STAT6 INHIBITORS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates to novel compounds which inhibit the Signal Transducer and Activator of Transcription protein 6 (STAT6). This invention also relates to pharmaceutical compositions containing them, processes for their preparation and their use in the treatment of several disorders.

BACKGROUND OF THE INVENTION

Signal Transducers and Activators of Transcription (STAT) are a family of transcription factors regulated by phosphorylation which play a key role in the signaling of several cytokines dependent on Janus kinases (JAK) activity. Cytokine-dependent JAK phosphorylation of STAT induces STAT homodimerization through SH2 domains and nuclear translocation to the nucleus where they regulate gene transcription through binding to the promoters of specific target genes. Although JAK play an important role in STAT activation, additional mechanisms also can play a key role in STAT regulation including phosphorylation by alternative protein kinases, acetylation, methylation, or ubiquitination among other mechanisms.

STAT6 is activated by interleukin-4 (IL-4) and IL-13 cytokines which mediate STAT6 phosphorylation and translocation to the nucleus where it can bind to specific DNA sequences, thereby regulating the expression of target genes. Other cytokines such as IL-3, IL-15, interferon α (IFNα), growth factors such as platelet-derived growth factor (PDGF) or stimulator of interferon genes (STING) agonists can also activate STAT6.

STAT6-mediated signaling pathway is required for the development of T-helper type 2 (Th2) cells and type II immune responses. Expression of Th2 cytokines, including IL-4, IL-13, and IL-5 is reduced in *STAT6*-deficient mice in comparison to wild-type mice. In preclinical models of allergic skin inflammation, *STAT6*-defient mice show inflammation amelioration, decreased expression of type II cytokines such as IL-4 or IL-5, lower immunoglobulin E (IgE) levels and preserved skin barrier function. STAT6 also plays a key role in preclinical models of asthma, and $STAT6^{-/-}$ mice are protected against developing lung inflammation and express lower levels of IL-4 and IL-5 than $STAT6^{+/+}$ mice.

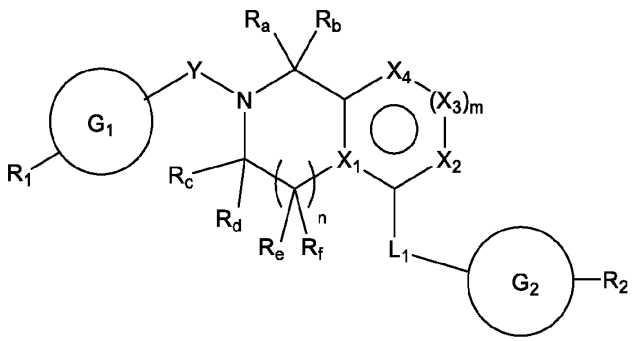
In humans, *STAT6* gain of function mutations (for instance p.D419H, p.E377K or p.D419N mutations) are associated with severe atopic dermatitis, food allergy and eosinophilic asthma highlighting the role of STAT6 in type II immunity. In addition,

different polymorphisms of the *STAT6* gene are associated to a higher risk of suffering atopic diseases. STAT6 controls different pathophysiological mechanisms key for the development of atopic and allergic diseases such as Th2 differentiation through controlling the expression of GATA3 gene, Ig class switching to IgE, macrophage polarization to M2 macrophages, differentiation of cytotoxic T cells type 2 (Tc2) for Tc2 cell production of IL-4, IL-13 and IL-5 and production of pro-inflammatory cytokines such as TARC by dendritic and monocytes/macrophages.

STAT6 expression is also dysregulated in certain forms of lymphomas such as in the Hodgkin lymphoma group, primary mediastinal and primary central nervous system lymphoma, as well as some follicular and T cell lymphomas, and mutations in *STAT6* gene have been shown in some of these patients. High levels of P-STAT6 are also found in cutaneous cell lymphomas (CTCL) and in $CD4^+$ Sezary syndrome (SS) T cells, and STAT6 regulates several common pathways in CTCL/SS malignant lymphocytes that are associated with control of cell-cycle progression and genomic stability as well as production of Th2 cytokines.

SUMMARY OF THE INVENTION

The present inventors have identified novel compounds which are inhibitors of STAT6. Such compounds typically exhibit low lipophilicity, and good permeability. The present invention therefore provides a heterocyclic compound, which heterocyclic compound is a compound of formula (I') or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, for use as a medicament,



(I')

wherein

- R_1 is C_1-C_6 haloalkyl, −L'−Z, −L'−C(O)R^y, −L'−C(O)NR^iR^y, −L'−C(O)OH, −L'−C(O)OR^y, −L'−$NR^iC(O)R^y$, −L'−$SO_2NR^iR^y$, or −L'−Het, wherein

  Het is 4- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−NR^iR^{ii}, and said heteroaryl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−NR^iR^{ii};

  Z is selected from −OR^i, −NR^iR^y and −SR^i;

  R^y is C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl, 3- to 7-membered carbocyclyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said carbocyclyl and heterocyclyl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−NR^iR^{ii}, and said phenyl and heteroaryl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−NR^iR^{ii};

  R^i and R^{ii} are the same or different and are selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

  L' is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene;

- R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−Z', −L"−C(O)R^z, −L"−C(O)OR^z, −L"−C(O)$NR^{iii}R^z$, −L"−C(O)NH_2, −L"−$NR^{iii}C(O)R^z$, −L"−$NR^{iii}C(O)OR^z$, −L"−$NR^{iii}C(O)NR^{iv}R^z$, −L"−$NR^{iii}C(O)C(O)NR^{iv}R^z$, −L"−$NR^{iii}SO_2R^z$, −L"−(4- to 10-membered heterocyclyl), or −L"−(5- to 7-membered heteroaryl), wherein said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii} and −L"−$NR^{iii}R^{iv}$, and wherein said heteroaryl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii} and −L"−$NR^{iii}R^{iv}$; wherein

  Z' is selected from −OH, −OR^{iii}, −NH_2, −$NR^{iii}R^z$ and −SR^{iii};

  R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, −Q"−Z', −A−A', −Q'−A−A', or −A−Q"−A, wherein

A is phenyl, 3- to 7-membered carbocyclyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said carbocyclyl and heterocyclyl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-OR^{iii}$, $-L''-NR^{iii}R^{iv}$, and $-L''-C(O)NR^{iii}R^{iv}$, and said phenyl and heteroaryl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-OR^{iii}$, $-L''-NR^{iii}R^{iv}$, and $-L''-C(O)NR^{iii}R^{iv}$;

A' is hydrogen, phenyl or 4- to 8-membered heterocyclyl, wherein said phenyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 7-membered carbocyclyl, 4- to 7-membered heterocyclyl, $-L''-OR^{iii}$, and $-L''-NR^{iii}R^{iv}$, and said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 7-membered carbocyclyl, 4- to 7-membered heterocyclyl, $-L''-OR^{iii}$, and $-L''-NR^{iii}R^{iv}$;

Q' is C_1-C_6 alkylene, C_1-C_6 haloalkylene, or $-Q''-O-L''-$;

Q'' is C_1-C_6 alkylene or C_1-C_6 haloalkylene;

L'' is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene;

R^{iii} and R^{iv} are the same or different and are selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety; and

- G_1 and G_2 are the same or different and are selected from phenyl, naphthyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 10-membered carbocyclyl, wherein said heterocyclyl and carbocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, and $-L^G-OR^G$, and wherein said phenyl, naphthyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-L^G-OR^G$, wherein

L^G is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene; and

R^G is selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

- Y is methylene or −C(O)−, wherein said methylene is unsubstituted or substituted by C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen or hydroxy;
- X_1 is C or N; m is 0 or 1; X_2 and X_3 are the same or different and are selected from N, NR' and CR", and X_4 is selected from N, NR' and CR'"; provided that when m is 0, either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 is selected from N and CR" and X_4 is selected from N and CR'", and X_1 is N; and when m is 1, X_1 is C, X_2 and X_3 are the same or different and are selected from N and CR", and X_4 is selected from N and CR'"; wherein R' is hydrogen or C_1-C_4 alkyl; R" is hydrogen, C_1-C_4 alkyl or halogen; and R'" is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, cyano or 3- to 5-membered carbocyclyl;
- L_1 is $-C(O)NR^v-Q-$, $-L_1'-NR^v-Q-$, or $-Het'-Q-$, wherein

  Q is a direct bond, linear or branched C_1-C_6 alkylene, or linear or branched C_1-C_6 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted or substituted by a hydroxy group;

  L_1' is a direct bond, linear or branched C_1-C_2 alkylene, linear or branched C_1-C_2 haloalkylene or 4- to 6-membered heterocyclylene;

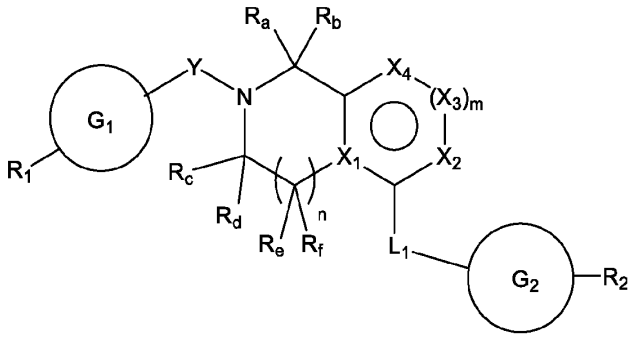
  Het' is a 4- to 6-membered heterocyclylene group or a 5- to 6-membered heteroarylene group, which group is unsubstituted or substituted by one, two or three C_1-C_3 alkyl groups which are the same or different; and

  R^v is hydrogen or C_1-C_3 alkyl;
- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered carbocyclyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl, or R_c and R_d together are oxo;
- R_e and R_f are the same or different and are selected from hydrogen, halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- n is 0 or 1.

The invention also provides a compound which compound is

(a) a heterocyclic compound of formula (I'), wherein R_1, R_2, G_1, G_2, Y, X_1, X_2, X_3, X_4, L_1, R_a, R_b, R_c, R_d, R_e, R_f, m and n are as defined herein; or

(b) a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative of said heterocyclic compound,



(I')

provided that said compound is not:

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[[5-Fluoro-2-(2,2,2-trifluoroethoxy)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[5-fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[[4-(trifluoromethyl)-2-pyrimidinyl]amino]pyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-hydroxypropyl)-2,5-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(4-Ethoxy-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(3,3,3-trifluoropropyl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, hydrate (1:1);

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, with 2-propanol (1:1);

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[3-[(4,6-Dimethyl-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

Methanone, [3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]-, acetate (1:1);

[3-[(2-Ethoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, [3-[(2,5-difluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2R,5S)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]-, *relative stereochemistry*;

Bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4- c]pyrazol-5(1H)-yl]methanone; or

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-2-methyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone.

DETAILED DESCRIPTION OF THE INVENTION

When describing the compounds, compositions, combinations and methods of the present invention, the following terms have the following meanings, unless otherwise indicated.

Definitions

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human patient which includes:

(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;

(c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

As used herein, a N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

As used in the present invention, the term tautomer means two or more forms or isomers of an organic compound that readily could be interconverted into each other via a common chemical reaction called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. The concept of tautomerizations is called tautomerism. Because of the rapid interconversion, tautomers are generally considered to be the same chemical compound. In solutions in which tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH.

The compounds of the invention may exist in both unsolvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of the invention in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

The invention also includes isotopically-labelled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine,

such as ^{36}CI, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Preferred isotopically-labelled compounds include deuterated derivatives of the compounds of the invention. As used herein, the term deuterated derivative embraces compounds of the invention where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^{2}H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015 molar %.

Isotopically-labelled compounds derivatives of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labelled reagent in place of the non-labelled reagent otherwise employed.

In the case of compounds of the invention that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystalline or polymorphic forms, or in an amorphous form, all of which are intended to be within the scope of the present invention.

Compounds of the present invention containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers.

As used herein, "alkyl" or "alkylene" is intended to include both branched and linear (straight-chain) saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1-C_6 alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. "C_1-C_3 alkyl" (or alkylene), is intended to include C_1, C_2 and C_3 alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. "C_1-C_3 alkyl" denotes alkyl having 1 to 3 carbon atoms. Typically, C_1-C_6 alkyl is preferably C_1-C_4 alkyl, more preferably C_1-C_3 alkyl, and is more preferably methyl. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl (for example n-propyl, i-propyl, preferably i-propyl) and butyl (for example n-butyl, i-butyl, sec-butyl and t-butyl, preferably t-butyl). Typically, C_1-C_6 alkylene is preferably C_1-C_4 alkylene, more preferably C_1-C_3 alkylene, and is more preferably methylene. Examples of alkylene include, but are not limited to, methylene, ethylene and propylene (for example n-propylene, i-propylene, preferably i-propylene). For the avoidance of doubt, where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine and is

preferably chlorine, bromine or fluorine, more preferably chlorine or fluorine, and most preferably fluorine.

As used herein, the term “haloalkyl” or “haloalkylene” is intended to include both branched and linear (straight-chain) saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, and which contains at least one halogen atom. The halogen is typically chlorine, fluorine, bromine or iodine, and is preferably chlorine, fluorine or bromine, more preferably chlorine or fluorine, and most preferably fluorine. Typically, C_1-C_6 haloalkyl is preferably C_1-C_4 haloalkyl, and more preferably C_1-C_3 haloalkyl, for example C_1-C_3 fluoroalkyl.

The term "carbocyclyl" (or “carbocyclylene”) refers to a monocyclic or polycyclic (e.g., bicyclic or tricyclic), non-aromatic, saturated or partially unsaturated ring system whose ring atoms consist of carbon atoms. Preferably, the carbocyclyl is a saturated ring system (i.e. in which all ring bonds between adjacent carbon atoms are single bonds), which is referred to herein as “cycloalkyl”. A polycyclic carbocyclyl may comprise fused rings (where a first ring and a second ring share two adjacent ring carbon atoms), bridged rings (where two non-adjacent ring carbon atoms of a first ring are shared with a second ring) and/or spirocyclic rings (where a first ring shares only a single ring carbon atom with a second ring). A tricyclic or higher order polycyclic cycloalkyl may comprise a mixture of fused, bridged and spirocyclic relationships between its constituent rings. Preferably, the carbocyclyl is a monocyclic or bicyclic carbocyclyl, more preferably a monocyclic or bicyclic bridged carbocyclyl. A typical carbocyclyl (or carbocyclylene) is 3- to 7-membered carbocyclyl, 4- to 10-membered carbocyclyl or 5- to 10-membered carbocyclyl, for example 5- to 7-membered carbocyclyl, 4- to 6-membered carbocyclyl, or 3- to 5-membered carbocyclyl. Example carbocyclyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, bicyclo[1.1.1]pentyl, and bicyclo[2.2.2]octanyl and the like. Typically, carbocylyl is preferably cyclopropyl, cyclobutyl, cyclopentyl or bicyclo[1.1.1]pentyl. A particularly preferred example of a carbocyclyl or cycloalkyl is cyclobutyl.

As used herein, "heterocyclyl", “heterocycle” or "heterocyclic" (or “heterocyclylene”) refers to a monocyclic or polycyclic (e.g., bicyclic or tricyclic), non-aromatic, saturated or partially unsaturated ring system whose ring atoms consist of carbon atoms and at least one heteroatom selected from O, S and N. The at least one heteroatom is commonly 1-3 heteroatoms, for instance 1-2 heteroatoms or 1 heteroatom. Preferably, the at least one heteroatom ring atom is selected from N and O, more preferably N. Preferably,

the heterocyclyl is monocyclic or bicyclic. More preferably, the heterocyclyl is monocyclic. In one embodiment, the heterocyclyl is saturated. In one embodiment, the heterocyclyl is unsaturated. Preferably, the heterocyclyl is saturated.

Typical examples of heterocycles include 4- to 10-membered heterocycles, wherein "X-membered" means that the total number of ring atoms in the heterocycle is X. Preferred heterocycles are 4- to 10-membered heterocycles, 9- to 10-membered heterocycles, 4- to 7-membered heterocycles, 4- to 6-membered heterocycles, 4- to 5-membered heterocycles and 5- to 6-membered heterocycles. Examples of heterocycles include, but are not limited to, azetidinyl, pyrrolidinyl, piperazinyl, pyrazolidinyl, piperadinyl, oxetanyl, dihydrotriazolyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, indolinyl, imidazolidinyl, tetrahydro-1H,3H-5l2-furo[3,4-c]pyrrole, 2-oxa-5-azabicyclo[2.2.1]heptane, oxa-8-azabicycloctane, 2-oxa-6-azaspiro[3.4]octane, 7-oxa-azaspiro[3.5]nonane, 6-oxa-3l2-azabicyclo[3.1.1]heptane, 2-oxazaspiro[3.5]nonane, 2-oxa-azaspiro[3.3]heptane, 1,2,3,4-tetrahydroquinoline, benzo[d][1,3]dioxole, and tetrahydropyrazolo[1,5-a]pyrazinyl. Preferred examples of heterocycles include azetidinyl, oxetanyl, piperidinyl, morpholinyl and pyrrolidinyl. As described herein, a heterocycle may be substituted by one or more oxo groups, typically one oxo group. Examples of heterocycles substituted by one oxo group include oxadiazolonyl, benzoxazolonyl, morpholinonyl, dihydrotriazolonyl, dihydroquinolinonyl, imidazolidinone, pyrimidinonyl, pyrrolidinonyl and oxoindolinyl.

As used herein, "heteroaryl" (or "heterarylene") refers to a monocyclic or polycyclic (e.g., bicyclic or tricyclic), aromatic ring system whose ring atoms consist of carbon atoms and at least one heteroatom selected from O, S and N. The at least one heteroatom is commonly 1-3 heteroatoms, for instance 1-2 heteroatoms or 1 heteroatom. Preferably, the at least one heteroatom ring atom is selected from N and O. More preferably, the at least one heteroatom ring atom is N. Preferably, the heteroaryl is monocyclic or bicyclic, more preferably monocyclic.

Typical examples of heteroaryls include 5- to 10-membered heteroaryls, wherein "X-membered" means that the total number of ring atoms in the heteroaryl is X. Preferred heteroaryls are 5- to 7-membered heteroaryls, 5-membered heteroaryls and 6-membered heteroaryls. Examples of heteroaryl groups include, without limitation, furanyl, thiophenyl, imidazolyl, thiazolyl, isothiazolyl, indolyl, benzimidazolyl, pyrrolyl (pyrryl), oxazolyl, indazolyl, isoxazolyl, pyrazolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl,

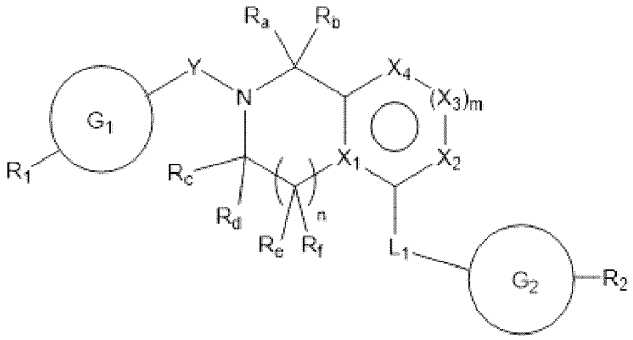
1,3,4-triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, tetrazolyl, and the like. Preferred examples of heteroaryls include imidazolyl, triazolyl, pyrazolyl, oxadiazolyl, oxazolyl, pyridinyl and tetrazolyl. A particularly preferred example of a heteroaryl is pyrazolyl.

The term "aryl" (or "arylene") is intended to mean an aromatic moiety containing, if specified, the specified number of carbon atoms. For example, C_6-C_{10} aryl is preferably phenyl or naphthyl. Preferably, C_6-C_{10} aryl is phenyl.

As used herein, a PROTAC refers to a proteolysis targeting chimera. PROTACs are heterobifunctional molecules that degrade a target protein by hijacking the ubiquitin–proteasome system, and are well-known to the person skilled in the art. In particular, PROTACs consist of two covalently linked protein-binding molecules: one capable of engaging an E3 ubiquitin ligase, and another that binds to a target protein meant for degradation (such as STAT6). Through binding to both the E3 ubiquitin ligase and the target protein in a cell, the PROTAC recruits the target protein to a ternary complex with the E3 ligase. The E3 ligase itself is in complex with an activated Ub-loaded E2 ligase, and the ternary complex formation brings the ensemble into close proximity with the target protein. This induces the (poly)-ubiquitination of the target protein at lysine residues, marking it for degradation by the 26S proteasome. This mechanism is catalytic, and PROTAC molecules freed from the ternary complex can elicit degradation of the target protein at multiple sites.

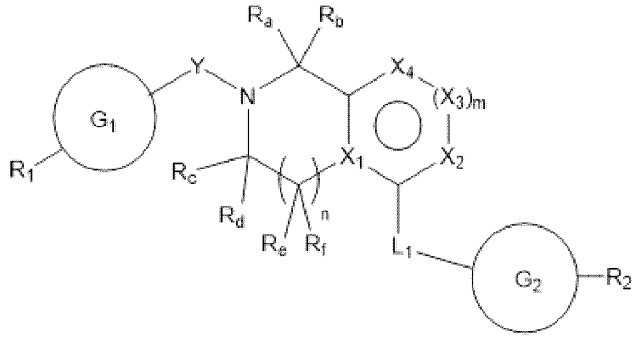
Compounds

The invention relates to compounds of formula (I') or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I')

In one aspect, the heterocyclic compound is a compound of formula (I) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof,



(I)

wherein:

- R_1, Y, L_1, R_a, R_b, R_c, R_d, R_e, R_f, and n are as defined above for formula (I');
- R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)OR^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, or $-L''-$(4- to 10-membered heterocyclyl), wherein said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-OR^{iii}$ and $-L''-NR^{iii}R^{iv}$; wherein

  Z' is selected from $-OH$, $-OR^{iii}$, $-NH_2$, $-NR^{iii}R^z$ and $-SR^{iii}$;

  R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-A-A'$, wherein

  A is phenyl, 3- to 7-membered carbocyclyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said carbocyclyl and heterocyclyl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-OR^{iii}$, and $-L''-NR^{iii}R^{iv}$, and said phenyl and heteroaryl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-L''-OR^{iii}$, and $-L''-NR^{iii}R^{iv}$;

  A' is hydrogen or 5- to 7-membered heterocyclyl which is unsubstituted or substituted by one, two or three C_1-C_3 alkyl groups which are the same or different;

L" is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene;

R^{iii} and R^{iv} are the same or different and are selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

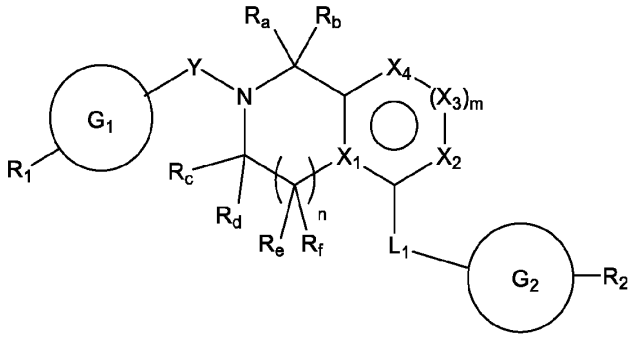
or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety; and

- G_1 and G_2 are the same or different and are selected from phenyl, naphthyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, and 4- to 10-membered carbocyclyl, wherein said heterocyclyl and carbocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo and hydroxy, and wherein said phenyl, naphthyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and hydroxy; and
- X_1 is C or N; m is 0 or 1; and X_2, X_3 and X_4 are the same or different and are selected from N, NR' and CR"; provided that when m is 0, either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 and X_4 are selected from N and CR", and X_1 is N; and when m is 1, X_1 is C and X_2, X_3 and X_4 are the same or different and are selected from N and CR"; wherein R' is hydrogen or C_1-C_4 alkyl, and R" is hydrogen, C_1-C_4 alkyl or halogen.

In one aspect, the compound is a compound which is

(a) a heterocyclic compound of formula (I'), wherein R_1, R_2, G_1, G_2, Y, X_1, X_2, X_3, X_4, L_1, R_a, R_b, R_c, R_d, R_e, R_f, m and n are as defined herein; or

(b) a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative of said heterocyclic compound,



(I')

provided that said compound is not:

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-

fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[[5-Fluoro-2-(2,2,2-trifluoroethoxy)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[5-fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[[4-(trifluoromethyl)-2-pyrimidinyl]amino]pyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-hydroxypropyl)-2,5-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(4-Ethoxy-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(3,3,3-trifluoropropyl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, hydrate (1:1);

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, with 2-propanol (1:1);

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[3-[(4,6-Dimethyl-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

Methanone, [3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]-, acetate (1:1);

[3-[(2-Ethoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, [3-[(2,5-difluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2R,5S)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]-, *relative stereochemistry*;

Bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4- c]pyrazol-5(1H)-yl]methanone; or

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-2-methyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone.

Preferably, the heterocyclic compound of the invention is a compound as described herein or a pharmaceutically acceptable salt, or a solvate, or a tautomer, or a stereoisomer thereof.

Preferably, in formula (I') or formula (I), R_1 is $-C_1$-C_4 haloalkyl, $-L'-Z$, $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, $-L'-SO_2NR^iR^y$, or $-L'-Het$. In this embodiment, R_1 is preferably $-L'-Z$, $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, or $-L'-Het$. Typically, R_1 is $-L'-C(O)NR^iR^y$. More preferably, R_1 is $-C_1$-C_4 haloalkyl, $-SR^i$, $-(C_1$-C_4 alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, $-SO_2NR^iR^y$, or $-Het$. In this embodiment, R_1 is more preferably $-(C_1$-C_4 alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, or $-Het$. More typically, R_1 is $-C(O)NR^iR^y$. Yet more preferably, R_1 is $-C_1$-C_3 haloalkyl, $-SR^i$, $-(C_1$-C_4 alkylene$)-OH$, $-C(O)R^y$, $-C(O)NR^i(C_1$-C_3 alkyl), $-C(O)OH$, $-C(O)O(C_1$-C_3 alkyl), $-NR^iC(O)(C_1$-C_3 alkyl), $-SO_2NR^i(C_1$-C_3 alkyl), 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group, or which is substituted by one oxo group and one C_1-C_3 alkyl group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one or two C_1-C_3 alkyl. In this embodiment, R_1 is yet more preferably $(C_1$-C_4 alkylene$)-OH$, $-C(O)R^y$, $-C(O)NR^i(C_1$-C_3 alkyl), $-C(O)OH$, $-C(O)O(C_1$-C_3 alkyl), $-NR^iC(O)(C_1$-C_3 alkyl), 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one C_1-C_3 alkyl. Yet more typically, R_1 is $-C(O)NR^i(C_1$-C_3 alkyl). Further preferably, R_1 is $-CF_2CH_3$, $-SCH_3$, C_4 alkylene$-OH$, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl), $-C(O)N(CH_2CH_3)_2$, $-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-SO_2NH(CH_3)$, or unsubstituted pyrrolidinone, or an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or a triazolyl moiety which is unsubstituted, substituted with one methyl group, or substituted with one oxo group and one methyl group, or an imidazolyl moiety which is unsubstituted, substituted with one or two methyl groups, or substituted with one oxo group and one methyl group, or a pyrazolyl moiety which is unsubstituted or substituted by one methyl group, or unsubstituted oxadiazolyl, or an oxazolyl moiety which is unsubstituted or substituted by one methyl group, or a furanyl moiety which is substituted with two methyl groups, or unsubstituted tetrahydrofuranyl, or unsubstituted tetrazolyl. In this embodiment, R_1 is further preferably C_4 alkylene$-OH$, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl),

$-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, unsubstituted pyrrolidinone, an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl. In this embodiment, R_1 is most preferably $-C(O)-$(unsubstituted pyrrolidinyl), $-C(O)N(CH_3)_2$, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl. Most typically, R_1 is $-C(O)N(CH_3)_2$.

Preferably, in formula (I') or formula (I), Het is 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-N(C_1$-C_4 alkyl$)_2$. More preferably, Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, C_1-C_4 alkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_4 alkyl. Yet more preferably, Het is 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group, or which is substituted by one oxo group and one C_1-C_3 alkyl group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one or two C_1-C_3 alkyl. In this embodiment, yet more preferably, Het is 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one C_1-C_3 alkyl. Further preferably, Het is unsubstituted pyrrolidinone, or an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or a triazolyl moiety which is unsubstituted, substituted with one methyl group, or substituted with one oxo group and one methyl group, or an imidazolyl moiety which is unsubstituted, substituted with one or two methyl groups, or substituted with one oxo group and one methyl group, or a pyrazolyl moiety which is unsubstituted or substituted by one methyl group, or unsubstituted oxadiazolyl, or an oxazolyl moiety which is unsubstituted or substituted by one methyl group, or a furanyl moiety which is substituted with two methyl groups, or unsubstituted tetrahydrofuranyl, or unsubstituted tetrazolyl. In this embodiment, further

preferably, Het is unsubstituted pyrrolidinone, an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, unsubstituted oxadiazolyl, or unsubstituted oxazolyl. Most preferably, Het is an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl.

Preferably, in formula (I') or formula (I), Z is $-OR^i$ or $-SR^i$. In this embodiment, preferably Z is $-OR^i$. More preferably, Z is $-OH$ or $-S(C_1\text{-}C_3$ alkyl). Most preferably, Z is $-OH$ or $-SCH_3$. In this embodiment, most preferably Z is $-OH$. In one embodiment, Z is selected from $-OR^i$ or $-NR^iR^y$.

Preferably, in formula (I') or formula (I), R^y is $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ haloalkyl, phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, $C_1\text{-}C_4$ alkyl, and $C_1\text{-}C_4$ haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl, and $C_1\text{-}C_4$ haloalkyl. More preferably, R^y is $C_1\text{-}C_4$ alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one $C_1\text{-}C_4$ alkyl group. Typically, R^y is $C_1\text{-}C_4$ alkyl. Yet more preferably, R^y is $C_1\text{-}C_3$ alkyl, or unsubstituted 4- to 6-membered heterocyclyl. More typically, R^y is $C_1\text{-}C_3$ alkyl. Further preferably, R^y is methyl, ethyl, i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl. In this embodiment, further preferably R^y is i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl. In this embodiment, further preferably R^y is unsubstituted pyrrolidinyl. Most typically, R^y is methyl.

Preferably, in formula (I') or formula (I), R^i and R^{ii} are the same or different and are selected from hydrogen and $C_1\text{-}C_4$ alkyl. More preferably, R^i and R^{ii} are the same or different and are selected from hydrogen and $C_1\text{-}C_3$ alkyl. Most preferably, R^i and R^{ii} are the same or different and are selected from hydrogen and methyl. Yet further preferably, R^i and R^{ii} are methyl.

Preferably, in formula (I') or formula (I), L' is a direct bond, $C_1\text{-}C_4$ alkylene or $C_1\text{-}C_4$ haloalkylene. More preferably, L' is a direct bond or $C_1\text{-}C_4$ alkylene. When R_1 is $-L'-Z$, preferably L' is a direct bond or C_4 alkylene (propylene). Typically, when R_1 is $-L'-Z$ and

Z is $-OR^i$, preferably L' is C_4 alkylene (propylene), more preferably i-propylene. Typically, when R_1 is $-L'-Z$ and Z is $-NR^iR^y$ or $-SR^i$, preferably L' is a direct bond. In one embodiment when R_1 is $-L'-Z$, preferably L' is C_4 alkylene (propylene), more preferably i-propylene. When R_1 is $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, $-L'-SO_2NR^iR^y$, or $-L'-$Het, preferably L' is a direct bond.

