1}H NMR δ (ppm) ($CDCl_3$): 8.40-8.07 (1H, m), 7.86 (1H, d), 7.49-7.37 (2H, m), 7.33 (2H, d), 7.27-6.75 (3H, m), 5.36-4.66 (1H, m), 4.62-4.42 (1H, m), 4.33-3.29 (7H, m), 2.85-2.33 (4H, m), 2.10-1.90 (3H, m)
152	^{1}H NMR δ (ppm) ($CDCl_3$): 8.16-8.03 (1H, m), 7.84-7.41 (4H, m), 7.40-6.89 (4H m), 5.11-4.47 (2H, m), 4.19-3.88 (4H, m), 3.75-3.05 (4H, m), 2.69-2.52 (1H, m), 2.43-2.13 (3H, m), 2.11-1.82 (5H, m), 1.32-1.17 (3H, m)
153	^{1}H NMR δ (ppm) ($CDCl_3$): 8.39-8.03 (2H, m), 7.94-7.66 (2H, m), 7.62-7.31 (3H, m), 7.19-6.93 (1H, m), 6.60 (1H, br s), 5.48-4.91 (1H, m), 4.73-4.51 (1H, m), 4.43-3.56 (5H, m), 3.34-3.04 (1H, m), 2.89-2.71 (1H, m), 2.50-2.20 (3H, m), 2.20-1.77 (5H, m), 1.32-1.13 (3H, m)
154	^{1}H NMR δ (ppm) ($CDCl_3$): 7.79-7.52 (2H, m), 7.48 (1H, dd), 7.44-7.23 (4H, m), 7.23-7.04 (2H, m), 4.81-4.34 (2H, m), 4.20-3.30 (6H, m), 2.76-2.48 (3H, m), 2.42-2.23 (1H, m), 1.96-1.78 (3H, d)
155	^{1}H NMR δ (ppm) ($CDCl_3$): 8.38-8.06 (1H, m), 7.86 (1H, d), 7.50-7.37 (2H, m), 7.33 (2H, d), 7.25-7.08 (2H, m), 6.99 (1H, br s), 5.28-4.68 (1H, m), 4.57-4.42 (1H, m), 4.09-3.79 (2H, m), 3.47-3.31 (1H, m), 3.10-2.56 (4H, m), 2.47-2.32 (1H, m), 2.14-1.89 (3H, m)
156	^{1}H NMR δ (ppm) ($CDCl_3$): 8.10-7.96 (1H, m), 7.80-7.34 (5H, m), 7.29-6.89 (3H, m), 5.06-4.44 (2H, m), 4.13-3.85 (2H, m), 3.80-2.96 (4H, m), 2.75-2.16 (4H, m), 2.05-1.79 (5H, m)
157	^{1}H NMR δ (ppm) ($CDCl_3$): 8.34-8.01 (2H, m), 7.90-7.62 (2H, m), 7.58-7.31 (3H, m), 7.18-6.74 (2H, m), 5.23-4.84 (1H, m), 4.70-4.48 (1H, m), 4.33-3.69 (3H, m), 3.27-3.10 (1H, m), 2.89-2.61 (1H, m), 2.53-2.23 (3H, m), 2.15-1.78 (5H, m)
158	^{1}H NMR δ (ppm) ($CDCl_3$): 8.34-8.09 (2H, m), 7.86 (1H, d), 7.50-7.37 (2H, m), 7.34 (2H, d), 7.27-7.09 (2H, m), 7.01-6.48 (1H, m), 5.44 (1H, br s), 5.21 (1H, br s), 4.43 (1H, d), 4.34-3.71 (3H, m), 3.30-3.09 (1H, m), 2.86-2.68 (1H, m), 2.48-2.24 (2H, m), 2.18-1.87 (5H, m)
159	^{1}H NMR δ (ppm) ($CDCl_3$): 7.74-7.55 (2H, m), 7.45-7.22 (2H, m), 7.02-6.70 (3H, m), 5.11-4.34 (2H, m), 4.19-3.66 (3H, m), 3.63-2.95 (3H, m), 2.65-2.48 (1H, m), 2.48-2.17 (9H, m), 2.01-1.75 (5H, m)
160	^{1}H NMR δ (ppm) ($CDCl_3$): 7.77-7.52 (4H, m), 7.48 (1H, dd), 7.43-7.19 (4H, m), 4.97-4.35 (2H, m), 4.04-3.87 (2H, m), 3.80-3.01 (4H, m), 2.66-2.49 (1H, m), 2.46-2.16 (3H, m), 2.02-1.79 (5H, m)
161	^{1}H NMR δ (ppm) ($CDCl_3$): 7.40-7.01 (4H, m), 7.01-6.85 (2H, m), 6.80 (1H, s), 5.02-4.23 (2H, m), 4.16-3.67 (3H, m), 3.61-2.99 (3H, m), 2.64-2.49 (1H, m), 2.45-2.18 (9H, m), 2.00-1.77 (5H, m)
162	^{1}H NMR δ (ppm) (MeOD, d_4): 7.85-7.76 (1H, m), 7.74-7.59 (1H, m), 7.57-7.36 (1H, m), 7.30-7.10 (1H, m), 7.03-6.83 (4H, m), 4.91-4.60 (2H, m), 4.16-4.01 (1H, m), 3.95-3.40 (3H, m), 3.40-3.11 (2H, m), 2.69-2.50 (1H, m), 2.47-2.20 (9H, m), 2.04-1.85 (5H, m)
163	^{1}H NMR δ (ppm) (MeOD, d_4): 8.33-8.04 (1H, m), 8.02-7.90 (1H, m), 7.81 (1H, d), 7.72-7.62 (1H, m), 7.61-7.40 (4H, m), 7.35-7.14 (1H, m), 6.89 (1H, m), 5.12-4.69 (2H, m), 4.39-3.95 (2H, m), 3.82-3.18 (2H, m), 2.85-2.46 (2H, m), 2.45-2.28 (2H, m), 2.23-1.86 (5H, m)
164	^{1}H NMR δ (ppm) (DMSO, d_6): 7.98 (1H, d), 7.78 (1H, dd), 7.72-7.57 (2H, m), 7.56-7.46 (2H, m), 7.33-7.15 (3H, m), 6.95 (1H, d), 4.82-4.51 (2H, m), 3.90-3.49 (4H, m), 3.20-3.01 (2H, m), 2.48-2.27 (2H, m), 2.26-2.09 (2H, m), 1.96-1.64 (5H, m)
165	^{1}H NMR δ (ppm) ($CDCl_3$): 7.74-7.56 (2H, m), 7.44-7.23 (2H, m), 7.03-6.69 (3H, m), 5.17-4.37 (2H, m), 4.12 (2H, q), 3.99-2.96 (6H, m), 2.68-2.48 (1H, m), 2.39-2.12 (9H, m), 2.02-1.76 (5H, m), 1.25 (3H, t)

Cpd	NMR data (δ)
166	^{1}H NMR δ (ppm) ($CDCl_3$): 7.76-7.57 (2H, m), 7.54-7.46 (1H, m), 7.44-7.00 (6H, m), 6.71-6.01 (1H, m), 5.58-5.26 (1H, m), 4.86-3.86 (4H, m), 3.73-3.08 (4H, m), 2.69-2.52 (1H, m), 2.43-2.17 (3H, m), 2.01-1.81 (5H, m)
167	^{1}H NMR δ (ppm) ($CDCl_3$): 7.81-7.57 (4H, m), 7.49 (1H, d), 7.44-7.20 (4H, m), 5.01-4.37 (2H, m), 4.12 (2H, q), 4.08-3.87 (2H, m), 3.80-2.83 (4H, m), 2.67-2.52 (1H, m), 2.46-2.15 (3H, m), 2.03-.1.80 (5H, m), 1.25 (3H, t)
168	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.22-7.00 (3H, m), 7.00-6.72 (3H, m), 6.53-6.41 (2H, m), 5.00-4.48 (2H, m), 4.47-4.16 (3H, m), 4.01-3.38 (10H, m), 3.31-2.91 (2H, m), 2.91-2.63 (2H, m), 2.61-2.45 (1H, m), 2.38-2.19 (7H, m), 2.01-1.76 (5H, m)
169	^{1}H NMR δ (ppm) ($CDCl_3$): 8.11-7.99 (1H, m), 7.74 (1H, d), 7.39-7.24 (2H, m), 7.21-6.78 (5H, m), 5.13 (1H, br s), 4.39 (1H, br s), 4.00-3.23 (4H, m), 2.77-2.54 (3H, m), 2.38-2.22 (1H, m), 2.05-1.81 (3H, br s)
170	^{1}H NMR δ (ppm) ($CDCl_3$): 7.85-7.57 (2H, m), 7.38-7.15 (5H, m), 7.14-6.89 (2H, m), 4.71-3.24 (8H, m), 2.66-2.34 (3H, m), 2.29-2.08 (1H, m), 1.74 (3H, d)
171	^{1}H NMR δ (ppm) ($CDCl_3$): 7.43-7.29 (2H, m), 7.22-6.99 (2H, m), 6.96-6.79 (3H, m), 5.30-5.01 (2H, m), 4.75 (1H, d), 4.59-4.14 (1H, m), 4.06-3.80 (2H, m), 3.79-3.58 (1H, m), 3.34-3.01 (5H, m), 2.61-2.43 (1H, m), 2.33-2.24 (6H, m), 2.24-2.12 (1H, m), 2.13-2.03 (2H, m), 1.84 (3H, br s)
172	^{1}H NMR δ (ppm) ($CDCl_3$): 8.40-8.11 (1H, m), 7.85 (1H, d), 7.51-7.36 (2H, m), 7.33-6.77 (5H, m), 5.34 (1H, br s), 4.62-4.41 (1H, m), 4.35-3.78 (3H, m), 3.71 (3H, s), 3.62-3.30 (1H, m), 2.91-2.62 (3H, m), 2.48-2.35 (1H, m), 2.19-1.90 (3H, m)
173	^{1}H NMR δ (ppm) ($CDCl_3$): 7.97-7.69 (2H, m), 7.47-7.27 (5H, m), 7.26-7.01 (2H, m), 4.90-4.35 (2H, m), 4.14-3.80 (3H, m), 3.77-3.29 (6H, m), 2.75-2.52 (3H, m), 2.35-2.25 (1H, m), 1.85 (3H, d)
174	^{1}H NMR δ (ppm) ($CDCl_3$): 7.48-7.31 (2H, m), 7.27-7.02 (2H, m), 7.02-6.76 (3H, m), 4.97-4.23 (3H, m), 4.09-3.85 (2H, m), 3.85-2.88 (6H, m), 2.88-2.65 (3H, m), 2.65-2.49 (1H, m), 2.42-2.18 (7H, m), 2.14-1.80 (5H, m)
175	^{1}H NMR δ (ppm) ($CDCl_3$): 8.11 (1H, d), 7.98-7.63 (3H, m), 7.47-4.31 (4H, m), 7.13-6.93 (1H, m), 4.93-4.55 (2H, m), 4.18-3.70 (4H, m), 3.67 (3H, d), 3.63-3.40 (2H, m), 2.74-2.55 (3H, m), 2.37-2.24 (1H, m), 2.05-1.80 (3H, m)
176	^{1}H NMR δ (ppm) (MeOD, d_4): 8.09 (1H, d), 8.06-7.75 (3H, m), 7.63-7.35 (4H, m), 7.23-7.02 (1H, m), 4.92-3.87 (4H, m), 3.86-3.44 (4H, m), 2.84-2.62 (3H, m), 2.61-2.40 (1H, m), 2.07-1.87 (3H, m)
177	^{1}H NMR δ (ppm) (MeOD, d_4): 8.42-8.17 (1H, m), 7.88-7.59 (3H, m), 7.58-7.45 (1H, m), 7.45-7.15 (4H, m), 6.93-6.57 (1H, m), 4.73-4.43 (1H, m), 4.17-3.89 (2H, m), 3.86-3.52 (3H, m), 3.46-3.23 (2H, m), 2.64-2.26 (2H, m), 2.26-2.07 (2H, m), 1.91-1.68 (5H, m)
178	^{1}H NMR δ (ppm) ($CDCl_3$): 7.92-7.67 (2H, m), 7.44-7.31 (4H, m), 7.30-7.26 (1H, m), 7.18-6.90 (3H, m), 6.51-6.34 (2H, m), 4.97-4.80 (1H, m), 4.75-4.30 (1H, m), 4.26-4.14 (2H, m), 4.02-3.84 (2H, m), 3.85-3.71 (7H, m), 3.63-3.30 (2H, m), 3.25-2.90 (1H, m), 2.88-2.62 (2H, m), 2.56-2.37 (2H, m), 2.55-2.35 (1H, m), 2.36-2.13 (1H, m), 1.97-1.78 (4H, m)
179	^{1}H NMR δ (ppm) ($CDCl_3$): 7.45-7.31 (2H, m), 7.22-6.80 (5H, m), 4.85-4.51 (2H, m), 4.03-3.81 (3H, m), 3.81-3.73 (5H, m), 3.52-3.10 (8H, m), 2.74-2.59 (1H, m), 2.34-2.19 (7H, m), 1.87 (3H, s)
180	^{1}H NMR δ (ppm) ($CDCl_3$): 7.42-7.28 (2H, m), 7.21-7.04 (2H, m), 6.96 (1H, br s), 6.87 (1H, br s), 6.81 (1H, br s), 4.98-4.45 (2H, m), 4.06-3.75 (3H, m), 3.80-3.64 (5H, m), 3.61-3.39 (1H, m), 3.40-3.07 (8H, m), 2.74-2.53 (1H, m), 2.33-2.15 (7H, m), 1.82 (3H, br s), 1.62-1.57 (4H, m)
181	^{1}H NMR δ (ppm) ($CDCl_3$): 7.90-7.71 (2H, m), 7.46-7.26 (5H, m), 7.19-6.89 (2H, m), 5.20-4.88 (2H, m), 4.70-4.34 (1H, m), 4.08-3.85 (2H, m), 3.80-3.44 (3H, m), 3.29-2.88 (3H, m), 2.59-2.37 (1H, m), 2.36-2.13 (1H, m), 2.09-1.98 (1H, m), 1.86 (3H, br s)
182	^{1}H NMR δ (ppm) ($CDCl_3$): 8.18-8.06 (1H, m), 7.82 (1H, d), 7.45-7.35 (2H, m), 7.33-7.29 (2H, m), 7.19-7.03 (3H, m), 5.16-4.99 (2H, m), 4.47-4.34 (1H, m), 4.08-3.80 (3H, m), 3.23-3.09 (2H, m), 2.79-2.65 (1H, m), 2.43-2.27 (1H, m), 2.23-2.08 (2H, m), 1.99 (3H, br s)

Cpd	NMR data (δ)
183	^{1}H NMR δ (ppm) ($CDCl_3$): 9.08 (1H, br s), 8.11-7.57 (4H, m), 7.50-7.27 (4H, m), 5.30 (2H, s), 5.03-4.40 (2H, m), 4.14-3.96 (1H, m), 3.78-3.42 (3H, m), 3.41-3.02 (2H, m), 2.74-2.45 (1H, m), 2.42-2.16 (3H, m), 1.92 (3H, br s)
184	^{1}H NMR δ (ppm) ($CDCl_3$): 9.01 (1H, br s), 8.11-7.95 (2H, m), 7.92-7.69 (2H, m), 7.45-7.25 (2H, m), 7.25-7.15 (1H, m), 7.10-6.46 (1H, m), 5.39-5.21 (1H, m), 4.69-4.35 (3H, m), 4.10-3.92 (1H, m), 3.90-3.72 (1H, m), 3.27-3.06 (1H, m), 2.90-2.70 (1H, m), 2.44-2.18 (3H, m), 2.11-1.84 (3H, m)
185	^{1}H NMR δ (ppm) ($CDCl_3$): 9.05 (1H, br s), 8.08-7.83 (2H, m), 7.45-7.27 (1H, m), 6.93 (1H, br s), 6.82 (1H, br s), 6.73 (1H, br s), 5.11-4.89 (1H, m), 4.84-4.37 (2H, m), 4.00-3.64 (3H, m), 3.62-3.33 (1H, m), 3.31-3.01 (2H, m), 2.71-2.43 (2H, m), 2.40-2.13 (9H, m), 1.99-1.80 (3H, m)
186	^{1}H NMR δ (ppm) ($CDCl_3$): 8.27-8.05 (1H, m), 7.89-7.76 (1H, m), 7.47-7.35 (2H, m), 7.34-7.27 (2H, m), 7.21-6.90 (3H, m), 5.31-4.90 (1H, m), 4.60-4.32 (1H, m), 4.05-3.75 (3H, m), 3.26-2.95 (2H, m), 2.89-2.66 (3H, m), 2.47-2.28 (1H, m), 2.18-2.05 (2H, m), 2.05-1.90 (3H, m), 1.77 (3H, br s)
187	^{1}H NMR δ (ppm) ($CDCl_3$): 8.19-8.08 (1H, m), 7.81 (1H, d), 7.46-7.32 (2H, m), 7.30-7.22 (3H, m), 7.21-7.14 (1H, m), 7.11-6.99 (1H, m), 5.24-5.02 (2H, m), 4.45-4.29 (1H, m), 4.08-3.96 (1H, m), 3.96-3.78 (2H, m), 3.25-3.02 (2H, m), 2.81-2.63 (1H, m), 2.44-2.26 (1H, m), 2.22-2.08 (2H, m), 2.05-1.90 (3H, m)
188	^{1}H NMR δ (ppm) ($CDCl_3$): 8.30-7.87 (2H, m), 7.81-7.67 (1H, m), 7.66-7.51 (1H, m), 7.49-7.38 (1H, m), 7.37-7.23 (3H, m), 7.06-6.80 (1H, m), 5.87-5.32 (2H, m), 5.16-4.91 (1H, m), 4.68-4.40 (1H, m), 4.12-3.92 (1H, m), 3.97-3.67 (1H, m), 3.61-3.37 (1H, m), 2.87-2.48 (2H, m), 2.41-2.15 (1H, m), 2.14-1.87 (3H, m)
189	^{1}H NMR δ (ppm) ($CDCl_3$): 7.91-7.70 (2H, m), 7.44-7.27 (6H, m), 7.21-6.92 (2H, m), 4.77-4.62 (1H, m), 4.59-4.15 (1H, m), 4.03-3.83 (2H, m), 3.83-3.48 (3H, m), 3.34-3.06 (1H, m), 3.06-2.84 (1H, m), 2.79-2.63 (1H, m), 2.58-2.40 (1H, m), 2.32-2.15 (1H, m), 2.06-1.92 (3H, m), 1.93-1.77 (3H, m)
190	^{1}H NMR δ (ppm) ($CDCl_3$): 8.22-8.07 (1H, m), 7.89-7.74 (2H, m), 7.49-7.31 (3H, m), 7.23-7.13 (2H, m), 7.13-6.82 (2H, m), 5.38-5.14 (1H, m), 4.62-4.31 (3H, m), 4.06-3.77 (4H, m), 3.27-3.09 (1H, m), 2.83-2.72 (1H, m), 2.47-2.31 (2H, m), 2.19-2.06 (3H, m), 2.06-1.90 (3H, m)
191	^{1}H NMR δ (ppm) (DMSO, d_6) at 80°C: 8.14-8.08 (1H, m), 7.99-7.93 (1H, m), 7.90 (1H, s), 7.44-7.31 (3H, m), 7.30-7.25 (2H, m), 7.22-7.16 (1H, m), 4.73-4.54 (2H, m), 4.11-3.98 (2H, m), 3.44-3.34 (1H, m), 3.26-3.15 (1H, m), 2.58-2.51 (1H, m), 2.41-2.32 (1H, m), 2.18 (2H, t), 1.85-1.76 (5H, m)
192	^{1}H NMR δ (ppm) ($CDCl_3$): 8.20 (1H, d), 7.83 (1H, d), 7.48-7.28 (5H, m), 7.20-7.07 (2H, m), 5.61-5.40 (1H, m), 4.96-4.78 (1H, m), 4.53-4.40 (1H, m), 4.38-4.20 (1H, m), 4.03-3.83 (1H, m), 3.47-3.12 (3H, m), 2.92-2.69 (1H, m), 2.42-2.23 (1H, m), 2.07-1.89 (3H, m)
193	^{1}H NMR δ (ppm) ($CDCl_3$): 8.20 (1H, d), 7.83 (1H, d), 7.47-7.29 (5H, m), 7.19-7.09 (2H, m), 5.31-5.11 (1H, m), 5.09-4.88 (1H, m), 4.61-4.41 (1H, m), 4.27-3.80 (3H, m), 3.48-3.35 (1H, m), 3.35-3.17 (2H, m), 2.42-2.24 (1H, m), 2.14-1.88 (3H, m), 1.68-1.47 (3H, m)
194	^{1}H NMR δ (ppm) ($CDCl_3$): 8.29 (1H, d), 7.82 (1H, d), 7.48-7.26 (6H, m), 7.10-6.95 (1H, m), 4.03-3.86 (1H, m), 3.86-3.59 (3H, m), 2.65-2.51 (1H, m), 2.46 (2H, t), 2.18-2.02 (1H, m), 1.99-1.84 (2H, m), 1.84-1.67 (3H, m)
195	^{1}H NMR δ (ppm) ($CDCl_3$): 8.13-8.03 (1H, m), 7.85-7.75 (1H, m), 7.46-7.31 (6H, m), 7.27-7.13 (4H, m), 7.10-6.98 (1H, m), 6.77-6.66 (1H, m), 5.56-5.31 (1H, m), 4.43-4.21 (1H, m), 4.09-3.80 (2H, m), 3.76-3.56 (1H, m), 3.08-2.90 (1H, m), 2.77-2.58 (2H, m), 2.59-2.10 (5H, m), 2.03-1.84 (2H, m), 1.15-1.01 (3H, m)
196	^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.30 (2H, m), 7.23-7.09 (2H, m), 6.84-6.72 (2H, m), 6.59-6.43 (1H, m), 5.10-4.73 (1H, m), 4.55-4.36 (1H, m), 4.10-3.81 (3H, m), 3.72-3.58 (1H, m), 3.20-3.04 (1H, m), 2.72-2.62 (1H, m), 2.44-2.30 (4H, m), 2.30-2.25 (6H, m), 1.90-1.80 (3H, m)