Preferably, in formula (I'), R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)OR^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-C(O)NH_2$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, $-L''-$(4- to 7-membered heterocyclyl), or $-L''-$(5- to 7-membered heteroaryl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. In this embodiment, in formula (I') or formula (I), R_2 is preferably hydrogen, C_1-C_4 alkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, or $-L''-$(4- to 7-membered heterocyclyl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. Alternatively, in formula (I'), preferably, R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)OR^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-C(O)NH_2$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, $-L''-$(4- to 7-membered heterocyclyl), or $-L''-$(5- to 7-membered heteroaryl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl. In this embodiment, in formula (I') or formula (I), R_2 is preferably hydrogen, C_1-C_4 alkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, or $-L''-$(4- to 7-membered heterocyclyl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl. Typically, in formula (I') or formula (I), R_2 is $-L''-NR^{iii}C(O)R^z$. More preferably, in formula

(I'), R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, −Z', $-C(O)R^z$, $-C(O)OR^z$, $-C(O)NR^{iii}R^z$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, −(4- to 7-membered heterocyclyl) which is unsubstituted or substituted by one oxo group, or −(5- to 7-membered heteroaryl) which is unsubstituted or substituted with one C_1-C_3 alkyl group; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. In this embodiment, in formula (I') or formula (I), R_2 is more preferably hydrogen, C_1-C_4 alkyl, −Z', $-C(O)R^z$, $-C(O)NR^{iii}R^z$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, or −4- to 7-membered heterocyclyl which is unsubstituted or substituted by one oxo group; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. Alternatively, more preferably in formula (I'), R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, −Z', $-C(O)R^z$, $-C(O)OR^z$, $-C(O)NR^{iii}R^z$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, −(4- to 7-membered heterocyclyl) which is unsubstituted or substituted by one oxo group, or −(5- to 7-membered heteroaryl) which is unsubstituted or substituted with one C_1-C_3 alkyl group. In this embodiment, in formula (I') or formula (I), R_2 is more preferably hydrogen, C_1-C_4 alkyl, −Z', $-C(O)R^z$, $-C(O)NR^{iii}R^z$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, or −4- to 7-membered heterocyclyl which is unsubstituted or substituted by one oxo group. More typically, in formula (I') or formula (I), R_2 is $-NR^{iii}C(O)R^z$. Yet more preferably, in formula (I'), R_2 is hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, −Z', $-C(O)(C_1$-C_3 alkyl), $-C(O)O(C_1$-C_4 alkyl), $-C(O)NR^{iii}(C_1$-C_3 alkyl), $-C(O)NR^{iii}(-A-A')$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)O(C_1$-C_4 alkyl), $-NR^{iii}C(O)O(-A-A')$, $-NR^{iii}C(O)NR^{iv}(C_1$-C_3 alkyl), $-NR^{iii}C(O)C(O)NR^{iv}(C_1$-$C_3$ alkyl), $-NHSO_2(C_1$-C_3 alkyl), 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group, or 5-membered heteroaryl which is unsubstituted or substituted with one C_1-C_3 alkyl group; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. In this embodiment, in formula (I') or formula (I), R_2 is more preferably hydrogen, C_1-C_3 alkyl, −Z', $-C(O)(C_1$-C_3 alkyl), $-C(O)NR^{iii}(C_1$-C_3 alkyl), $-NR^{iii}C(O)R^z$, $-NHC(O)O(C_1$-C_4 alkyl), $-NHC(O)N(C_1$-C_3 alkyl)$_2$, $-NHSO_2(C_1$-C_3 alkyl), or 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. Alternatively, yet more preferably in formula (I'), R_2 is hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, −Z', $-C(O)(C_1$-C_3 alkyl), $-C(O)O(C_1$-C_4 alkyl), $-C(O)NR^{iii}(C_1$-C_3 alkyl), $-C(O)NR^{iii}(-A-A')$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)O(C_1$-C_4 alkyl), $-NR^{iii}C(O)O(-A-A')$, $-NR^{iii}C(O)NR^{iv}(C_1$-C_3 alkyl), $-NR^{iii}C(O)C(O)NR^{iv}(C_1$-$C_3$ alkyl), $-NHSO_2(C_1$-C_3 alkyl), 5-membered heterocyclyl which is unsubstituted or substituted with

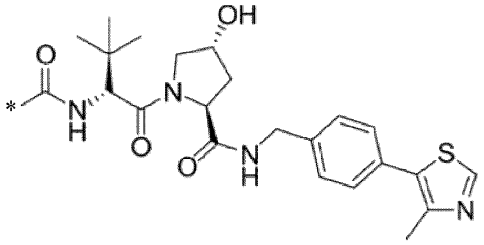
one oxo group, or 5-membered heteroaryl which is unsubstituted or substituted with one C_1-C_3 alkyl group. In this embodiment, in formula (I') or formula (I) R_2 is yet more preferably hydrogen, C_1-C_3 alkyl, −Z', −C(O)(C_1-C_3 alkyl), −C(O)NR^{iii}(C_1-C_3 alkyl), −NR^{iii}C(O)R^z, −NHC(O)O(C_1-C_4 alkyl), −NHC(O)N(C_1-C_3 alkyl)$_2$, −$NHSO_2$(C_1-C_3 alkyl), or 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group. Further preferably, in formula (I'), R_2 is hydrogen, methyl, −CH_2F, −Z', −C(O)CH_3, −C(O)O(*tert*-butyl), −C(O)NH(CH_3), −C(O)N(CH_3)$_2$, −C(O)NH(−A−A'), −C(O)NH_2, −N(CH_3)C(O)CH_3, −NHC(O)R^z, −NHC(O)O(C_3-C_4 alkyl), −NHC(O)O(unsubstituted phenyl), −NHC(O)N(CH_3)$_2$, −NHC(O)N(CH_3)(CH_2CH_3), −NHC(O)NH(CH_3), −NHC(O)C(O)N(CH_3)$_2$, −$NHSO_2$(CH_3), unsubstituted pyrrolidinone, unsubstituted dihydrotriazolone, unsubstituted oxadiazolone, imidazolyl which is unsubstituted or substituted with one methyl group, triazolyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrazolyl; or R_2 is −L_2-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. In this embodiment, in formula (I') or formula (I), R_2 is further preferably hydrogen, methyl, −Z', −C(O)CH_3, −C(O)NH(CH_3), −C(O)N(CH_3)$_2$, −N(CH_3)C(O)CH_3, −NHC(O)R^z, −NHC(O)O(C_4 alkyl), −NHC(O)N(CH_3)$_2$, −$NHSO_2$(CH_3), or unsubstituted pyrrolidinone; or R_2 is −L_2-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. Alternatively, in formula (I'), further preferably R_2 is hydrogen, methyl, −CH_2F, −Z', −C(O)CH_3, −C(O)O(*tert*-butyl), −C(O)NH(CH_3), −C(O)N(CH_3)$_2$, −C(O)NH(−A−A'), −C(O)NH_2, −N(CH_3)C(O)CH_3, −NHC(O)R^z, −NHC(O)O(C_3-C_4 alkyl), −NHC(O)O(unsubstituted phenyl), −NHC(O)N(CH_3)$_2$, −NHC(O)N(CH_3)(CH_2CH_3), −NHC(O)NH(CH_3), −NHC(O)C(O)N(CH_3)$_2$, −$NHSO_2$(CH_3), unsubstituted pyrrolidinone, unsubstituted dihydrotriazolone, unsubstituted oxadiazolone, imidazolyl which is unsubstituted or substituted with one methyl group, triazolyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrazolyl. In this embodiment, in formula (I') or formula (I), R_2 is further preferably hydrogen, methyl, −Z', −C(O)CH_3, −C(O)NH(CH_3), −C(O)N(CH_3)$_2$, −N(CH_3)C(O)CH_3, −NHC(O)R^z, −NHC(O)O(C_4 alkyl), −NHC(O)N(CH_3)$_2$, −$NHSO_2$(CH_3), or unsubstituted pyrrolidinone. Most preferably, in formula (I') or formula (I), R_2 is −NHC(O)R^z, −NHC(O)O(*tert*-butyl), or −NHC(O)N(CH_3)$_2$; or R_2 is −L_2-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety. Alternatively, most preferably in formula (I') or formula (I), R_2 is −NHC(O)R^z, −NHC(O)O(*tert*-butyl), or −NHC(O)N(CH_3)$_2$. In one embodiment, R_2 is not hydrogen.

Typically, in formula (I') or formula (I), R_2 is −NR^{iii}C(O)R^z. In this embodiment, in formula (I'), R_2 is typically −NR^{iii}C(O)(−A−A'), −NR^{iii}C(O)(C_1-C_5 alkyl), −NR^{iii}C(O)(C_1-

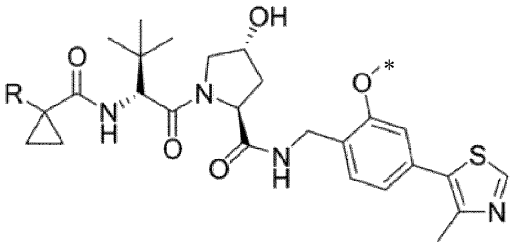
C_3 haloalkyl), $-NR^{iii}C(O)-Q''-OR^{iii}$, $-NR^{iii}C(O)-Q''-OH$, or $-NR^{iii}C(O)-Q''-NR^{iii}(C_1$-$C_3$ alkyl). More typically, R_2 is $-NHC(O)R^z$. In this embodiment, in formula (I'), R_2 is more typically $-NHC(O)(-A-A')$, $-NHC(O)(C_1$-C_5 alkyl), $-N(CH_3)C(O)(C_1$-C_3 alkyl), $-NHC(O)(C_1$-C_3 haloalkyl), $-NHC(O)-(C_1$-C_2 alkylene)$-OCH_3$, $-NHC(O)-(C_1$-C_2 alkylene)$-OH$, or $-NHC(O)CH_2CH_2N(C_1$-C_3 alkyl)$_2$. Yet more typically, in formula (I') or formula (I), R_2 is $-NHC(O)(-A-A')$. Even further typically, in formula (I'), R_2 is $-NHC(O)$((5- to 7-membered heteroaryl which is unsubstituted or substituted with one C_1-C_3 alkyl group)$-$(4- to 7-membered heterocyclyl which is unsubstituted or substituted with one 3- to 5-membered carbocyclyl group or one C_1-C_3 haloalkyl group)), or $-NHC(O)$((unsubstituted phenyl)$-$(4- to 6-membered heterocyclyl which is unsubstituted or substituted with one $-OR^{iii}$ group)). Yet further typically, in formula (I'), R_2 is $-NHC(O)$((5-membered heteroaryl which is substituted with one methyl group)$-$(6-membered heterocyclyl which is substituted with one cyclobutyl group or one C_2 haloalkyl group)), or $-NHC(O)$((unsubstituted phenyl)$-$(4-membered heterocyclyl which is substituted with one methoxy group)), or $-NHC(O)$((unsubstituted phenyl)$-$(unsubstituted 6-membered heterocyclyl)). Most typically, in formula (I'), R_2 is $-NHC(O)$((pyrazolyl which is substituted with one methyl group)$-$(piperidinyl which is substituted with one cyclobutyl group or one $-CH_2CHF_2$ group)), or $-NHC(O)$((unsubstituted phenyl)$-$(azetidinyl which is substituted with one methoxy group)), or $-NHC(O)$((unsubstituted phenyl)$-$(unsubstituted morpholinyl)).

When R_2 contains or is L_2-LBM in formula (I') or formula (I), the compound of the invention may be used as a PROTAC. L_2 is any linker which is suitable for covalently linking the ligase binding moiety LBM to the remainder of the compound of the invention. Suitable L_2 groups are known to the person skilled in the art and include alkylene groups, polyethylene glycol chains, other glycol chains and triazolylene moieties. For example, L_2 may comprise a C_2 to C_{20} alkylene group and/or a polyethylene glycol (PEG) chain with a molecular weight of from 50 g/mol to 500 g/mol. Preferably, L_2 is $-NHC(O)-L_2'-Z^L-$, wherein L_2' is selected from C_2-C_{20} alkylene, $-L_2''-(Het^L)-L_2''-$, and $-L_2'''-(OCH_2CH_2)_p-$; Z^L is a direct bond or $-NH-L_2'''-$; each L_2'' is the same or different and is a direct bond or C_1-C_{10} alkylene; L_2''' is a direct bond or C_1-C_3 alkylene; Het^L is 5- to 7-membered heterocyclylene or 5- to 7-membered heteroarylene; and p is from 1 to 20. Preferably, Het^L is 6-membered heterocyclylene. More preferably, Het^L is piperazinylene. Preferably, p is from 1 to 10.

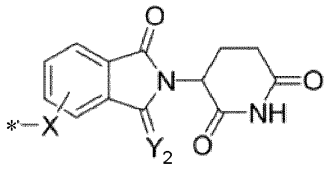
LBM is a ligase binding moiety which binds to the E3 ubiquitin (Ub) ligase, preferably at the substrate binding domain of the E3 Ub ligase. Suitable LBM moieties are known the person skilled in the art and include any moiety which is suitable for binding to one of the human proteome's E3 ligases. Preferably, LBM is selected from formulae (a) to (f) below, where * represents the point of attachment to L_2:



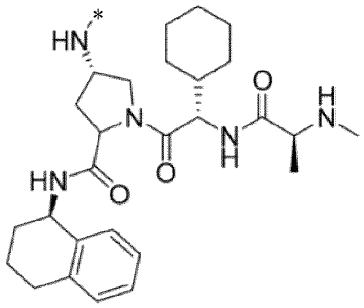
(a)



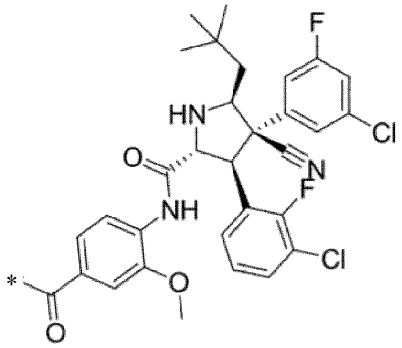
(b)



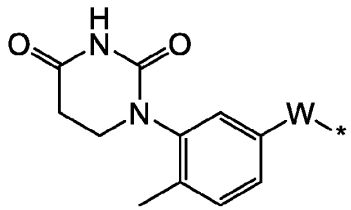
(c)



(d)



(e)



(f)

wherein

R is F or CN; Y_2 is O or CH_2; X is NH, O or −NHC(O)−; and W is −C(O)NH− or −C(O)−.

Preferably, in formula (I') or formula (I), Z' is selected from −OH, $-OR^{iii}$, $-NH_2$, and $-NR^{iii}R^z$. In this embodiment, Z' is preferably selected from $-NH_2$ or $-NR^{iii}R^z$. More preferably, Z' is selected from −OH, $-O(C_1\text{-}C_3$ alkyl), $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), $-NR^{iii}(C_1\text{-}C_3$ haloalkyl), a −NH−(5- to 6-membered heteroaryl) group which is unsubstituted, and a −NH−(4- to 6-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, or one $C_1\text{-}C_3$ alkyl group and one oxo group. In this embodiment, Z' is more preferably selected from $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), a −NH−(5- to 6-membered heteroaryl) group which is unsubstituted, or a −NH−(4- to 6-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group. Yet more preferably, Z' is $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), $-NR^{iii}(C_1\text{-}C_3$ haloalkyl), a −NH−(6-membered heteroaryl) group which is unsubstituted, a −NH−(4-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, or a −NH−(6-membered heterocyclyl) group which is substituted with one $C_1\text{-}C_3$ alkyl group and one oxo group. In this embodiment, Z' is yet more preferably $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), a −NH−(6-membered heteroaryl) group which is unsubstituted, or a −NH−(4-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group. Most preferably, Z' is $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$,

$-NHCH_2CF_3$, a $-NH-$pyridinyl group which is unsubstituted, a $-NH-$oxetanyl group which is unsubstituted or substituted with one methyl group, or a $-NH-$(unsubstituted pyrimidinone) group. In this embodiment, Z' is most preferably $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, a $-NH-$pyridinyl group which is unsubstituted, or a $-NH-$oxetanyl group which is unsubstituted or substituted with one methyl group.

Preferably, in formula (I'), R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-(C_1$-C_3 alkylene$)-Z'$, $-A-A'$, $-(C_1$-C_3 alkylene$)-A-A'$, $-(C_1$-C_3 alkylene$-O-C_1$-C_3 alkylene$)-A-A'$, or $-A-(C_1$-C_3 alkylene$)-A$. In this embodiment, in formula (I') or formula (I), R^z is preferably C_1-C_6 alkyl or $-A-A'$. Typically, in formula (I') or formula (I), R^z is $-A-A'$. More preferably, in formula (I'), R^z is C_1-C_5 alkyl, or 3- to 5-membered cycloalkyl which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, and $-OR^{iii}$, or 4- to 10 membered heterocyclyl which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, C_1-C_3 alkyl, and oxo, or phenyl$-A'$ wherein said phenyl is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(C_1$-C_3 alkyl$)_2$, and $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), or (5- to 6-membered heteroaryl$)-A'$ wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl. In this embodiment, in formula (I') or formula (I), R^z is more preferably C_1-C_5 alkyl, unsubstituted 3- to 5-membered cycloalkyl, unsubstituted 6-membered heteroaryl, unsubstituted 4-membered heterocyclyl, 9- to 10-membered heterocyclyl which is unsubstituted or substituted with one C_1-C_3 alkyl group, or phenyl$-A'$ wherein said phenyl is unsubstituted or substituted with one C_1-C_3 alkyl group. More typically, in formula (I'), R^z is phenyl$-A'$ wherein said phenyl is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(C_1$-C_3 alkyl$)_2$, and $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), or (5- to 6-membered heteroaryl$)-A'$ wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl. Yet more preferably, in formula (I'), R^z is methyl, *tert*-butyl, *iso*-butyl, $-CH_2-$(*tert*-butyl), cyclopropyl which is unsubstituted or substituted with one halogen group, cyclobutyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, oxadiazolyl which is substituted with one methyl group, unsubstituted thiazolyl, benzodioxazolyl which is unsubstituted or substituted with one or two halogen groups, oxetanyl which is unsubstituted or substituted with one methyl group, azetidinyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted

pyrrolidinyl, pyrimidinonyl which is unsubstituted or substituted with one methyl group, indolinyl which is unsubstituted or substituted with one methyl group, morpholinyl which is unsubstituted or substituted with one methyl group, piperidinyl which is unsubstituted or substituted with one methyl group, piperazinyl which is unsubstituted or substituted with one methyl group, tetrahydroquinoline which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and methyl, unsubstituted tetrahydrofuranyl, unsubstituted tetrahydropyranyl, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, tetrahydro-1H,3H-5l2-furo[3,4-c]pyrrole which is substituted with one or two methyl groups, unsubstituted oxa-azaspiroheptane, unsubstituted oxa-azaspirooctane, unsubstituted oxa-azaspirononane, unsubstituted oxa-azabicycloheptane, unsubstituted oxa-azabicyclooctane, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one substituent selected from methyl, propyl, halogen, $-N(CH_3)_2$, and –(ethylene)−C(O)NH(CH_3), or (imidazolyl)−A' wherein said imidazolyl is unsubstituted or substituted with one methyl group, or (pyrazolyl)−A' wherein said pyrazolyl is unsubstituted or substituted with one or two methyl groups, or (pyridinyl)−A' wherein said pyridinyl is unsubstituted or substituted with one C_1-C_3 alkyl group or one halogen group, or (pyrimidinyl)−A' wherein said pyrimidinyl is unsubstituted or substituted with one methyl group. In this embodiment, in formula (I') or formula (I), R^z is yet more preferably methyl, *tert*-butyl, $-CH_2-$(*tert*-butyl), unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, unsubstituted oxetanyl, indolinyl which is unsubstituted or substituted with one methyl group, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one propyl group. In this embodiment, in formula (I') or formula (I), R^z is most preferably methyl, *tert*-butyl, $-CH_2-$(*tert*-butyl), unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl−A' wherein said phenyl is unsubstituted. Yet more typically, in formula (I') or formula (I), R^z is (unsubstituted phenyl)−A', or (pyrazolyl)−A' wherein said pyrazolyl is substituted with one methyl group. Most typically, in formula (I'), R^z is (pyrazolyl which is substituted with one methyl group)−(piperidinyl which is substituted with one cyclobutyl group or one $-CH_2CHF_2$ group), or (unsubstituted phenyl)−(azetidinyl which is substituted with one methoxy group), or (unsubstituted phenyl)−(unsubstituted morpholinyl).

Preferably, in formula (I'), A is phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said cycloalkyl and

heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, $-OR^{iii}$, oxo, C_1-C_4 alkyl and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-N(C_1$-C_3 alkyl$)_2$, $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl. In this embodiment, in formula (I') or formula (I), A is preferably phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. More preferably, in formula (I'), A is a phenyl moiety which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(C_1$-C_3 alkyl$)_2$, and $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), a 3- to 7-membered cycloalkyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_3 alkyl, halogen, cyano, and $-OR^{iii}$, a 5- to 7-membered heteroaryl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl, or a 4- to 10-membered heterocyclyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, C_1-C_3 alkyl, and oxo. In this embodiment, in formula (I'), A is more preferably a phenyl moiety, a 3- to 7-membered cycloalkyl moiety, a 5- to 7-membered heteroaryl moiety or a 4- to 10-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one C_1-C_3 alkyl group. Typically, in formula (I'), A is a phenyl moiety which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(C_1$-C_3 alkyl$)_2$, and $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), or a 5- to 7-membered heteroaryl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl. Yet more preferably, in formula (I'), A is a 3- to 6-membered cycloalkyl moiety which moiety is unsubstituted or substituted with one halogen group, one cyano group or one methoxy group, a 5- to 6- membered heteroaryl moiety which moiety is unsubstituted or substituted with one or two substituents which are the same or different and are selected from C_1-C_3 alkyl and halogen, a 4- to 5-membered heterocyclyl moiety which moiety is unsubstituted or substituted with one methyl group, one cyano group, or one methoxy group, a 6-membered heterocyclyl moiety which moiety is

unsubstituted or substituted with one methyl group and one oxo group, or one methyl group, a 7- to 10-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl, or phenyl which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(CH_3)_2$, and –(ethylene)–$C(O)NH(CH_3)$. In this embodiment, in formula (I') or formula (I), A is yet more preferably unsubstituted 3- to 5-membered cycloalkyl, unsubstituted 6-membered heteroaryl, unsubstituted 4-membered heterocyclyl, 9- to 10-membered heterocyclyl moiety which moiety is unsubstituted or substituted with one C_1-C_3 alkyl group, or phenyl which is unsubstituted or substituted with one C_1-C_3 alkyl group. Yet more typically, in formula (I'), A is phenyl which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(CH_3)_2$, and –(ethylene)–$C(O)NH(CH_3)$, or a 5- to 6- membered heteroaryl moiety which moiety is unsubstituted or substituted with one or two substituents which are the same or different and are selected from C_1-C_3 alkyl and halogen. Further preferably, in formula (I'), A is cyclopropyl which is unsubstituted or substituted with one halogen group, cyclobutyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, oxadiazolyl which is substituted with one methyl group, unsubstituted thiazolyl, benzodioxazolyl which is unsubstituted or substituted with one or two halogen groups, oxetanyl which is unsubstituted or substituted with one methyl group, azetidinyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted pyrrolidinyl, pyrimidinonyl which is unsubstituted or substituted with one methyl group, indolinyl which is unsubstituted or substituted with one methyl group, morpholinyl which is unsubstituted or substituted with one methyl group, piperidinyl which is unsubstituted or substituted with one methyl group, piperazinyl which is unsubstituted or substituted with one methyl group, tetrahydroquinoline which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and methyl, unsubstituted tetrahydrofuranyl, unsubstituted tetrahydropyranyl, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, tetrahydro-1H,3H-5l2-furo[3,4-c]pyrrole which is substituted with one or two methyl groups, unsubstituted oxa-azaspiroheptane, unsubstituted oxa-azaspirooctane, unsubstituted oxa-azaspirononane, unsubstituted oxa-azabicycloheptane, unsubstituted oxa-azabicycloctane, phenyl which is unsubstituted or substituted with one substituent selected from methyl, propyl, halogen, $-N(CH_3)_2$, and –(ethylene)–$C(O)NH(CH_3)$, imidazolyl which is unsubstituted or substituted with one methyl

group, pyrazolyl which is unsubstituted or substituted with one or two methyl groups, pyridinyl which is unsubstituted or substituted with one C_1-C_3 alkyl group or one halogen group, or pyrimidinyl which is unsubstituted or substituted with one methyl group. In this embodiment, in formula (I') or formula (I), A is further preferably unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, unsubstituted oxetanyl, indolinyl moiety which is unsubstituted or substituted with one methyl group, tetrahydropyrazolo[1,5-a]pyrazinyl moiety which is unsubstituted or substituted with one methyl group, or phenyl which is unsubstituted or substituted with one propyl group. In this embodiment, in formula (I') or formula (I), A is most preferably unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl which is unsubstituted. Further typically, in formula (I'), A is phenyl which is unsubstituted or substituted with one substituent selected from methyl, propyl, halogen, $-N(CH_3)_2$, and –(ethylene)–C(O)NH(CH_3), or pyrazolyl which is unsubstituted or substituted with one or two methyl groups. Most typically, in formula (I') or formula (I), A is unsubstituted phenyl or pyrazolyl which is substituted with one methyl group.

In formula (I'), where a compound contains two A groups, for the avoidance of doubt the two A groups may be the same or different.

Preferably, in formula (I'), A' is hydrogen, a phenyl moiety which moiety is unsubstituted or substituted with $-(C_1$-C_3 alkylene)$-NR^{iii}R^{iv}$, or a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$. In this embodiment, in formula (I') or formula (I), A' is preferably hydrogen or 5- to 7-membered heterocyclyl which is unsubstituted or substituted by one C_1-C_3 alkyl group. Typically, in formula (I'), A' is a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$. More preferably, in formula (I'), A' is hydrogen, phenyl which is substituted with $-(C_1$-C_3 alkylene)$-NH(CH_3)$, a 4-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, cyclopropyl, cyclobutyl, and methoxy, a 5-membered heterocyclyl which is unsubstituted or substituted with one methoxy group, a 6-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, ethyl, C_2 haloalkyl, cyclopropyl, cyclobutyl, oxetanyl, oxo, and methoxy, or an unsubstituted 7- to 8-membered heterocyclyl. In this embodiment, in

formula (I') or formula (I), A' is more preferably hydrogen or 6-membered heterocyclyl which is unsubstituted or substituted with one methyl group. More typically, in formula (I'), A' is a 4-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, cyclopropyl, cyclobutyl, and methoxy, or a 6-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, ethyl, C_2 haloalkyl, cyclopropyl, cyclobutyl, oxetanyl, oxo, and methoxy. Most preferably, in formula (I'), A' is hydrogen, phenyl which is substituted with $-(CH_2)-NH(CH_3)$, azetidinyl which is substituted with one substituent selected from methyl, methoxy, cyclopropyl, and cyclobutyl, piperidinyl which is substituted with one substituent selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH_2CH_2F$, $-CH_2CHF_2$, methoxy, and oxetanyl, morpholinyl which is unsubstituted or substituted with one methyl group or one oxo group, piperazinyl which is substituted with one substituent selected from methyl, cyclopropyl, and cyclobutyl, tetrahydropyridinyl which is substituted with one methyl group, pyrrolidinyl which is substituted with one methoxy group, or unsubstituted oxazaspiroheptane, unsubstituted oxazaspirooctane, or unsubstituted tetrahydropyranyl. In this embodiment, in formula (I') or formula (I), A' is most preferably hydrogen, piperidinyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrahydropyranyl. Yet more typically, in formula (I'), A' is piperidinyl which is substituted with one substituent selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH_2CH_2F$, $-CH_2CHF_2$, methoxy, and oxetanyl, or azetidinyl which is substituted with one substituent selected from methyl, methoxy, cyclopropyl, and cyclobutyl, or morpholinyl which is unsubstituted or substituted with one methyl group or one oxo group. Most typically, in formula (I'), A' is piperidinyl which is substituted with one substituent selected from cyclobutyl and $-CH_2CHF_2$, or azetidinyl which is substituted with one methoxy group, or unsubstituted morpholinyl.

Preferably, in formula (I'), Q' is C_1-C_6 alkylene or $-(C_1$-C_6 alkylene$)-O-L''-$. More preferably, Q' is C_1-C_3 alkylene or $-(C_1$-C_3 alkylene$)-O-(C_1$-C_3 alkylene$)-$. Most preferably, Q' is methylene or $-(CH_2)-O-(CH_2)-$.

Preferably, in formula (I'), Q'' is C_1-C_6 alkylene. More preferably, Q'' is C_1-C_3 alkylene. Most preferably, Q'' is C_1-C_2 alkylene.

Preferably, in formula (I') or formula (I), L'' is a direct bond, C_1-C_3 alkylene or C_1-C_3 haloalkylene. More preferably, L'' is a direct bond or C_1-C_3 alkylene. Most preferably, L'' is a direct bond.

Preferably, in formula (I') or formula (I), R^{iii} and R^{iv} are the same or different and are selected from hydrogen and C_1-C_4 alkyl. More preferably, R^{iii} and R^{iv} are the same or

different and are selected from hydrogen and C_1-C_3 alkyl. Most preferably, R^{iii} and R^{iv} are the same or different and are selected from hydrogen and methyl.

Preferably, in formula (I'), G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, $-OR^G$ and $-(C_1$-C_3 alkylene$)-OR^G$, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^G$ and $-(C_1$-C_3 alkylene$)-OR^G$. In this embodiment, in formula (I') or formula (I), G_1 is preferably selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. In this embodiment, in formula (I') or formula (I), more preferably G_1 is selected from a phenyl moiety, a 4- to 7-membered heterocyclyl moiety, a 5- to 7-membered heteroaryl moiety, or a 4- to 7-membered cycloalkyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. More preferably, in formula (I') or formula (I), G_1 is selected from a phenyl moiety, a 5- to 7-membered heterocyclyl moiety, a 5- to 7-membered heteroaryl moiety, or a 5- to 7-membered cycloalkyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. Yet more preferably, in formula (I') or formula (I), G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered cycloalkyl, 5- to 6-membered heteroaryl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl. In this embodiment, in formula (I') or formula (I), G_1 is yet more preferably unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered heteroaryl, unsubstituted 5- to 6-membered cycloalkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl. Yet more typically, in formula

(I') or formula (I), G_1 is phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl. Further preferably, in formula (I') or formula (I), G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, unsubstituted pyrimidinyl, pyridinyl which is unsubstituted or substituted with one methyl group, one fluorine group, or one chlorine group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and methyl. In this embodiment, in formula (I') or formula (I), G_1 is further preferably unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. Most preferably, in formula (I') or formula (I), G_1 is phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. Most typically, in formula (I') or formula (I), G_1 is unsubstituted phenyl.

In formula (I') or formula (I), when G_1 is a 6-membered monocyclic ring (such as phenyl, 6-membered monocyclic heterocyclyl, 6-membered monocyclic heteroaryl or 6-membered carbocyclyl), the R_1 moiety is preferably at the para position in relation to moiety Y.

Preferably, in formula (I'), G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L^G-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-O-(C_1$-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl. In this embodiment, in formula (I') or formula (I), G_2 is preferably selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. More preferably, in formula (I'), G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one substituent selected from C_1-C_4 alkyl, $-(C_1$-C_4 alkylene)$-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted

or substituted by one or two substituents which are the same or different and are selected from halogen, −O−(C_1-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl. In this embodiment, in formula (I') or formula (I), G_2 is more preferably selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, and 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one substituent selected from C_1-C_4 alkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. Yet more preferably, in formula (I'), G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; 5- to 6-membered cycloalkyl which is unsubstituted or substituted with one hydroxy group; 5- to 10- membered heteroaryl which is unsubstituted or substituted with one halogen group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from halogen, −O−(C_1-C_3 alkyl) and C_1-C_3 alkyl. In this embodiment, in formula (I') or formula (I), G_2 is yet more preferably G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; unsubstituted 5- to 6- membered cycloalkyl; unsubstituted 5- to 10- membered heteroaryl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl. Yet more typically, in formula (I'), G_2 is phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from halogen, −O−(C_1-C_3 alkyl) and C_1-C_3 alkyl. Further preferably, in formula (I'), G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted pyrrolidinyl, unsubstituted tetrahydropyranyl, unsubstituted bicyclo[1.1.1]pentyl, cyclohexyl which is unsubstituted or substituted with one hydroxy group, unsubstituted indolinyl, unsubstituted oxoindolinyl, unsubstituted benzoxazolonyl, unsubstituted dihydroquinolinonyl, pyridinyl which is unsubstituted or substituted with one chlorine group, unsubstituted pyrimidinyl, unsubstituted indolyl, unsubstituted oxazolyl, unsubstituted thiazolyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine, chlorine, methoxy and methyl. In this embodiment, in formula (I') or formula (I), G_2 is further preferably unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted indolinyl, unsubstituted oxoindolinyl or unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. Most preferably, in formula (I') or formula (I), G_2 is phenyl which is unsubstituted or substituted with one or two substituents

selected from fluorine and methyl. Most typically, in formula (I') or formula (I), G_2 is unsubstituted phenyl.

In formula (I') or formula (I), when G_2 is a 6-membered monocyclic ring (such as phenyl, 6-membered monocyclic heterocyclyl, 6-membered monocyclic heteroaryl or 6-membered carbocyclyl), the R_2 moiety is preferably at the para position in relation to moiety L_1.

Preferably, in formula (I'), L^G is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene. More preferably, L^G is a direct bond or C_1-C_3 alkylene. Yet more preferably, L^G is a direct bond or methylene. Most preferably, L^G is a direct bond.

Preferably, in formula (I'), R^G is selected from hydrogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. More preferably, R^G is selected from hydrogen and C_1-C_3 alkyl. Yet more preferably, R^G is selected from hydrogen and methyl. In one preferred embodiment, R^G is hydrogen. In an alternative preferred embodiment, R^G is methyl.

Preferably, in formula (I') or formula (I), Y is methylene or −C(O)−. Most preferably, Y is methylene.

In formula (I') or formula (I), X_1, X_2, X_3, X_4 and m together define a monocyclic, 5- or 6-membered aromatic ring, preferably a monocyclic 5-membered heteroaryl ring. For example, the ring defined by X_1, X_2, X_3, X_4 and m may be pyrrolyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, phenyl, or pyridinyl. Preferably, the ring defined by X_1, X_2, X_3, X_4 and m is pyrrolyl, imidazolyl, pyrazolyl, or 1,2,4-triazolyl. More preferably, the ring defined by X_1, X_2, X_3, X_4 and m is pyrrolyl or imidazolyl. In this embodiment, more preferably, the ring defined by X_1, X_2, X_3, X_4 and m is pyrrolyl. In one embodiment, more preferably, the ring defined by X_1, X_2, X_3, X_4 and m is imidazolyl. In formula (I') or formula (I), preferably, m is 0. In formula (I') or formula (I), preferably, X_1 is N. In formula (I') or formula (I), preferably, X_2 is CR''. In one preferred embodiment in formula (I') or formula (I), X_2 is N. In formula (I'), preferably, X_4 is CR'''. In this embodiment, in formula (I') or formula (I), preferably X_4 is CR''. In one preferred embodiment in formula (I') or formula (I), X_4 is N.

Preferably, in formula (I'), m is 0, X_1 is N, X_2 is selected from N and CR'' and X_4 is selected from N and CR'''. In this embodiment, in formula (I') or formula (I), preferably m is 0, X_1 is N and X_2 and X_4 are selected from N and CR''. More preferably, in formula (I'), m is 0, X_1 is N, X_2 is N or CR'', and X_4 is CR'''. In this embodiment, in formula (I') or formula (I), more preferably, m is 0, X_1 is N and X_2 and X_4 are CR''. Yet more preferably, in formula (I'), m is 0, X_1 is N, X_2 is N, CH, CF or $C(CH_3)$ and X_4 is CR'''. In this embodiment, in formula (I') or formula (I), yet more preferably, m is 0, X_1 is N, X_2 is CH and X_4 is CR''.

Further preferably, in formula (I'), m is 0, X_1 is N, X_2 is N, CH, CF or $C(CH_3)$ and X_4 is CH, CF, CCl, CBr, $C(CH_3)$, C(cyclopropyl), or C(CN). In this embodiment, in formula (I') or formula (I), further preferably, m is 0, X_1 is N, X_2 is CH and X_4 is CH or CF. Most preferably, in formula (I') or formula (I), m is 0, X_1 is N, X_2 is CH and X_4 is CH. Alternatively, most preferably in formula (I') or formula (I), m is 0, X_1 is N, X_2 is N and X_4 is CH or $C(CH_3)$.

Preferably, in formula (I') or formula (I), R' is hydrogen or methyl. More preferably, R' is hydrogen. Preferably, in formula (I') or formula (I), R" is hydrogen, methyl or fluorine. More preferably, R" is hydrogen or fluorine. Most preferably, R" is hydrogen. Preferably, in formula (I'), R'" is hydrogen, halogen, methyl, trifluoromethyl, cyano or 3-to 4-membered carbocyclyl. More preferably, R'" is hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl, cyano, or cyclopropyl. Most preferably, R'" is hydrogen or methyl. Preferably, the ring defined by X_1, X_2, X_3, X_4 and m contains no more than two R', R" or R'" groups which are not hydrogen. More preferably, the ring defined by X_1, X_2, X_3, X_4 and m contains no more than one R', R" or R'" groups which are not hydrogen.