Cpd	NMR data (δ)
197	^{1}H NMR δ (ppm) ($CDCl_3$): 8.07-7.99 (1H, m), 7.86 (1H, d), 7.52-7.14 (7H, m), 4.24-3.83 (2H, m), 3.64-3.44 (1H, m), 2.99-2.82 (1H, m), 2.82-2.68 (1H, m), 2.54-2.20 (3H, m), 2.15-1.78 (5H, m), 1.73 (3H, d)
198	^{1}H NMR δ (ppm) ($CDCl_3$): 8.27-8.16 (1H, m), 7.85 (1H, d), 7.75-7.61 (1H, m), 7.48-7.35 (2H, m), 7.36-7.29 (2H, m), 7.25-7.15 (2H, m), 5.53-5.31 (1H, m), 4.29-4.09 (1H, m), 4.09-3.90 (1H, m), 3.62-3.44 (1H, m), 2.90-2.61 (2H, m), 2.48-2.21 (3H, m), 2.17-1.99 (2H, m), 1.96-1.73 (3H, m), 1.67 (3H, d)
199	^{1}H NMR δ (ppm) (DMSO, d_6): 8.31-8.16 (1H, m), 8.08-7.90 (2H, m), 7.85-7.68 (1H, m), 7.52-7.20 (10H, m), 4.80-4.56 (2H, m), 4.09-3.83 (2H, m), 3.44-3.22 (1H, m), 3.22-3.06 (1H, m), 3.04-2.87 (2H, m), 2.45-2.33 (2H, m), 2.23 (2H, t), 1.91-1.71 (2H, m)
200	^{1}H NMR δ (ppm) ($CDCl_3$): 9.82-9.74 (1H, m), 7.44-7.40 (1H, m), 7.39-7.34 (1H, m), 7.26-7.21 (1H, m), 7.20-7.15 (2H, m), 7.13-7.11 (1H, m), 6.68 (1H, s), 4.79-4.62 (1H, m), 4.51-4.36 (1H, m), 4.19-3.97 (1H, m), 3.72-3.47 (2H, m), 3.36-3.10 (2H, m), 2.80-2.65 (1H, m), 2.48-2.35 (2H, m), 2.32 (3H, s), -2.30 (3H, s), 1.99-1.91 (2H, m), 1.82-1.71 (3H, m)
201	^{1}H NMR δ (ppm) (MeOD, d_4): 7.49-7.26 (4H, m), 7.03-6.85 (2H, m), 6.70-6.58 (1H, br s), 4.84-4.54 (2H, m), 3.50-3.35 (1H, m), 3.36-3.20 (1H, m), 3.20-3.05 (3H, m), 2.94-2.65 (1H, m), 2.43-2.18 (9H, m), 2.16-1.96 (1H, m), 1.96-1.78 (5H, m)
202	^{1}H NMR δ (ppm) (MeOD, d_4): 7.54-7.14 (8H, m), 4.76-4.45 (2H, m), 4.30-3.98 (1H, m), 3.97-3.78 (1H, m), 3.58-3.09 (1H, m), 2.75-2.43 (2H, m), 2.36-2.22 (2H, m), 2.07-1.75 (5H, m)
203	^{1}H NMR δ (ppm) ($CDCl_3$): 8.10-7.97 (1H, m), 7.86-7.73 (1H, m), 7.48-7.31 (2H, m), 7.24-7.11 (3H, m), 7.09-6.95 (1H, m), 6.73-6.61 (1H, m), 4.42 (1H, d), 4.18-3.89 (2H, m), 3.68-3.52 (1H, m), 3.05-2.75 (3H, m), 2.62-2.22 (4H, m), 2.09-1.84 (2H, m), 1.34-1.23 (3H, m), 1.06-0.95 (3H, m)
204	^{1}H NMR δ (ppm) ($CDCl_3$): 8.13-7.97 (1H, m), 7.81 (1H, d), 7.48-7.31 (2H, m), 7.28-7.14 (3H, m), 7.10-6.95 (1H, m), 6.78-6.62 (1H, m), 5.60-5.37 (1H, m), 4.46-4.27 (1H, m), 4.09-3.83 (2H, m), 3.75-3.53 (1H, m), 3.10-2.88 (1H, m), 2.83-2.64 (1H, m), 2.61-2.28 (4H, m), 2.25-2.07 (1H, m), 2.02-1.84 (2H, m), 1.60-1.35 (2H, m), 1.12-0.89 (3H, m)
205	^{1}H NMR δ (ppm) (MeOD, d_4): 7.50-6.98 (8H, m), 4.77-4.49 (2H, m), 4.24-3.94 (2H, m), 3.94-3.80 (1H, m), 3.57-3.38 (1H, m), 3.33-3.06 (2H, m), 2.71-2.42 (2H, m), 2.35-2.07 (5H, m), 1.95-1.77 (3H, m)
206	^{1}H NMR δ (ppm) (MeOD, d_4): 7.52-7.31 (4H, m), 7.07-6.91 (2H, m), 6.72-6.63 (1H, m), 4.87-4.61 (2H, m), 3.50-3.41 (1H, m), 3.23-3.10 (3H, m), 3.01-2.74 (2H, m), 2.44-2.23 (9H, m), 1.99-1.82 (5H, m), 1.39-1.10 (2H, m)
207	^{1}H NMR δ (ppm) ($CDCl_3$): 8.17 (1H, d), 7.83 (1H, d), 7.50-7.34 (2H, m), 7.33-7.22 (3H, m), 7.21-7.14 (1H, m), 7.13-7.01 (1H, m), 5.19-4.87 (1H, m), 4.43-4.28 (1H, m), 4.22-4.04 (1H, m), 4.03-3.87 (1H, m), 3.86-3.61 (1H, m), 3.30-3.07 (4H, m), 2.84-2.64 (1H, m), 2.42-2.22 (3H, m), 2.13-1.77 (5H, m)
208	^{1}H NMR δ (ppm) ($CDCl_3$): 8.16-7.93 (1H, m), 7.80-7.64 (1H, m), 7.37-7.21 (2H, m), 7.20-6.89 (4H, m), 6.87-6.69 (1H, m), 6.12-5.67 (2H, m), 4.38-4.18 (1H, m), 3.94-3.74 (2H, m), 3.68-3.50 (1H, m), 3.11-2.35 (6H, m), 2.14-1.91 (4H, m), 1.02-0.90 (3H, br s)
209	^{1}H NMR δ (ppm) ($CDCl_3$): 8.26-8.05 (1H, m), 7.85 (1H, t), 7.70 (1H, br s), 7.47-7.37 (2H, m), 7.34 (1H, d), 7.30 (1H, d), 7.25-7.11 (2H, m), 5.68-5.00 (2H, m), 4.28-3.85 (2H, m), 3.82-3.53 (1H, m), 3.20-2.64 (4H, m), 2.42-2.29 (1H, m), 2.27-1.91 (3H, m), 1.66 (3H, d), 1.61 (3H, br s)
211	^{1}H NMR δ (ppm) (MeOD, d_4): 7.87-7.80 (1H, m), 7.59-7.56 (1H, m), 7.47-7.22 (7H, m), 4.78-4.54 (1H, m), 4.34-4.08 (1H, m), 3.93 (1H, br s), 3.88-3.60 (1H, m), 3.28-3.12 (1H, m), 2.74-2.51 (2H, m), 2.38-2.24 (2H, m), 2.11-1.82 (6H, m)
216	^{1}H NMR δ (ppm) ($CDCl_3$): 8.25-8.02 (1H, m), 7.83 (1H, d), 7.46-7.34 (2H, m), 7.31 (2H, d), 7.10 (2H, d), 6.92 (1H, br s), 5.27-4.61 (3H, m), 4.36 (1H, d), 4.09-3.60 (3H, m), 3.27-2.92 (3H, m), 2.79-2.43 (3H, m), 2.28-1.99 (3H, m), 1.09 (3H, br s)

Cpd	NMR data (δ)
217	^{1}H NMR δ (ppm) ($CDCl_3$): 8.16-7.98 (1H, m), 7.90-7.77 (1H, m), 7.49-7.31 (2H, m), 7.30-7.11 (4H, m), 7.10-6.70 (1H, m), 5.75 (1H, d), 5.04-4.83 (2H, m), 4.42 (1H, d), 4.29-3.92 (2H, m), 3.76-3.58 (1H, m), 3.24-2.73 (5H, m), 2.58-2.48 (1H, m), 2.27-1.97 (2H, m), 1.30-1.24 (4H, m), 1.05-0.95 (2H, m)
218	^{1}H NMR δ (ppm) ($CDCl_3$): 7.39-7.08 (5H, m), 6.84-6.46 (3H, m), 5.00-4.70 (1H, m), 4.58-4.30 (1H, m), 4.18-3.85 (2H, m), 3.78 (3H, s), 3.70-3.46 (1H, m), 3.23-3.01 (1H, m), 2.79-2.21 (4H, m), 2.02-1.75 (5H, m)
219	^{1}H NMR δ (ppm) ($CDCl_3$): 8.35-8.20 (1H, m), 7.82 (1H, d), 7.45 (1H, t), 7.42-7.30 (3H, m), 7.29-7.04 (4H, m), 6.96 (3H, t), 5.34-4.73 (1H, m), 4.68-4.34 (1H, m), 4.18 (1H, d), 4.00-3.48 (2H, m), 3.34-2.98 (3H, m), 2.60-2.20 (4H, m), 2.07-1.84 (2H, m)
221	^{1}H NMR δ (ppm) ($CDCl_3$): 8.37-8.21 (1H, m), 7.81 (1H, d), 7.43 (1H, t), 7.37 (1H, t), 7.33-6.90 (8H, m), 6.79 (1H, d), 5.29-4.73 (1H, m), 4.70-4.35 (1H, m), 4.33-4.11 (1H, m), 3.99-3.69 (2H, m), 3.66 (3H, s), 3.38-3.00 (3H, m), 2.58-2.21 (4H, m), 2.07-1.88 (2H, m)
227	^{1}H NMR δ (ppm) ($CDCl_3$): 7.41-7.04 (7H, m), 6.89 (1H, br s), 4.93-4.30 (2H, m), 4.17-3.82 (2H, m), 3.71-2.99 (2H, m), 2.73-2.26 (7H, m), 2.00-1.75 (5H, m)
228	^{1}H NMR δ (ppm) ($CDCl_3$): 8.12 (1H, d), 7.83 (1H, d), 7.46-7.35 (2H, m), 7.29-7.23 (2H, m), 7.21-7.14 (1H, m), 7.09-7.00 (1H, m), 6.97-6.89 (1H, m), 5.31 (1H, d), 4.32 (1H, d), 4.05-3.88 (2H, m), 3.82-3.70 (1H, m), 3.35-3.22 (3H, m), 3.18-3.03 (1H, m), 2.80-2.59 (2H, m), 2.58-2.46 (1H, m), 2.45-2.27 (2H, m), 2.21-2.06 (1H, m), 2.05-1.81 (3H, m), 1.18-1.02 (3H, m)
229	^{1}H NMR δ (ppm) ($CDCl_3$): 8.15 (1H, d), 7.83 (1H, d), 7.48-7.35 (2H, m), 7.30-7.27 (2H, m), 7.20-7.15 (1H, m), 7.09-7.03 (1H, m), 6.96-6.89 (1H, m), 6.02-5.88 (1H, m), 5.44-5.30 (2H, m), 5.27 (1H, d), 4.31 (1H, d), 4.13-4.01 (1H, m), 3.99-3.87 (1H, m), 3.83-3.72 (1H, m), 3.55-3.45 (1H, m), 3.37-3.27 (3H, br s), 3.11-3.02 (1H, m), 2.87-2.77 (1H, m), 2.68-2.50 (2H, m), 2.47-2.29 (2H, m), 2.02-1.87 (2H, m), 1.57-1.53 (1H, m)
230	^{1}H NMR δ (ppm) ($CDCl_3$): 8.28 (1H, d), 7.85 (1H, d), 7.49 (1H, t), 7.46-7.34 (3H, m), 7.34-7.16 (7H, m), 7.15-7.05 (1H, m), 5.17 (1H, d), 4.40 (1H, d), 4.16 (1H, m), 4.10-3.98 (1H, m), 3.86-3.73 (1H, m), 3.39-3.18 (4H, m), 3.19-3.04 (2H, m), 2.55-2.37 (4H, m), 1.99-1.86 (2H, m)
231	^{1}H NMR δ (ppm) ($CDCl_3$): 8.20 (1H, d), 7.87 (1H, d), 7.78 (1H, br s), 7.46-7.36 (2H, m), 7.34 (2H, d), 7.18 (2H, d), 5.08 (1H, br s), 4.26-4.17 (1H, m), 4.07-3.98 (1H, m), 3.79-3.67 (1H, m), 3.21 (3H, br s), 2.82-2.72 (1H, m), 2.62-2.53 (1H, m), 2.45-2.22 (3H, m), 2.22-2.06 (3H, m), 2.06-1.82 (2H, m), 1.79-1.60 (4H, m)
232	^{1}H NMR δ (ppm) ($CDCl_3$): 8.09 (1H, d), 7.82 (1H, d), 7.47-7.34 (2H, m), 7.31-7.21 (2H, m), 7.17 (1H, br s), 7.10-7.00 (1H, m), 6.85 (1H, br s), 5.42 (1H, d), 4.32 (1H, d), 4.03-3.89 (2H, m), 3.80-3.68 (1H, m), 3.31 (3H, s), 3.18-3.05 (1H, m), 2.76-2.47 (3H, m), 2.46-2.27 (2H, m), 2.21-2.06 (1H, m), 2.05-1.87 (2H, m), 1.61-1.42 (2H, m), 1.05 (3H, t)
233	^{1}H NMR δ (ppm) ($CDCl_3$): 8.06 (1H, d), 7.81 (1H, d), 7.65-7.47 (2H, m), 7.46-7.11 (3H, m), 7.03 (1H, br s), 6.72 (1H, br s), 5.74 (1H, d), 4.37 (1H, d), 4.26-3.91 (2H, m), 3.70-3.58 (1H, m), 3.31 (3H, s), 3.09-2.96 (1H, m), 2.95-2.73 (2H, m), 2.58-2.48 (1H, m), 2.47-2.28 (2H, m), 2.07-1.89 (2H, m), 1.29 (4H, d), 1.05 (2H, br s)
234	^{1}H NMR δ (ppm) ($CDCl_3$): 8.40 (1H, d), 7.87 (1H, d), 7.48 (1H, t), 7.42 (1H, t), 7.30-7.20 (5H, m), 4.30-4.21 (1H, m), 4.07-3.99 (1H, m), 3.77-3.71 (1H, m), 3.46-3.31 (4H, m), 2.66-2.45 (3H, m), 2.09-1.94 (2H, m), 1.88-1.74 (5H, m)
237	^{1}H NMR δ (ppm) (MeOD, d_4): 8.00-7.87 (1H, m), 7.54 (2H, br s), 7.40-6.97 (6H, m), 6.66-6.45 (1H, m), 4.72-4.49(1H, m), 4.45-4.23 (1H, m), 4.19-3.95 (1H, m), 3.73-3.52 (1H, m), 3.45-3.05 (2H, m), 2.86-2.66 (1H, m), 2.53-2.40 (1H, m), 2.37-2.20 (2H, m), 2.11-1.79 (5H, m)
240	^{1}H NMR δ (ppm) ($CDCl_3$): 8.15 (1H, d), 7.83 (1H, d), 7.49 (1H, t), 7.42 (1H, t), 7.39-7.25(5H, m), 7.21 (1H, br s), 7.16-7.06 (1H, m), 6.96 (2H, t), 5.09 (1H, d), 4.42 (1H, d), 4.16 (1H, d), 4.07-3.77 (2H, m), 3.30 (3H, s), 3.27-3.02 (3H, m), 2.57-2.32 (4H, m), 2.03-1.82 (2H, m)

Cpd	NMR data (δ)
241	^{1}H NMR δ (ppm) ($CDCl_3$): 8.29 (1H, d), 7.85 (1H, d), 7.46-7.36 (2H, m), 7.35-7.27 (2H, m), 7.27-7.07 (3H, m), 5.02 (1H, d), 4.36 (1H, d), 4.15-4.05 (1H, m), 4.02-3.80 (2H, m), 3.27 (3H, s), 3.20-3.02 (1H, m), 2.78-2.68 (1H, m), 2.52-2.26 (3H, m), 2.08-1.89 (5H, m)
242	^{1}H NMR δ (ppm) ($CDCl_3$): 8.29 (1H, d), 7.83 (1H, d), 7.56-7.14 (7H, m), 7.10 (1H, br s), 7.02-6.83 (2H, m), 6.79 (1H, d), 5.17-4.70 (1H, m), 4.56-4.34 (1H, m), 4.30-4.11 (1H, m), 4.00-3.73 (2H, m), 3.63 (3H, s), 3.34-3.02 (6H, m), 2.56-2.18 (4H, m), 2.05-1.76 (2H, m)
243	^{1}H NMR δ (ppm) ($CDCl_3$): 8.29 (1H, d), 7.84 (1H, d), 7.57 (1H, br s), 7.54-7.44 (2H, m), 7.40 (1H, t), 7.36-7.20 (4H, m), 7.19-7.11 (1H, m), 7.05 (2H, t), 4.84 (1H, d), 4.53 (1H, d), 4.13 (1H, d), 3.96 (1H, q), 3.74-3.65 (1H, m), 3.42 (1H, d), 3.31-3.13 (5H, m), 2.60-2.23 (4H, m), 2.06-1.90 (1H, m), 1.84-1.74 (1H, m)
245	^{1}H NMR δ (ppm) ($CDCl_3$): 8.19 (1H, d), 7.87 (1H, d), 7.67 (1H, br s), 7.45 (1H, t), 7.40 (1H, t), 7.35 (2H, d), 7.25-7.15 (2H, m), 5.57-5.01 (3H, m), 4.26-4.13 (1H, m), 3.91-3.78 (1H, m), 3.69-3.55 (1H, m), 3.18-2.91 (3H, m), 2.84-2.56 (2H, m), 2.50-2.39 (1H, m), 2.26-2.12 (1H, m), 2.09-1.91 (2H, m), 1.69-1.58 (6H, m)
246	^{1}H NMR δ (ppm) ($CDCl_3$): 8.29 (1H, d), 7.84 (1H, d), 7.43 (1H, t), 7.39 (1H, t), 7.35-7.27 (4H, m), 7.00 (1H, s), 5.23 (2H, s), 3.93-3.84 (1H, m), 3.82-3.69 (2H, m), 3.56-3.49 (1H, m), 3.34-3.19 (2H, m), 2.61-2.42 (2H, m), 2.24-2.09 (3H, m), 1.97-1.87 (1H, m), 0.92 (3H, t)
248	^{1}H NMR δ (ppm) ($CDCl_3$): 8.32 (1H, d), 7.82 (1H, d), 7.46-7.31 (3H, m), 7.30-7.20 (3H, m), 7.07 (1H, br s), 3.97 (1H, q), 3.76 (2H, t), 3.64 (1H, q), 2.67-2.57 (1H, m), 2.45 (2H, t), 2.16-2.09 (1H, m), 1.96-1.63 (5H, m)
250	^{1}H NMR δ (ppm) ($CDCl_3$): 8.43 (1H, d), 8.28 (1H, d), 7.81 (1H, d), 7.49 (1H, d), 7.41 (1H, t), 7.36 (1H, t), 7.28 (1H, s), 7.12 (1H, br s), 4.02-3.90 (2H, m), 3.81 (1H, q), 3.73-3.63 (1H, m), 2.99-2.90 (1H, m), 2.40 (2H, t), 2.13-2.05 (1H, m), 1.94-1.82 (2H, m), 1.76 (3H, br s)
251	^{1}H NMR δ (ppm) ($CDCl_3$): 8.28 (1H, d), 7.81 (1H, d), 7.42 (1H, t), 7.36 (1H, t), 7.34-7.24 (4H, m), 7.02 (1H, br s), 3.93 (1H, q), 3.81-3.61 (3H, m), 2.63-2.53 (1H, m), 2.42 (2H, t), 2.13-2.02 (1H, m), 1.96-1.66 (5H, m)
252	^{1}H NMR δ (ppm) ($CDCl_3$): 8.37 (1H, d), 8.33 (1H, d), 7.81 (1H, d), 7.42 (1H, t), 7.37 (1H, t), 7.32 (1H, s), 7.23-7.13 (2H, m), 4.05-3.91 (2H, m), 3.82-3.68 (2H, m), 3.00 (1H, q), 2.47 (2H, t), 2.15-2.06 (1H, m), 1.98-1.84 (2H, m), 1.77 (3H, br s)