Preferably, in formula (I') or formula (I), L_1 is $-C(O)NR^v-Q-$, $-L_1'-NR^v-Q-$, or –(5- to 6-membered heteroarylene)–Q–. In this embodiment, preferably L_1 is $-C(O)NR^v-Q-$, or $-L_1'-NR^v-Q-$. More preferably, L_1 is $-C(O)NR^v-Q-$, –(4-membered heterocyclylene)–NR^v–Q–, $-NR^v-Q-$ or –(5-membered heteroarylene)–Q–. In this embodiment, more preferably L_1 is $-C(O)NR^v-Q-$, or $-NR^v-Q-$. Yet more preferably, L_1 is $-C(O)NR^v-Q-$, –(oxetanylene)–NR^v–Q–, or –(triazolylene)–Q–. In this embodiment, yet more preferably L_1 is $-C(O)NR^v-Q-$. Most preferably, L_1 is $-C(O)NH-CH_2-$, $-C(O)N(CH_3)-CH_2-$, $-C(O)NH-$, $-C(O)NH-CH(CH_3)-$, $-C(O)NH-C(^2H)_2-$, (oxetanylene)–$NH-CH_2-$, or –(triazolylene)–CH_2-. In this embodiment, most preferably, L_1 is $-C(O)NH-CH_2-$. In one embodiment, L_1 is not $-NH-$.

Preferably, in formula (I') or formula (I), Q is a direct bond, linear or branched C_1-C_4 alkylene, or linear or branched C_1-C_4 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted. More preferably, Q is a direct bond, or unsubstituted C_1-C_2 alkylene. Yet more preferably, Q is a direct bond or methylene. Most preferably, Q is methylene.

Preferably, in formula (I') or formula (I), L_1' is a direct bond, linear or branched C_1-C_2 alkylene, linear or branched C_1-C_2 haloalkylene or 4- to 5-membered heterocyclyene. More preferably, L_1' is a direct bond, linear or branched C_1-C_2 alkylene, linear or branched C_1-C_2 haloalkylene or 4-membered heterocyclyene. Yet more preferably, L_1' is a direct bond, linear or branched C_1-C_2 alkylene, linear or branched C_1-C_2 haloalkylene or

oxetanylene. In this embodiment, further preferably, L_1' is a direct bond, linear or branched C_1-C_2 alkylene, or linear or branched C_1-C_2 haloalkylene. In this embodiment, more preferably, L_1' is a direct bond. More preferably, L_1' is oxetanylene.

Preferably, in formula (I') or formula (I), Het' is a 5- to 6-membered heteroarylene group which is unsubstituted or substituted by one, two or three C_1-C_3 alkyl groups which are the same or different. More preferably, Het' is a 5- to 6-membered heteroarylene group which is unsubstituted or substituted by one C_1-C_3 alkyl group. Further preferably, Het' is an unsubstituted 5- to 6-membered heteroarylene group. Most preferably, Het' is an unsubstituted triazolylene group.

Preferably, in formula (I') or formula (I), R^v is hydrogen or methyl. More preferably, R^v is hydrogen.

Preferably, in formula (I') or formula (I), R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl. More preferably, R_a and R_b are the same or different and are C_1-C_4 alkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl. In this embodiment, more preferably, R_a and R_b are the same or different and are C_1-C_4 alkyl; or R_a and R_b together with the carbon to which they are attached form a 4- to 6-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl. More typically, R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl. Yet more preferably, R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 3- to 7-membered cycloalkyl which is unsubstituted or substituted by one or two substituents selected from fluorine and C_1-C_3 alkyl. In this embodiment, yet more preferably, R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an

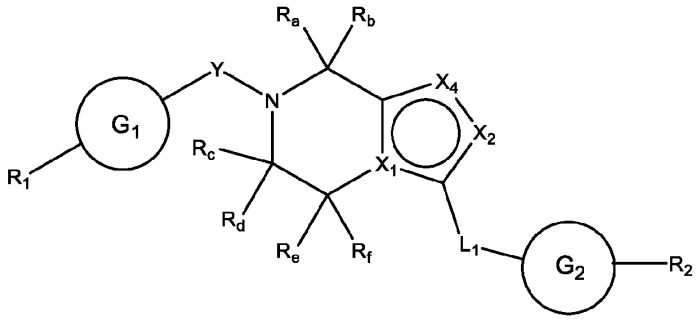
unsubstituted 4- to 6-membered heterocyclyl, or a 4- to 6-membered cycloalkyl which is unsubstituted or substituted by two substituents selected from fluorine and C_1-C_3 alkyl. Yet more typically, R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 3- to 7-membered cycloalkyl which is unsubstituted or substituted by one or two substituents selected from fluorine and C_1-C_3 alkyl. Yet further typically, R_a and R_b together with the carbon to which they are attached form an unsubstituted 4-membered heterocyclyl, or an unsubstituted 4-membered cycloalkyl. Further preferably, R_a and R_b are the same or different and are methyl, or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted tetrahydrofuranyl, unsubstituted cyclopropyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. In this embodiment, further preferably, R_a and R_b are the same or different and are methyl, or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. Yet further preferably, R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted tetrahydrofuranyl, unsubstituted cyclopropyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. In this embodiment, yet further preferably, R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl. Most preferably, R_a and R_b together with the carbon to which they are attached form unsubstituted oxetantyl, or a cyclobutyl group which is unsubstituted or substituted by two substituents selected from fluorine and methyl. In this embodiment, most preferably, R_a and R_b together with the carbon to which they are attached form a cyclobutyl group which is unsubstituted or substituted by two substituents selected from fluorine and methyl. Typically, R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl or unsubstituted cyclobutyl.

Preferably, in formula (I') or formula (I), R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl. More preferably, R_c and R_d are the same or different and are selected from hydrogen and methyl. Most preferably, R_c and R_d are hydrogen.

Preferably, in formula (I') or formula (I), R_e and R_f are the same or different and are selected from hydrogen and C_1-C_4 alkyl. More preferably, R_e and R_f are the same or different and are selected from hydrogen and methyl. Most preferably, R_e and R_f are hydrogen.

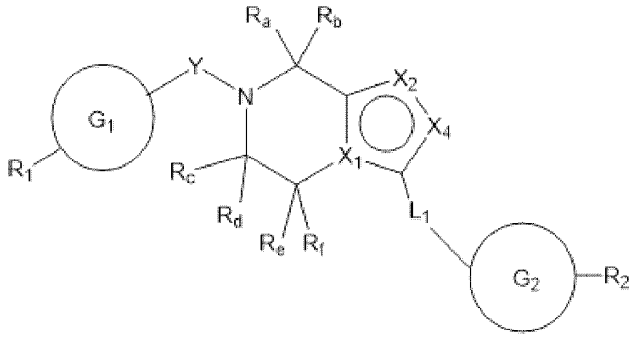
Preferably, in formula (I') or formula (I), n is 1.

Preferably, the heterocyclic compound is a compound of formula (I'i) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'i)

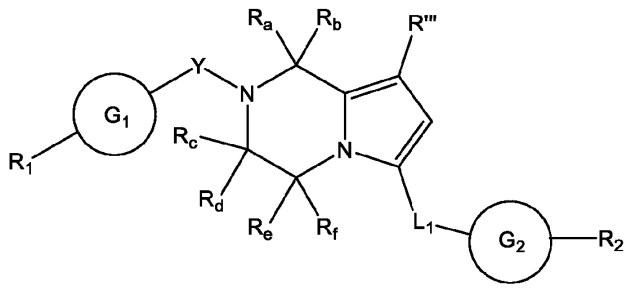
wherein R_1, R_2, G_1, G_2, Y, X_1, X_2, X_4, L_1, R_a, R_b, R_c, R_d, R_e and R_f are as defined above for formula (I'). In this embodiment, preferably the heterocyclic compound is a compound of formula (Ii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



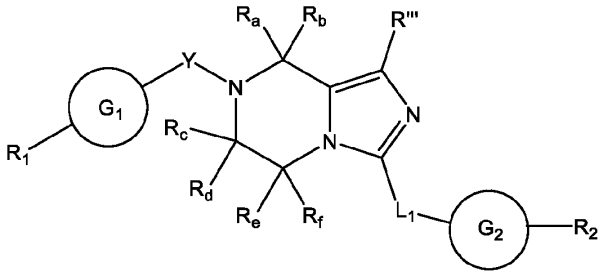
(Ii)

wherein R_1, R_2, G_1, G_2, Y, X_1, X_2, X_4, L_1, R_a, R_b, R_c, R_d, R_e and R_f are as defined above for formula (I).

More preferably, the heterocyclic compound is a compound of formula (I'ii(a)) or (I'ii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:

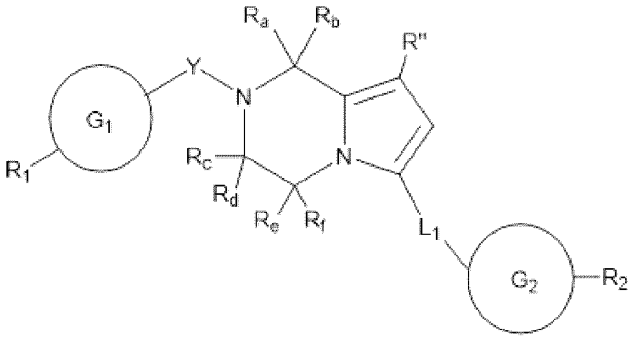


(I'ii(a))



(I'ii(b))

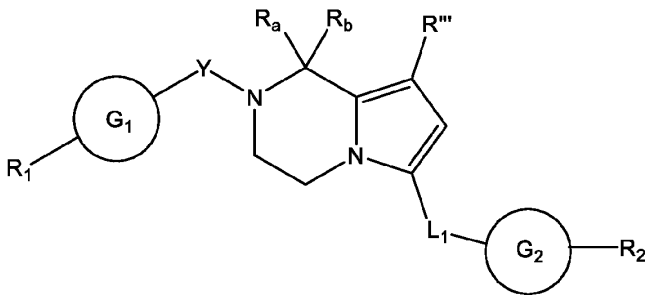
wherein R_1, R_2, G_1, G_2, Y, L_1, R''', R_a, R_b, R_c, R_d, R_e and R_f are as defined above for formula (I'). In this embodiment, more preferably, the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



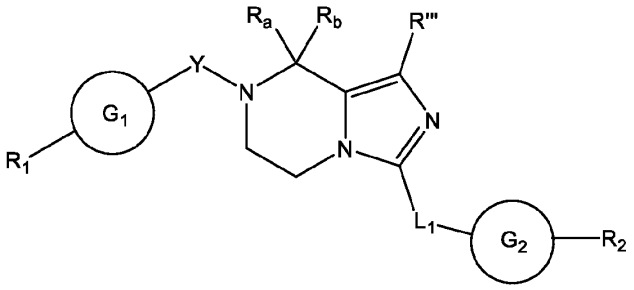
(Iii)

wherein R_1, R_2, G_1, G_2, Y, L_1, R'', R_a, R_b, R_c, R_d, R_e and R_f are as defined above for formula (I).

Yet more preferably, the heterocyclic compound is a compound of formula (I'iii(a)) or (I'iii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:

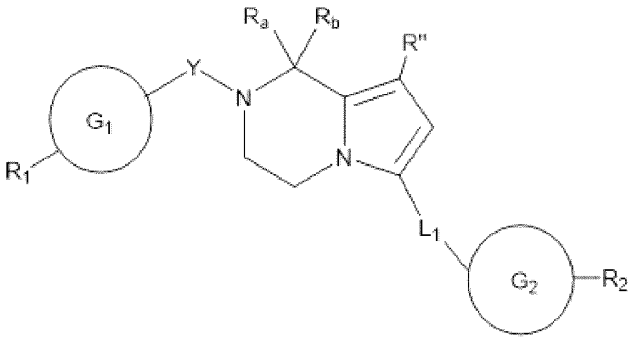


(I'iii(a))



(I'iii(b))

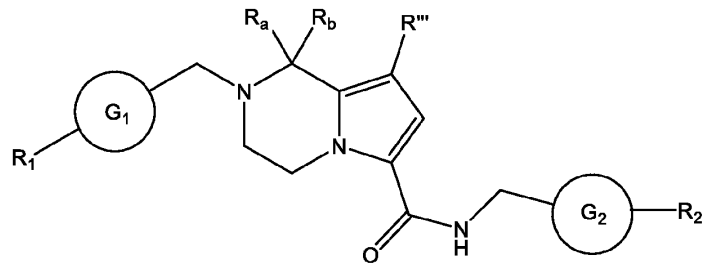
wherein R_1, R_2, G_1, G_2, Y, L_1, R''', R_a, and R_b are as defined above for formula (I'). In this embodiment, yet more preferably, the heterocyclic compound is a compound of formula (Iiii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



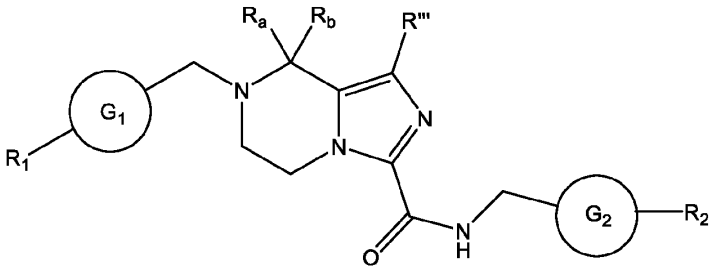
(Iiii)

wherein R_1, R_2, G_1, G_2, Y, L_1, R'', R_a, and R_b are as defined above for formula (I).

Further preferably, the heterocyclic compound is a compound of formula (I'iv(a)) or (I'iv(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:

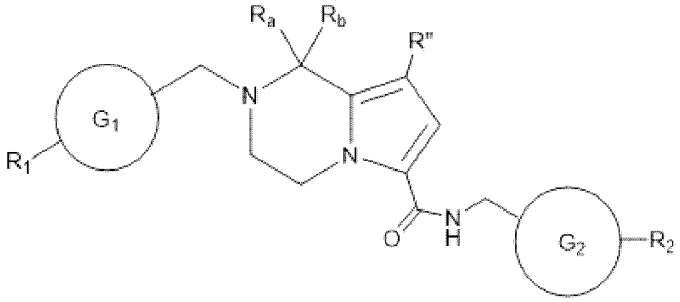


(I'iv(a))



(I'iv(b))

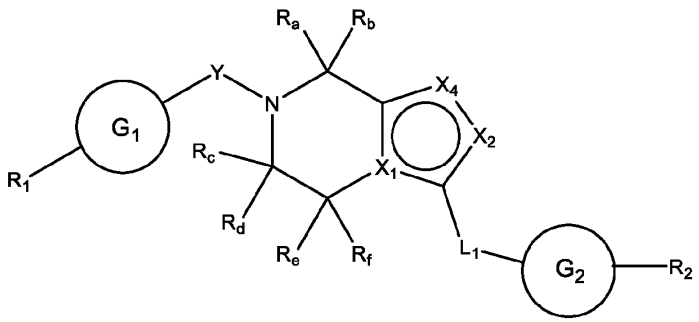
wherein R_1, R_2, G_1, G_2, R''', R_a, and R_b are as defined above for formula (I'). In this embodiment, further preferably, the heterocyclic compound is a compound of formula (Iiv) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Iiv)

wherein R_1, R_2, G_1, G_2, R'', R_a, and R_b are as defined above for formula (I).

In one preferred embodiment, the heterocyclic compound is a compound of formula (I'i) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'i)

wherein

- R_1 is C_1-C_4 haloalkyl, −L'−Z, −L'−C(O)R^y, −L'−C(O)NR^iR^y, −L'−C(O)OH, −L'−C(O)OR^y, −L'−$NR^iC(O)R^y$, −L'−$SO_2NR^iR^y$, or −L'−Het, wherein

  Het is 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and −N(C_1-C_4 alkyl)$_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, −N(C_1-C_4 alkyl)$_2$;

  Z is selected from $-OR^i$, $-NR^iR^y$ and $-SR^i$;

  R^y is C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

  R^i is selected from hydrogen and C_1-C_4 alkyl; and

  L' is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;

- R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, −L"−Z', −L"−C(O)R^z, −L"−C(O)OR^z, −L"−C(O)$NR^{iii}R^z$, −L"−C(O)NH_2, −L"−$NR^{iii}C(O)R^z$, −L"−$NR^{iii}C(O)OR^z$, −L"−$NR^{iii}C(O)NR^{iv}R^z$, −L"−$NR^{iii}C(O)C(O)NR^{iv}R^z$, −L"−$NR^{iii}SO_2R^z$, −L"−(4- to 7-membered heterocyclyl), or −L"−(5- to 7-membered heteroaryl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and wherein said

heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl; wherein

Z' is selected from −OH, $-OR^{iii}$, $-NH_2$, and $-NR^{iii}R^z$;

R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, −(C_1-C_3 alkylene)−Z', −A−A', −(C_1-C_3 alkylene)−A−A', −(C_1-C_3 alkylene−O−C_1-C_3 alkylene)−A−A', or −A−(C_1-C_3 alkylene)−A, wherein

A is phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, $-OR^{iii}$, oxo, C_1-C_4 alkyl and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-N(C_1$-C_3 alkyl)$_2$, −(C_1-C_3 alkylene)−C(O)NR^{iii}(C_1-C_3 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl;

A' is hydrogen, a phenyl moiety which moiety is unsubstituted or substituted with −(C_1-C_3 alkylene)−$NR^{iii}R^{iv}$, or a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$;

L" is a direct bond, C_1-C_3 alkylene or C_1-C_3 haloalkylene; and

R^{iii} is selected from hydrogen and C_1-C_4 alkyl;

- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, $-OR^G$ and −(C_1-C_3 alkylene)−OR^G, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^G$ and −(C_1-C_3 alkylene)−OR^G;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L^G-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are

the same or different and are selected from halogen, −O−(C_1-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl;

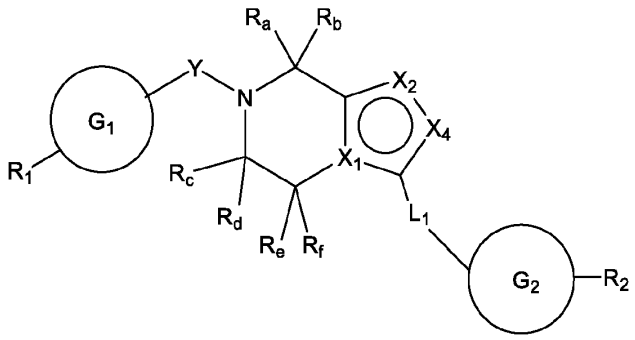
- L^G is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;
- R^G is selected from hydrogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- Y is linear or branched C_1-C_4 alkylene, linear or branched C_1-C_4 haloalkylene, or −C(O)−;
- X_1 is C or N; and X_2 is selected from N, NR' and CR"; and X_4 is selected from N, NR' and CR'"; provided that either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 is selected from N and CR" and X_4 is selected from N and CR'", and X_1 is N; wherein R' is hydrogen or C_1-C_4 alkyl, R" is hydrogen, C_1-C_4 alkyl or halogen, and R'" is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, cyano or 3- to 5-membered carbocyclyl;
- L_1 is −C(O)NR^v−Q−, −L_1'−NR^v−Q−, or −(5- to 6-membered heteroarylene)−Q−, wherein

  Q is a direct bond, linear or branched C_1-C_4 alkylene, or linear or branched C_1-C_4 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted;

  L_1' is a direct bond, linear or branched C_1-C_2 alkylene, or linear or branched C_1-C_2 haloalkylene, or 4- to 5-membered heterocyclyene; and

  R^v is hydrogen or C_1-C_3 alkyl;
- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl; and
- R_e and R_f are the same or different and are selected from hydrogen and C_1-C_4 alkyl.

In this embodiment, preferably the heterocyclic compound is a compound of formula (Ii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Ii)

wherein

- R_1 is $-L'-Z$, $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, or $-L'-Het$, wherein

  Het is 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-N(C_1$-C_4 alkyl$)_2$;

  Z is selected from $-OR^i$ or $-NR^iR^y$;

  R^y is C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

  R^i is selected from hydrogen and C_1-C_4 alkyl; and

  L' is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;

- R_2 is hydrogen, C_1-C_4 alkyl, $-L''-Z'$, $-L''-C(O)R^z$, $-L''-C(O)NR^{iii}R^z$, $-L''-NR^{iii}C(O)R^z$, $-L''-NR^{iii}C(O)OR^z$, $-L''-NR^{iii}C(O)NR^{iv}R^z$, $-L''-NR^{iii}SO_2R^z$, or $-L''-$(4- to 7-membered heterocyclyl), wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl; wherein

  Z' is selected from $-NH_2$ or $-NR^{iii}R^z$;

  R^z is C_1-C_6 alkyl or $-A-A'$, wherein

A is phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;

A' is hydrogen or 5- to 7-membered heterocyclyl which is unsubstituted or substituted by one C_1-C_3 alkyl group;

L" is a direct bond, C_1-C_3 alkylene or C_1-C_3 haloalkylene; and

R^{iii} is selected from hydrogen and C_1-C_4 alkyl;

- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- Y is linear or branched C_1-C_4 alkylene, linear or branched C_1-C_4 haloalkylene, or $-C(O)-$;
- X_1 is C or N; and X_2 and X_4 are the same or different and are selected from N, NR' and CR"; provided that either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 and X_4 are selected from N and CR", and X_1 is N; wherein R' is hydrogen or C_1-C_4 alkyl, and R" is hydrogen, C_1-C_4 alkyl or halogen;
- L_1 is $-C(O)NR^v-Q-$, or $-L_1'-NR^v-Q-$ wherein

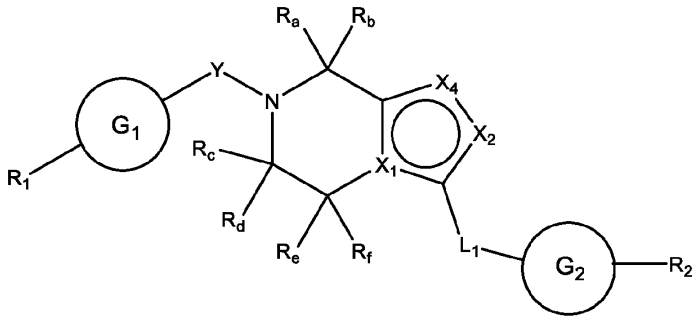
  Q is a direct bond, linear or branched C_1-C_4 alkylene, or linear or branched C_1-C_4 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted;

L_1' is a direct bond, linear or branched C_1-C_2 alkylene, or linear or branched C_1-C_2 haloalkylene; and

R^y is hydrogen or C_1-C_3 alkyl;

- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl; and
- R_e and R_f are the same or different and are selected from hydrogen and C_1-C_4 alkyl.

Alternatively, in one preferred embodiment, the heterocyclic compound is a compound of formula (I'i) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'i)

wherein

- R_1 is C_1-C_4 haloalkyl, $-L'-Z$, $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, $-L'-SO_2NR^iR^y$, or $-L'-Het$, wherein

Het is 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-N(C_1$-C_4 alkyl$)_2$;

Z is selected from $-OR^i$, $-NR^iR^y$ and $-SR^i$;

R^y is C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

R^i is selected from hydrogen and C_1-C_4 alkyl; and

L' is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;

- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, $-OR^G$ and $-(C_1$-C_3 alkylene$)-OR^G$, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^G$ and $-(C_1$-C_3 alkylene$)-OR^G$;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L^G-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-O-(C_1$-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- L^G is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;
- R^G is selected from hydrogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- Y is linear or branched C_1-C_4 alkylene, linear or branched C_1-C_4 haloalkylene, or $-C(O)-$;
- X_1 is C or N; and X_2 is selected from N, NR' and CR"; and X_4 is selected from N, NR' and CR'"; provided that either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 is selected from N and CR" and X_4 is selected from N and CR'", and X_1 is N; wherein R' is hydrogen or C_1-C_4 alkyl, R" is hydrogen, C_1-C_4 alkyl or halogen, and R'" is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, cyano or 3- to 5-membered carbocyclyl;

- L_1 is $-C(O)NR^v-Q-$, $-L_1'-NR^v-Q-$, or –(5- to 6-membered heteroarylene)–Q–, wherein

  Q is a direct bond, linear or branched C_1-C_4 alkylene, or linear or branched C_1-C_4 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted;

  L_1' is a direct bond, linear or branched C_1-C_2 alkylene, or linear or branched C_1-C_2 haloalkylene, or 4- to 5-membered heterocyclyene; and

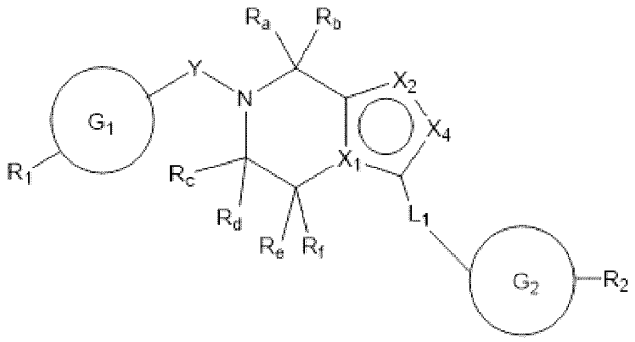
  R^v is hydrogen or C_1-C_3 alkyl;

- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;

- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl; and

- R_e and R_f are the same or different and are selected from hydrogen and C_1-C_4 alkyl.

In this embodiment, preferably the heterocyclic compound is a compound of formula (Ii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Ii)

wherein

- R_1 is $-L'-Z$, $-L'-C(O)R^y$, $-L'-C(O)NR^iR^y$, $-L'-C(O)OH$, $-L'-C(O)OR^y$, $-L'-NR^iC(O)R^y$, or $-L'-Het$, wherein

  Het is 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or

substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-N(C_1$-C_4 alkyl$)_2$;

Z is selected from $-OR^i$ or $-NR^iR^y$;

R^y is C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl, 3- to 7-membered cycloalkyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 haloalkyl, and said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

R^i is selected from hydrogen and C_1-C_4 alkyl; and

L' is a direct bond, C_1-C_4 alkylene or C_1-C_4 haloalkylene;

- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- Y is methylene or $-C(O)-$, wherein said methylene is unsubstituted or substituted by C_1-C_4 alkyl, C_1-$_4$ haloalkyl, halogen or hydroxy;
- X_1 is C or N; and X_2 and X_4 are the same or different and are selected from N, NR' and CR"; provided that either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 and X_4 are selected from N and CR", and X_1 is N; wherein R' is hydrogen or C_1-C_4 alkyl, and R" is hydrogen, C_1-C_4 alkyl or halogen;
- L_1 is $-C(O)NR^v-Q-$, or $-L_1'-NR^v-Q-$ wherein

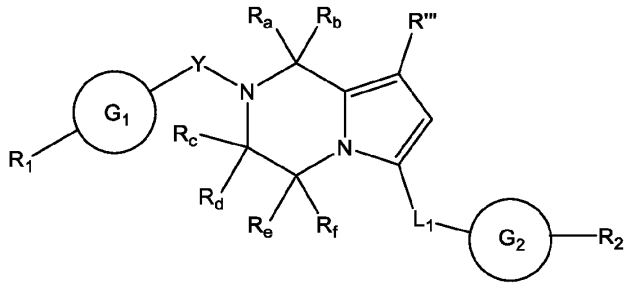
Q is a direct bond, linear or branched C_1-C_4 alkylene, or linear or branched C_1-C_4 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted;

L_1' is a direct bond, linear or branched C_1-C_2 alkylene, or linear or branched C_1-C_2 haloalkylene; and

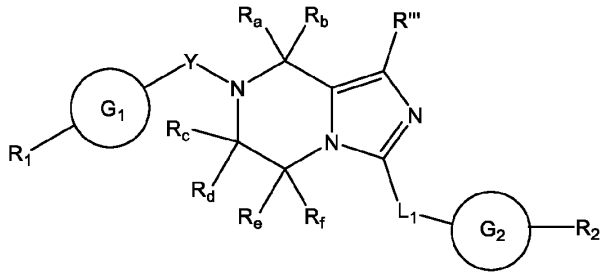
R^y is hydrogen or C_1-C_3 alkyl;

- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl; and
- R_e and R_f are the same or different and are selected from hydrogen and C_1-C_4 alkyl.

In a more preferred embodiment, the heterocyclic compound is a compound of formula (I'ii(a)) or (I'ii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'ii(a))



(I'ii(b))

wherein

- R_1 is $-C_1$-C_4 haloalkyl, $-SR^i$, $-(C_1$-C_4 alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, $-SO_2NR^iR^y$, or $-$Het, wherein

Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, C_1-C_4 alkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_4 alkyl;

R^y is C_1-C_4 alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one C_1-C_4 alkyl group; and

R^j is selected from hydrogen and C_1-C_4 alkyl;

- R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-Z'$, $-C(O)R^z$, $-C(O)OR^z$, $-C(O)NR^{iii}R^z$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, $-$(4- to 7-membered heterocyclyl) which is unsubstituted or substituted by one oxo group, or $-$(5- to 7-membered heteroaryl) which is unsubstituted or substituted with one C_1-C_3 alkyl group; wherein

  Z' is selected from $-OH$, $-O(C_1$-C_3 alkyl), $-NH_2$, $-NR^{iii}(C_1$-C_3 alkyl), $-NR^{iii}(C_1$-C_3 haloalkyl), a $-NH-$(5- to 6-membered heteroaryl) group which is unsubstituted, and a $-NH-$(4- to 6-membered heterocyclyl) group which is unsubstituted or substituted with one C_1-C_3 alkyl group, or one C_1-C_3 alkyl group and one oxo group;

  R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-(C_1$-C_3 alkylene$)-Z'$, $-A-A'$, $-(C_1$-C_3 alkylene$)-A-A'$, $-(C_1$-C_3 alkylene$-O-C_1$-C_3 alkylene$)-A-A'$, or $-A-(C_1$-C_3 alkylene$)-A$, wherein

  A is a phenyl moiety which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, $-N(C_1$-C_3 alkyl$)_2$, and $-(C_1$-C_3 alkylene$)-C(O)NR^{iii}(C_1$-C_3 alkyl), a 3- to 7-membered cycloalkyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_3 alkyl, halogen, cyano, and $-OR^{iii}$, a 5- to 7-membered heteroaryl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl, or a 4- to 10-membered heterocyclyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, C_1-C_3 alkyl, and oxo;

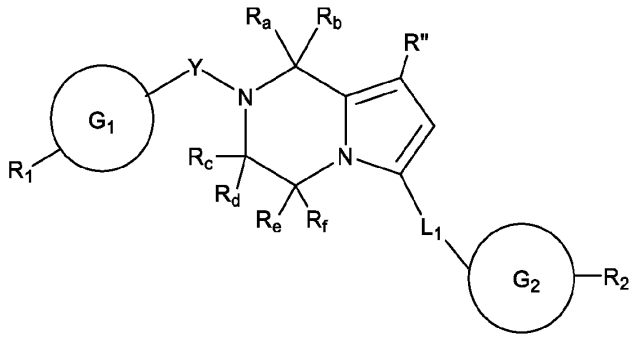
A' is hydrogen, a phenyl moiety which moiety is unsubstituted or substituted with $-(C_1\text{-}C_3$ alkylene$)-NR^{iii}R^{iv}$, or a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from $C_1\text{-}C_3$ alkyl, $C_1\text{-}C_3$ haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$; and

R^{iii} is selected from hydrogen and $C_1\text{-}C_4$ alkyl;

- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ haloalkyl, oxo, $-OR^G$ and $-(C_1\text{-}C_3$ alkylene$)-OR^G$, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ haloalkyl, $-OR^G$ and $-(C_1\text{-}C_3$ alkylene$)-OR^G$;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ haloalkyl, $-L^G-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-O-(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_4$ haloalkyl;
- L^G is a direct bond or $C_1\text{-}C_3$ alkylene;
- R^G is selected from hydrogen and $C_1\text{-}C_3$ alkyl;
- Y is methylene or $-C(O)-$, wherein said methylene is unsubstituted or substituted by $C_1\text{-}C_4$ alkyl, $C_1\text{-}_4$ haloalkyl, halogen or hydroxy;
- R''' is hydrogen, $C_1\text{-}C_4$ alkyl, halogen, $C_1\text{-}C_4$ haloalkyl, cyano or 3- to 5-membered carbocyclyl;
- L_1 is $-C(O)NR^v-Q-$, –(4-membered heterocyclylene)$-NR^v-Q-$, $-NR^v-Q-$ or –(5-membered heteroarylene)$-Q-$, wherein Q is a direct bond, or unsubstituted $C_1\text{-}C_2$ alkylene, and R^v is hydrogen or $C_1\text{-}C_3$ alkyl;
- R_a and R_b are the same or different and are $C_1\text{-}C_4$ alkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and $C_1\text{-}C_4$ alkyl;

- R_c and R_d are the same or different and are selected from hydrogen and methyl; and
- R_e and R_f are the same or different and are selected from hydrogen and methyl.

In this embodiment, more preferably the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Iii)

wherein

- R_1 is $-(C_1\text{-}C_4$ alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, or $-$Het, wherein

  Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, $C_1\text{-}C_4$ alkyl, and $-N(C_1\text{-}C_4$ alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from $C_1\text{-}C_4$ alkyl;

  R^y is $C_1\text{-}C_4$ alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one $C_1\text{-}C_4$ alkyl group; and

  R^i is selected from hydrogen and $C_1\text{-}C_4$ alkyl;

- R_2 is hydrogen, $C_1\text{-}C_4$ alkyl, $-Z'$, $-C(O)R^z$, $-C(O)NR^{iii}R^z$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, or $-$4- to 7-membered heterocyclyl which is unsubstituted or substituted by one oxo group; wherein

  Z' is selected from $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), a $-NH-$(5- to 6-membered heteroaryl) group which is unsubstituted, or a $-NH-$(4- to 6-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group;

  R^z is $C_1\text{-}C_6$ alkyl or $-A-A'$, wherein

A is a phenyl moiety, a 3- to 7-membered cycloalkyl moiety, a 5- to 7-membered heteroaryl moiety or a 4- to 10-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one C_1-C_3 alkyl group;

A' is hydrogen or 5- to 7-membered heterocyclyl which is unsubstituted or substituted by one C_1-C_3 alkyl group; and

R^{iii} is selected from hydrogen and C_1-C_4 alkyl;

- G_1 is selected from a phenyl moiety, a 4- to 7-membered heterocyclyl moiety, a 5- to 7-membered heteroaryl moiety, or a 4- to 7-membered cycloalkyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one substituent selected from C_1-C_4 alkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- Y is methylene or $-C(O)-$, wherein said methylene is unsubstituted or substituted by C_1-C_4 alkyl, C_{1-4} haloalkyl, halogen or hydroxy;
- R'' is hydrogen, C_1-C_4 alkyl or halogen;
- L_1 is $-C(O)NR^v-Q-$, or $-NR^v-Q-$ wherein Q is a direct bond, or unsubstituted C_1-C_2 alkylene, and R^v is hydrogen or C_1-C_3 alkyl;
- R_a and R_b are the same or different and are C_1-C_4 alkyl; or R_a and R_b together with the carbon to which they are attached form a 4- to 6-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl;
- R_c and R_d are the same or different and are selected from hydrogen and methyl; and
- R_e and R_f are the same or different and are selected from hydrogen and methyl.