Biological Examples

Example 1 – *in vitro* assays

Example 1.1 Cell based assay: Calcium mobilization assay without probenecid

[00298] The following assay can be used for determination of GPR43 activation. The assay measures intracellular calcium release induced by activation of GPR43. On day 1, GPR43 stably expressing cells were detached with mild trypsinization (Trypsin, 0.25% with EDTA 4Na, 5x diluted in PBS) centrifuged at 1000 rpm for 5 min and resuspended at 6.000 cells/25 µL medium (DMEM supplemented with 10% FBS, 10µg/mL puromycin and 1% Pen/Strep). The cells were distributed in poly-D-lysine coated 384 well plates (black with clear bottom, 25 µL/well) and incubated overnight at 37°C 10% CO_2. On day 2, 25 µL of a fluorescent Ca^{2+} indicator (Calcium 4 assay; Molecular Devices) was added on top of the cells and incubated for 2h at 37°C. Subsequently, compounds at increasing concentration (10 µL/well) were added to the plate and incubated for 15 min at 37°C. Finally the cells were triggered with sodium acetate at EC_{80} concentration (concentration which gives 80% of the activity of the GPR43) and the Ca-flux was measured simultaneously to the trigger injection on a fluorescence plate reader (FlexStation3), this measures the

antagonist activity of the compounds. To measure agonist activity of the compounds, compound was added to the well and the Ca-flux was measured simultaneously to the injection of compound.

[00299] TABLE III: GPR43 assay without probenicid IC_{50} (nM) of selected Compounds of the Invention.

na: not active

* > 1001 nM

** 501-1000 nM

*** 101-500 nM

**** 0.01- 100 nM

Cpd #	GPR43
1	***
2	*
3	*
4	*
5	*
6	**
7	***
8	**
9	*
10	*
11	*
12	*
13	***
14	**
15	*
16	*
17	*
18	*
20	*
21	*
22	*
23	*
24	*
25	*
26	*
27	*
28	*
29	*
30	*
31	**
32	*
33	**
34	*
35	***
36	*
37	**
38	na
42	*

Cpd #	GPR43
43	*
44	*
45	*
46	*
47	***
48	**
49	***
50	*
51	*
52	*
53	***
54	**
55	*
56	*
57	*
58	***
59	*
60	*
61	****
62	**
63	***
64	***
65	*
66	***
67	****
68	***
69	*
70	***
71	*
72	**
74	*
75	***
77	*
78	***
79	*
80	*
81a	na
82	***

Cpd #	GPR43
83	*
84	***
85	*
86	***
87	**
88	***
89	****
90	****
91	*
92	*

Cpd #	GPR43
93	*
94	*
95	**
96	***
97	***
98	***
100	****
101	***
102	**

Example 1.2

Cell based assay: Calcium mobilization assay with probenecid.

[00300] The following assay can be used for determination of GPR43 activation. The assay measures intracellular calcium release induced by activation of GPR43. On day 1, GPR43 stably expressing cells were detached with mild trypsinization (Trypsin, 0.25% with EDTA 4Na,5x diluted in PBS) centrifuged at 1000 rpm for 5 min and resuspended at 6.000 cells/25 µL medium (DMEM supplemented with 10% FBS, 10µg/mL puromycin and 1% Pen/Strep). The cells were distributed in poly-D-lysine coated 384 well plates (black with clear bottom, 25 µL/well) and incubated overnight at 37°C 10% CO_2.

[00301] On day 2, 25 µL of a fluorescent Ca^{2+} indicator (Calcium 4 assay; Molecular Devices) supplemented with 2.5 mM probenecid was added on top of the cells and incubated for 2h at 37°C. Subsequently, compounds at increasing concentration (10 µL/well) were added to the plate and incubated for 15 min at 37°C.

[00302] Finally the cells were triggered with sodium acetate at EC_{80} concentration (concentration which gives 80% of the activity of the GPR43) and the Ca^{2+}-flux was measured simultaneously to the trigger injection on a fluorescence plate reader (FlexStation3), this measures the antagonist activity of the compounds. To measure agonist activity of the compounds, compound was added to the well and the Ca^{2+}-flux was measured simultaneously to the injection of compound.

[00303] TABLE IV: GPR43 assay with probenicid__ IC50_(nM) of selected Compounds of the Invention.

na = not active

* > 1001 nM

** 501-1000 nM

*** 101-500 nM

**** 0.01-100 nM

Cpd #	GPR43
2	*
4	na
5	na
6	*
7	***
9	na
10	na
11	na

Cpd #	GPR43
12	na
15	na
16	na
17	na
18	na
19	*
20	na
21	na

Cpd #	GPR43
22	*
23	na
24	na
25	na
26	na
27	*
28	na
29	na
30	na
31	*
32	*
33	*
34	na
35	***
36	*
37	*
38	na
39	*
41	*
42	na
43	*
44	*
45	*
46	*
48	**
49	***
50	*
51	*
52	na
53	***
54	*
55	*
56	*
57	*
58	***
59	*
60	**
61	****
63	***
66	**
67	*
68	***
69	**
71	**
72	***
73	**
74	*
75	***
76	*
77	***
78	***
79	*
80	*
81	***

Cpd #	GPR43
82	***
83	*
84	***
85	***
86	****
87	**
88	***
89	****
90	***
91	*
94	*
95	*
96	***
97	**
98	***
99	***
100	****
101	***
102	***
103	***
104	**
105	*
106	*
107	*
108	*
109	***
110	***
111	**
112	**
113	****
114	**
115	****
116	*
117	*
118	*
119	*
120	*
121	*
122	***
123	***
124	**
125	*
126	*
127	*
128	****
129	****
130	****
131	****
132	****
133	****
134	****
135	**
136	***
137	****

Cpd #	GPR43
138	*
139	*
140	*
141	*
142	*
143	*
144	****
145	***
146	****
147	**
148	**
149	*
150	***
151	***
152	***
153	***
154	*
155	****
156	***
157	***
158	***
159	**
160	***
161	*
162	**
163	***
164	***
165	**
166	***
167	*
168	*
169	****
170	***
171	***
172	***
173	***
174	***
175	****
176	***
177	*
178	*
179	*
180	**
181	****
182	****
183	****
184	***
185	**
186	***
187	****
188	**
189	****
190	****
191	****

Cpd #	GPR43
192	****
193	***
194	****
195	****
196	****
197	**
198	****
199	***
200	*
201	*
202	*
203	****
204	****
205	*
206	****
207	****
208	****
209	***
210	*
211	****
213	*
215	*
216	***
217	***
218	***
219	***
220	**
221	***
222	*
223	*
224	*
225	**
226	*
227	**
228	****
229	****
230	***
231	****
232	***
233	***
234	****
235	*
236	*
237	*
238	*
239	*
240	***
241	**
242	**
243	**
244	*
245	***
246	***
247	*

Cpd #	GPR43
248	***
249	*
250	**

Cpd #	GPR43
251	***
252	**
253	*

Example 1.3 Binding assay: GTPγS assay

[00304] The [35S]GTPγS binding assay measures the level of G protein activation following agonist occupation of a GPCR, by determining the binding of the non-hydrolysable analog [35S]GTPγS to Gα subunits.

[00305] The assay was performed in a 96 well plate where the following reagents were added. First 50 µL compound was added into the assay plate, followed by addition of 20 µL Sodium acetate at EC80 concentration (concentration which give 80% of the activity of the GPR43). In a last step, 30 µL of a mixture consisting of membranes-GTPγS-SpA beads was added (mixture consists of 10 µg/well membranes derived from stable cell line over expressing GPR43 (membranes were pre-incubated with 3 µM GDP for 15 minutes at 4°C), 0.1 nM [35S]GTPγS (Perkin Elmer, NEG030) and 0.5 mg/well PVT-WGA SpA beads (perkin Elmer, RPNQ0001)). All components were diluted in assay buffer containing 20mM Hepes pH 7.4; 10mM $MgCl_2$; 250mM NaCl and 37.5 µg/mL saponin. Reactions were incubated for 240 minutes at room temperature followed by centrifugation at 2000 rpm for 15 minutes. Plates were read on a Topcount immediately after centrifugation (readout time, 1 minute/well).

[00306] TABLE V: GTPγS assay IC_{50}(nM) of selected Compounds of the invention.

* > 501 nM

** 101-500 nM

*** 51-100 nM

Cpd #	GTPγS IC_{50}
67	**
115	**
128	**
134	*
144	***
146	**
155	*
169	*
182	**
187	**
191	***
194	*
195	**
198	**

Example 2. Cellular assays

Example 2.1 Neutrophil migration assay

[00307] G Protein-Coupled Receptor 43 (GPR43) was described as an essential player in the process of neutrophil recruitment during intestinal inflammation. It has been shown that sodium acetate and sodium propionate, two natural ligands of GPR43, act as chemoattractants for neutrophils and thus induce neutrophil migration (Brown, A. J., S. M. Goldsworthy, et al. (2003). "The Orphan G Protein-coupled Receptors GPR41 and GPR43 Are Activated by Propionate and Other Short Chain Carboxylic Acids" J. Biol. Chem. 278(13): 11312-11319.)

[00308] The effect of agonists or antagonists for GPR43 can therefore be assayed in a neutrophil migration test. In the neutrophil migration assay, neutrophils, isolated from buffy coats from human volunteers, are treated with a compound for 30 minutes. Subsequently, the neutrophils are transferred to the upper wells of a Corning HTS transwell 96 permeable support system, of which the lower wells are filled with a sodium acetate solution. After 1 h of incubation, migration of the neutrophils towards the sodium acetate can be quantified by measuring the ATP-content of the lower wells using the ATPlite luminescence ATP detection assay system (Perkin Elmer, Cat. N°.: 436110).

1.1.1 *Neutrophil migration assay protocol*

[00309] The ACD buffer consists of 140 mM citric acid, 200 mM sodium citrate and 220 mM dextrose. The 6% dextran/0.9% NaCl solution consists of 15 g dextran T2000 and 2.25 g NaCl dissolved in 250 mL H_2O.

[00310] The chemotaxis buffer, freshly made for each experiment, consists of RPMI 1640 medium, supplemented with 10 mM HEPES.

Isolation of neutrophils from human buffy coat

[00311] A human buffy coat is diluted with an equal volume of ice cold DPBS. 20 mL of the diluted buffy coat is gently mixed with 4 mL of ACD buffer. Then, 12 mL of the 6% dextran/0.9% NaCl solution is added to the mixture and the samples are inverted gently up to 20 times. The total volume is transferred to a new recipient and incubated at room temperature for 1 h for complete separation of the two phases to occur. The yellowish supernatant is then transferred to a clean centrifugation tube and centrifuged for 12 minutes at 1300 rpm and 4°C. After centrifugation, the supernatant is discarded and the remaining cell pellet is rapidly resuspended in 12 mL of ice-cold H_2O for red blood cell lysis to occur. After 20 seconds, 4 mL of ice-cold 0.6 M KCl is added. Samples are mixed carefully and centrifuged for 6 minutes at 1300 rpm, 4°C. The supernatant is discarded and the red blood cell lysis procedure is repeated one more time. Subsequently, the cell pellet is resuspended in 4 mL of DPBS and layered over 5 mL of Lymphoprep (Nycomed Pharma, Cat. N°.: 1114545) in a 15 mL centrifuge tube. After centrifugation for 12 min at 1300 rpm, 4°C, the supernatant is removed and the cell pellet, containing the neutrophils, is resuspended in 25 mL chemotaxis buffer.

Migration assay

[00312] A cell suspension of $8.9x10^6$ cells per milliliter is prepared. 20 µL of compound solution in chemotaxis buffer is added to 180 µL cell suspension. The mixture is incubated at 37°C for 30 minutes with Intermediate resuspension of the cells after 15 minutes. Following this, 70 µL cell suspension is transferred to the upper compartment of a Corning HTS transwell 96 permeable support system with 5.0 µm pore size

polycarbonate membrane (Corning, Cat.N°.: 3387). The receiver well of the transwell system is then filled with 200 µL chemotaxis buffer containing compound and chemotactic agent (sodium acetate). After incubation at 37°C in 5% CO_2 for 1 h, the upper plate of the transwell system is removed and the cell suspension in the receiver plate is transferred to a 96-well V-bottom plate. 50 µL of DPBS is added to the receiver plate to prevent remaining cells from drying out. The V-bottom plate is centrifuged for 6 minutes at 1500 rpm. The supernatant is removed and the cells are resuspended in 50 µL DPBS. The cells are then transferred back to the receiver plate of the transwell system. After this, 100 µL ATPlite solution (Perkin Elmer, Cat. N°: 436110) is added to the cells. The plate is incubated for 10 minutes in the dark, while shaking. 170 µL of cell lysate is then transferred to a white 96-well plate and luminescence is measured. The detected luminescent signal is considered as linearely related to the number of migrated cells.

[00313] **TABLE VI: human neutrophil migration inhibition**

* > 1001 nM

** 501-1000 nM

*** 101-500 nM

**** 0.01-100 nM

Cpd #	EC_{50} (nM)
61	****
89	****
90	****
96	****
103	**
110	***
113	****
115	****
122	***
123	****
128	****
130	***
131	***
132	***
134	****
137	****
144	****
146	****
155	****
157	****
169	***
191	****

Example 3: ADME, PK and Safety Models

Example 3.1 Aqueous Solubility

[00314] Starting from a 10mM stock in DMSO, a serial dilution of the compound is prepared in DMSO. The dilution series is transferred to a 96 NUNC Maxisorb plate F-bottom and 0.1M phosphate buffer pH 7.4 or 0.1M citrate buffer pH3.0 at room temperature is added.

[00315] The final concentrations range from 18.75 to 300 µM in 5 equal dilution steps. The final DMSO concentration does not exceed 3%.

[00316] 200µM Pyrene is added to the corner points of each 96 well plate and serves as a reference point for calibration of Z-axis on the microscope.

[00317] The assay plates are sealed and incubated for 1 h at 37°C while shaking at 230rpm. The plates are then scanned under a white light microscope, yielding individual pictures of the precipitate per concentration. The precipitate is analyzed and converted into a number by a custom-developed software tool. The first concentration at which the compound appears completely dissolved is the concentration reported, however the true concentration lies somewhere between this concentration and one dilution step higher.

[00318] Solubility values are reported in µM and in µg/mL.

Example 3.2 Thermodynamic solubility

[00319] Two individual solutions of 2 mg/mL of compound are prepared in a 0.1 M phosphate buffer pH 7.4 or a 0.1 M citrate buffer pH 3.0 at room temperature in a 2mL glass vial.

[00320] After addition of a magnetic stir, the samples are stirred at room temperature for 24 h.

[00321] After 24 h, the vials are centrifuged 10 min at 1400 rpm. The supernatant of the sample is then transferred to a MultiscreenR Solubility Plate (Millipore, MSSLBPC50) and filtered (10-12" Hg) with the aid of a vacuum manifold into a clean Greiner polypropylene V-bottom 96 well plate. Per sample, two dilutions (factor 10 and 100) are made in DMSO. Other dilutions can be made if the acquired peak area is not within the standard curve.

[00322] A 10mM DMSO stock, made from dry matter, is used to make a 200µg/mL working stock. The standard curve for the compound is prepared in DMSO starting from the 200µg/mL working stock. Eight concentrations and two quality control samples (QC) are made in 2mL tubes. The first 3 concentrations (50, 35 and 15µg/mL) and the first QC sample (20µg/mL) are made starting with the 200µg/mL working stock. The 4^{th} concentration (5µg/mL) is made with the 50µg/mL solution and the 5^{th} concentration (1µg/mL) with the 15µg/mL. The last three concentrations (0.2, 0.1 and 0.05µg/mL) are made with the 1µg/mL solution. The second QC sample (0.5µg/mL) is made with the first QC sample.

[00323] Of every step of the dilution series, quality control and sample dilutions, a volume is transferred to a 96-well Deepwell plate. The samples are injected on a LC-MS/MS system (API2000 from Applied Biosystems).

[00324] The samples are analyzed on LC-MS/MS with a flow rate of 0.5mL/min. Solvent A is 0.1% Formic Acid in water and solvent B is 0.1% Formic Acid in methanol . The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 minutes and ranges from 10% B to 100% B.

[00325] The thermodynamic solubility samples are analyzed with the aid of QuanLynx software. For the standard curve a linear or quadratic curve can be used in the analysis. Samples of the standard curve that

have more than 15% deviation are excluded; the lowest concentrations of the curve may vary up to 20%. Peak areas of the samples are plotted against the standard curve to obtain the solubility of the compound.

[00326] Solubility values are reported in μM or μg/mL.

Example 3.3 Microsomal stability

[00327] A 10 mM stock solution of compound in DMSO is 1,668 fold diluted in a 105 mM phosphate buffer pH 7.4. Of this compound dilution, 50 μL is transferred in two 96 assay plates: one for time point 0 min (T0 plate) and one for time point 30 min (T30 plate) and pre-warmed at 37°C.

[00328] In the time zero reference sample (T0 plate), 100 μL MeOH (1:1) is added to the wells. In each assay plate (T0 and T30 min), 50 μL of microsomal mix is then added.

[00329] Final reaction concentrations are: 3 μM compound, 0.5 mg/mL microsomes, 0.4 U/mL GDPDH, 3.3 mM $MgCl_2$, 3.3 mM glucose-6-phosphate and 1.3 mM $NADP^+$.

[00330] The T30 plate is incubated at 37°C, 300 rpm and after 30 minutes of incubation the reaction is stopped with MeOH (1:1). The samples are mixed, centrifuged and the supernatant is harvested for analysis on LC-MS/MS (API2000 from Applied Biosystems).

[00331] The samples are analyzed on LC-MS/MS with a flow rate of 0.5mL/min. Solvent A is 0.1% Formic Acid in water and solvent B is 0.1% Formic Acid in methanol. The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 minutes and ranges from 10% B to 100% B.Peak area from the parent compound at time 0 is considered to be 100% remaining. The percentage remaining after 30 minutes incubation is calculated from time 0. The solubility of the compound in the final test concentration in buffer is inspected by microscope and results are also reported.

Example 3.4 Hepatocyte stability.

[00332] Test compounds (1 μM initial concentration, n=2) are incubated in Williams' Medium E, containing 4 mM L-gutamine and 2 mM magnesium sulphate, with pooled cryopreserved hepatocytes (Celsis International) in suspension at cell densities of 0.25-0.5 million viable cells/mL. The incubations are performed at 37°C in a shaking water bath with 100 μL samples taken from the incubation at 0, 10, 20, 45 and 90 minutes, and reactions terminated by addition of 100 μL of acetonitrile containing carbamazepine as analytical internal standard. Samples are centrifuged and the supernatant fractions analysed by LC-MS/MS. The instrument responses (*i.e.* peak heights) are referenced to the zero time-point samples (as 100%) in order to determine the percentage of compound remaining. Ln plots of the % remaining for each compound are used to determine the half-life for the hepatocyte incubations. Half-life values are calculated from the relationship: $T_{1/2}$ (min) = -0.693/λ, where λ is the slope of the Ln concentration *vs* time curve. Standard compounds testosterone, midazolam, and 4-methylumbelliferone are included in the assay design.