In a yet more preferred embodiment, the heterocyclic compound is a compound of formula (I'ii(a)) or (I'ii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, wherein

- R_1 is C_1-C_3 haloalkyl, $-SR^i$, (C_1-C_4 alkylene)$-OH$, $-C(O)R^y$, $-C(O)NR^i(C_1$-C_3 alkyl), $-C(O)OH$, $-C(O)O(C_1$-C_3 alkyl), $-NR^iC(O)(C_1$-C_3 alkyl), $-SO_2NR^i(C_1$-C_3 alkyl), 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-

C_3 alkyl group or one $-N(C_1\text{-}C_3$ alkyl$)_2$ group, or which is substituted by one oxo group and one $C_1\text{-}C_3$ alkyl group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one or two $C_1\text{-}C_3$ alkyl, wherein

R^y is $C_1\text{-}C_3$ alkyl, or unsubstituted 4- to 6-membered heterocyclyl; and

R^i is hydrogen or $C_1\text{-}C_3$ alkyl;

- R_2 is hydrogen, $C_1\text{-}C_3$ alkyl, $C_1\text{-}C_3$ haloalkyl, −Z', $-C(O)(C_1\text{-}C_3$ alkyl), $-C(O)O(C_1\text{-}C_4$ alkyl), $-C(O)NR^{iii}(C_1\text{-}C_3$ alkyl), $-C(O)NR^{iii}(-A-A')$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)O(C_1\text{-}C_4$ alkyl), $-NR^{iii}C(O)O(-A-A')$, $-NR^{iii}C(O)NR^{iv}(C_1\text{-}C_3$ alkyl), $-NR^{iii}C(O)C(O)NR^{iv}(C_1\text{-}C_3$ alkyl), $-NHSO_2(C_1\text{-}C_3$ alkyl), 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group, or 5-membered heteroaryl which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, wherein

Z' is $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), $-NR^{iii}(C_1\text{-}C_3$ haloalkyl), a −NH−(6-membered heteroaryl) group which is unsubstituted, a −NH−(4-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, or a −NH−(6-membered heterocyclyl) group which is substituted with one $C_1\text{-}C_3$ alkyl group and one oxo group;

R^z is $C_1\text{-}C_5$ alkyl, or 3- to 5-membered cycloalkyl which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, and $-OR^{iii}$, or 4- to 10 membered heterocyclyl which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, $C_1\text{-}C_3$ alkyl, and oxo, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one substituent selected from $C_1\text{-}C_3$ alkyl, halogen, $-N(C_1\text{-}C_3$ alkyl$)_2$, and $-(C_1\text{-}C_3$ alkylene$)-C(O)NR^{iii}(C_1\text{-}C_3$ alkyl), or (5- to 6-membered heteroaryl)−A' wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and $C_1\text{-}C_3$ alkyl, wherein

A' is hydrogen, phenyl which is substituted with $-(C_1\text{-}C_3$ alkylene$)-NH(CH_3)$, a 4-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, cyclopropyl, cyclobutyl, and methoxy, a 5-membered heterocyclyl which is unsubstituted or substituted with one methoxy group, a 6-membered heterocyclyl which is unsubstituted or substituted with one substituent selected from methyl, ethyl, C_2 haloalkyl, cyclopropyl, cyclobutyl, oxetanyl, oxo, and methoxy, or an unsubstituted 7- to 8-membered heterocyclyl, and

R^{iii} is hydrogen or C_1-C_3 alkyl;

- G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered cycloalkyl, 5- to 6-membered heteroaryl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl;
- G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; 5- to 6- membered cycloalkyl which is unsubstituted or substituted with one hydroxy group; 5- to 10- membered heteroaryl which is unsubstituted or substituted with one halogen group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from halogen, −O−(C_1-C_3 alkyl) and C_1-C_3 alkyl;
- Y is methylene or −C(O)−;
- R''' is hydrogen, halogen, methyl, trifluoromethyl, cyano or 3-to 4-membered carbocyclyl;
- L_1 is −C(O)NR^v−Q−, −(oxetanylene)−NR^v−Q−, or −(triazolylene)−Q−, wherein Q is a direct bond or methylene and R^v is hydrogen or C_1-C_3 alkyl; and

R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 3- to 7-membered cycloalkyl which is unsubstituted or substituted by one or two substituents selected from fluorine and C_1-C_3 alkyl.

In this embodiment, yet more preferably the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, wherein

- R_1 is (C_1-C_4 alkylene)−OH, −C(O)R^y, −C(O)NR^i(C_1-C_3 alkyl), −C(O)OH, −C(O)O(C_1-C_3 alkyl), −NR^iC(O)(C_1-C_3 alkyl); 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one −N(C_1-C_3 alkyl)$_2$ group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one C_1-C_3 alkyl, wherein

R^y is C_1-C_3 alkyl, or unsubstituted 4- to 6-membered heterocyclyl; and

R^i is hydrogen or C_1-C_3 alkyl;

- R_2 is hydrogen, C_1-C_3 alkyl, −Z', −C(O)(C_1-C_3 alkyl), −C(O)NR^{iii}(C_1-C_3 alkyl), −NR^{iii}C(O)R^z, −NHC(O)O(C_1-C_4 alkyl), −NHC(O)N(C_1-C_3 alkyl)$_2$, −$NHSO_2$(C_1-C_3 alkyl),

or 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group, wherein

Z' is $-NH_2$, $-NR^{iii}(C_1\text{-}C_3$ alkyl), a $-NH-$(6-membered heteroaryl) group which is unsubstituted, or a $-NH-$(4-membered heterocyclyl) group which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group;

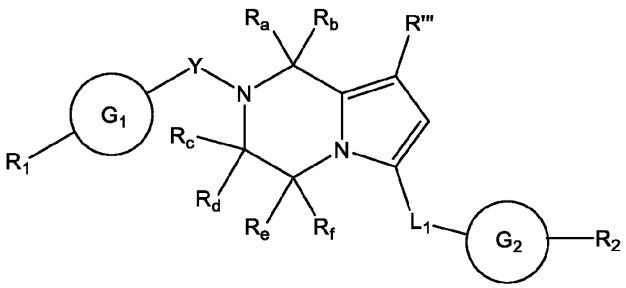
R^Z is $C_1\text{-}C_5$ alkyl, unsubstituted 3- to 5-membered cycloalkyl, unsubstituted 6-membered heteroaryl, unsubstituted 4-membered heterocyclyl, 9- to 10-membered heterocyclyl which is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, or phenyl$-$A' wherein said phenyl is unsubstituted or substituted with one $C_1\text{-}C_3$ alkyl group, wherein

A' is hydrogen or 6-membered heterocyclyl which is unsubstituted or substituted with one methyl group, and

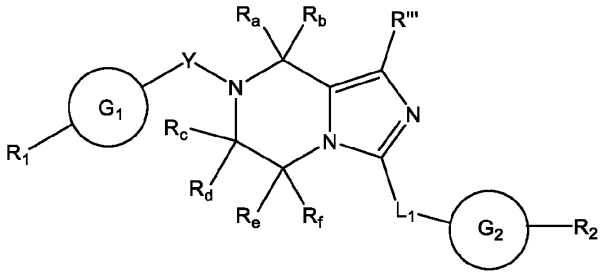
R^{iii} is hydrogen or $C_1\text{-}C_3$ alkyl;

- G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered heteroaryl, unsubstituted 5- to 6-membered cycloalkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and $C_1\text{-}C_3$ alkyl;
- G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; unsubstituted 5- to 6- membered cycloalkyl; unsubstituted 5- to 10- membered heteroaryl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and $C_1\text{-}C_3$ alkyl;
- Y is methylene or $-C(O)-$;
- R'' is hydrogen or fluorine;
- L_1 is $-C(O)NR^v-Q-$, wherein Q is a direct bond or methylene and R^v is hydrogen or $C_1\text{-}C_3$ alkyl; and
- R_a and R_b are the same or different and are $C_1\text{-}C_3$ alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 4- to 6-membered cycloalkyl which is unsubstituted or substituted by two substituents selected from fluorine and $C_1\text{-}C_3$ alkyl.

Alternatively, in a more preferred embodiment, the heterocyclic compound is a compound of formula (I'ii(a)) or (I'ii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'ii(a))



(I'ii(b))

wherein

- R_1 is $-C_1$-C_4 haloalkyl, $-SR^i$, $-(C_1$-C_4 alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, $-SO_2NR^iR^y$, or $-$Het, wherein

  Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, C_1-C_4 alkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_4 alkyl;

  R^y is C_1-C_4 alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one C_1-C_4 alkyl group; and

  R^i is selected from hydrogen and C_1-C_4 alkyl;

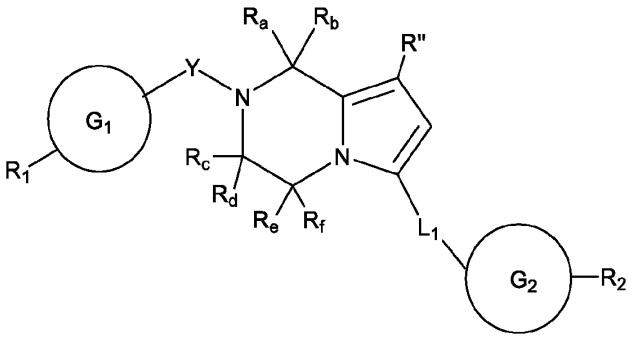
- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;

- G_1 is selected from phenyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, $-OR^G$ and $-(C_1$-C_3 alkylene$)-OR^G$, and wherein said phenyl, and heteroaryl are unsubstituted or substituted by

one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^G$ and $-(C_1$-C_3 alkylene)$-OR^G$;

- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-L^G-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-O-(C_1$-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- L^G is a direct bond or C_1-C_3 alkylene;
- R^G is selected from hydrogen and C_1-C_3 alkyl;
- Y is methylene or $-C(O)-$, wherein said methylene is unsubstituted or substituted by C_1-C_4 alkyl, C_1-$_4$ haloalkyl, halogen or hydroxy;
- R''' is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, cyano or 3- to 5-membered carbocyclyl;
- L_1 is $-C(O)NR^v-Q-$, –(4-membered heterocyclylene)$-NR^v-Q-$, $-NR^v-Q-$ or –(5-membered heteroarylene)$-Q-$, wherein Q is a direct bond, or unsubstituted C_1-C_2 alkylene, and R^v is hydrogen or C_1-C_3 alkyl;
- R_a and R_b are the same or different and are C_1-C_4 alkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl;
- R_c and R_d are the same or different and are selected from hydrogen and methyl; and
- R_e and R_f are the same or different and are selected from hydrogen and methyl.

In this embodiment, more preferably the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Iii)

wherein

- R_1 is $-(C_1\text{-}C_4$ alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, or $-$Het, wherein

  Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, $C_1\text{-}C_4$ alkyl, and $-N(C_1\text{-}C_4$ alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from $C_1\text{-}C_4$ alkyl;

  R^y is $C_1\text{-}C_4$ alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one $C_1\text{-}C_4$ alkyl group; and

  R^i is selected from hydrogen and $C_1\text{-}C_4$ alkyl;

- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is selected from a phenyl moiety, a 4- to 7-membered heterocyclyl moiety, a 5- to 7-membered heteroaryl moiety, or a 4- to 7-membered cycloalkyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_4$ haloalkyl;
- G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one substituent selected from $C_1\text{-}C_4$ alkyl and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_4$ haloalkyl;
- Y is methylene or $-C(O)-$;
- R" is hydrogen, $C_1\text{-}C_4$ alkyl or halogen;

- L_1 is $-C(O)NR^v-Q-$, or $-NR^v-Q-$ wherein Q is a direct bond, or unsubstituted C_1-C_2 alkylene, and R^v is hydrogen or C_1-C_3 alkyl;
- R_a and R_b are the same or different and are C_1-C_4 alkyl; or R_a and R_b together with the carbon to which they are attached form a 4- to 6-membered cycloalkyl moiety or 4- to 6-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_4 alkyl;
- R_c and R_d are the same or different and are selected from hydrogen and methyl; and
- R_e and R_f are the same or different and are selected from hydrogen and methyl.

In this embodiment, yet more preferably the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, wherein

- R_1 is (C_1-C_4 alkylene)$-OH$, $-C(O)R^y$, $-C(O)NR^i(C_1$-C_3 alkyl), $-C(O)OH$, $-C(O)O(C_1$-C_3 alkyl), $-NR^iC(O)(C_1$-C_3 alkyl); 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl)$_2$ group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one C_1-C_3 alkyl, wherein

  R^y is C_1-C_3 alkyl, or unsubstituted 4- to 6-membered heterocyclyl; and

  R^i is hydrogen or C_1-C_3 alkyl;

- R_2 is hydrogen, C_1-C_3 alkyl, $-Z'$, $-C(O)(C_1$-C_3 alkyl), $-C(O)NR^{iii}(C_1$-C_3 alkyl), $-NR^{iii}C(O)R^z$, $-NHC(O)O(C_1$-C_4 alkyl), $-NHC(O)N(C_1$-C_3 alkyl)$_2$, $-NHSO_2(C_1$-C_3 alkyl), or 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group, wherein

  Z' is $-NH_2$, $-NR^{iii}(C_1$-C_3 alkyl), a $-NH-$(6-membered heteroaryl) group which is unsubstituted, or a $-NH-$(4-membered heterocyclyl) group which is unsubstituted or substituted with one C_1-C_3 alkyl group;

  R^z is C_1-C_5 alkyl, unsubstituted 3- to 5-membered cycloalkyl, unsubstituted 6-membered heteroaryl, unsubstituted 4-membered heterocyclyl, 9- to 10-membered heterocyclyl which is unsubstituted or substituted with one C_1-C_3 alkyl group, or phenyl$-A'$ wherein said phenyl is unsubstituted or substituted with one C_1-C_3 alkyl group, wherein

  A' is hydrogen or 6-membered heterocyclyl which is unsubstituted or substituted with one methyl group, and

  R^{iii} is hydrogen or C_1-C_3 alkyl;

- G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered heteroaryl, unsubstituted 5- to 6-membered cycloalkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl;
- G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; unsubstituted 5- to 6- membered cycloalkyl; unsubstituted 5- to 10- membered heteroaryl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl;
- Y is methylene or −C(O)−;
- R'' is hydrogen or fluorine;
- L_1 is $-C(O)NR^v-Q-$, wherein Q is a direct bond or methylene and R^v is hydrogen or C_1-C_3 alkyl; and
- R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 4- to 6-membered cycloalkyl which is unsubstituted or substituted by two substituents selected from fluorine and C_1-C_3 alkyl.

In a yet more preferred embodiment, the heterocyclic compound is a compound of formula (I'ii(a)) or (I'ii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, wherein

- R_1 is C_1-C_3 haloalkyl, $-SR^i$, (C_1-C_4 alkylene)−OH, $-C(O)R^y$, $-C(O)NR^i(C_1$-C_3 alkyl), −C(O)OH, $-C(O)O(C_1$-C_3 alkyl), $-NR^iC(O)(C_1$-C_3 alkyl), $-SO_2NR^i(C_1$-C_3 alkyl), 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group, or which is substituted by one oxo group and one C_1-C_3 alkyl group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one or two C_1-C_3 alkyl, wherein

  R^y is C_1-C_3 alkyl, or unsubstituted 4- to 6-membered heterocyclyl; and

  R^i is hydrogen or C_1-C_3 alkyl;
- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered cycloalkyl, 5- to 6-membered heteroaryl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl;

- G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; 5- to 6- membered cycloalkyl which is unsubstituted or substituted with one hydroxy group; 5- to 10- membered heteroaryl which is unsubstituted or substituted with one halogen group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from halogen, $-O-(C_1-C_3$ alkyl) and C_1-C_3 alkyl;
- Y is methylene or $-C(O)-$;
- R''' is hydrogen, halogen, methyl, trifluoromethyl, cyano or 3-to 4-membered carbocyclyl;
- L_1 is $-C(O)NR^v-Q-$, $-$(oxetanylene)$-NR^v-Q-$, or $-$(triazolylene)$-Q-$, wherein Q is a direct bond or methylene and R^v is hydrogen or C_1-C_3 alkyl; and

R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 3- to 7-membered cycloalkyl which is unsubstituted or substituted by one or two substituents selected from fluorine and C_1-C_3 alkyl.

In this embodiment, yet more preferably the heterocyclic compound is a compound of formula (Iii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, wherein

- R_1 is $(C_1-C_4$ alkylene$)-OH$, $-C(O)R^y$, $-C(O)NR^i(C_1-C_3$ alkyl), $-C(O)OH$, $-C(O)O(C_1-C_3$ alkyl), $-NR^iC(O)(C_1-C_3$ alkyl); 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1-C_3$ alkyl$)_2$ group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one C_1-C_3 alkyl, wherein

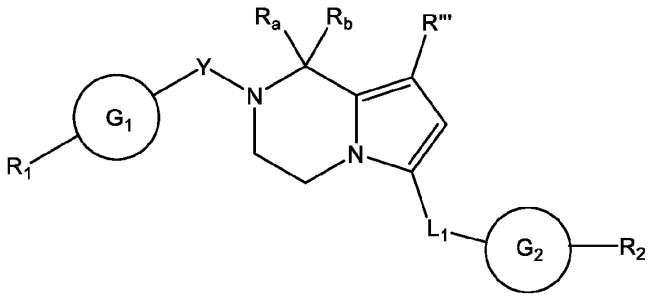
  R^y is C_1-C_3 alkyl, or unsubstituted 4- to 6-membered heterocyclyl; and

  R^i is hydrogen or C_1-C_3 alkyl;
- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is unsubstituted 5- to 6-membered heterocyclyl, unsubstituted 5- to 6-membered heteroaryl, unsubstituted 5- to 6-membered cycloalkyl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl;
- G_2 is 5- to 10-membered heterocyclyl which is unsubstituted or substituted with one oxo group; unsubstituted 5- to 6- membered cycloalkyl; unsubstituted 5- to 10- membered

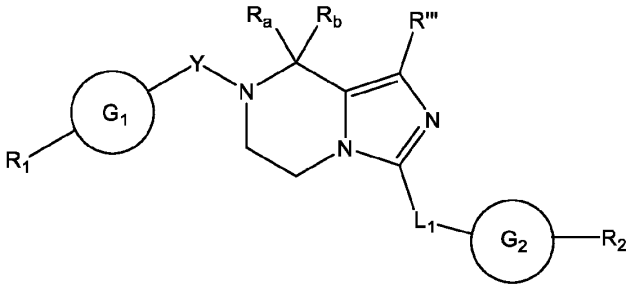
heteroaryl, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine and C_1-C_3 alkyl;

- Y is methylene or −C(O)−;
- R'' is hydrogen or fluorine;
- L_1 is $-C(O)NR^v-Q-$, wherein Q is a direct bond or methylene and R^v is hydrogen or C_1-C_3 alkyl; and
- R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 4- to 6-membered cycloalkyl which is unsubstituted or substituted by two substituents selected from fluorine and C_1-C_3 alkyl.

In a further preferred embodiment, the heterocyclic compound is a compound of formula (I'iii(a)) or (I'iii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iii(a))



(I'iii(b))

wherein

- R_1 is CF_2CH_3, $-SCH_3$, C4 alkylene−OH, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl), $-C(O)N(CH_2CH_3)_2$, $-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-SO_2NH(CH_3)$, or unsubstituted pyrrolidinone, or an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or a

triazolyl moiety which is unsubstituted, substituted with one methyl group, or substituted with one oxo group and one methyl group, or an imidazolyl moiety which is unsubstituted, substituted with one or two methyl groups, or substituted with one oxo group and one methyl group, or a pyrazolyl moiety which is unsubstituted or substituted by one methyl group, or unsubstituted oxadiazolyl, or an oxazolyl moiety which is unsubstituted or substituted by one methyl group, or a furanyl moiety which is substituted with two methyl groups, or unsubstituted tetrahydrofuranyl, or unsubstituted tetrazolyl, wherein

R^y is methyl, ethyl, i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl;

- R_2 is hydrogen, methyl, $-CH_2F$, $-Z'$, $-C(O)CH_3$, $-C(O)O$(*tert*-butyl), $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH(-A-A')$, $-C(O)NH_2$, $-N(CH_3)C(O)CH_3$, $-NHC(O)R^z$, $-NHC(O)O(C_3\text{-}C_4$ alkyl), $-NHC(O)O$(unsubstituted phenyl), $-NHC(O)N(CH_3)_2$, $-NHC(O)N(CH_3)(CH_2CH_3)$, $-NHC(O)NH(CH_3)$, $-NHC(O)C(O)N(CH_3)_2$, $-NHSO_2(CH_3)$, unsubstituted pyrrolidinone, unsubstituted dihydrotriazolone, unsubstituted oxadiazolone, imidazolyl which is unsubstituted or substituted with one methyl group, triazolyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrazolyl, wherein

  Z' is $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-NHCH_2CF_3$, a $-NH-$pyridinyl group which is unsubstituted, a $-NH-$oxetanyl group which is unsubstituted or substituted with one methyl group, or a $-NH-$(unsubstituted pyrimidinone) group;

  R^z is methyl, *tert*-butyl, *iso*-butyl, $-CH_2-$(*tert*-butyl), cyclopropyl which is unsubstituted or substituted with one halogen group, cyclobutyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, oxadiazolyl which is substituted with one methyl group, unsubstituted thiazolyl, benzodioxazolyl which is unsubstituted or substituted with one or two halogen groups, oxetanyl which is unsubstituted or substituted with one methyl group, azetidinyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted pyrrolidinyl, pyrimidinonyl which is unsubstituted or substituted with one methyl group, indolinyl which is unsubstituted or substituted with one methyl group, morpholinyl which is unsubstituted or substituted with one methyl group, piperidinyl which is unsubstituted or substituted with one methyl group, piperazinyl which is unsubstituted or substituted with one methyl group, tetrahydroquinoline which is unsubstituted or substituted by one or two substituents which are the same or

different and are selected from halogen and methyl, unsubstituted tetrahydrofuranyl, unsubstituted tetrahydropyranyl, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, tetrahydro-1H,3H-5l2-furo[3,4-c]pyrrole which is substituted with one or two methyl groups, unsubstituted oxa-azaspiroheptane, unsubstituted oxa-azaspirooctane, unsubstituted oxa-azaspirononane, unsubstituted oxa-azabicycloheptane, unsubstituted oxa-azabicyclooctane, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one substituent selected from methyl, propyl, halogen, $-N(CH_3)_2$, and –(ethylene)−C(O)NH(CH_3), or (imidazolyl)−A' wherein said imidazolyl is unsubstituted or substituted with one methyl group, or (pyrazolyl)−A' wherein said pyrazolyl is unsubstituted or substituted with one or two methyl groups, or (pyridinyl)−A' wherein said pyridinyl is unsubstituted or substituted with one C_1-C_3 alkyl group or one halogen group, or (pyrimidinyl)−A' wherein said pyrimidinyl is unsubstituted or substituted with one methyl group, wherein

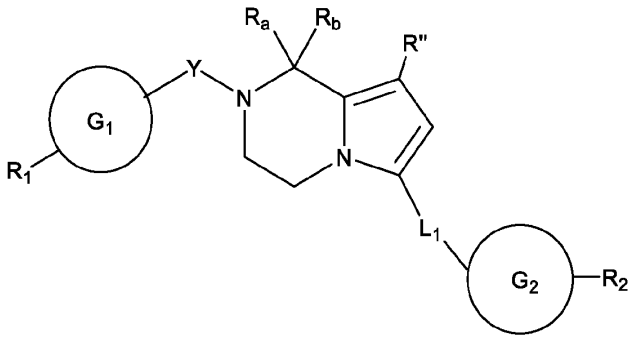
A' is hydrogen, phenyl which is substituted with $-(CH_2)-NH(CH_3)$, azetidinyl which is substituted with one substituent selected from methyl, methoxy, cyclopropyl, and cyclobutyl, piperidinyl which is substituted with one substituent selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH_2CH_2F$, $-CH_2CHF_2$, methoxy, and oxetanyl, morpholinyl which is unsubstituted or substituted with one methyl group or one oxo group, piperazinyl which is substituted with one substituent selected from methyl, cyclopropyl, and cyclobutyl, tetrahydropyridinyl which is substituted with one methyl group, pyrrolidinyl which is substituted with one methoxy group, or unsubstituted oxazaspiroheptane, unsubstituted oxazaspirooctane, or unsubstituted tetrahydropyranyl;

- G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, unsubstituted pyrimidinyl, pyridinyl which is unsubstituted or substituted with one methyl group, one fluorine group, or one chlorine group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and methyl;
- G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted pyrrolidinyl, unsubstituted tetrahydropyranyl, unsubstituted bicyclo[1.1.1]pentyl, cyclohexyl which is unsubstituted or substituted with one hydroxy group, unsubstituted indolinyl, unsubstituted oxoindolinyl, unsubstituted benzoxazolonyl, unsubstituted

dihydroquinolinonyl, pyridinyl which is unsubstituted or substituted with one chlorine group, unsubstituted pyrimidinyl, unsubstituted indolyl, unsubstituted oxazolyl, unsubstituted thiazolyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine, chlorine, methoxy and methyl;

- Y is methylene or −C(O)−;
- R''' is hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl, cyano, or cyclopropyl;
- L_1 is −C(O)NR^v−Q−, –(oxetanylene)−NR^v−Q−, or –(triazolylene)−Q−, wherein Q is a direct bond or methylene, and R^v is hydrogen or methyl;
- R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted tetrahydrofuranyl, unsubstituted cyclopropyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl.

In this embodiment, further preferably the heterocyclic compound is a compound of formula (Iiii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Iiii)

wherein

- R_1 is C_4 alkylene−OH, −C(O)R^y, −C(O)$NHCH_3$, −C(O)$N(CH_3)_2$, −C(O)$N(CH_3)(C_3$ alkyl), −C(O)OH, −C(O)OCH_3, −$NHC(O)CH_3$, −$N(CH_3)C(O)CH_3$, unsubstituted pyrrolidinone, an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one −$N(CH_3)_2$ group, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl, wherein

R^y is i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl;

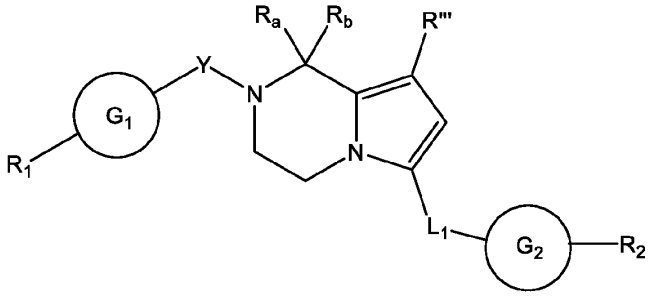
- R_2 is hydrogen, methyl, −Z', −C(O)CH_3, −C(O)NH(CH_3), −C(O)N(CH_3)$_2$, −N(CH_3)C(O)CH_3, −NHC(O)R^z, −NHC(O)O(C_4 alkyl), −NHC(O)N(CH_3)$_2$, −$NHSO_2$(CH_3), or unsubstituted pyrrolidinone, wherein

  Z' is −NH_2, −NH(CH_3), −N(CH_3)$_2$, a −NH−pyridinyl group which is unsubstituted, or a −NH−oxetanyl group which is unsubstituted or substituted with one methyl group;

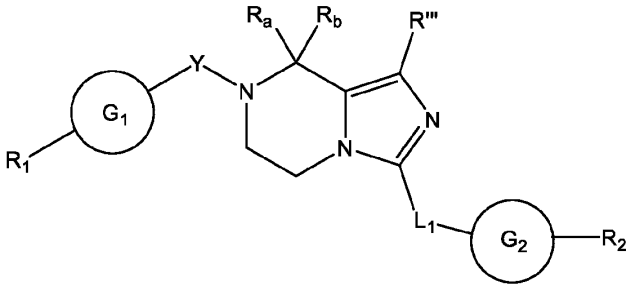
  R^z is methyl, *tert*-butyl, −CH_2−(*tert*-butyl), unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, unsubstituted oxetanyl, indolinyl which is unsubstituted or substituted with one methyl group, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one propyl group, wherein A' is hydrogen, piperidinyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrahydropyranyl;

- G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted indolinyl, unsubstituted oxoindolinyl or unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- Y is methylene or −C(O)−;
- R'' is hydrogen or fluorine;
- L_1 is −C(O)NR^v−Q−, wherein Q is a direct bond or methylene, and R^v is hydrogen or methyl;
- R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl.

Alternatively, in a further preferred embodiment, the heterocyclic compound is a compound of formula (I'iii(a)) or (I'iii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iii(a))



(I'iii(b))

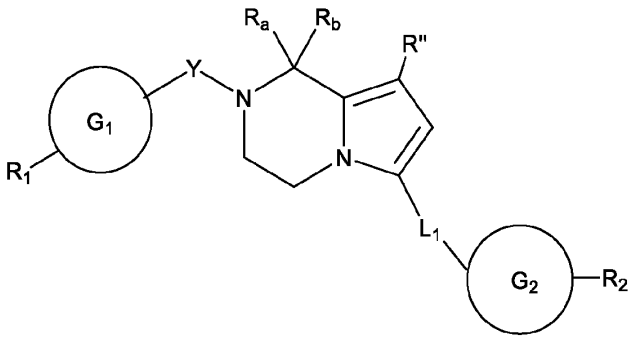
- R_1 is CF_2CH_3, $-SCH_3$, C4 alkylene–OH, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl), $-C(O)N(CH_2CH_3)_2$, $-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-SO_2NH(CH_3)$, or unsubstituted pyrrolidinone, or an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or a triazolyl moiety which is unsubstituted, substituted with one methyl group, or substituted with one oxo group and one methyl group, or an imidazolyl moiety which is unsubstituted, substituted with one or two methyl groups, or substituted with one oxo group and one methyl group, or a pyrazolyl moiety which is unsubstituted or substituted by one methyl group, or unsubstituted oxadiazolyl, or an oxazolyl moiety which is unsubstituted or substituted by one methyl group, or a furanyl moiety which is substituted with two methyl groups, or unsubstituted tetrahydrofuranyl, or unsubstituted tetrazolyl, wherein

  R^y is methyl, ethyl, i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl;

- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety

- G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, unsubstituted pyrimidinyl, pyridinyl which is unsubstituted or substituted with one methyl group, one fluorine group, or one chlorine group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and methyl;
- G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted pyrrolidinyl, unsubstituted tetrahydropyranyl, unsubstituted bicyclo[1.1.1]pentyl, cyclohexyl which is unsubstituted or substituted with one hydroxy group, unsubstituted indolinyl, unsubstituted oxoindolinyl, unsubstituted benzoxazolonyl, unsubstituted dihydroquinolinonyl, pyridinyl which is unsubstituted or substituted with one chlorine group, unsubstituted pyrimidinyl, unsubstituted indolyl, unsubstituted oxazolyl, unsubstituted thiazolyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine, chlorine, methoxy and methyl;
- Y is methylene or $-C(O)-$;
- R''' is hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl, cyano, or cyclopropyl;
- L_1 is $-C(O)NR^v-Q-$, $-$(oxetanylene)$-NR^v-Q-$, or $-$(triazolylene)$-Q-$, wherein Q is a direct bond or methylene, and R^v is hydrogen or methyl;
- R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted tetrahydrofuranyl, unsubstituted cyclopropyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl.

In this embodiment, further preferably the heterocyclic compound is a compound of formula (Iiii) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(Iiii)

wherein

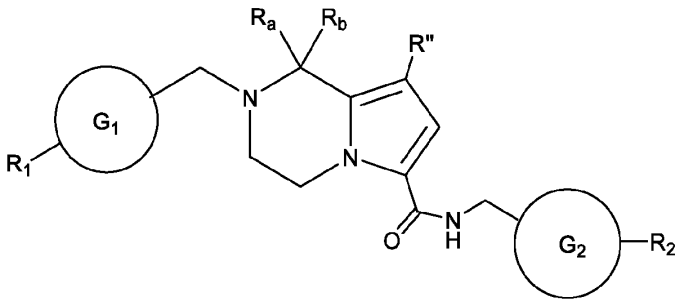
- R_1 is C_4 alkylene–OH, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl), $-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, unsubstituted pyrrolidinone, an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl, wherein

  R^y is i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl;

- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted indolinyl, unsubstituted oxoindolinyl or unsubstituted pyridinyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- Y is methylene or $-C(O)-$;
- R" is hydrogen or fluorine;
- L_1 is $-C(O)NR^v-Q-$, wherein Q is a direct bond or methylene, and R^v is hydrogen or methyl;
- R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted cyclopentyl, unsubstituted

cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl.

In a most preferred embodiment, the heterocyclic compound is a compound of formula (Iiv) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:

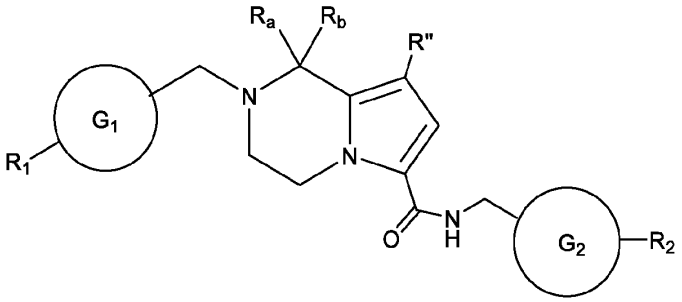


(Iiv)

wherein

- R_1 is –C(O)–(unsubstituted pyrrolidinyl), –C(O)N(CH_3)$_2$, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl;
- R_2 is –NHC(O)R^z, –NHC(O)O(*tert*-butyl), or –NHC(O)N(CH_3)$_2$, wherein
  R^z is methyl, *tert*-butyl, –CH_2–(*tert*-butyl), unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted pyridinyl, or phenyl–A' wherein said phenyl is unsubstituted and A' is hydrogen, piperidinyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrahydropyranyl;
- G_1 is phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- G_2 is phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- R" is hydrogen or fluorine; and
- R_a and R_b together with the carbon to which they are attached form a cyclobutyl group which is unsubstituted or substituted by two substituents selected from fluorine and methyl.

Alternatively, in a most preferred embodiment, the heterocyclic compound is a compound of formula (Iiv) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:

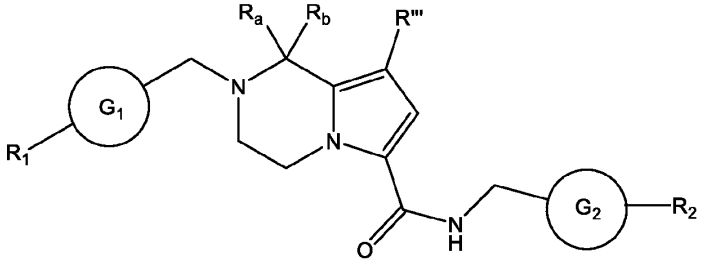


(Iiv)

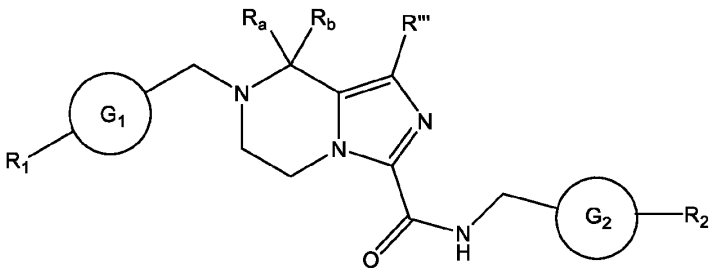
wherein

- R_1 is −C(O)−(unsubstituted pyrrolidinyl), −C(O)N(CH_3)$_2$, an imidazolyl or triazolyl moiety which is unsubstituted or substituted with one methyl group, or unsubstituted pyrazolyl, or unsubstituted oxadiazolyl, or unsubstituted oxazolyl;
- R_2 is −L_2-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- G_2 is phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl;
- R" is hydrogen or fluorine; and
- R_a and R_b together with the carbon to which they are attached form a cyclobutyl group which is unsubstituted or substituted by two substituents selected from fluorine and methyl.

In a yet further most preferred embodiment, the heterocyclic compound is a compound of formula (I'iv(a)) or (I'iv(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iv(a))

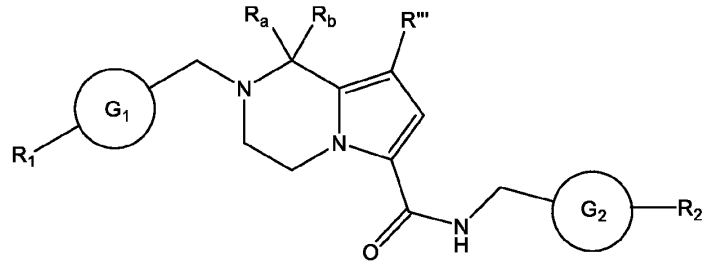


(I'iv(b))

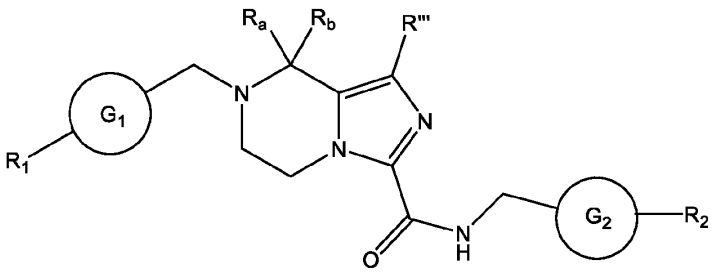
wherein

- R_1 is $-C(O)N(CH_3)_2$;
- R_2 is $-NHC(O)(-A-A')$, wherein A is unsubstituted phenyl or pyrazolyl which is substituted with one methyl group, and A' is piperidinyl which is substituted with one substituent selected from cyclobutyl and $-CH_2CHF_2$, or azetidinyl which is substituted with one methoxy group, or unsubstituted morpholinyl;
- G_1 is unsubstituted phenyl;
- G_2 is unsubstituted phenyl;
- R''' is hydrogen or methyl; and
- R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl or unsubstituted cyclobutyl.

Alternatively, in a most preferred embodiment, the heterocyclic compound is a compound of formula (I'iv(a)) or (I'iv(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iv(a))



(I'iv(b))

wherein

- R_1 is $-C(O)N(CH_3)_2$;
- R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety;
- G_1 is unsubstituted phenyl;
- G_2 is unsubstituted phenyl;
- R''' is hydrogen or methyl; and

R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl or unsubstituted cyclobutyl.

Preferred compounds of formula (I') are:

- *N*-(4-acetamidobenzyl)-2'-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(isopropyl(methyl)carbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3,5-dimethylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(4-methyl-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(1,3,4-oxadiazol-2-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-acetamidobenzyl)-2'-(4-(oxazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((1-isobutyrylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(1*H*-pyrazol-1-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-methyloxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- Methyl 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylate;
- 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-(dimethylamino)oxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((3-(dimethylcarbamoyl)bicyclo[1.1.1]pentan-1-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-hydroxy-2-methylpropyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(2-methyl-4-(1*H*-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-isobutyrylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((2-((3R,5S)-3,5-Dimethylpiperazin-1-yl)pyrimidin-4-yl)methyl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine
- *N*-(4-acetamidobenzyl)-2'-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-(dimethylamino)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-benzyl-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylpiperidin-4-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(azetidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(pyrrolidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(piperidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(morpholine-4-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-methylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3,5-dimethylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-oxoindolin-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-methyl-1*H*-benzo[d]imidazol-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-((3-methyloxetan-3-yl)amino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylindolin-5-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*,2'-bis(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- Tert-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate;
- *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-isopropylbenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(isonicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-pivalamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(cyclobutanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-benzamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(nicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-2-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(tetrahydro-2*H*-pyran-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-(bicyclo[1.1.1]pentane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(pyridin-2-ylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-6-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(3,3-dimethylbutanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(picolinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-benzamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((3-acetamidobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide; and
- *N*-(4-acetamidobenzyl)-2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxamide.
- *N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1*H*-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide

- *N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(2-chloro-4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1*H*-pyrazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-((3-chloro-5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- *N*-(4-(1*H*-imidazol-2-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-(4*H*-1,2,4-triazol-3-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((1-(methylcarbamoyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-((4-acetamidophenyl)methyl-d2)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- isopropyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate
- *N*-(4-((2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamido)methyl)phenyl)morpholine-4-carboxamide
- *N*-(4-acetamidobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(methylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide

- *N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(isoxazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- N-(4-acetamidobenzyl)-2'-((4-(dimethylcarbamoyl)phenyl)methyl-d2)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-N-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-N-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-N-((5-(1-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-N-((5-(1-methyl-1H-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7''-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6'',7''-dihydro-5''H-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide

- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methoxypropanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(2-cyclopropylacetamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1R,2R)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-(methylamino)-3-oxopropyl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2'-((methylamino)methyl)-[1,1'-biphenyl]-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-hydroxypropanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-ethylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-(oxetan-3-yl)piperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylazetidin-3-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1,5-dimethyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1H-pyrazole-3-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((1r,3r)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((1s,3s)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- (1R,4R)-N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxamide
- (1R,5S)-N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.4]octane-6-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(tetrahydrofuran-2-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- (S)-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- (R)-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)morpholine-4-carboxamide
- N-(4-(cyclohexanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(pyrrolidine-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(azetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-ethyl-3-methylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(3-cyanoazetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methoxyazetidine-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1s,3s)-3-methoxycyclobutane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- isobutyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylazetidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(1-cyclobutylpiperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(4-(1-cyclobutylpiperidin-4-yl)benzamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(2-fluoro-4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-morpholinonicotinamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- N1-(4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)-N2,N2-dimethyloxalamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- isobutyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-morpholinopyrimidine-5-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxypyrrolidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- 4-((7'-(4-acetamidobenzyl)-6'-oxo-3',4',6',7',8',9'-hexahydro-2'H-spiro[cyclobutane-1,1'-pyrido[4',3':4,5]pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-N,N-dimethylbenzamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(1-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(1-methyl-1H-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(1-methyl-1H-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(3-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methoxypiperidin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-oxomorpholino)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- tert-butyl (4-((1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate
- 1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-N-(3-chloro-4-(3,3-dimethylureido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(3-chloro-4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N2,N2-dimethyloxalamide

- 7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(2-methoxy-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((4-morpholinophenyl)carbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-((1-(1-cyclopropylpiperidin-4-yl)-1H-imidazol-4-yl)carbamoyl)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(3-methoxyazetidin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-N-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-1'-methyl-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(4-(3-oxomorpholino)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(1-cyclopropylazetidin-3-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide.

- Preferred compounds of formula (I) are:
- *N*-(4-acetamidobenzyl)-2'-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(isopropyl(methyl)carbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3,5-dimethylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(4-methyl-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(1,3,4-oxadiazol-2-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(oxazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((1-isobutyrylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(1*H*-pyrazol-1-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-methyloxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- Methyl 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylate;
- 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-(dimethylamino)oxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-acetamidobenzyl)-2'-((3-(dimethylcarbamoyl)bicyclo[1.1.1]pentan-1-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-hydroxy-2-methylpropyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(2-methyl-4-(1*H*-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-isobutyrylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((2-((3R,5S)-3,5-Dimethylpiperazin-1-yl)pyrimidin-4-yl)methyl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine
- *N*-(4-acetamidobenzyl)-2'-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(dimethylamino)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-benzyl-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylpiperidin-4-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(azetidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(pyrrolidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(piperidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(morpholine-4-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-methylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3,5-dimethylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-oxoindolin-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-methyl-1*H*-benzo[d]imidazol-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-((3-methyloxetan-3-yl)amino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylindolin-5-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*,2'-bis(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- Tert-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate;
- *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-isopropylbenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(isonicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-pivalamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-(cyclobutanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-benzamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(nicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-2-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(tetrahydro-2*H*-pyran-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(bicyclo[1.1.1]pentane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(pyridin-2-ylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-6-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(3,3-dimethylbutanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(picolinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-benzamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-((3-acetamidobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide; and
- *N*-(4-acetamidobenzyl)-2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide.

Preferred compounds of formula (I') and formula (I) where R_2 is $-L_2-$LBM are:

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((S)-15-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-16,16-dimethyl-13-oxo-4,7,10-trioxa-14-azaheptadecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14-tetraoxa-2-azaheptadecan-17-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N10-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15,18-hexaoxahenicosan-21-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-

tetraoxapentadecan-15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N15-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12-trioxa-3-azapentadecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N11-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-

hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N21-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12,15,18-pentaoxa-3-azahenicosanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(7-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11-trioxa-2-azatetradecan-14-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14,17-pentaoxa-2-azaicosan-20-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15-

pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N12-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)dodecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-

2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide.

Uses and Methods

Compounds of the invention as described herein are inhibitors of STAT6. Preferably, the heterocyclic compound of the invention has an IC_{50} against STAT6 of no more than 10,000 nM, more preferably no more than 1,000 nM, or no more than 100 nM, or no more than 10 nM. Most preferably, the heterocyclic compound of the invention has an IC_{50} against STAT6 of no more than 5 nM.

The compounds of the present invention may be used in the treatment of a condition or disease susceptible to amelioration by inhibition of STAT6. Said condition or disease susceptible to amelioration by inhibition of STAT6 includes an atopic disease, an allergic disease, an inflammatory disease and lymphoma. For instance, the condition or disease can be selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers

including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas. Preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

The invention therefore provides a method of treating a subject, the method comprising administering to said subject a therapeutically effective amount of a heterocyclic compound of the invention, or a pharmaceutical composition of the invention. The invention therefore provides a method of treating a condition or disease selected from an atopic disease, an allergic disease, an inflammatory disease or lymphoma in a subject, the method comprising administering to said subject a therapeutically effective amount of a heterocyclic compound of the invention, or a pharmaceutical composition of the invention. For instance, the condition or disease can be selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas. Preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

The invention also provides the use of a heterocyclic compound of the invention, or a pharmaceutical composition of the invention, for the manufacture of a medicament. The invention also provides the use of a heterocyclic compound of the invention, or a pharmaceutical composition of the invention, for the manufacture of a medicament for treating a condition or disease selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen

sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas. Preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

Pharmaceutical compositions, dosage and formulation

The compounds of the invention, when used in a method of treatment, can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. Thus, preferably, the compounds of the present invention can be included in a pharmaceutical composition. Preferably the pharmaceutical composition is suitable for oral administration. Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. One exemplary such pharmaceutical composition is a solid dosage form suitable for oral administration (e.g., a tablet, capsule (each of which includes a sustained release or timed release formulation), pill, powder, or granule). Another exemplary such pharmaceutical composition is a liquid dosage form suitable for oral administration (e.g., an elixir, tincture, suspension, syrup, solution or emulsion).

However, the compounds of the invention may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen for the compounds of the invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian

can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day.

Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of the invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of the invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered alongside suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, com sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these

pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

General synthetic schemes

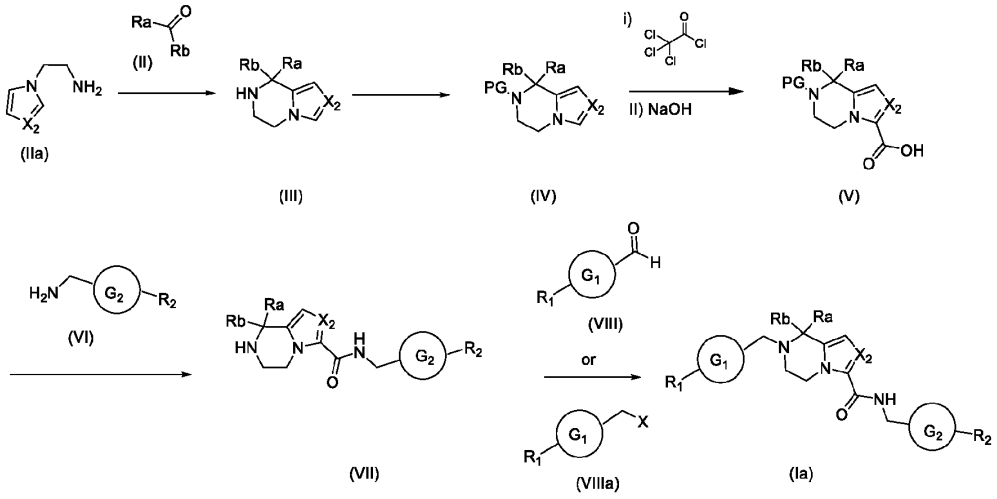
Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Commercial intermediates are referred to in the experimental section by their IUPAC name. Ether refers to diethyl ether, unless otherwise specified. Concentration or evaporation refer to evaporation under vacuum using a Büchi rotatory evaporator.

Standard synthetic methods are described the first time they are used. Compounds synthesized with similar methods are referred to only by their starting materials, without full experimental detail. Slight modifications to the general experimental methods used are permitted in these cases. Specific synthetic transformations already described in the literature are referred to only by their bibliographical reference. Other specific methods are also described in full.

The compounds of the invention can be prepared using the methods and procedures described herein or using similar 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.

Processes for preparing compounds of the invention are provided as further embodiments of the invention and are illustrated by the procedures below. In the following Schemes 1-15, compounds are depicted where L_1 is $-C(O)NH-CH_2-$. For compounds where L_1 is another embodiment of $-C(O)NR^v-Q-$, or is $-L_1'-NR^v-Q-$ or $-Het'-Q-$ as defined herein, analogous synthetic processes can be used which are well-known to the person skilled in the art. In the following Schemes 1-7, compounds are depicted where m is 0, n is 1, X_1 is N and X_2, X_4 are CR".

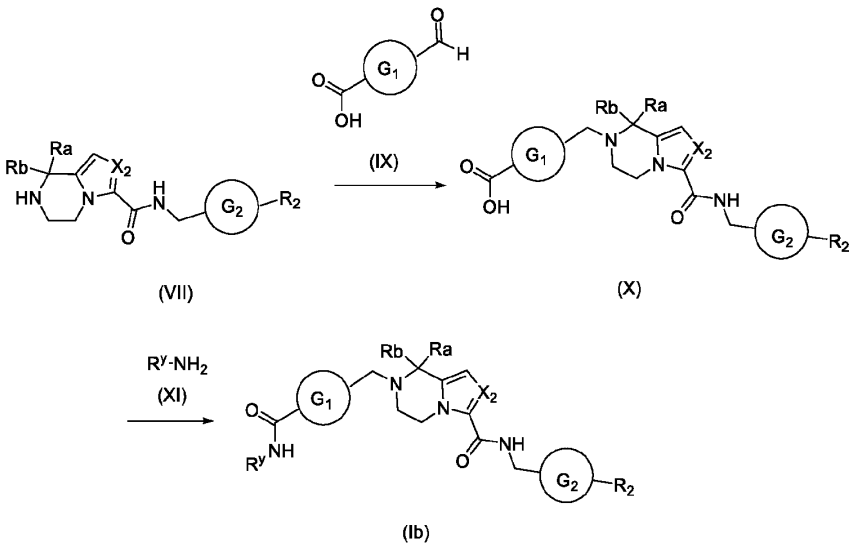
According to one embodiment of the present invention, compounds of Formula Ia may be prepared by the following a 5 steps synthetic route as illustrated in Scheme 1:



Scheme 1

Pictet-Spengler condensation of ethan-1-amines of Formula IIa with ketones of Formula II, in a solvent such as ethanol or dichloromethane, in the presence of an acid such as p-toluene sulphonic acid or trifluoroacetic acid, at temperatures ranging from 25-80 °C gives rise to dihydro-pyrrolopyrazines of Formula III. Treatment of the protected amine of Formula IV with 2,2,2-trichloroacetyl chloride in the presence of triethylamine in a solvent such as dichloromethane, at temperatures ranging from 0-25 °C, gives rise to carboxylic acids of Formula V after treatment with a base such as NaOH, in a solvent such as tetrahydrofuran or water, at room temperature. Reaction with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate / *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature furnishes amides of Formula VII, after deprotection of the corresponding amine. Compounds of Formula Ia are obtained from amines of Formula VII by reductive amination with aldehydes of Formula VIII, in a solvent such as dichloromethane or dichloroethane, in the presence of a reductive reagent such as sodium triacetoxyborohydride, in the presence of an acid such as acetic acid, at room temperature. Alternatively, compounds of Formula Ia can be obtained by treatment with alkylating agents of Formula VIIIa, in a solvent such as acetonitrile, in the presence of a base such as diisopropylethylamine at 60°C.

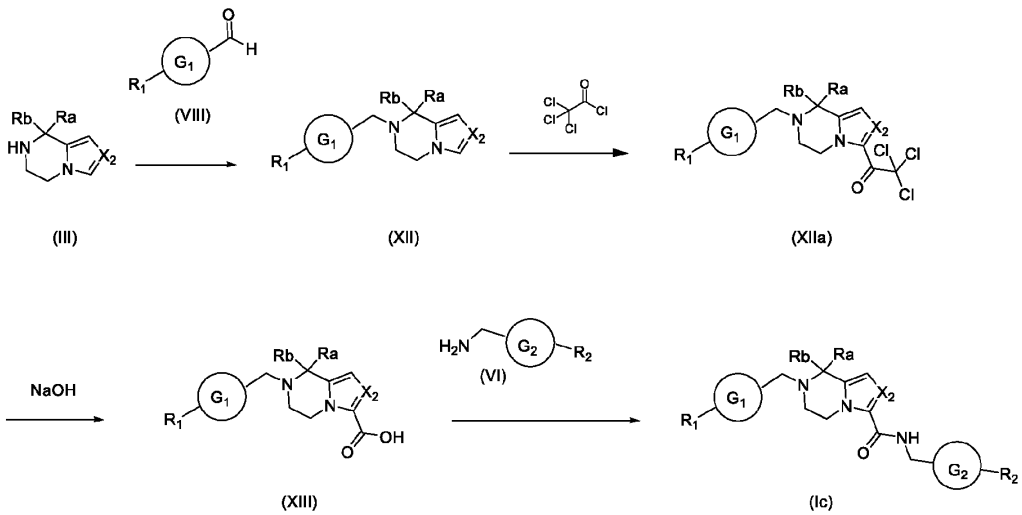
In the particular case where R_1 in Scheme 1 is a carboxylic acid, compounds of Formula Ib may be prepared by the following a 2-step synthetic route as illustrated in Scheme 2:



Scheme 2

Compounds of Formula X are obtained from amines of Formula VII by reductive amination with aldehydes of Formula IX, in a solvent such as dichloromethane or dichloroethane, in the presence of a reductive reagent such as sodium triacetoxyborohydride, in the presence of an acid such as acetic acid, at room temperature. Treatment of the resulting acids with amines of Formula XI in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate as a coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N*,*N*-dimethylformamide at room temperature gives rise to compounds of Formula Ib.

In the particular case where carboxylic acids of Formula XIII are substituted on nitrogen, compounds of Formula Ic may be prepared as illustrated in Scheme 3:

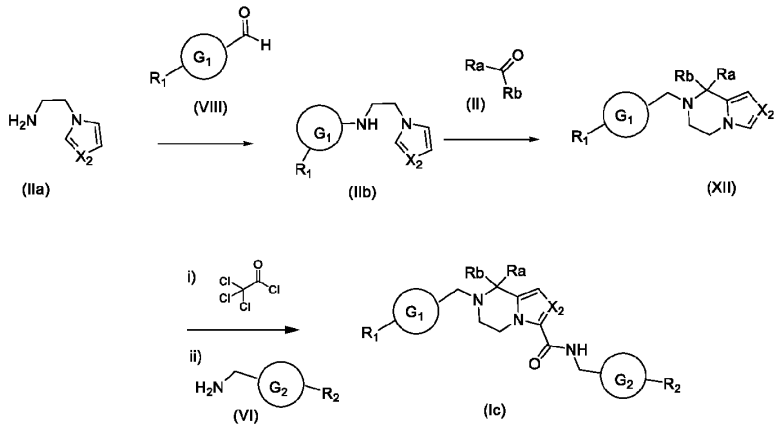


Scheme 3

Compounds of Formula XII are obtained from amines of Formula III by reductive amination with aldehydes of Formula VIII, in a solvent such as dichloromethane or dichloroethane, in the presence of a reductive reagent such as sodium triacetoxyborohydride, in the presence of an acid such as acetic acid, at room temperature. Treatment of compounds of Formula XII with 2,2,2-trichloroacetyl chloride in the presence of triethylamine in a solvent such as dichloromethane, at temperatures ranging from 0-25 °C, gives rise to trichloroacetyl derivatives of Formula XIIa, that give rise to carboxylic acids of Formula XIII after treatment with a base such as NaOH, in a solvent such as tetrahydrofuran or water, at room temperature. Alternatively, carboxylic acids of Formula XIII can be obtained directly from compounds of Formula XII in a one pot reaction. Compounds of Formula Ic may be prepared directly by amide coupling of acids of Formula XIII with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate / *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature. Alternatively, compounds of Formula Ic can be obtained directly from compounds of Formula XII by treatment with 2,2,2-trichloroacetyl chloride in the presence of a base such as triethylamine in a solvent such as dichloromethane, at 0 °C, followed by treatment of with amines of Formula VI in the presence of a base such as triethylamine, in a solvent such as dicholoromethane at room temperature. Finally, compounds of Formula Ic can be also

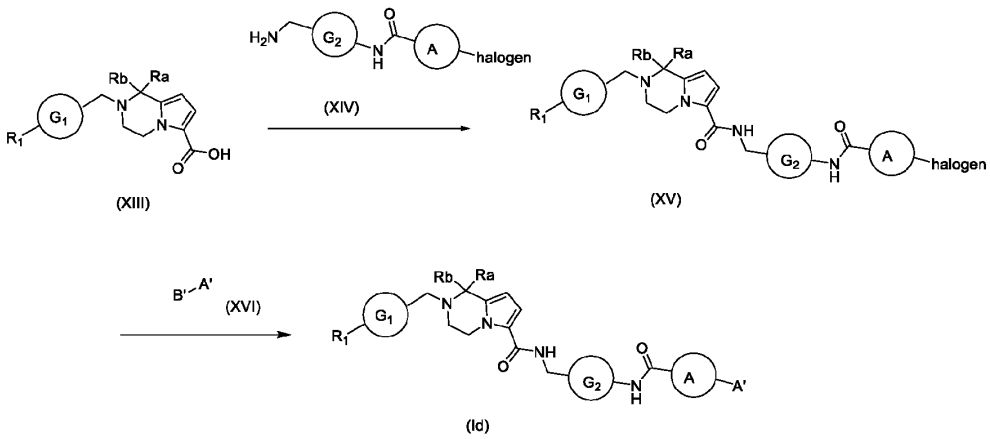
obtained from compounds of Formula XIIa in a one pot reaction by treatment of with amines of Formula VI in the presence of a base such as triethylamine, in a solvent such as dicholoromethane at room temperature.

Alternatively, compounds of Formula XII can be obtained by treatment of ethan-1-amines of Formula IIa with ketones of Formula VIII, in a solvent such as methanol, in the presence palladium on carbon as a catalyst by treatment with hydrogen under pressure (15 psi), at room temperature, followed by Pictet-Spengler reaction by treatment with a ketone of Formula II in a solvent such as ethanol or dichloromethane, in the presence of an acid such as *p*-toluene sulphonic acid or trifluoroacetic acid, at temperatures ranging from 25-80°C. Through synthetic processes well-known to the person skilled in the art, further derivatization of compounds of formula XII may lead to the final compounds of Formula Ic as described in Scheme 3b.



Scheme 3b

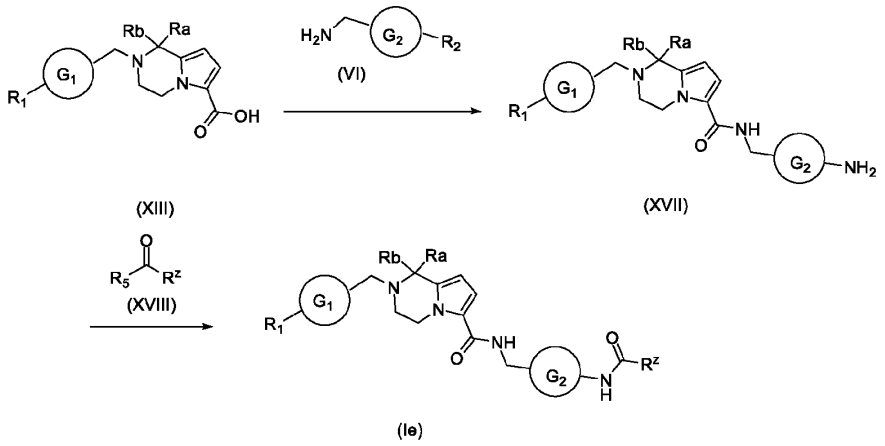
In the particular case where compounds of Formula XIII are coupled with amines of Formula XIV where A is as defined herein, compounds of Formula Id may be prepared as illustrated in Scheme 4:



Scheme 4

Compounds of Formula XV may be prepared by amide coupling of acids of Formula XIII with amines of Formula XIV, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate and *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature. Compounds of Formula Id may be prepared from halides of Formula XV by reaction with boronic acids or boronic esters of Formula XVI under Suzuki–Miyaura reaction conditions (Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457). In the Formula XVI, the B' group represents a boronic acid or a boronic ester. Such reactions may be catalyzed by a suitable palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex or tris(dibenzylideneacetone)dipalladium (0) in a solvent such as dioxane, dimethoxyethane, toluene or N,N'-dimethylformamide with or without water as a cosolvent, in the presence of a base such as cesium carbonate, potassium carbonate, sodium carbonate or potassium phosphate, at temperatures ranging from 80-120 °C with or without the use of microwave irradiation.

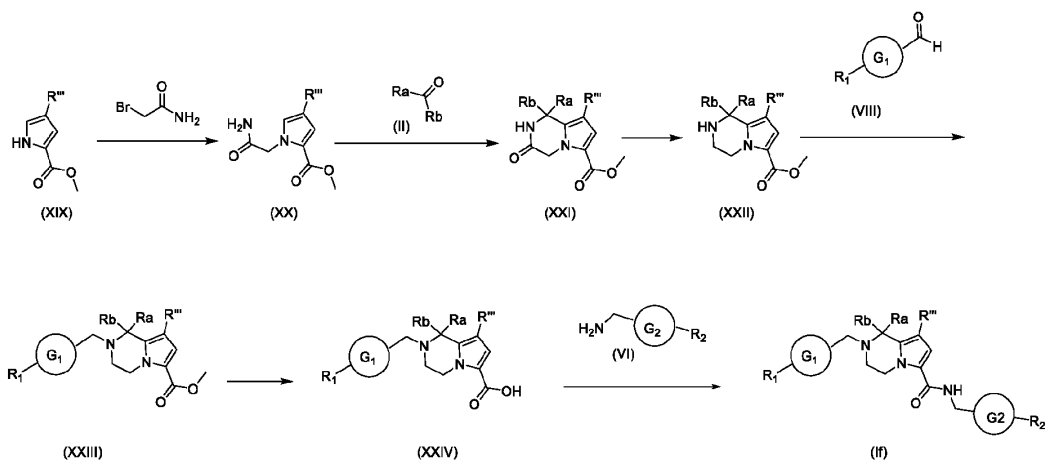
In the particular case where carboxylic acids of Formula XIII are coupled with amines of Formula VI where R2 is NH-PG compounds of Formula Ie may be prepared as illustrated in Scheme 5:



Scheme 5

Compounds of Formula XVII may be prepared by amide coupling of acids of Formula XIII with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate and *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature, after deprotection of the corresponding amine. Compound of Formula Ie may be prepared by treatment with compound of Formula XVIII where R_5 can be OH or Cl and R^z is as defined herein. In the particular case where R_5 is OH, compounds of Formula Ie may be prepared by amide coupling by treatment with amines of Formula XVII and carboxylic acids of Formula XVIII, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate and *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature. In the particular case where R_5 is Cl, compounds of Formula Ie may be prepared by amide fomation by treatment with amines of Formula XVII and acyl chlorides of Formula XVIII, in the presence of a suitable base such as diisopropylethylamine in a solvent such as dichloromethane at temperatures ranging from 0 to 25°C.

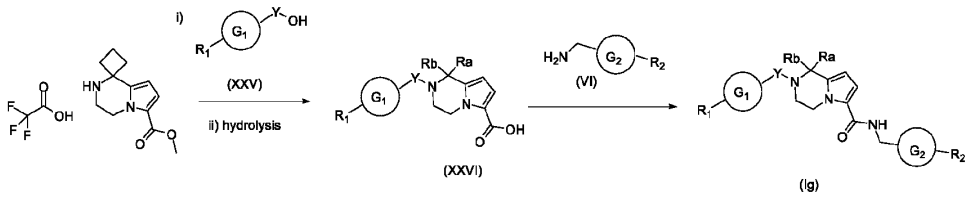
In the particular case where X_4 is CR''' (in particular where R''' is not hydrogen, for example, C_{1-4} alkyl or halogen) compounds of Formula If may be prepared as illustrated in Scheme 6:



Scheme 6

Compounds of Formula XX may be prepared by treatment of compounds of Formula XIX with 2-bromoacetamide, in the presence of a suitable base such as cesium carbonate, in a solvent such as *N*,*N*-dimethylformamide at room temperature. Treatment of compounds of Formula XX with ketones of Formula II in the presence of a suitable condensation agent such as Eaton's reagent at 85°C, gives rise to compounds of Formula XXI. Compounds of Formula XXII may be prepared by reaction of compounds of Formula XXI with a suitable reducing agent such as borane dimethylsulfide, in a suitable solvent such as tetrahydrofuran at temperatures ranging from 0-80°C. Reductive amination of amines of Formula XXII with aldehydes of Formula VIII, in a suitable solvent such as dichloromethane or dichloroethane, in the presence of a suitable reductive reagent such as sodium triacetoxyborohydride, in the presence of a suitable acid such as acetic acid, at room temperature gives rise to compounds of Formula XXIII. Compounds of Formula If may be prepared by hydrolysis of compounds of Formula XXIII in the presence of a suitable base such as lithium hydroxide, in a suitable solvent such as tetrahydrofuran or methanol, at room temperature, followed by amide coupling of the resultant acids of Formula XIV with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate as coupling reagent, in the presence of a suitable base such as diisopropylethylamine, in a suitable solvent such as *N*,*N*-dimethylformamide at room temperature.

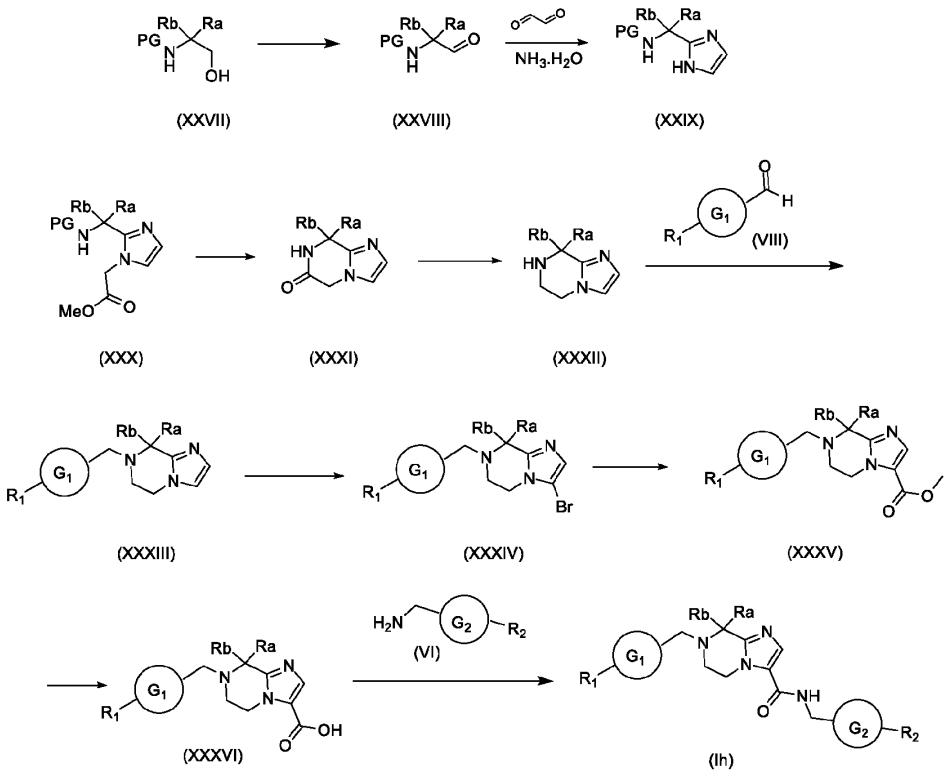
In the particular case where Y is C(=O) compounds of Formula Ig may be prepared as illustrated in Scheme 7:



Scheme 7

Compounds of Formula XXVI may be prepared by amide coupling of methyl 3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate 2,2,2-trifuoroacetic acid with carboxcylic acids of Formula XXV, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate as a coupling reagent, in the presence of a suitable base such as diisopropylethylamine, in a suitable solvent such as *N*,*N*-dimethylformamide at room temperature, followed by hydrolysis of the resulting ester in the presence of a suitable base such as sodium hydroxide, in a suitable solvent such as tetrahydrofuran or methanol, at room temperature. Compounds of Formula Ig may be prepared by amide coupling of compounds of Formula XXVI with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate as coupling reagent, in the presence of a suitable base such as diisopropylethylamine, in a suitable solvent such as *N*,*N*-dimethylformamide at room temperature.