Example 3.5 Plasma Protein Binding (Equilibrium Dialysis)

[00333] A 10mM stock solution of the compound in DMSO is diluted with a factor 10 in DMSO. This solution is further diluted in freshly thawed human, rat, mouse or dog plasma (BioReclamation INC) with a final concentration of 5μM and final DMSO concentration of 0.5%.

[00334] A Pierce Red Device plate with inserts (ThermoScientific) is prepared and filled with 450μL PBS in the buffer chamber and 300μL of the spiked plasma in the plasma chamber. The plate is incubated for 4 h at 37°C while shaking at 100rpm. After incubation, 120μL of both chambers is transferred to 480μL methanol in a 96-well round bottom, PP deep-well plates (Nunc) and sealed with an aluminum foil lid. The samples are mixed and immediately centrifuged 30 min at 1400 rcf at 4°C and the supernatant is transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LC-MS/MS (API2000 from Applied Biosystems).

[00335] The samples are analyzed on LC-MS/MS with a flow rate of 0.5mL/min. Solvent A is 0.1% formic acid in water and solvent B is 0.1% formic acid in methanol. The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 minutes and ranges from 10% B to 100% B.

[00336] Peak area from the compound in the buffer chamber and the plasma chamber are considered to be 100% compound. The percentage bound to plasma is derived from these results and is reported as percentage bound to plasma.

[00337] The solubility of the compound in the final test concentration in PBS is inspected by microscope to indicate whether precipitation is observed or not.

Example 3.6 Caco2 Permeability

[00338] Bi-directional Caco-2 assays are performed as described below. Caco-2 cells are obtained from European Collection of Cell Cultures (ECACC, cat 86010202) and used after a 21 day cell culture in 24-well Transwell plates (Corning, cell growth area: 0.33 cm^2, Membrane pore size: 0.4 μM, membrane diameter: 6.5 mm)..

[00339] $2x10^5$ cells/well are seeded in plating medium consisting of DMEM + GlutaMAX™-I + 1% NEAA + 10% FBS (FetalClone II) + 1% Pen/Strep. The medium is changed every 2 – 3 days.

[00340] Test and reference compounds (propranolol and rhodamine123 or vinblastine, all purchased from Sigma) are prepared in Hanks' Balanced Salt Solution containing 25 mM HEPES (pH7.4) and added to either the apical (125μL) or basolateral (600μL) chambers of the Transwell plate assembly at a concentration of 10 μM with a final DMSO concentration of 0.25%.

[00341] 50μM Lucifer Yellow (Sigma) is added to the donor buffer in all wells to assess integrity of the cell layers by monitoring Lucifer Yellow permeation. As Lucifer Yellow (LY) cannot freely permeate lipophilic barriers, a high degree of LY transport indicates poor integrity of the cell layer.

[00342] After a 1 h incubation at 37°C while shaking at an orbital shaker at 150rpm, 70μL aliquots are taken from both apical (A) and basal (B) chambers and added to 100μL 50:50 acetonitrile:water solution containing analytical internal standard (0.5μM carbamazepine) in a 96 well plate.

[00343] Lucifer yellow is measured with a Spectramax Gemini XS (Ex 426nm and Em 538nm) in a clean 96 well plate containing 150µL of liquid from basolateral and apical side.

[00344] Concentrations of compound in the samples are measured by high performance liquid-chromatography/mass spectroscopy (LC-MS/MS).

[00345] Apparent permeability (P_{app}) values are calculated from the relationship:

$P_{app} = [compound]_{acceptor\ final} \times V_{acceptor} / ([compound]_{donor\ initial} \times V_{donor}) / T_{inc} \times V_{donor}$ / surface area $\times 60 \times 10^{-6}$ cm/s

V = chamber volume

T_{inc} = incubation time.

Surface area = $0.33cm^2$

[00346] The Efflux ratios, as an indication of active efflux from the apical cell surface, are calculated using the ratio of P_{app} B>A/ P_{app} A>B.

[00347] The following assay acceptance criteria are used:

Propranolol: P_{app} (A>B) value $\geq 20(\times 10^{-6}$ cm/s)

Rhodamine 123 or Vinblastine: P_{app} (A>B) value < 5 ($\times 10^{-6}$ cm/s) with Efflux ratio ≥ 5.

Lucifer yellow permeability: ≤ 100 nm/s

Example 3.7 Liability for QT prolongation

[00348] Potential for QT prolongation is assessed in the hERG manual patch clamp assay.

3.7.1 Conventional whole-cell patch-clamp

[00349] Whole-cell patch-clamp recordings are performed using an EPC10 amplifier controlled by Pulse v8.77 software (HEKA). Series resistance is typically less than 10 MΩ and compensated by greater than 60%, recordings are not leak subtracted. Electrodes are manufactured from GC150TF pipette glass (Harvard).

[00350] The external bathing solution contains: 135 mM NaCl, 5 mM KCl, 1.8 mM $CaCl_2$, 5 mM Glucose, 10 mM HEPES, pH 7.4.

[00351] The internal patch pipette solution contains: 100mM Kgluconate, 20 mM KCl, 1mM $CaCl_2$, 1 mM $MgCl_2$, 5mM Na_2ATP, 2mM Glutathione, 11 mM EGTA, 10 mM HEPES, pH 7.2.

[00352] Drugs are perfused using a Biologic MEV-9/EVH-9 rapid perfusion system.

[00353] All recordings are performed on HEK293 cells stably expressing hERG channels. Cells are cultured on 12 mm round coverslips (German glass, Bellco) anchored in the recording chamber using two platinum rods (Goodfellow). hERG currents are evoked using an activating pulse to +40 mV for 1000 ms followed by a tail current pulse to –50 mV for 2000 ms, holding potential is -80 mV. Pulses are applied every 20s and all experiments are performed at room temperature.

3.7.2 Data Analysis

[00354] IC_{50} values are calculated for each compound tested. The fold difference between the IC_{50} in the manual hERG patch clamp and the unbound IC_{50} in the whole blood assay is calculated.

[00355] For the concentration response curves, peak tail current amplitude is measured during the voltage step to -50 mV. Curve-fitting of concentration-response data is performed using the equation:

$$y = a + [(b - a)/ (1 + 10^{\wedge} ((\log c - x) d)]$$

[00356] where a is minimum response, b is maximum response and d is Hill slope, this equation can be used to calculate both IC_{50} (where y = 50 and c is the IC_{50} value) and IC_{20} (where y = 20 and c is the IC_{20} value). GraphPad® Prism® (Graphpad® Software Inc.) software is used for all curve fitting. A difference of 100 fold or greater indicates a low potential for QT prolongation.

Example 3.8 Pharmacokinetic study

3.8.1 Single dose pharmacokinetic study in rats

[00357] Compounds are formulated in PEG200/physiological saline mixtures for the intravenous route and in PEG400/0.5% methylcellulose (10/90 v/v) for the oral route. Test compounds are orally dosed as a single esophageal gavage at 5-10 mg/kg and intravenously dosed as a bolus via the caudal vein at 1 mg/kg to male Sprague-Dawley rats. Each group consists of 3 rats. Blood samples are collected either via the jugular vein using cannulated rats or at the retro-orbital sinus with lithium heparin as anti-coagulant at the time points in the following range: 0.05 to 8 h (intravenous route), and 0.25 to 6 or 24 h (oral route). Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

3.8.2 Multiple dose pharmacokinetic study in rats

[00358] Compounds are formulated in PEG400/0.5% methylcellulose (10/90 v/v) for the oral route. Test compounds are orally dosed as an esophageal daily gavage at 30 or 300 mg/kg to male Sprague-Dawley rats for 14 days. Each group consists of 3 rats. Blood samples are collected via the tail vein with lithium heparin as anti-coagulant at the following time points on day 1, 7 and 14: 0.25, 1, 4, 8 and 24 h. In addition, on day 2 blood samples are taken at 0.25, 1 and 4 h and at day 4 and 11 at 0.25 h. Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

3.8.3 Quantification of compound levels in plasma

[00359] Plasma concentrations of each test compound are determined by an LC-MS/MS method in which the mass spectrometer is operated in positive or negative electrospray mode.

3.8.4 Determination of pharmacokinetic parameters

[00360] Pharmacokinetic parameters are calculated using Winnonlin® (Pharsight®, US).

Example 3.9 7-Day rat toxicity study

[00361] A 7-day oral toxicity study with test compounds is performed in Sprague-Dawley male rats to assess their toxic potential and toxicokinetics, at daily doses of 100, 300 and 1000 mg/kg/day, by gavage, at the constant dosage-volume of 10 mL/kg/day.

[00362] The test compounds are formulated in PEG400/0.5% methylcellulose (10/90, v/v). Each group includes 6 principal male rats as well as 3 satellite animals for toxicokinetics. A fourth group is given PEG400/0.5% methylcellulose (10/90, v/v) only, at the same frequency, dosage volume and by the same route of administration, and acts as the vehicle control group.

[00363] The goal of the study is to determine the lowest dose that results in no adverse events being identified (no observable adverse effect level - NOAEL).

Example 3.10 CD11b whole blood assay

[00364] G Protein-Coupled Receptor 43 (GPR43) expression has been shown in polymorphonuclear leukocytes (PMN) and purified neutrophils ((Le Pouls et al., 2003, The Journal of Biological Chemistry, 278, 28, 25481-25489; Brown et al., 2003, The Journal of Biological Chemistry, 278, 13, 11312-11319; Stoddart et al., 2008, Pharmacological Reviews, 60, 405-417).

[00365] The effect of agonists or antagonists for GPR43 is therefore assayed for neutrophil activation measured by CD11b expression level at the surface of neutrophil.

[00366] Human blood is collected by venipuncture from human volunteers, who gave informed consent, in acid-citrate-dextrose (ACD) vacutubes, mixed well and processed as soon as possible, the latest within 90 mn after blood collection.

[00367] Blood is diluted 1/1 in RPMI1640. Diluted blood is treated simultaneously with a compound in DMSO solution or with DMSO (max. 0.3% of DMSO), and with 20µg/mL cytochalasin B, TNFalpha 2ng/mL. Blood is incubated at 37°C for 15 mn without shaking. Then GPR43 agonist (sodium acetate) is added to blood. Blood is gently mixed and incubated at 37°C for 30 mn without shaking.