In the particular case where X_1 and X_4 are N, compounds of Formula Ih may be prepared as illustrated in Scheme 8:

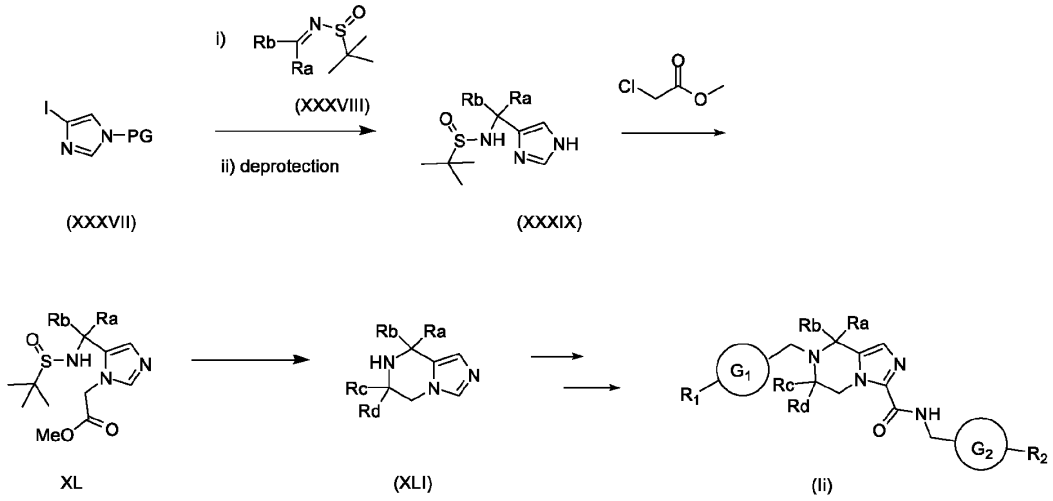


Scheme 8

Compounds of Formula XXVIII may be prepared by Dess-Martin oxidation of amino alcohols of Formula XXVII by treatment with Dess Martin reagent in a suitable solvent such as dichloromethane at room temperature. Cyclisation of the resulting aldehyde by treatment with oxoaldehyde in the presence of an aqueous solution of ammonia in a suitable solvent such as methanol at room temperature gives rise to compounds of Formula XXIX. Compounds of Formula XXX may be prepared by treatment of the resulting imidazole with methyl chloroacetate, in the presence of a suitable base such as potassium carbonate, in a suitable solvent such as *N*,*N*-dimethylformamide at room temperature. Condensation of the resulting amino ester in the presence of a suitable acid such as trifluoroacetic acid in a suitable solvent such as dichloromethane at room temperature gives rise to bicycles of Formula XXXI. Compounds of Formula XXXII may be prepared by reduction by treatment with borane dimethyl sulfide, in a suitable solvent such as tetrahydrofuran, at temperatures ranging from 0-20°C. Reductive amination of the resulting amine with aldehydes of Formula VIII, in a suitable solvent such as dichloromethane or dichloroethane, in the presence of a suitable reductive reagent such as sodium triacetoxyborohydride, in the presence of a

suitable acid such as acetic acid, at room temperature gives rise to compounds of Formula XXXIII. Compounds of Formula XXXIV may be prepared by bromination of compounds of Formula XXXIII by treatment with *N*-bromosuccinimide in a suitable solvent such as dichloromethane at room temperature. Compounds of Formula XXXV may be prepared by treatment of the corresponding bromo derivative with carbon monoxide, in the presence of a suitable catalyst such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), in the presence of a suitable base such as triethylamine, in a suitable solvent such as methanol or *N,N*-dimethylformamide at temperatures ranging from 60-80°C. Compounds of Formula Ih may be prepared by hydrolysis of compounds of Formula XXXV in the presence of a suitable base such as sodium hydroxide, in a suitable solvent such as tetrahydrofuran or methanol, at room temperature, followed by amide coupling of the resultant acids of Formula XXXVI with amines of Formula VI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate as coupling reagent, in the presence of a suitable base such as diisopropylethylamine, in a suitable solvent such as *N,N*-dimethylformamide at room temperature.

In the particular case where X_1 and X_2 are N, compounds of Formula Ii may be prepared as illustrated in Scheme 9:

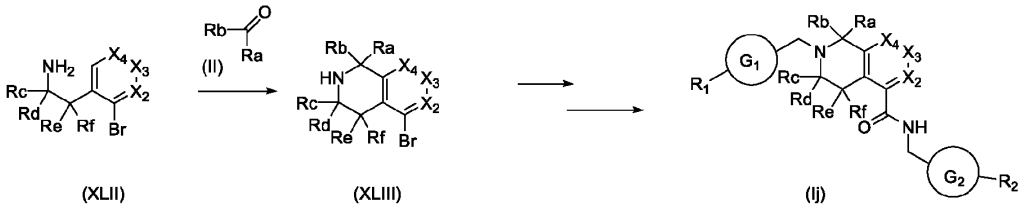


Scheme 9

Compounds of Formula XXXIX may be prepared by Grignard reaction of imidazoles of Formula XXXVII with sulfinamides of Formula XXXVIII, in the presence of a suitable Grignard reagent such as ethylmagnesium bromide, in a suitable solvent such as

dichloromethane, at temperature ranging from 0-20°C, followed by deprotection of the corresponding protecting group. Treatment of the resulting imidazole with methyl 2-chloroacetate, in a suitable solvent such as *N*,*N*-dimethylformamide, in the presence of a suitable base such as potassium carbonate, at room temperature, gives rise to compounds of Formula XL. Compounds of Formula XLI may be prepared by condensation in the presence of a suitable acid such as trifluoroacetic acid, in a suitable solvent such as dichloromethane, at room temperature. Through synthetic processes well-known to the person skilled in the art, further derivatization of compounds of formula XLI may lead to the final compounds of Formula Ii.

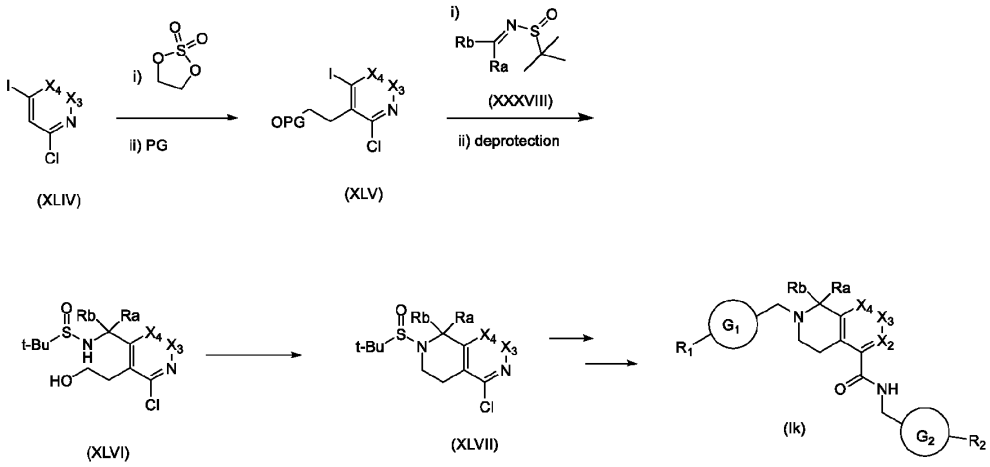
In the particular case where m and n are 1 and X_1 is C, compounds of Formula Ij may be prepared as illustrated in Scheme 10.



Scheme 10

Compounds of Formula XLIII may be prepared by condensation of compounds of Formula XLII with ketones of Formula II, in a suitable solvent such as ethanol or dichloromethane, in the presence of a suitable acid such as *p*-toluene sulphonic acid or trifluoroacetic acid, at temperatures ranging from 25-80 °C. Through synthetic processes well-known to the person skilled in art, further derivatization of compounds of formula XLIII may lead to the final compounds of Formula Ij.

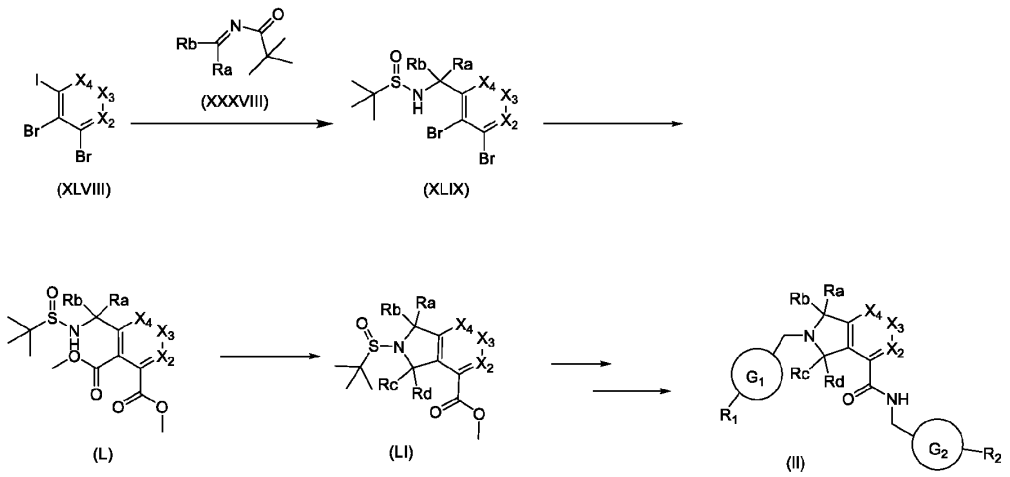
In the particular case where X_1 is C and X_2 is N compounds of Formula Ik may be prepared as illustrated in Scheme 11.



Scheme 11

Compounds of Formula XLV may be prepared by reaction with 1,3,2-dioxathiolane 2,2-dioxide, in a suitable solvent such as tetrahydrofuran, in the presence of a suitable base such as lithium diisopropylamide, at temperatures ranging from -78-20°C, followed by treatment with a suitable acid such as hydrochloric acid at temperatures ranging from 0-20°C and further protection of the resulting alcohol. Compounds of Formula XLVI may be prepared by Grignard reaction with sulfinamides of Formula XXXVIII, in the presence of a suitable Grignard reagent such as ethylmagnesium bromide, in a suitable solvent such as dichloromethane, at temperature ranging from 0-20°C, followed by deprotection of the corresponding protecting group. Compounds of Formula XLVII may be prepared by ciclyzation of compounds of Formula XLVI. Through synthetic processes well-known to the person skilled in art, further derivatization of compounds of formula XLVII may lead to the final compounds of Formula Ik.

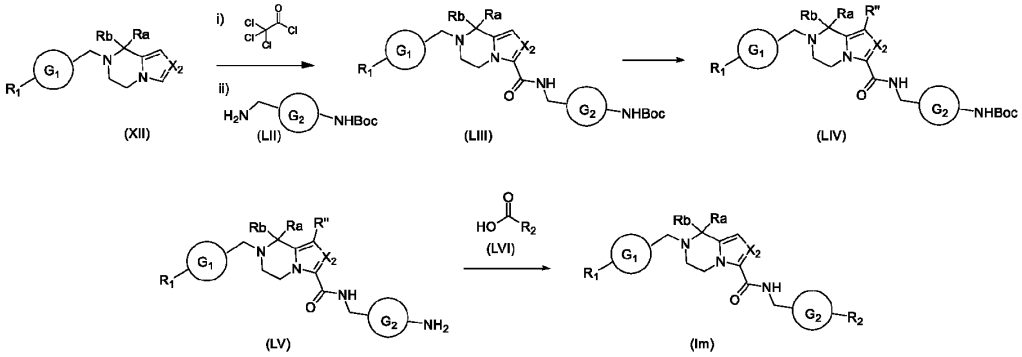
In the particular case where m is 1 and n is 0 and X_1 is C, compounds of Formula Il may be prepared as illustrated in Scheme 12.



Scheme 12

Compounds of Formula XLIX may be prepared by Grignard reaction of compounds of Formula XLVIII with sulfinamides of Formula XXXVIII, in the presence of a suitable Grignard reagent such as isopropylmagnesium choride, in a suitable solvent such as tetrahydrofuran, at temperature ranging from 0-20°C. Compounds of Formula L may be prepared by treatment of the corresponding bromo derivative with carbon monoxide, in the presence of a suitable base such as triethylamine, in the presence of a suitable catalyst such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), in a suitable solvent such as methanol or *N*,*N*-dimethylformamide at temperatures ranging from 60-80°C. Compounds of Formula LI may be prepared by cyclization of compounds of Formula L, in the presence of a suitable acid such as hydrochloric acid. Through synthetic processes well-known to the person skilled in art, further derivatization of compounds of Formula LI may lead to the final compounds of Formula Il.

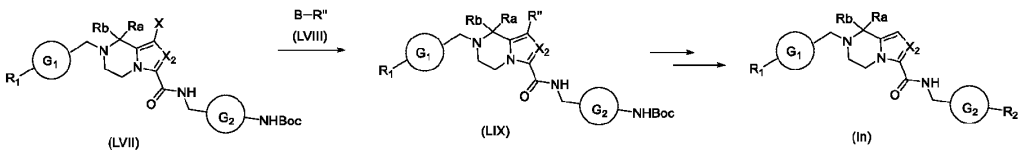
In the particular case where R" is a halogen compounds of Formula Im may also be prepared as illustrated in Scheme 13:



Scheme 13

Compounds of Formula LIII may be prepared by a one pot reaction by treatment of compounds of Formula XII with 2,2,2-trichloroacetyl chloride in the presence of a base such as triethylamine in a solvent such as dichloromethane, at 0 °C, followed by treatment of with amines of Formula LII having a Boc protected amino group in the presence of a base such as triethylamine, in a solvent such as dicholoromethane at room temperature. Halogenated compounds of Formula LV may be prepared by treatment of compounds of Formula LIII with the corresponding *N*-halogenated succinimide reagents in a solvent such as acetone at room temperature, followed by Boc group deprotection by treatment of resulting compounds of Formula LIV with an acid such as trifluoroacetic acid or hydrochloric acid in a solvent such as dichloromethane or dioxane at room temperature. Compounds of Formula Im may be prepared by amide coupling by treatment of amines of Formula LV with carboxylic acids of Formula LVI, in the presence of 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate or *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate and *N*-methylimidazole as coupling reagent, in the presence of a base such as diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide at room temperature.

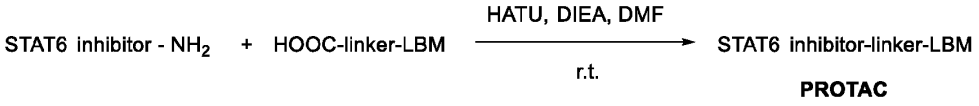
In the particular case where R'' is C_{1-4} alkyl, C_{1-4} haloalkyl or 3- to 5-membered carbocyclyl, compounds of Formula In may also be prepared as illustrated in Scheme 14:



Scheme 14

Compounds of Formula LIX may be prepared by Suzuki coupling of halogenated compounds of Formula LVII with a boronated reagent of Formula LVIII in the presence of a base such as cesium carbonate and a palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex in a solvent such as dioxane at 120°C. Through synthetic processes well-known to the person skilled in art, further derivatization of compounds of Formula LIX may lead to the final compounds of Formula Im.

Compounds of formula (I') or formula (I) wherein R_2 is L_2-LBM may be prepared following the synthetic pathway described in Scheme 15:



Scheme 15

For compounds where m, n, and X_1-X_4 define alternative heterocyclic cores, analogous synthetic processes can be used which are well-known to the person skilled in the art. Specific synthetic processes not covered by Schemes 1-15 are described in detail in the experimental section.

In any step of the synthetic sequences described above, any reactant and intermediate can be used in a protected form to prevent certain functional groups from undergoing undesired reactions. In these cases, standard methods for the introduction and subsequent removal of these protecting groups can be used at any suitable step of the synthesis. Numerous protecting groups, their introduction and their removal are described in T. W. Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

The syntheses of the compounds of the invention are illustrated by the following Examples (1 to 322) and PROTAC Examples (1 to 88) including Intermediates (1 to 153), and are given in order to provide a person skilled in the art with a sufficiently clear and complete explanation of the present invention, but should not be considered as limiting of the essential aspects of its subject, as set out in the preceding portions of this description.

Starting compounds are commercially available or may be obtained following the conventional synthetic methods already known in the art.

Examples

The syntheses of the compounds of the invention are illustrated by the following Examples which do not limit the scope of the invention in any way.

Preparative Examples

Abbreviations:

Ac_2O	Acetic anhydride
ACN	Acetonitrile
AcOH	Acetic acid
Al_2O_3	Aluminium oxide
BH_3-Me_2S	Borane dimethylsulfide
bb	Broad band
Boc_2O	Di-*tert*-butyl decarbonate
BOP	(Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate)
BrettPhos Pd G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate methanesulfonate
br	Broad
BuOH	Buthanol
CAN	Cerium ammonium nitrate
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CO	Carbon monoxide
Cs_2CO_3	Cesium carbonate
CuI	Copper iodide
d	Doublet
dd	Doublet of doublets
DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMC·HCl	2-Chloro-1,3-dimethyl-4,5-dihydroimidazol-1-ium chloride

DME	Dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated Dimethylsulfoxide
dtbbpy	4-Tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
H_2	Hydrogen
HATU	2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HCHO	Formaldehyde
HCl	Hydrochloric acid
IPA	Isopropanol
$(Ir(dF(CF_3)ppy)_2(dtbbpy))PF_6$:	Bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridyl]phenyl]iridium(1+);4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine;hexafluorophosphate
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
KPNH	Amine Functionalized Stationary Phase
LRMS	Low Resolution Mass Spectrometry
LC	Liquid Chromatography
m	Multiplet
MeI	Iodomethane
MeOH	Methanol
MeOD	Deuterated methanol
$MgSO_4$	Magnesium sulfate
min	Minutes
MPLC	Medium Pressure Liquid Chromatography
MS	Mass Spectrometry
MsCl	Methanesulfonyl chloride
mw	Microwave

N_2	Nitrogen
$NaBH_4$	Sodium borohydride
$NaBH_3CN$	Sodium cyanoborohydride
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
NaCN	Sodium cyanide
NaH	Sodium Hydride
$NaHCO_3$	Sodium bicarbonate
Na_2CO_3	Sodium carbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NBS	*N*-bromosuccinimide
NCS	N-Chlorosuccinimide
NH_3	Ammonia
NH_4Cl	Ammonium Chloride
NH_2-$NH_2 \cdot H_2O$	Hydrazine hydrate
$NiCl_2$ glyme	dichloronickel;1,2-dimethoxyethane
Ni Raney	Nickel Raney
NMI	*N*-methylimidazole
NMR	Nuclear magnetic resonance
PBr_3	Phosphorus tribromide
PCy_3	Tricyclohexylphosphine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2.CH_2Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex
$Pd(OAc)_2$	Palladium acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
p-TsOH	*para*-Toluenesulfonic acid
q	Quartet
r.t.	Room temperature
Ru	Ruthenium
s	Singlet
SiO_2	Silicon dioxide
$SOCl_2$	Thionyl chloride
t	Triplet

T4P	2,4,6-Tributyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide
T^a	Temperature
TBAF	Tetrabuthylammonium floride
*t*Bu	*Tert*-butyl
TCFH	*N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate
td	Triple doublet
TFA	Trifluoroacetic acid
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSOK	Potassium trimethylsilanolateTTMSS Tris(trimethylsilyl)silane
UPLC	Ultra Pressure Liquid Chromatography
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd G3	Methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct

Analytical methods:

LCMS method 1, LCMS (1)

Apparatus: Waters Acquity UPLC I-Class system; Bin. Pump: BSM, SM with SO; PDA; TQD; ESI, pos/neg 160-900; column: Waters Acquity UPLC BEH C-18, 50x2.1mm, 1.7µm, Temp: 50°C, Flow rate: 0.65 mL/min, Gradient: from 5% B to 95% B, Run time: 5 min, Eluent A: 0.05% formic acid + 0.0125% ammonia in water, Eluent B: 0.04% formic acid + 0.01% ammonia in ACN/MeOH (1:1). Sample concentration: 1 mM in DMSO. Injection volume: 0.5 µL. Chromatograms were processed at 210 nm.

LCMS methods 2

Detection methods are Evaporarive Light-scattering detector (ELSD) and diode array (DAD). MS mode was positive and negative electrospray ionization. MS range was 50-2000. Chromatograms were processed at 210 and 254 nm.

LCMS method 2a, LCMS (2a)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 50-2000; column: Halo C18 3.0*30 mm, 5 µm, Temp: 40°C, Flow rate: 0.2 mL/min, Gradient: 10-100% B in 0.90 min, Eluent A: 0.04% TFA in water, Eluent B: 0.02% TFA in HPLC grade ACN.

LCMS method 2b, LCMS (2b)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos/neg 50-2000; column: Xtimate C18 2.1*30mm, 5 µm, Temp: 40°C, Flow rate: 1.5 mL/min, Gradient: 10-100% B in 0.5 min and holding at 100% for 0.4 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2c, LCMS (2c)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos/neg 50-2000; column: XBridge C18 2.1*30mm, 5 µm, Temp: 40°C, Flow rate: 1.2 mL/min, Gradient: 5%-95% B in 1.5 min and holding at 95% B for 0.50 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2d, LCMS (2d)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 50-2000; column: Luna C18 30*2.0 mm, 3 µm, Temp: 40°C, Flow rate: 1.2 mL/min, Gradient: 5%-95% B in 3.5 min, Eluent A: 0.04% TFA in water, Eluent B: 0.02% TFA in HPLC grade ACN.

LCMS method 2e, LCMS (2e)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Xbridge C18 2.1*50 mm column, 5 µm, Temp: 40°C, Flow rate: 0.8 mL/min, Gradient: 5-95% B at 0.40-5.50 min, and then 95-100% B at 5.50-7.00 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2f, LCMS (2f)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Xbridge C18 2.1*50 mm column, 5 µm, Temp: 40°C, Flow rate: 0.8 mL/min, Gradient: 25%-65% B in 8 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2g, LCMS (2g)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Xbridge C18 2.1*50 mm column, 5 µm, Temp: 40°C, Flow rate: 1.2 mL/min, Gradient: 0%-60% B in 1.5 min and holding at 60% B for 0.50 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2h, LCMS (2h)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Xbridge C18 2.1*30 mm column, 5 µm, Temp: 40°C, Flow rate: 1.2 mL/min, Gradient: 0-30% B in 1.5 min, 30-90% B in 0.5 min , 90-0% B in 0.01 min , and then hold at 0% B for 0.49 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2i, LCMS (2i)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Xtimate C18 2.1*30mm, 5µm, Temp: 40°C, Flow rate: 1.5 mL/min, Gradient: 10-100% B in 0.90 min .10% B in 0.01 min, 10-100% B (0.01-0.50 min) with a hold at 100% B for 0.40 min, Eluent A: 10 mM NH_4HCO_3 in water, Eluent B: HPLC grade ACN.

LCMS method 2j, LCMS (2j)

Apparatus: Agilent 1200 HPLC, MSD:6120 single quadrupole MSD, pos 100-1000; column: Luna C18 50*2.0mm, 5 µm, Temp: 40°C, Flow rate: 1.0 mL/min, Gradient: 5%B in 0.40 min and 5-95% B in 2.60 min, hold on 95% B in 1.00 min, and then 95-5%B in 0.01 min, Eluent A: 0.04% TFA in water, Eluent B: 0.02% TFA in HPLC grade ACN.

LCMS method 3, LCMS (3)

Apparatus: Agilent 1290 Infinity II; Bin. Pump: 1290 High speed Pump, 1290 Multisampler; 1290 DAD WR; LC/MSD IQ; ESI, pos/neg 100-1000; column: Infinitylab Poroshell 120 EC-C18 2,1X50mm, 50x2.1mm, 1.9µm, Temp column: 50°C, Flow rate: 0.65 mL/min, Gradient: from 4% B to 98% B, Run time: 3 min, Eluent A: 0.05% formic acid + 0.0125% ammonia in water, Eluent B: 0.04% formic acid + 0.01% ammonia in ACN/MeOH (1:1).

LCMS method 4a, LCMS (4a)

Apparatus: Waters ACQUITYTM UPLCTM system; Bin. Pump: Waters ACQUITY TM Quaternary Solvent manager; PDA; Waters ACQUITY™ PDA detector; Waters QDa mass detector; ESI, pos/neg 100-1000; column: Waters UPLCTM BEHTM C18 2.1x50mm, 1.7 µm, Temp: 40°C, Flow rate: 0.9 mL/min, Gradient: from 5% B to 100% B, Run time: 1.1 min, Eluent A: 0.1% formic acid in water, Eluent B: 0.1% formic acid in ACN/MeOH (1:1). Sample concentration: 1 mM. Injection volume: 1 µL. Chromatograms were processed at 215 nm.

LCMS method 4b, LCMS (4b)

Apparatus: Waters ACQUITYTM UPLCTM system; Bin. Pump: Waters ACQUITY TM Quaternary Solvent manager; Waters H Class Sample Manager and Organiser; PDA; Waters ACQUITY™ PDA detector; Waters SQDa mass detector; ESI, pos/neg 100-1000; column:

Phenomenex Kinetex® Evo C18 column 2.1 mm × 50 mm, 1.7 µm, Temp: 40°C, Flow rate: 1.0 mL/min, Gradient: from 1% B to 100% B then 100% B for 0.25 min, Run time: 1.1 min, Eluent A: water + 0.2% ammonium hydroxide, Eluent B: HPLC grade ACN. Sample concentration: 1 mM. Injection volume: 1 µL. Chromatograms were processed at 215 nm.

LCMS method 4c, LCMS (4c)

Apparatus: Waters ACQUITYTM UPLCTM system; Bin. Pump: Waters ACQUITY TM Quaternary Solvent manager; Waters H Class Sample Manager and Organiser; PDA; Waters ACQUITY™ PDA detector; Waters SQDa mass detector; ESI, pos/neg 100-1000; column: Phenomenex Kinetex® Evo C18 column 2.1 mm × 50 mm, 1.7 µm, Temp: 40°C, Flow rate: 0.6 mL/min, Gradient: from 5% B to 100% Run time: 1.1 min, Eluent A: water + 0.2% ammonium hydroxide, Eluent B: HPLC grade ACN. Sample concentration: 1 mM. Injection volume: 1 µL. Chromatograms were processed at 215 nm.

LCMS method 4d, LCMS (4d)

Apparatus: Waters ACQUITYTM UPLCTM system; Bin. Pump: Waters ACQUITY TM Quaternary Solvent manager; Waters H Class Sample Manager and Organiser; PDA; Waters ACQUITY™ PDA detector; Waters SQDa mass detector; ESI, pos/neg 100-1000; column: Phenomenex Kinetex® Evo C18 column (2.1 mm × 50 mm, 1.7 µm), Temp: 40°C, Flow rate: 0.6 mL/min, Gradient: from 5% B to 100% Run time: 5.3 min, Eluent A: water + 0.2% ammonium hydroxide, Eluent B: HPLC grade ACN. Sample concentration: 1 mM. Injection volume: 1 µL. Chromatograms were processed at 215 nm.

LCMS method 4e, LCMS (4e)

Apparatus: Waters ACQUITYTM UPLCTM system; Bin. Pump: Waters ACQUITY TM Quaternary Solvent manager; Waters H Class Sample Manager and Organiser; PDA; Waters ACQUITY™ PDA detector; Waters SQDa mass detector; ESI, pos/neg 100-1000; column: Phenomenex Kinetex® Evo C18 column (2.1 mm × 50 mm, 1.7 µm), Temp: 40°C, Flow rate: 0.6 mL/min, Gradient: from 5% B to 100% B over 5.30 min then 100% B for 0.5 min, Run time: 1.18 min, Eluent A: water + 0.2% ammonium hydroxide, Eluent B: ACN. Sample concentration: 1 mM. Injection volume: 1 µL. Chromatograms were processed at 215 nm.

NMR

^{1}H Nuclear Magnetic Resonance Spectra were recorded using the following instruments:

Varian Mercury plus 400MHz

Bruker Avance III HD 400 MHz

Bruker Avance III HD 500 MHz

Agilent VNMRS DD2 600 MHz equipped with a cold probe

Samples were dissolved in the specified deuterated solvent. Tetramethylsilane was used as reference.

Preparative methods

Reaction products were purified, when necessary, by one or several of the following methods, as indicated in the examples:

Flash chromatography

Instrument type: Grace Reveleris X2® C-815 Flash; Detection: UV 200-400nm, combination of up to 4 UV signals and scan of entire UV range, ELSD; Column sizes: 4-330 g on instrument.

Instrument type: Biotage Isolera® automated purification system equipped with a silica gel (40-63 µm) column (column sizes: 4-330 g).

Where specified, the column can be Amine Functionalized Stationary Phase (KPNH) (40-65 µm) column (column sizes: 11-380 g).

The solvent system and gradients used are indicated in the preparations. The appropriate fractions were collected, and the solvents evaporated under reduced pressure.

Reverse phase chromatography

Purifications in reverse phase were made in a Biotage Isolera® automated purification system equipped with a C18 column and using a gradient, unless otherwise stated, of water-acetonitrile/MeOH (1:1) from 0% to 100% acetonitrile/MeOH (1:1) in 40 column volumes. The conditions "formic acid buffer" refer to the use of 0.1% v/v formic acid in both phases. The appropriate fractions were collected, and the solvents evaporated under reduced pressure and/or lyophilised.

Preparative-HPLC

(1) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Phenomenex Gemini-NX C18 75*30 mm*3 um, Eluent A: H_2O (10 mM ammonium formate); Eluent B: ACN, Gradient: B from 5.00% to 45.00% in 7.00 min, Flow rate: 60.0 mL/min. Monitor wavelength: 220 and 254nm

(1b) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Phenomenex Luna C18 100*30mm*5µm, Eluent A: H2O (0.1% TFA); Eluent B: ACN, Gradient: B from 1.00% to 28.00% in 8.00min, Flow rate: 60.0 mL/min. Monitor wavelength: 220&254nm**(2)** Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Waters Xbridge Prep OBD C18 150*40 mm*10 µm,

Eluent A: H_2O (10 mM ammonium formate); Eluent B: ACN, Gradient: B from 5.00% to 45.00% in 7.00 min, Flow rate: 60.0 mL/min. Monitor wavelength: 220 and 254nm

(2b) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Waters Xbridge BEH C18 100*30 mm*10 um, Eluent A: H2O (10 mM ammonium carbonate); Eluent B: ACN, Gradient: B from 40.00% to 75.00% in 8.00 min, Flow rate: 25.0 mL/min. Monitor wavelength: 220 and 254nm

(3) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Waters WePure Biotech XP tC18 150*40*7um, Eluent A: H_2O (10 mM ammonium carbonate); Eluent B: ACN, Gradient: B from 15.00% to 40.00% in 10.00 min, Flow rate: 60.0 mL/min. Monitor wavelength: 220 and 254nm

(4) Preparative HPLC method: Instrument: Agela-600 Preparative HPLC system, Column: Welch Xtimate C18 250*100 mm*10 um, Eluent A: H2O (10 mM ammonium carbonate); Eluent B: ACN, Gradient: B from 1.00% to 45.00% in 20.00 min, Flow rate: 300 mL/min. Monitor wavelength: 220 and 254nm

(5a) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Waters SunfireTM C18 Part no. 186002572 30 mm × 100 mm, 5 µm, Eluent A: H2O + 0.1% formic acid; Eluent B: ACN + 0.1% formic acid, Gradient: B 10% for 1.9 min then a gradient of 10% to 95% in 14.1 min Flow rate: 40.00 mL/min, UV 215 nm.

(5b) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Waters XBridgeTM C18 Part no.186002982 30 mm × 100 mm, 5 µm, Eluent A: H2O + 0.2% ammonium hydroxide; Eluent B: ACN, Gradient: B 10% for 2.0 min then a gradient of 10% to 95% in 14.0 min Flow rate: 40.00 mL/min, UV 215 nm.

(5c) Preparative HPLC method: Instrument: Gilson 281 Semi-preparative HPLC system, Column: Waters XBridgeTM C18 Part no.186002982 30 mm × 100 mm, 5 µm, Eluent A: H2O + 0.2% ammonium hydroxide; Eluent B: ACN, Gradient: B 30% for 2.0 min then a gradient of 30% to 95% in 9.50 min Flow rate: 40.00 mL/min, UV 215 nm.

(6) Preparative HPLC method: Instrument: Agilent 1290, Column: Daicel Chiralpak AD 5µm x 250mm x 20 mm, Eluent A: heptane; Eluent B: EtOH + 0.2% DEA, , Flow rate: 20.0 mL/min. Monitor wavelength: 270 nm

COware gas reactor

STW1 apparatus (20 mL)

Flow chemistry hydrogenation

Apparatus: Automatic hydrogenation reactor OU SHISENG Inc, H-flow-S10

Microwave reactor

Biotage Initiator+

Photochemical reactor

Merk Photoreactor M2 (365/420/455 nm, blue LEDs

INTERMEDIATES

INTERMEDIATE 1

***N*-(4-acetamidobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]

2-(1*H*-Pyrrol-1-yl)ethan-1-amine (5.00 g, 45.4 mmol) and cyclobutanone (3.4 mL, 45.4 mmol) were dissolved in EtOH (50 mL) and p-TsOH was added (0.78 g, 4.54 mmol). The mixture was stirred at 70°C for 4 h. After the reaction completion, the mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$/IPA (3:1, 50 mL) and treated with saturated $NaHCO_3$ solution (100 mL). The resulting mixture was extracted with $CHCl_3$/IPA (3:1), the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (6.6 g, 84% yield, 93% purity) as a yellow oil, which was used in next step without further purification.

LRMS (m/z): 163 $[M+1]^+$

LC (2b) r.t. (min.): 0.41

b) *Tert*-butyl 3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (15 g, 92.5 mmol) was dissolved in THF (150 mL) and TEA (19 mL, 137 mmol) and Boc_2O (30 g, 139 mmol) were added. The mixture was stirred at r.t. for 4 h. After reaction completion, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc,3:1) to give the title compound (20.6 g, 77%, purity 91% yield) as a yellow oil, which was used in next step without further purification.

LRMS (m/z): 263 $[M+1]^+$

LC (2c) r.t. (min.): 1.40

c) *Tert*-butyl 6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Tert-butyl 3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (2.00 g, 7.62 mmol) was dissolved in $CHCl_3$ (20 mL) and TEA (1.59 mL, 11.4 mmol) and 2,2,2-trichloroacetyl chloride (1.70 mL, 15.2 mmol) were added at 0°C. The mixture was stirred at 15°C for 4 h. After reaction completion, the mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$/IPA (3:1). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 1:1) to give the title compound (2.1 g, 67% yield, 91% purity) as a white solid.

LRMS (m/z): 351, 353 $[M-t\text{Bu}+1]^+$

LC (2e) r.t. (min.): 5.11

d) 2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Tert-butyl 6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (500 mg, 1.23 mmol) was dissolved in THF (4 mL) and water (1 mL) and NaOH was added (196 mg, 4.91 mmol). The mixture was stirred at r.t. for 12 h and after reaction completion the reaction mixture was diluted with water and extracted with EtOAc. The aqueous layer was adjusted to pH = 2 with 1N aqueous HCl. The precipitate was collected by filtration, washed with water and dried in the oven to give the title compound (320 mg, 77% yield, 90% purity) as white solid.

LRMS (m/z): 207 $[M-t\text{Bu}+1]^+$

LC (2d) r.t. (min.): 1.65

e) *Tert*-butyl 6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (320 mg, 1.04 mmol) and *N*-[4-(aminomethyl)phenyl]acetamide (206 mg, 1.25 mmol) were dissolved in DMF (3 mL). HATU (437 mg, 1.15 mmol) and DIEA (545 µL, 3.13 mmol) were added and the mixture was stirred at r.t. for 2 h. After reaction completion, the mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was

purified by prep-TLC (SiO_2, petroleum ether/EtOAc,1:3) to give the title compound (400 mg, 76% yield, 90% purity) as white solid.

LRMS (m/z): 475 $[M+23]^+$

LC (2d) r.t. (min.): 1.67

f) *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Tert-butyl 6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (400 mg, 0.88 mmol) was dissolved in a mixture DCM/TFA 3:1 (6 mL). The mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated under reduced pressure to remove volatile material, and the residue was diluted with water and the solution was adjusted to pH = 10 with saturated aqueous Na_2CO_3. The mixture was extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (300 mg, 91% yield, 95% purity) as white solid. The product was directly used in next step without further purification.

LRMS (m/z): 353 $[M+1]^+$

LC (2d) r.t. (min.): 0.8

INTERMEDIATE 2

***N*-(4-formylphenyl)-*N*-methylacetamide**

N-(4-formylphenyl)acetamide (200 mg, 1.23 mmol) was dissolved in THF (4 mL), the mixture was cooled to 0°C and NaH (58 mg, 1.47 mmol, 60% dispersion in mineral oil) was added in portions.. After stirring for 0.5 h at 0°C, MeI (114 µL, 1.84 mmol) was added dropwise at 0°C. The mixture was stirred at 20°C for 2 h. After reaction completion, the mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) at 0°C and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2, EtOAc 100%) to give the title compound (120 mg, 55% yield, 95% purity) as a white solid.

LRMS (m/z): 178 $[M+1]^+$

LC (2a) r.t. (min.): 0.30

INTERMEDIATE 3

4-Formyl-*N*-isopropyl-*N*-methylbenzamide

Obtained as a white solid (73% yield, 92% purity) from 4-formylbenzoic acid and *N*-methylpropan-2-amine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 206 $[M+1]^+$

LC (2b) r.t. (min.): 0.42

INTERMEDIATE 4

4-Formyl-*N*,*N*,2-trimethylbenzamide

Obtained as a colorless oil (77% yield, 90% purity) from 4-formyl-2-methyl-benzoic acid and *N*-methylmethanamine 2 mol/L following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 192 $[M+1]^+$

LC (2d) r.t. (min.): 1.51

INTERMEDIATE 5

6-Formyl-*N*,*N*-dimethylnicotinamide

Obtained as a white solid (59% yield, 95% purity) from 6-formylnicotinic acid and *N*-methylmethanamine 2 mol/L following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 179 $[M+1]^+$

LC (2c) r.t. (min.): 0.75

INTERMEDIATE 6

4-(1-Methyl-1*H*-imidazol-2-yl)benzaldehyde

2-(4-Bromophenyl)-1-methyl-imidazole (100 mg, 0.42 mmol) was dissolved in DMSO (5 mL) and 2-isocyano-2-methyl-propane (190 µL, 1.69 mmol), potassium formate (284 mg, 3.37 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (34 mg, 0.42 mmol) were added. The mixture was stirred at 120°C for 1 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and purified by prep-TLC (SiO_2, EtOAc 100%) to give the title compound (43 mg, 49% yield, 90% purity) as yellow oil.

LRMS (m/z): 187 $[M+1]^+$

LC (2c) r.t. (min.): 0.18

INTERMEDIATE 7

4-(4-Methyl-4*H*-1,2,4-triazol-3-yl)benzaldehyde

a) 3-(4-Bromophenyl)-4-methyl-4*H*-1,2,4-triazole

4-Bromobenzohydrazide (1.0 g, 4.65 mmol) was dissolved in DMF-DMA (10 mL) and was stirred at 100°C for 3 h. The mixture was cooled to 25°C and concentrated under reduced pressure. The residue was dissolved in EtOH (10 mL) followed by the addition of methylamine (1.93 g, 18.6 mmol, 30% purity in EtOH) and AcOH (1.60 mL, 27.9 mmol). The mixture was stirred at 75°C for 12 h and after reaction completion, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, EtOAc 100%) to the title compound (0.70 g, 63% yield, 97% purity) as a white solid.

LRMS (m/z): 238 $[M+1]^+$

LC (2a) r.t. (min.): 0.32

b) 4-(4-Methyl-4*H*-1,2,4-triazol-3-yl)benzaldehyde

Obtained as a red solid (22% yield, 96% purity) from 3-(4-bromophenyl)-4-methyl-1,2,4-triazole and 2-isocyano-2-methyl-propane following the synthetic procedure as described for Intermediate 6.

LRMS (m/z): 188 $[M+1]^+$

LC (2a) r.t. (min.): 0.37

INTERMEDIATE 8

4-(1,3,4-Oxadiazol-2-yl)benzaldehyde

Obtained as a white solid (63% yield, 98% purity) from 2-(4-bromophenyl)-1,3,4-oxadiazole and 2-isocyano-2-methyl-propane following the synthetic procedure as described for Intermediate 6.

LRMS (m/z): 175 $[M+1]^+$

LC (2) r.t. (min.): 1.15

INTERMEDIATE 9

4-(Oxazol-2-yl)benzaldehyde

A mixture of 2-bromooxazole (100 mg, 0.68 mmol) and (4-formylphenyl)boronic acid (152 mg, 1.01 mmol) was dissolved in a mixture of DME (1.80 mL) and water (0.60 mL) and Na_2CO_3 (143 mg, 1.35 mmol) and $Pd(PPh_3)_4$ (78 mg, 0.67 mmol) were added. The mixture was stirred at 100°C for 5 h and after reaction completion, the mixture was poured into water

and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (SiO_2, EtOAc/petroleum ether, 1:1) to give the title compound (60 mg, 46% yield, 90% purity) as a yellow solid.

LRMS (m/z): 174 $[M+1]^+$

LC (2) r.t. (min.): 0.38

INTERMEDIATE 10

***N*-(4-acetamidobenzyl)-2'-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) Methyl 2'-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Methyl 3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate (trifluoroacetate salt) (50 mg, 0.15 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (36 mg, 0.17 mmol) were dissolved in DCM (1.5 mL) and the resulting solution was stirred at r.t. for 10 min before $NaBH(OAc)_3$ (65 mg, 0.31 mmol) was added. The mixture was then stirred at r.t. overnight. Additional *tert*-butyl 4-formylpiperidine-1-carboxylate (25 mg, 0.12 mmol) and $NaBH(OAc)_3$ (30 mg, 0.14 mmol) were added and the mixture was allowed to stir for additional 24 h at r.t. 4% w/v aqueous $NaHCO_3$ was added to the reaction mixture and the resulting biphasic solution was stirred for 1 h. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford 81.5 mg of a colourless oil. The residue was purified by flash chromatography (MeOH-DCM, 0:100 rising to 10:90) to give the title compound (21 mg, 34% yield, 98% purity) as a colourless oil.

LRMS (m/z): 418 $[M+1]^+$

LC (3) r.t. (min.): 2.09

b) 2'-((1-(*Tert*-butoxycarbonyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Methyl 2'-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro [cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate (21 mg, 0.50 mmol) was dissolved in a mixture of THF (1 mL) and water (0.4 mL). To this solution, lithium hydroxide monohydrate (8 mg, 0.19 mmol) was added and the mixture was stirred at r.t. overnight. MeOH was then added to the mixture (0.4 mL) and stirring was continued for 4 h. The organic volatiles were evaporated, and the aqueous phase was acidified to pH =3 with 2N HCl. DCM was added, the aqueous phase was further extracted with DCM and the resulting

organic extracts were washed with brine and filtered through a Phase Separator. The filtered solution was then evaporated under reduced pressure to give the title compound (16.8 mg, 83% yield, 94% purity) as a colourless oil, which was used in next step without further purification.

LRMS (m/z): 404 $[M+1]^+$

LC (3) r.t. (min.): 1.61

c) *Tert*-butyl 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)piperidine-1-carboxylate

Obtained as a colourless oil (89% yield, 98% purity) from 2'-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro [cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 550 $[M+1]^+$

LC (3) r.t. (min.): 1.56

d) *N*-(4-acetamidobenzyl)-2'-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a light yellow gum (84% yield, 89% purity) from *tert*-butyl 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro [cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 450 $[M+1]^+$

LC (3) r.t. (min.): 0.82

INTERMEDIATE 11

2'-(4-(1*H*-Pyrazol-1-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a colourless oil (32% yield, 83% purity) from 3-(4-bromophenyl)-3-methyl-oxetane and 2-isocyano-2-methyl-propane following the synthetic procedure as described for Intermediate 6.

LRMS (m/z): 177 $[M+1]^+$

LC (2d) r.t. (min.): 0.54

INTERMEDIATE 12

4-[3-(Dimethylamino)oxetan-3-yl]benzaldehyde

a) 3-(4-Bromophenyl)-*N*,*N*-dimethyl-oxetan-3-amine

3-(4-Bromophenyl)oxetan-3-amine hydrochloride (300 mg, 1.13 mmol) was dissolved in a mixture THF/DCM 1:1 (2 mL) and formaldehyde (4.6 g, 56.70 mmol, 37% purity) was added, followed by $NaBH(OAc)_3$ (649 mg, 3.06 mmol) at 0°C. The mixture was stirred at 20°C for 12 h. After reaction completion, the mixture was quenched by the addition of 1N aqueous NaOH solution (1 mL), diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the title compound (200 mg, 69% yield, 97% purity) as a white solid.

LRMS (m/z): 256 $[M+1]^+$

LC (2a) r.t. (min.): 0.30

b) 4-[3-(Dimethylamino)oxetan-3-yl]benzaldehyde

Obtained (40 mg) from 3-(4-bromophenyl)-*N*,*N*-dimethyl-oxetan-3-amine and 2-isocyano-2-methyl-propane following the synthetic procedure as described for Intermediate 6. The crude product was used in the next step without further purification.

LRMS (m/z): 206 $[M+1]^+$

LC (2b) r.t. (min.): 0.37

INTERMEDIATE 13

4-(1-Hydroxy-2-methylpropyl)benzaldehyde

A 2M solution of isopropyl magnesium chloride in THF (1.5 mL, 3.00 mmol) was added dropwise to a stirred solution of 4-(diethoxymethyl)benzaldehyde (520 mg, 2.5 mmol) in dry diethyl ether (5 mL) under an atmosphere of argon. After 1 h, the mixture was quenched with water (20 mL) and 5M aqueous HCl (0.70 mL) and stirring was continued at r.t.. After 30 min, the mixture was diluted with brine and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (diethyl ether-hexane gradient, 0:100 rising to 100:0) to give the title compound (0.14 g, 31% yield, 99% purity) as a colourless oil.

LRMS (m/z): 179 $[M+1]^+$

LC (3) r.t. (min.): 1.45

INTERMEDIATE 14

3-Fluoro-4-formyl-*N*,*N*-dimethylbenzamide

3-Fluoro-4-formylbenzoic acid (0.20 g, 1.19 mmol) was suspended in dry DCM (2 mL), cooled in an ice bath and oxalyl chloride (0.13 mL, 1.52 mmol) was added dropwise followed by 2 drops of DMF. The mixture was warmed to ambient temperature and stirred for 2 h. The mixture was evaporated to dryness, redissolved in DCM (2 mL) and cooled in an ice bath. A 2M solution of dimethylamine in THF (0.9 mL, 1.80 mmol) and DIEA (0.25 mL, 1.44 mmol) dissolved in DCM (1 mL) were added and the mixture was stirred overnight at ambient temperature. The mixture was diluted with DCM and washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (0.24 g, 100% yield, 97% purity) as a colourless oil.

LRMS (m/z): 196 $[M+1]^+$

LC (3) r.t. (min.): 0.98

INTERMEDIATE 15

2-Methyl-4-(1,2,4-triazol-1-yl)benzaldehyde

To a solution of 1*H*-1,2,4-triazole (100 mg, 1.45 mmol) and 4-fluoro-2-methyl-benzaldehyde (0.2 g, 1.45 mmol) in DMF (4 mL) was added K_2CO_3 (400 mg, 2.90 mmol). The mixture was stirred at 100°C for 12 h. After the reaction completion, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, EtOAc 100%) to give the title compound (0.12 g, 44%, yield, 96% purity) as a white solid.

LRMS (m/z): 188 $[M+1]^+$

LC (2c) r.t. (min.): 0.84

INTERMEDIATE 16

4-(2-Oxopyrrolidin-1-yl)benzaldehyde

To a solution of 4-bromobenzaldehyde (200 mg, 1.08 mmol) and pyrrolidin-2-one (138 mg, 1.62 mmol) in toluene (2 mL) were added Cs_2CO_3 (1.06 g, 3.24 mmol), $Pd_2(dba)_3$ (49 mg, 54 µmol) and Xantphos (63 mg, 108 µmol) under a N_2 atmosphere. The mixture was stirred at 100°C for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, EtOAc/MeOH=10/1) to give the title compound (150 mg, 66% yield, 90% purity) as yellow solid.

LRMS (m/z): 190 $[M+1]^+$

LC (2c) r.t. (min.): 0.78

INTERMEDIATE 17

***N*-(4-(dimethylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl 6'-((4-(dimethylamino)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

To a solution of 4-(aminomethyl)-*N*,*N*-dimethylaniline (39 mg, 0.260 mmol) and 2'-(*tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d, 80 mg, 0.26 mmol) in DMF (3 mL) was added NMI (42.6 mg, 0.52 mmol) and the resulting mixture was stirred at r.t. for 5 min before TCFH (146 mg, 0.52 mmol) was added. The reaction mixture was stirred at r.t. until reaction completion. Then the mixture was quenched with water and extracted with EtOAc and the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by MPLC to give the title compound (41 mg, 36% yield).

b) *N*-(4-(dimethylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Tert-butyl 6'-((4-(dimethylamino)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (41 mg, 0.93 mmol) was dissolved in 4 M HCl in 1,4-dioxane (5 mL), and the resulting mixture was stirred at r.t. for 30 min before it was concentrated to yield the title compound, that was used in the next step without further purification (57 mg).

INTERMEDIATE 18

***N*-(4-acetamidobenzyl)-N-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *N*-(4-formylphenyl)acetamide

To a stirred solution of 4-aminobenzaldehyde (200 mg, 1.65 mmol) in DCM (2 mL) was added TEA (460 µL, 3.30 mmol,). The resulting reaction mixture was stirred at r.t. for 10 min before Ac_2O (169 mg, 1.65 mmol) was added. Stirring was continued at r.t. until

reaction completion. Then the reaction mixture was purified by MPLC to give the title compound (214 mg, 79% yield).

b) *N*-(4-((methylamino)methyl)phenyl)acetamide

To a mixture of *N*-(4-formylphenyl)acetamide (214 mg, 1.31 mmol) in 30% methylamine in MeOH (5 mL) was added $NaBH_4$ (124 mg, 3.28 mmol). The mixture was stirred at r.t. for 2 h until reaction completion. The reaction mixture was purified by MPLC to give the title compound (112 mg, 48% yield) as a white solid.

c) *Tert*-butyl 6'-((4-acetamidobenzyl)(methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (49% yield) from *N*-(4-((methylamino)methyl)phenyl)acetamide and 2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d) following the synthetic procedure as described for Intermediate 17a.

d) *N*-(4-acetamidobenzyl)-N-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained from *tert*-butyl 6'-((4-acetamidobenzyl)(methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification (32 mg).

INTERMEDIATE 19

***N*-benzyl-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl 6'-(benzylcarbamoyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (90% yield) from phenylmethanamine and 2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d) following the synthetic procedure as described for Intermediate 17a.

b) *N*-benzyl-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained from *tert*-butyl 6'-(benzylcarbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for

Intermediate 1f. The crude product was used in the next step without further purification (50 mg).

INTERMEDIATE 20

***N*-((1-acetylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

***a) Tert*-butyl ((1-acetylpiperidin-4-yl)methyl)carbamate**

Obtained from *tert*-butyl (piperidin-4-ylmethyl)carbamate (214 mg, 999 μmol), DIEA (174 μL, 999 μmol) and Ac_2O (102 mg, 999 μmol) following the synthetic procedure as described for Intermediate 18a. The crude product was used in the next step without further purification (300 mg).

b) 1-(4-(Aminomethyl)piperidin-1-yl)ethan-1-one

Obtained (180 mg) from *tert*-butyl ((1-acetylpiperidin-4-yl)methyl) following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

c) *Tert*-butyl 6'-(((1-acetylpiperidin-4-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (55% yield) from 1-(4-(aminomethyl)piperidin-1-yl)ethan-1-one and 2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d) following the synthetic procedure as described for Intermediate 17a.

d) *N*-((1-acetylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (40 mg) from *tert*-butyl 6'-(((1-acetylpiperidin-4-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

INTERMEDIATE 21

4-((6'-((4-Acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzoic acid

N-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 1f, 150 mg, 0.43 mmol) was dissolved in DCM (2 mL) and 4-formylbenzoic acid (96 mg, 0.64 mmol), AcOH (2 μL) and $NaBH(OAc)_3$ (180 mg, 0.85 mmol) were added at 0°C and the mixture was stirred at 25°C for 12 h. After reaction

completion, the mixture was purified by prep-HPLC (1a, B from 5.00% to 45.00% in 7.00 min) to give the title compound (80 mg, 38.6% yield, 90% purity) as white solid.

LRMS (m/z): 487 $[M+1]^+$

LC (2b) r.t. (min.): 0.39

INTERMEDIATE 22

4-((6'-((4-Acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluorobenzoic acid

Obtained as a white foam (62% yield, 97% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 1f) and 3,5-difluoro-4-formylbenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 523 [M+1]+

LC (3) r.t. (min.): 2.34

INTERMEDIATE 23

***Tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)(methyl)carbamate**

a) 4-((3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a white solid (64% yield, 93% purity) from 3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 1a) and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 324 $[M+1]^+$

LC (2b) r.t. (min.): 0.54

b) *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a yellow oil (79% yield, 86% purity)from 4-((3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c, but stirring the reaction mixture at 60ºC for 12 h. The crude product was used in the next step without further purification.

LRMS (m/z): 468 $[M+1]^+$

LC (2b) r.t. (min.): 0.66

c) 2'-(4-(Dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

N,*N*-dimethyl-4-[[6-(2,2,2-trichloroacetyl)spiro[3,4-dihydropyrrolo [1,2-a]pyrazine-1,1'-cyclobutane]-2-yl]methyl]benzamide (12 g, 25.6 mmol) was dissolved in THF (100 mL) and H_2O (25 mL) and NaOH was added (3.07 g, 76.8 mmol). The mixture was stirred at 25°C for 2 h. After the reaction completion, the mixture was poured into water (100 mL) and the two phases were separated. The aqueous phase was extracted with EtOAc and was then adjusted to pH = 3-4 with 1 M aqueous HCl solution. The precipitate was collected by filtration and dried under reduced pressure to give the title compound (6.00 g, 62% yield, 97% purity) as a yellow solid.

LRMS (m/z): 368 $[M+1]^+$

LC (2e) r.t. (min.): 2.45

d) *Tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)(methyl)carbamate

Obtained as a white solid (56% yield) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and tert-butyl (4-(aminomethyl)phenyl)(methyl)carbamate following the synthetic procedure as described for Intermediate 17a.

INTERMEDIATE 24

***N*-(6-(aminomethyl)pyridin-3-yl)acetamide**

a) *N*-(6-cyanopyridin-3-yl)acetamide

To a solution of 5-aminopicolinonitrile (0.3 g, 2.52 mmol) in Ac_2O (0.9 mL) was added AcOH (865 µL,15.1 mmol) at 0°C. The mixture was stirred at 25°C for 12 h. After reaction completion, the mixture was concentrated under reduced pressure to give the title compound (0.28 g, 68% yield, 98% purity 98%) as a yellow solid, which was used in next step without further purification.

LRMS (m/z): 162 $[M+1]^+$

LC (2b) r.t. (min.): 0.32

b) *N*-(6-(aminomethyl)pyridin-3-yl)acetamide

To a solution of *N*-(6-cyanopyridin-3-yl)acetamide (100 mg, 0.62 mmol) in MeOH (10 mL) was added Raney-Ni (106 mg, 10% wt%) and a 28% aqueous solution of ammonia (357 µL, 2.60 mmol) under a N_2 atmosphere. The suspension was degassed and purged twice with H_2.

The mixture was stirred under H_2 (15 PSI) at 25°C for 2 h. After reaction completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (80 mg, 78% yield, 90% purity) as a white solid.

LRMS (m/z): 166 $[M+1]^+$

LC (2b) r.t. (min.): 0.13

INTERMEDIATE 25

***N*-(4-(aminomethyl)-2-methylphenyl)acetamide**

a) *N*-(4-cyano-2-methylphenyl)acetamide

Obtained as a yellow solid (58% yield, 99% purity) from 4-amino-3-methyl-benzonitrile following the synthetic procedure as described for Intermediate 24a.

LRMS (m/z): 175 $[M+1]^+$

LC (2a) r.t. (min.): 0.32

b) *N*-(4-(aminomethyl)-2-methylphenyl)acetamide

Obtained as a white solid (62% yield, 80% purity) from *N*-(4-cyano-2-methyl-phenyl)acetamide following the synthetic procedure as described for Intermediate 24b.

LRMS (m/z): 357 $[M+1]^+$

LC (2b) r.t. (min.): 0.14

INTERMEDIATE 26

***N*-(4-(aminomethyl)-2,6-dimethylphenyl)acetamide**

***a) N*-(4-cyano-2,6-dimethylphenyl)acetamide**

Obtained as a grey solid (69% yield, 99% purity) from 4-amino-3,5-dimethyl-benzonitrile following the synthetic procedure as described for Intermediate 24a.

LRMS (m/z): 189 $[M+1]^+$

LC (2d) r.t. (min.): 0.82

b) *N*-(4-(aminomethyl)-2,6-dimethylphenyl)acetamide

Obtained as a white solid (65% yield, 88% purity) from *N*-(4-cyano-2,6-dimethyl-phenyl)acetamide following the synthetic procedure as described for Intermediate 24b.

LRMS (m/z): 385 $[M+1]^+$

LC (2c) r.t. (min.): 0.31

INTERMEDIATE 27

***N*-[3-(aminomethyl)phenyl]acetamide;hydrochloride**

a) *Tert*-butyl (3-acetamidobenzyl)carbamate

Tert-butyl (3-aminobenzyl)carbamate (1.2 g, 5 mmol) was dissolved in DCM (20 mL) and TEA was added (3.8 mL, 25.3 mmol). The solution was cooled in an ice bath, acetyl chloride (0.43 mL, 6.05 mmol) was slowly added dropwise and the mixture was stirred at 0ºC for 40 min. The mixture was diluted with water and the organic layer was washed with 0.1 M aqueous HCl, dried over Na_2SO_4, filtrated and evaporated under reduced pressure to give the title compound (quantitative yield, 99% purity) as a colorless oil, that was used directly in the next reaction step without further purification.

LRMS (m/z): 263 $[M+1]^+$

LC (3) r.t. (min.): 1.43

b) *N*-[3-(aminomethyl)phenyl]acetamide;hydrochloride

Obtained as a beige solid (quantitative yield, 95% purity) from *N*-(4-cyano-2,6-dimethyl-phenyl)acetamide following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 165 $[M+1]^+$

LC (3) r.t. (min.): 0.35

INTERMEDIATE 28

***N*-(4-(aminomethyl)-2-fluorophenyl)acetamide**

***a) N*-(4-cyano-2-fluorophenyl)acetamide**

Obtained as a white solid (64% yield, 90% purity) from 4-amino-3-fluorobenzonitrile following the synthetic procedure as described for Intermediate 24a.

LRMS (m/z): 179.5 $[M+1]^+$

LC (2b) r.t. (min.): 0.39

b) *N*-(4-(aminomethyl)-2-fluorophenyl)acetamide

Obtained as a white solid (79% yield, 90% purity) from *N*-(4-cyano-2-fluorophenyl)acetamide following the synthetic procedure as described for Intermediate 24b.

LRMS (m/z): 181.5 $[M+1]^+$

LC (2b) r.t. (min.): 0.14

INTERMEDIATE 29

***N*-(4-(aminomethyl)phenyl)-N-methylacetamide**

***a) Tert*-butyl (4-(methylamino)benzyl)carbamate**

A mixture of tert-butyl (4-aminobenzyl)carbamate (1.50 g, 6.70 mmol) and 1*H*-benzotriazole (0.81 g, 6.80 mmol) was dissolved in ethanol (7 mL) and a 37% aqueous formaldehyde solution (0.5 mL, 6.70 mmol) was added. After 30 mins, further ethanol (6 mL) was added to the viscous mixture to facilitate stirring and stirring was continued at r.t. After 3 days, the mixture was filtered and the solid was washed with a 1:1 mixture of ethanol-water, then ethanol and then dried in vacuo (40 °C). The solid (1.68 g) was suspended in dry THF (20 mL), sodium borohydride (0.40 g) was added and the mixture was stirred at r.t. overnight. The mixture was concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc-hexane gradient, 0:100 rising to 40:60) to give the title compound (0.95 g, 60% yield, 97% purity) as a colourless oil.

LRMS (m/z): 237 $[M+1]^+$

LC (3) r.t. (min.): 1.33

b) *Tert*-butyl (4-(*N*-methylacetamido)benzyl)carbamate

Obtained as a colourless oil (quantitative yield, 99% purity) from *Tert*-butyl (4-(methylamino)benzyl)carbamate following the synthetic procedure as described for Intermediate 24a.

LRMS (m/z): 279 $[M+1]^+$

LC (3) r.t. (min.): 1.51

c) *N*-(4-(aminomethyl)phenyl)-N-methylacetamide

Obtained as a white solid (quantitative yield, 83% purity based on mass) from *Tert*-butyl (4-(*N*-methylacetamido)benzyl)carbamate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 179 $[M+1]^+$

LC (3) r.t. (min.): 0.35

INTERMEDIATE 30

4-(Aminomethyl)-*N*-methylbenzamide

a) *Tert*-butyl (4-(methylcarbamoyl)benzyl)carbamate

Obtained as an off white solid (48% yield, 86% purity based on mass) from 4-(((*tert*-butoxycarbonyl)amino)methyl)benzoic acid following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 265 $[M+1]^+$

LC (3) r.t. (min.): 1.37

b) 4-(Aminomethyl)-N-methylbenzamide

Obtained as a sticky white solid from *Tert*-butyl (4-(methylcarbamoyl)benzyl)carbamate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

LRMS (m/z): 165 $[M+1]^+$

LC (3) r.t. (min.): 0.26

INTERMEDIATE 31

***N*-(4-(aminomethyl)phenyl)-3-methyloxetan-3-amine**

***a) Tert*-butyl (4-((3-methyloxetan-3-yl)amino)benzyl)carbamate**

A mixture of 3-isopropyloxetan-3-amine (61 mg, 0.70 mmol), *tert*-butyl (4-bromobenzyl)carbamate (100 mg, 0.35 mmol), K_2CO_3 (104 mg, 1.05 mmol) and BrettPhos Pd G3 (35 mg, 10 mol%) were suspended in *tert*-butanol (2 mL) in a Schlenk tube. The mixture was purged with argon and then the mixture was stirred and heated to 110°C. After 12 h, the reaction mixture was partitioned between EtOAc and water and the organic layer was washed with water, brine, dried over MgSO4 and evaporated in vacuo. The residue was purified by flash chromatography (MeOH-DCM gradient, 0:100 rising to 10:90) to give the title compound (93 mg, 74% yield, 81% purity) as a colourless oil.

LRMS (m/z): 293 $[M+1]^+$

LC (3) r.t. (min.): 1.60

b) *N*-(4-(aminomethyl)phenyl)-3-methyloxetan-3-amine

Obtained (92 mg) from *tert*-butyl (4-((3-methyloxetan-3-yl)amino)benzyl)carbamate following the synthetic procedure as described for Intermediate 1f. The crude product, contaminated with inorganic material, was used in the next step without further purification.

LRMS (m/z): 193 $[M+1]^+$

LC (3) r.t. (min.): 0.45

INTERMEDIATE 32

***N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 6-(Aminomethyl)pyridin-3-amine

Obtained (600 mg) from 5-aminopicolinonitrile following the synthetic procedure as described for Intermediate 24b. The crude product was used in the next step without further purification.

LRMS (m/z): 124.2 $[M+1]^+$

LC (2c) r.t. (min.): 0.13

b) *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (54% yield, 94% purity) from 6-(aminomethyl)pyridin-3-amine following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 473 $[M+1]^+$

LC (2c) r.t. (min.): 1.07

INTERMEDIATE 33

1-(5-(Aminomethyl)indolin-1-yl)ethan-1-one

a) 1-Acetylindoline-5-carbonitrile

Indoline-5-carbonitrile (300 mg, 2.08 mmol) was dissolved in DCM (2 mL) and $NaHCO_3$ (2.1 g, 24.9 mmol) was added at 20°C. The reaction mixture was cooled to 0°C, and acetyl chloride (327 mg, 4.16 mmol) was added dropwise. Then the ice bath was removed, and the mixture was stirred at 20°C for 2 h. After reaction completion, the reaction mixture was diluted with water, extracted with DCM and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give the title compound (300 mg, 78% yield, 90% purity) as white solid.

LRMS (m/z): 187 $[M+1]^+$

LC (2a) r.t. (min.): 0.37

b) 1-(5-(Aminomethyl)indolin-1-yl)ethan-1-one

Obtained as a white solid (65% yield, 90% purity) from 1-acetylindoline-5-carbonitrile following the synthetic procedure as described for Intermediate 24b.

LRMS (m/z): 187 $[M+1]^+$

LC (2a) r.t. (min.): 0.37

INTERMEDIATE 34

2'-(4-(Dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 3',4'-Dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]

Obtained from 2-(1*H*-pyrrol-1-yl)ethan-1-amine and oxetan-3-one following the synthetic procedure as described for Intermediate 1a. The crude product was used in the next step without further purification (132 mg)

LRMS (m/z): 165 $[M+1]^+$

LC (3) r.t. (min.): 0.30

b) 4-((3',4'-Dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a white solid (23% yield, 100% purity) from 3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine] and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 326 $[M+1]^+$

LC (3) r.t. (min.): 1.49

c) *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained from 4-((3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification (117 mg)

LRMS (m/z): 470 $[M+1]^+$

LC (3) r.t. (min.): 2.08

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained from *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c. The crude product was used in the next step without further purification (73 mg)

LRMS (m/z): 370 [M+1]+

LC (3) r.t. (min.): 1.38

INTERMEDIATE 35

2-(1-(4-(Dimethylcarbamoyl)phenyl)cyclopentyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

a) 3',4'-Dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]

Obtained from 2-(1*H*-pyrrol-1-yl)ethan-1-amine and cyclopentanone following the synthetic procedure as described for Intermediate 1a. The crude product was used in the next step without further purification (263 mg)

LRMS (m/z): 177 $[M+1]^+$

LC (3) r.t. (min.): 0.75

b) 4-(1-(3,4-Dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclopentyl)-*N*,*N*-dimethylbenzamide

Obtained as a colourless oil (36% yield, 98% purity) from 3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine] and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 338 $[M+1]^+$

LC (3) r.t. (min.): 1.15

c) *N*,*N*-dimethyl-4-(1-(6-(2,2,2-trichloroacetyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclopentyl)benzamide

Obtained from 4-(1-(3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclopentyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification (261 mg)

LRMS (m/z): 482 $[M+1]^+$

LC (3) r.t. (min.): 2.48

d) 2-(1-(4-(Dimethylcarbamoyl)phenyl)cyclopentyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

Obtained from *N*,*N*-dimethyl-4-(1-(6-(2,2,2-trichloroacetyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclopentyl)benzamide following the synthetic procedure as described for Intermediate 23c. The crude product was used in the next step without further purification (95 mg)

LRMS (m/z): 382 $[M+1]^+$

LC (3) r.t. (min.): 1.31

INTERMEDIATE 36

2-(1-(4-(Dimethylcarbamoyl)phenyl)cyclohexyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

a) 3',4'-Dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]

Obtained as a brown oil (60% yield, 90% purity) from 2-(1*H*-pyrrol-1-yl)ethan-1-amine and cyclohexanone following the synthetic procedure as described for Intermediate 1a.

LRMS (m/z): 191 $[M+1]^+$

LC (3) r.t. (min.): 0.88

b) 4-(1-(3,4-Dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclohexyl)-*N*,*N*-dimethylbenzamide

Obtained as from 3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine] and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21. The crude product was used in the next step without further purification (97 mg)

LRMS (m/z): 352 $[M+1]^+$

LC (3) r.t. (min.): 1.54

c) *N*,*N*-dimethyl-4-(1-(6-(2,2,2-trichloroacetyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclohexyl)benzamide

Obtained from 4-(1-(3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclohexyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification (218 mg)

LRMS (m/z): 496, 498, 500 $[M+1]^+$

LC (3) r.t. (min.): 2.46

d) 2-(1-(4-(Dimethylcarbamoyl)phenyl)cyclohexyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

Obtained from *N*,*N*-dimethyl-4-(1-(6-(2,2,2-trichloroacetyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)cyclohexyl)benzamide following the synthetic procedure as described for Intermediate 23c. The crude product was used in the next step without further purification (68 mg)

LRMS (m/z): 396 $[M+1]^+$

LC (3) r.t. (min.): 1.92

INTERMEDIATE 37

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]

Obtained as a green oil (44% yield, 92% purity) from 2-(1*H*-pyrrol-1-yl)ethan-1-amine and 3,3-difluorocyclobutan-1-one following the synthetic procedure as described for Intermediate 1a.