[00368] Neutrophil surface expression of CD45, CD66b and CD11b markers is determined by flow cytometry. Unspecific binding of antibodies was blocked by addition of 2µg/sample of normal mouse IgG (Invitrogen, Cat. No. 10400C) and incubation for 10 mn at +4°C in the dark. Then 2 µL of CD45 V450 antibody (ref. 560367, BD Biosciences), 2.5 µL of CD11b APC Mouse Anti-Human CD11b/Mac-1 antibody (activation epitope; ref 17-0113-42, eBiosciences) and 10µL of CD66b FITC antibody (ref. 555724. BD Biosciences) are added to blood at the same time and samples incubated for 30 mn at +4°C in the dark. Red blood cells are lysed and samples fixed by addition of RBC lysing Buffer (1x solution from BD FACS™ Lysing Solution 10X, cat. 349202, BD Pharmigen) and incubated for 10 mn at room temperature in the dark. The cells are centrifuged, 550g for 10 mn at +4°C and washed once with PBS (550g for 5 mn at +4°C). The cells are resuspended in cold 300 µL wash/staining buffer (PBS + 2% FBS), transferred to polystyrene 5 mL tube and placed on ice protected from light until analysed with FACScan/CytekDev XDP8 and FlowJo Collector's, FlowJo V7.6 software. Neutrophils are gated and selected according to morphological characteristics using FSC and SSC parameters and immunophenotype

as CD45high+CD66b high+CD11b(AE) + cells. Cellular expression of CD11b activation epitope is determined by determination of MFI units (Mean Fluorescence Intensity).

[00369] REFERENCES

- Prentki *et al.*, 2008, Endocrine Review, 29(6), 647-676
- Sellin *et al.*, 1999, News. Physiol. Sci, 14, 58-64
- Le Pouls *et al.*, 2003, The Journal of Biological Chemistry, 278, 28, 25481-25489
- Brown *et al.*, 2003, The Journal of Biological Chemistry, 278, 13, 11312-11319
- Stoddart *et al.*, 2008, Pharmacological Reviews, 60, 405-417
- Dass *et al.*, 2007, Neurogastroenterl. Motil., 19:66-74
- Karaki *et al.*, 2006, Cell Tissue Res., 324/353-360
- Maslowski *et al.*, 2009, Nature, 461, 1282-1287
- Sina *et al.*, 2009, The Journal of Immunology, 183:7514-7522
- Bjursel *et al.*, 2010, Am. J. Physiol. Endocrinol. Metab. in press
- Hatanaka *et al.*, 2010, Cancer Sci, 101: 54-59
- Bjursel *et al.*, 2010, Am. J. Physiol. Endocronl. Metab.,in press
- Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985
- Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania
- T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991
- EP101004
- Lee *et al.*, Tetrahedron, 1995, 4909–4922
- Turner *et al.* A., J. Org. Chem. 1983, 3401-3408
- WO2009/104155 A1
- Rao *et al.*, Tetrahedron Letters, 1983 5023 – 5024
- McGinnity *et al.* Drug Metabolism and Disposition **2008**, 32, *11*, 1247

[00370] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[00371] From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

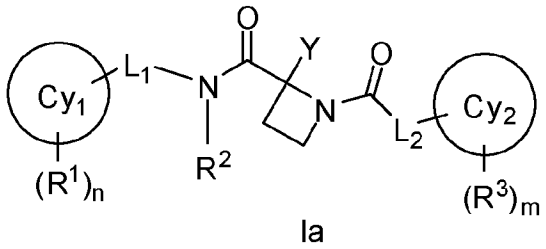
[00372] It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the *in vitro* biochemical and cellular assays.

[00373] At least some of the chemical names of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

[00374] Chemical structures shown herein were prepared using either ChemDraw® or ISIS® /DRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

WHAT IS CLAIMED IS:

1. A compound according to Formula Ia:



Ia

,

wherein

L_1 is a single bond, or CR^aR^b;

L_2 is a single bond, O, NR^e or CR^cR^d;

each of R^a, R^b, R^c, and R^d is independently selected from H, and C_{1-4} alkyl; or

R^a and R^b together with the carbon to which they are attached may form a C_{3-7} cycloalkyl; or

R^c and R^d together with the carbon to which they are attached may form a C_{3-7} cycloalkyl;

R^e is C_{1-4} alkyl;

Y is

- C_{1-4} alkyl optionally substituted with one or more groups independently selected from fluoro, OH, and phenyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, halo and cyano), or
- C_{1-4} alkenyl comprising 1 double bond;

each of Cy_1 and Cy_2 is independently C_{6-10} aryl, or 5-10 membered heteroaryl;

each R^1 is independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), and C_{1-4} alkoxy (optionally substituted with one or more halo);

R^2 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^{2a} groups,
- C_{3-7} cycloalkyl optionally substituted with one or more independently selected R^{2a} groups,

R^{2a} is

- halo,
- C_{1-6} alkoxy,
- OH,
- $C(=O)R^4$,
- $S(O)_2R^4$,
- CN,
- $NHC(=O)R^5$,
- $NHSO_2R^5$,
- 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-4} alkyl, and oxo), or

- 5-6 membered heteroaryl (optionally substituted with one or more groups independently selected from halo, OH, C_{1-4} alkoxy and C_{1-4} alkyl);

R^3 is selected from halo, C_{1-6} alkyl (optionally substituted with one or more halo), C_{1-6} alkoxy (optionally substituted with one or more halo, or phenyl), C_{1-6} thioalkoxy, phenyl (optionally substituted with one or more groups independently selected from halo, C_{1-4} alkyl (optionally substituted with one or more halo), C_{1-4} alkoxy, C(=O)-C_{1-4} alkoxy and CN);

R^4 is

- -OH,
- -C_{1-6} alkoxy,
- -*N*-linked 5-7 membered heterocycloalkyl (optionally substituted with one or more groups independently selected from C_{1-6} alkyl, and oxo),
- -$NR^{4a}R^{4b}$, or
- -$NHSO_2R^{4c}$;

Each of R^{4a} and R^{4b} is independently H, C_{1-4} alkyl (optionally substituted with phenyl (optionally substituted with one or more groups independently selected from halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy)), or C_{3-7} cycloalkyl;

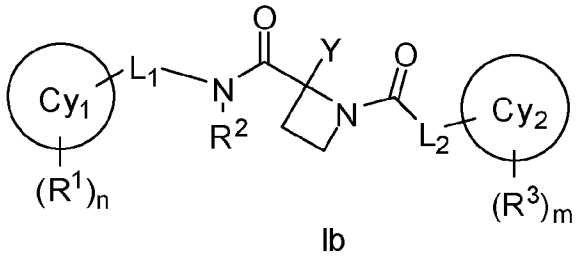
R^{4c} is phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl (optionally substituted with one or more C_{1-4} alkyl) or C_{1-4} alkyl (optionally substituted with one or more halo);

R^5 is C_{1-4} alkyl (optionally substituted with one or more halo) or phenyl; and

the subscripts n and m are independently selected from 0, 1, and 2;

or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

2. A compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula Ib:



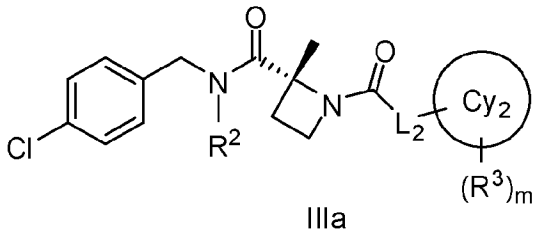
Ib

,

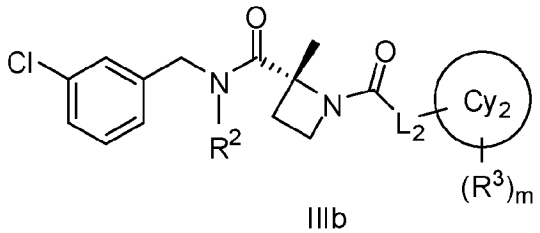
wherein L_1, L_2, R^1, R^2, R^3, Cy^1, Cy^2, R^a, R^b, R^c, R^d, R^e, Y, n, and m are as described in claim 1.

3. A compound or pharmaceutically acceptable salt thereof according to claims 1or 2, wherein Y is Me, Et, Pr, iPr, or $-CH_2-Ph$.

4. A compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein the compound is according to Formulae IIIa or IIIb:



IIIa



IIIb

wherein R^2, L_2, Cy_2, R^3 and m are as described in claim 1.

5. A compound or pharmaceutically acceptable salt thereof according to claims 1-4, wherein R^2 is $-(CH_2)$-COOH, $-(CH_2)_3$-COOH, $-(CH_2)_3$-SO_2NH_2, or $-(CH_2)_3$-SO_2NHMe.

6. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-5, wherein Cy_2 is phenyl, or naphthalene.

7. A compound or pharmaceutically acceptable salt thereof, according to claim 1-5, wherein Cy_2 is thiophenyl, benzothiophenyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl or indolyl.

8. A compound or pharmaceutically acceptable salt thereof according to any one of claim 1-7, wherein m is 1 or 2.

9. A compound or pharmaceutically acceptable salt thereof according to claim 8, wherein each R^3 group is independently selected from F, Cl, Br, Me, CF_3, and OMe.

10. A compound or pharmaceutically acceptable salt thereof according to any one of claim 1-7, wherein m is 0.

11. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-10, wherein L_2 is a single bond.

12. A compound or pharmaceutically acceptable salt thereof according to claim 1-10, wherein L_2 is $-CH_2$-.

13. A compound according to claim 1, wherein the compound is 4-[[(R)-1-(Benzo[b]thiophene-3-carbonyl)-2-methyl-azetidine-2-carbonyl]-(3-chloro-benzyl)-amino]-butyric acid; or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salt.

14. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof, according to any of claims 1-13, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition according to claim 14 comprising a further therapeutic agent.

16. A compound, or pharmaceutically acceptable salt thereof, according to any of claims 1-15 for use as a medicament.

17. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-13, or the pharmaceutical composition according to claims 14 or 15, for use in the treatment or prophylaxis of inflammatory conditions, infectious diseases, autoimmune diseases, diseases involving impairment of immune cell functions, cardiometabolic diseases, and/or proliferative diseases.