LRMS (m/z): 199 $[M+1]^+$

LC (2c) r.t. (min.): 1.18

b) 4-((3,3-Difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (65% yield, 95% purity) from 3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 360 $[M+1]^+$

LC (2c) r.t. (min.): 1.22

c) 4-((3,3-Difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a white solid (56% yield, 95% purity) from 4-((3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 504 $[M+1]^+$

LC (2c) r.t. (min.): 1.47

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 23c. The crude product was used in the next step without further purification (450 mg)

LRMS (m/z): 404 $[M+1]^+$

LC (2c) r.t. (min.): 0.82

INTERMEDIATE 38

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]

Obtained as a yellow oil (52% yield, 98% purity) from 2-(1*H*-pyrrol-1-yl)ethan-1-amine and 3,3-dimethylcyclobutan-1-one following the synthetic procedure as described for Intermediate 1a.

LRMS (m/z): 191 $[M+1]^+$

LC (2c) r.t. (min.): 1.51

b) 4-((3,3-Dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (45% yield, 92% purity) from 3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 352 $[M+1]^+$

LC (2b) r.t. (min.): 0.62

c) 4-((3,3-Dimethyl-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a white solid (66% yield, 95% purity) from 4-((3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 496 $[M+1]^+$

LC (2c) r.t. (min.): 1.67

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a white solid (86% yield, 95% purity) from 4-((3,3-dimethyl-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 396 $[M+1]^+$

LC (2c) r.t. (min.): 0.91

INTERMEDIATE 39

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl (4-(4-bromobenzamido)benzyl)carbamate

To a solution of (4-aminobenzyl)carbamate (1.00 g, 4.50 mmol, 1 eq) and DIEA (1.56 mL, 9.00 mmol) in $CHCl_3$ (5 mL) was added dropwise a solution of *tert*-butyl 4-bromobenzoyl chloride (1.09 g, 4.95 mmol) in $CHCl_3$ (5 mL). The resulting mixture was stirred at 25°C for 2 h. After reaction completion, the mixture was poured into water and the aqueous phase was extracted with DCM. The organic layer was washed with 10% aqueous citric acid (20 mL), saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.5 g, 78% yield, 95% purity) as yellow solid.

LRMS (m/z): 429 $[M+Na]^+$

LC (2a) r.t. (min.): 0.53

b) *N*-(4-(aminomethyl)phenyl)-4-bromobenzamide

Obtained as yellow solid (75% yield, 90% purity based on mass) from *tert*-butyl (4-(4-bromobenzamido)benzyl)carbamate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 306 $[M+1]^+$

LC (2a) r.t. (min.): 0.35

c) *N*-(4-(4-bromobenzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl) -3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (77% yield, 95% purity) from *N*-(4-(aminomethyl)phenyl)-4-bromobenzamide and 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 656 $[M+1]^+$

LC (2a) r.t. (min.): 0.41

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

N-(4-(4-bromobenzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (100 mg, 0.15 mmol) and 1-

methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (51 mg, 0.23 mmol) were dissolved in dioxane (2 mL) and H_2O (0.4 mL), and K_2CO_3 (63 mg, 0.46 mmol) and $Pd(dppf)Cl_2$ (11 mg, 15.2 µmol) were added under N_2. The resulting mixture was stirred at 90°C for 12 h. After reaction completion, the mixture was poured into water and the two phases were separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (SiO_2, Petroleum ether/EtOAc/EtOH, 4:3:1) to give the title compound (81 mg, 79% yield, 95% purity) as a yellow solid.

LRMS (m/z): 671 $[M+1]^+$

LC (2b) r.t. (min.): 0.57

INTERMEDIATE 40

4-(tetrahydro-2*H*-pyran-4-yl)benzoic acid

a) Methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate

To a solution of methyl 4-bromobenzoate (200 mg, 0.93 mmol, 1 eq) and 4-bromotetrahydropyran (153 mg, 0.93 mmol) in DME (2 mL) were added $(Ir(dF(CF_3)ppy)_2(dtbbpy))PF_6$ (10 mg, 9.30 µmol), Na_2CO_3 (197 mg, 1.86 mmol), dtbbpy (1.25 mg, 4.65 µmol), TTMSS (231 mg, 0.93 mmol) and $NiCl_2$.glyme (1.02 mg, 4.65 µmol) under an argon atmosphere. The mixture was stirred at 25°C for 12 h under blue LED irradiation. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO4, filtered and concentrated under reduced pressure to give a residue which was purified by prep-TLC (SiO_2, Petroleum ether/EtOAc,1:1) to give the title compound (100 mg, 38% yield, 79% purity) as a white solid.

LRMS (m/z): 221 $[M+1]^+$

LC (2a) r.t. (min.): 0.47

b) 4-(Tetrahydro-2*H*-pyran-4-yl)benzoic acid

Obtained as a white solid (48% yield, 90% purity) from methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 205 $[M+1]^+$

LC (2c) r.t. (min.): 0.95

INTERMEDIATE 41

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (49% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 472 $[M+1]^+$

LC (2d) r.t. (min.): 0.78

b) *Tert*-butyl 3-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4*H*)-carboxylate

Obtained as a brown oil (52% yield, 81% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 721 $[M+1]^+$

LC (2c) r.t. (min.): 1.37

c) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

A mixture of *tert*-butyl 3-[[4-[[[2-[[4-(dimethylcarbamoyl)phenyl]methyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carbonyl]amino]methyl]phenyl]carbamoyl]-6,7-dihydro-4*H*-pyrazolo[1,5-a]pyrazine-5-carboxylate (70 mg, 0.97 mmol) in 1M HCl/EtOAc (2 mL) was stirred at 20°C for 2 h. The reaction mixture was filtered. The filter cake was washed with EtOAc (10 mL) and dried to give the title compound (45 mg, 67% yield, 95% purity) as a brown solid.

LRMS (m/z): 621 $[M+1]^+$

LC (2c) r.t. (min.): 1.11

INTERMEDIATE 42

1-Methylindoline-6-carboxylic acid

1-Methylindole-6-carboxylic acid (100 mg, 0.57 mmol) was dissolved in AcOH (1 mL) and $NaBH_3CN$ (215 mg, 3.42 mmol) was added. The mixture was stirred at 20°C for 12 h. After reaction completion, the mixture was concentrated under reduced pressure and purified by preparative-HPLC (2, B from 5.00% to 45.00%) to give the title compound (80 mg, 79% yield, 94% purity) as a white solid.

LRMS (m/z): 178 $[M+1]^+$

LC (2c) r.t. (min.): 0.68

INTERMEDIATE 43

***Tert*-butyl (3-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)bicyclo[1.1.1]pentan-1-yl)carbamate**

a) (3-((*Tert*-butoxycarbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate

Tert-butyl (3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (0.27 g, 1.26 mmol) was dissolved in a mixture of dichloromethane (5 mL) and triethylamine (0.27 mL, 1.94 mmol) and the mixture was stirred and cooled in an ice bath. Methane sulphonyl chloride (0.12 mL, 1.51 mmol) was added dropwise and the mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was partitioned between water and EtOAc and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (0.35 g, 96% yield, 98% purity) as a white solid.

LRMS (m/z): 238 $[M-56+1]^+$

LC (3) r.t. (min.): 1.51

b) *Tert*-butyl (3-(azidomethyl)bicyclo[1.1.1]pentan-1-yl)carbamate

(3-((*Tert*-butoxycarbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate (0.35 g, 1.20 mmol) was dissolved in dry DMF (2 mL) under an argon atmosphere and sodium azide (0.10 g, 1.57 mmol) was added. The mixture was stirred and heated to 75 °C for 1.5 h and then allowed to cool to ambient temperature. The reaction mixture was partitioned between water and diethyl ether and the organic layer was washed with water, brine, dried over MgSO4, filtered and concentrated under reduced pressure to give the title compound (0.28 g, 97% yield, 95% purity) as a white solid.

1H NMR (400 MHz, CDCl3) δ 4.94 (br s, 1H), 3.36 (s, 2H), 2.04 (s, 6H), 1.44 (s, 9H).

c) *Tert*-butyl (3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl)carbamate

Tert-butyl (3-(azidomethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (0.28 g, 1.16 mmol) was dissolved in THF (1.5 mL) under an argon atmosphere and triphenyl phosphine (0.48 g, 1.74 mmol) was added followed by water (42 µL, 2.33 mmol) and the mixture was stirred at ambient temperature. After 3 h, the mixture was evaporated to dryness and the residue was triturated with two portions of hexanes (2 x 20 mL). The insoluble residue was dried to give the crude title compound contaminated with triphenyl phosphine oxide (344 mg), that was used directly in the next reaction step without further purification.

LRMS (m/z): 213 $[M+1]^+$

LC (3) r.t. (min.): 0.90 min

d) *Tert*-butyl (3-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)bicyclo[1.1.1]pentan-1-yl)carbamate

Obtained (223 mg) from tert-butyl (3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl)carbamate and *N*-(4-(aminomethyl)phenyl)-4-bromobenzamide and 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) following the synthetic procedure as described for Intermediate 1e. The crude product was used in the next step without further purification.

LRMS (m/z): 562 $[M+1]^+$

LC (3) r.t. (min.): 1.75

INTERMEDIATE 44

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) Methyl 1-(2-amino-2-oxoethyl)-4-fluoro-1*H*-pyrrole-2-carboxylate

2-Bromoacetamide (1.74 g, 12.6 mmol) and methyl 4-fluoro-1*H*-pyrrole-2-carboxylate (1.5 g, 10.5 mmol) were dissolved in DMF (15 mL) and Cs_2CO_3 (3.41 g, 10.5 mmol) was added. The mixture was stirred at 20°C for 12 h. After reaction completion, 30 mL of water was added to the reaction mixture and the solid that precipitated was collected by filtration and dried under reduced pressure to give the title compound (1.4 g, 57% yield, 85% purity) as a white solid.

LRMS (m/z): 201 $[M+1]^+$

LC (2c) r.t. (min.): 0.70

b) Methyl 8'-fluoro-3'-oxo-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Methyl 1-(2-amino-2-oxo-ethyl)-4-fluoro-pyrrole-2-carboxylate (1.4 g, 6.70 mmol, 1 eq) was dissolved in Eaton's reagent (14 mL) and cyclobutanone (1.47 g, 21.0 mmol) was added. The mixture was stirred at 85°C for 1 h. After reaction completion, the mixture was treated with 4% aqueous $NaHCO_3$ (200 mL) until a pH = 7 was obtained, then extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether/EtOAc, 1:4) to give the title compound (0.42 g, 24% yield, 96% purity) as a brown solid.

LRMS (m/z): 253 $[M+1]^+$

LC (2c) r.t. (min.): 1.01

c) Methyl 8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Methyl 8-fluoro-3-oxo-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxylate (0.50 g, 1.98 mmol) was dissolved in THF (10 mL) and 10 M BH_3-Me_2S complex (1.98 mL, 19.0 mmol) was added dropwise under N_2 at 0°C. The mixture was stirred at 25°C for 12 h. After reaction completion, the mixture was quenched with MeOH (5 mL) and heated to 80°C. The mixture was stirred at 80°C for 1 h and the resulting mixture was concentrated under reduced pressure to give the title compound (250 mg, 82% purity) as a yellow oil, that was used in next step without further purification.

LRMS (m/z): 239 $[M+1]^+$

LC (2c) r.t. (min.): 1.08

d) Methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Obtained as a yellow oil (48% yield, 92% purity) from methyl 8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 400 $[M+1]^+$

LC (2a) r.t. (min.): 0.37

e) 2'-(4-(Dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a colorless oil (67% yield, 88% purity) from methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-

pyrrolo[1,2-a]pyrazine]-6'-carboxylate following the synthetic procedure as described for Intermediate 10b. The crude product was used in next step without further purification.

LRMS (m/z): 386 $[M+1]^+$

LC (2a) r.t. (min.): 0.34

INTERMEDIATE 45

2-(4-(Dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

a) Methyl 1-(2-((tert-butoxycarbonyl)amino)ethyl)-1*H*-pyrrole-2-carboxylate

Methyl 1*H*-pyrrole-2-carboxylate (2.68 g, 21.4 mmol) was dissolved in DMF (20 mL) and NaH (2.57 g, 64.2 mmol, 60% in mineral oil) was added. The resulting reaction mixture was stirred at r.t. for 10 min before tert-butyl (2-bromoethyl)carbamate (5.76 g, 25.7 mmol) was added. Once the reaction was complete, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc. The combined organic phase was purified by a column of silica gel to give the title compound (1.36 g, 24% yield) as a white solid.

b) Methyl 1-(2-aminoethyl)-1*H*-pyrrole-2-carboxylate

Obtained (852 mg) from Methyl 1-(2-((tert-butoxycarbonyl)amino)ethyl)-1*H*-pyrrole-2-carboxylate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

c) Methyl 1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylate

Methyl 1-(2-aminoethyl)-1*H*-pyrrole-2-carboxylate (852 mg, 5.07 mmol) was dissolved in TFA (10 mL) and acetone (3.72 mL, 50.7 mmol) was added. The resulting mixture was stirred at 120 °C for 2 h. Once the reaction was complete, the mixture was purified by MPLC to give the title compound (832 mg, 79% yield)

d) Methyl 2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylate

Methyl 1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylate (50 mg, 0.24 mmol) and 4-formyl-*N*,*N*-dimethylbenzamide (70 mg, 395 μmol) were dissolved in DCE (10 mL) and $NaBH(OAc)_3$ (152 mg, 0.72 mmol) and DIEA (167 μL, 0.96 mmol) were added. The resulting mixture was stirred at 60 °C for 3 h. Once the reaction was complete, the mixture was purified by MPLC to give the title compound (56 mg, 63% yield).

e) 2-(4-(Dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid

Methyl 2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylate (56 mg, 0.15 mmol) was dissolved in MeOH (8 mL) and H_2O (2 mL) and NaOH (121 mg, 3.03 mmol) was added. The resulting mixture was stirred at 50 °C for 2 h. Once the reaction was complete, 1N aqueous HCl was added to the mixture until a pH of 5 was achieved. The mixture was concentrated under reduced pressure, and the residue was then purified by MPLC to give the title compound (53 mg, 0.151 mmol, 99.9% yield).

INTERMEDIATE 46

3,5-Difluoro-4-formyl-*N*,*N*-dimethylbenzamide

Obtained as a white solid (52% yield, 94% purity) from 3,5-difluoro-4-formylbenzoic acid and dimethylamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 214 $[M+1]^+$

LC (2b) r.t. (min.): 0.37

INTERMEDIATE 47

***N*-((5-acetamidopyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl 6'-(((5-aminopyridin-2-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (54% yield, 90% purity) from 2-*tert*-butoxycarbonylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxylic acid (Intermediate 1d) and 6-(aminomethyl)pyridin-3-amine (Intermediate 32a) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 412 $[M+1]^+$

LC (2b) r.t. (min.): 0.51

b) *Tert*-butyl 6'-(((5-acetamidopyridin-2-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Tert-butyl 6'-(((5-aminopyridin-2-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (200 mg, 0.49 mmol) was dissolved in DCM (3 mL), Ac_2O (59 mg, 583 µmol) and TEA (148 mg, 1.46 mmol) were added and the mixture was stirred at 20°C for 12 h. After reaction completion, the reaction mixture was diluted in water extracted with $CHCl_3$/IPA (3:1) and the combined organic

layers were washed with brine, dried over Na_2SO4, filtered and concentrated under reduced pressure to give the title compound (0.15 g, 68% yield, 90% purity) as a yellow solid.

LRMS (m/z): 454 $[M+1]^+$

LC (2c) r.t. (min.): 1.19

c) *N*-((5-acetamidopyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (77% yield, 95% purity) from *tert*-butyl 6'-(((5-acetamidopyridin-2-yl)methyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 354 $[M+1]^+$

LC (2c) r.t. (min.): 0.84

INTERMEDIATE 48

4-Formyl-*N*,*N*,3-trimethylbenzamide

Obtained as a white solid (43% yield, 80% purity) from 4-bromo-*N*,*N*,3-trimethyl-benzamide and 2-isocyano-2-methyl-propane following the synthetic procedure as described for Intermediate 6.

LRMS (m/z): 192 $[M+1]^+$

LC (2c) r.t. (min.): 0.80

INTERMEDIATE 49

4-(5-Methyl-1*H*-1,2,4-triazol-1-yl)benzaldehyde

Obtained as a white solid (15% yield, 50% purity) from 5-methyl-1*H*-1,2,4-triazole and 4-fluorobenzaldehyde following the synthetic procedure as described for Intermediate 15.

LRMS (m/z): 188 $[M+1]^+$

LC (2f) r.t. (min.): 0.38

INTERMEDIATE 50

4-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzaldehyde

Obtained as a yellow solid (58% yield, 84% purity) from 5-bromo-1-methyl-1*H*-1,2,4-triazole and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde following the synthetic procedure as described for Intermediate 39d.

LRMS (m/z): 188 $[M+1]^+$

LC (2c) r.t. (min.): 0.69

INTERMEDIATE 51

3-Chloro-4-formyl-*N*,*N*-dimethylbenzamide

Obtained as a white solid (66% yield, 85% purity) from 3-chloro-4-formylbenzoic acid and dimethylamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 212 $[M+1]^+$

LC (2c) r.t. (min.): 0.81

INTERMEDIATE 52

***N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl (4-(methylcarbamoyl)benzyl)carbamate

Obtained as a white solid (96% yield, 87% purity) from 4-(((*tert*-butoxycarbonyl)amino)methyl)benzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 265 $[M+1]^+$

LC (3) r.t. (min.): 1.36

b) 4-(Aminomethyl)-*N*-methyl-benzamide hydrochloride

Tert-butyl (4-(methylcarbamoyl)benzyl)carbamate (454 mg, 1.49 mmol) was dissolved in 4 M HCl in 1,4-dioxane (3.7 mL, 14.8 mmol) and DCM (10 mL), and the resulting mixture was stirred at r.t. for 1h before it was concentrated to yield the title compound, that was used in the next step without further purification (420 mg).

LRMS (m/z): 165 $[M+1]^+$

LC (3) r.t. (min.): 0.30

c) *Tert*-butyl 6'-((4-(methylcarbamoyl)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (96% yield, 98% purity) from 4-(aminomethyl)-*N*-methyl-benzamide hydrochloride and 2'-(*tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 453 $[M+1]^+$

LC (3) r.t. (min.): 1.90

d) *N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (190 mg) from *tert*-butyl 6'-((4-(methylcarbamoyl)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

LRMS (m/z): 353 $[M+1]^+$

LC (3) r.t. (min.): 0.83

INTERMEDIATE 53

4-(5-Methyl-1*H*-pyrazol-1-yl)benzaldehyde

Obtained as a brown oil (60% yield, 99% purity) from 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole following the synthetic procedure as described for Intermediate 6.

LRMS (m/z): 187 $[M+1]^+$

LC (2b) r.t. (min.): 0.45

INTERMEDIATE 54

2'-((5-Bromo-3-chloropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl (4-(3,3-dimethylureido)benzyl)carbamate

Bis(2,5-dioxopyrrolidin-1-yl) carbonate (3.03 g, 11.8 mmol) was added to a thick suspension of *tert*-butyl (4-aminobenzyl)carbamate (2.5 g, 11.0 mmol) in ACN (25 mL). After 1h, *N*-methylmethanamine hydrochloride (1.10 g, 13.0 mmol) and DIEA (5.88 mL, 33.8 mmol) were added, and the reaction mixture was stirred at r.t. overnight. After reaction completion, the mixture was concentrated under vacuum and purified by flash chromatography (EtOAc-hexane gradient, 0:100 rising to 100:0) to give the title compound (2.54g, 77% yield, 100% purity) as an off white solid.

LRMS (m/z): 294 $[M+1]^+$

LC (4a) r.t. (min.): 0.72

b) 3-(4-(Aminomethyl)phenyl)-1,1-dimethylurea hydrochloride

Tert-butyl (4-(3,3-dimethylureido)benzyl)carbamate (2.54 g, 8.66 mmol) was dissolved in 4 M HCl in 1,4-dioxane (10.9 mL, 43.6 mmol) and stirred at r.t. for 2h. The reaction mixture was concentrated under vacuum to give the title compound (2.05 g, 8.21 mmol, 95% yield, 92% purity).

LRMS (m/z): 194 $[M+1]^+$

LC (4c) r.t. (min.): 0.41

c) *Tert*-butyl 6'-((4-(3,3-dimethylureido)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white powder (47% yield, 100% purity) from 2'-(*Tert*-butoxycarbonyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 1d) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 382 $[M+1]^+$-Boc

LC (4c) r.t. (min.): 0.84

d) *N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide hydrochloride

Obtained as a yellow powder (98% yield, 99% purity) from *tert*-butyl 6'-((4-(3,3-dimethylureido)benzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 54b.

LRMS (m/z): 382 $[M+1]^+$

LC (4c) r.t. (min.): 0.59

e) 2'-((5-bromo-3-chloropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

5-bromo-3-chloro-pyridine-2-carbaldehyde (211 mg, 0.96 mmol) and *N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide hydrochloride (70 mg, 0.17 mmol) were dissolved in DMF (2 mL). $NaBH_3CN$ (45 mg, 0.72) was added and the reaction mixture was stirred at r.t. overnight. After completion, th mixture was diluted with sat.Na_2CO_3 and extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO4 and concentrated under vacuum. The crude was purified by flash chromatography KPNH (EtOAc-hexane gradient, 0:100 rising to 100:0) to afford the title compound (42 mg, 37% yield, 87% purity) as a yellow oil.

LRMS (m/z): 585, 587 $[M+1]^+$

LC (4a) r.t. (min.): 0.73

INTERMEDIATE 55

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (94% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 583 $[M+1]^+$

LC (3) r.t. (min.): 1.96

INTERMEDIATE 56

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) 2-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole

2-Iodo-1*H*-imidazole (0.50 g, 2.58 mmol) was dissolved in THF (13 mL) and NaH (123 mg, 3.08 mmol, 60% in mineral oil) was added. The resulting reaction mixture was stirred at r.t. for 10 min before (2-(chloromethoxy)ethyl)trimethylsilane (0.55 mL, 3.11 mmol) was added. Once the reaction was complete, the mixture was quenched with saturated aqueous NH4Cl (10 mL) and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO4 and concentrated under vacuum. The crude was purified by flash chromatography (DCM-DCM/MeOH 90:10, 100:0 rising to 40:60) to afford the title compound (55 mg, 59% yield, 90% purity) as a white solid.

LRMS (m/z): 325 $[M+1]^+$

LC (3) r.t. (min.): 1.86

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (112 mg) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 55) and 2-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole following the synthetic procedure as described

for Intermediate 39d. The crude product was used in the next step without further purification.

LRMS (m/z): 653 $[M+1]^+$

LC (3) r.t. (min.): 1.80

INTERMEDIATE 57

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-((2-(trimethylsilyl)ethoxy)methyl)-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) 3-Bromo-4-((2-(trimethylsilyl)ethoxy)methyl)-4*H*-1,2,4-triazole

Obtained as a white solid (49% yield, 100% purity) from 5-bromo-1*H*-1,2,4-triazole following the synthetic procedure as described for Intermediate 56a.

LRMS (m/z): 278, 280 $[M+1]^+$

LC (3) r.t. (min.): 1.91

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-((2-(trimethylsilyl)ethoxy)methyl)-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (71% yield, 86% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 55) and 3-bromo-4-((2-(trimethylsilyl)ethoxy)methyl)-4*H*-1,2,4-triazole following the synthetic procedure as described for Intermediate 39d.

LRMS (m/z): 654 $[M+1]^+$

LC (3) r.t. (min.): 2.01

INTERMEDIATE 58

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)piperidine-1-carboxylate

Obtained as a beige oil (100% yield, 94% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

(Intermediate 23c) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 564 $[M+1]^+$

LC (3) r.t. (min.): 1.82

b) 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (77 mg) from *tert*-butyl 4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f. The crude product was used in the next step without further purification.

LRMS (m/z): 464 $[M+1]^+$

LC (3) r.t. (min.): 0.88

INTERMEDIATE 59

***N*-(4-(aminomethyl-d2)phenyl)acetamide**

To a solution of Raney-Ni (321 mg, 3.75 mmol, 50% purity) in THF (4 mL) was added the mixture of *N*-(4-cyanophenyl) acetamide (0.2 g, 1.25 mmol) in NH3/MeOH (2 mL) under argon atmosphere. The suspension was degassed and purged with for 3 times. The mixture was stirred under D2 (50 Psi) at 50°C for 12 h. After the reaction completion, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give the title compound (91 mg, 42% yield, 96% purity) as a white solid.

LRMS (m/z): 165 $[M+1]^+$

LC (2c) r.t. (min.): 0.70

INTERMEDIATE 60

Isopropyl (4-(aminomethyl)phenyl)carbamate hydrochloride

a) Isopropyl (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)carbamate

To a stirred solution of *tert*-butyl *N*-[(4-aminophenyl)methyl]carbamate (200 mg, 0.90 mmol) and K_2CO_3 (143 mg, 1.44 mmol) in acetone (6 mL) under nitrogen atmosphere was added 2M isopropyl carbonochloridate in dioxane (472 µL, 0.94 mmol, 2 mol/L) dropwise and the reaction mixture was stirred at r.t. over the weekend. The excess solid was filtered off. The filtrate was collected and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc-heptane gradient, 0:100 rising to

50:50) to give the title compound (164 mg, 0.53 mmol, 56% yield, 100% purity) as a white solid.

LRMS (m/z): 331 $[M+Na]^+$

LC (4d) r.t. (min.): 3.42

b) Isopropyl (4-(aminomethyl)phenyl)carbamate hydrochloride

Obtained (79 mg) from isopropyl (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 54b. The crude product was used in the next step without further purification.

LRMS (m/z): no mass ion present

LC (4d) r.t. (min.): 1.16

INTERMEDIATE 61

3-(6-(Aminomethyl)pyridin-3-yl)-1,1-dimethylurea

a) 3-(6-Cyanopyridin-3-yl)-1,1-dimethylurea

To a solution of 5-aminopicolinonitrile (1.00 g, 8.39 mmol) in pyridine (10 mL) was added DMAP (1.03 g, 8.39 mmol) and *N,N*-dimethylcarbamoyl chloride (4.84 g, 33.6 mmol) at 0°C. The mixture was stirred at 80°C for 20 h. After the reaction completion, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with ethyl acetate, filtered and dried in high vacuum to give the title compound (500 mg, 27% yield, 85% purity) as a yellow solid.

LRMS (m/z): 191 $[M+1]^+$

LC (2c) r.t. (min.): 1.16

b) 3-(6-(Aminomethyl)pyridin-3-yl)-1,1-dimethylurea

Obtained (220 mg) from 3-(6-cyanopyridin-3-yl)-1,1-dimethylurea following the synthetic procedure as described for Intermediate 24b.

LRMS (m/z): 195 $[M+1]^+$

LC (2g) r.t. (min.): 0.71

INTERMEDIATE 62

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 3-Fluoro-4-formyl-*N*,*N*-dimethylbenzamide

Obtained as a white solid (84% yield, 98% purity) from 3-fluoro-4-formylbenzoic acid and dimethylamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 196 $[M+1]^+$

LC (2c) r.t. (min.): 0.72

b) 4-((3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (54% yield, 95% purity) from **3**-fluoro-4-formyl-*N*,*N*-dimethylbenzamide and 3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 1a) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 342 $[M+1]^+$

LC (2c) r.t. (min.): 1.23

c) 3-Fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a yellow solid (59% yield, 88% purity) from 4-((3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 486 $[M+1]^+$

LC (2c) r.t. (min.): 1.54

d) 2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a white solid (58% yield, 95% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 386 $[M+1]^+$

LC (2c) r.t. (min.): 0.79

INTERMEDIATE 63

7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid

a) Benzyl (2-(4-methyl-1*H*-imidazol-1-yl)ethyl)carbamate and benzyl (2-(5-methyl-*1*H-imidazol-1-yl)ethyl)carbamate

Obtained as a mixture of regioisomers (60:40, 11% yield, 87% purity) from 4-methyl-1*H*-imidazole and benzyl (2-bromoethyl)carbamate following the synthetic procedure as described for Intermediate 2.

LRMS (m/z): 260 $[M+1]^+$

LC (2c) r.t. (min.): 0.95

b) 2-(4-Methyl-1*H*-imidazol-1-yl)ethan-1-amine and 2-(5-methyl-1*H*-imidazol-1-yl)ethan-1-amine

To a mixture of Pd/C (500 mg, 0.47 mmol, 10% purity) in MeOH (25 mL) was added a mixture of benzyl (2-(4-methyl-1*H*-imidazol-1-yl)ethyl)carbamate and benzyl (2-(5-methyl-1*H*-imidazol-1-yl)ethyl)carbamate (60:40, 0.5 g, 1.93 mmol) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25°C for 2 h. Another three additional vials were set up as described above. After the reaction completion, all reaction mixtures were combined, filtered over celite and concentrated under reduced pressure to give the title compound as a mixture of regioisomers (60:40, 0.8 g, 81% yield, 98% purity) as a yellow oil. The crude product was used for the next step without purification.

LRMS (m/z): 126 $[M+1]^+$

LC (2c) r.t. (min.): 0.20

c) *N*,*N*-dimethyl-4-(((2-(4-methyl-1*H*-imidazol-1-yl)ethyl)amino)methyl)benzamide and *N*,*N*-dimethyl-4-(((2-(5-methyl-1*H*-imidazol-1-yl)ethyl)amino)methyl)benzamide

Obtained as a mixture of regioisomers (60:40, 66% yield, 80% purity) from 2-(4-methyl-1*H*-imidazol-1-yl)ethan-1-amine and 2-(5-methyl-1*H*-imidazol-1-yl)ethan-1-amine following the synthetic procedure as described for Intermediate 63b.

LRMS (m/z): 287 $[M+1]^+$

LC (2c) r.t. (min.): 0.80

d) *N*,*N*-dimethyl-4-((1'-methyl-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide

A solution of the mixture of regioisomers *N*,*N*-dimethyl-4-(((2-(4-methyl-1*H*-imidazol-1-yl)ethyl)amino)methyl)benzamide and *N*,*N*-dimethyl-4-(((2-(5-methyl-1*H*-imidazol-1-

yl)ethyl)amino)methyl)benzamide (60:40, 0.8 g, 2.79 mmol) and cyclobutanone (490 mg, 6.98 mmol) in AcOH (8 mL) was stirred at 80°C for 12 h. After the reaction completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (3, B from 15.00% to 40.00%) to give the title compound (0.12 g, 12% yield, 97% purity) as a yellow oil.

LRMS (m/z): 339 $[M+1]^+$

LC (2c) r.t. (min.): 0.99

e) *N,N*-dimethyl-4-((1'-methyl-3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide

Obtained as a yellow solid (78% yield, 90% purity) from *N,N*-dimethyl-4-((1'-methyl-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 483, 485 $[M+1]^+$

LC (2c) r.t. (min.): 1.40

f) 7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid

Obtained as a white solid (78% yield, 90% purity) from *N,N*-dimethyl-4-((1'-methyl-3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 383 $[M+1]^+$

LC (2c) r.t. (min.): 0.90

INTERMEDIATE 64

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

a) 4-(((2-(1*H*-Imidazol-1-yl)ethyl)amino)methyl)-*N,N*-dimethylbenzamide

Obtained as a yellow oil (80% yield, 94% purity) from 2-(1*H*-imidazol-1-yl)ethan-1-amine and 4-formyl-*N,N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 63c.

LRMS (m/z): 273 $[M+1]^+$

LC (2c) r.t. (min.): 0.76

b) 4-((5',6'-Dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-*N*,*N*-dimethylbenzamide

To a solution of 4-[(2-imidazol-1-ylethylamino)methyl]-*N*,*N*-dimethyl-benzamide (25 g, 91.8 mmol) in n-BuOH (500 mL) were added cyclobutanone (32.2 g, 459 mmol) and TFA (10.5 g, 91.8 mmol). The mixture was stirred at 120°C for 12 h. After the reaction completion, the reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (4, from 1.00% to 45.00% in 20.00 min) to give the title compound (18 g, 60% yield, 100% purity) as yellow oil.

LRMS (m/z): 325 $[M+1]^+$

LC (2c) r.t. (min.): 0.94

c) *N*,*N*-dimethyl-4-((3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide

Obtained (crude) from 4-((5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification.

LRMS (m/z): 469 $[M+1]^+$

LC (2c) r.t. (min.): 1.35

d) 7'-(4-(Dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid

Obtained as a yellow solid (71% yield, 92% purity) from *N*,*N*-dimethyl-4-((3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 369 $[M+1]^+$

LC (2e) r.t. (min.): 2.23

e) *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

To a solution of 7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro [cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid (0.5 g, 1.36 mmol) and 4-((methylamino)methyl)aniline (185 mg, 1.36 mmol) in DMF (3 mL) was added T4P (1.47 g, 2.04 mmol, 50% purity) and TEA (412 mg, 4.07 mmol). The mixture was stirred at 25°C for 2 h. After the reaction completion, the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (1b, from 1.00% to 28.00% in 8.00min) to give the title compound (0.35 g, 53.00% yield, 88% purity) as white solid.

LRMS (m/z): 487 $[M+1]^+$

LC (2e) r.t. (min.): 0.39

f) *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (36% yield, 91% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 778 $[M+1]^+$

LC (2c) r.t. (min.): 0.46

g) 7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (98% yield, 90% purity) from *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 41c.

LRMS (m/z): 340 $[M/2+1]^+$

LC (2c) r.t. (min.): 0.35

INTERMEDIATE 65

3-(4-(Bromomethyl)phenyl)isoxazole

a) 3-(*p*-Tolyl)isoxazole

To a solution of *N*-hydroxy-4-methyl-benzenesulfonamide (256 mg, 1.37 mmol) in MeOH (6 mL) and H2O (1 mL) was added K_2CO_3 (473 mg, 3.42 mmol). Then a solution of (*E*)-3-(p-tolyl)prop-2-enal (0.1 g, 684 μmol) in MeOH (6 mL) was added. The mixture was stirred at 20°C for 12 h and additional K_2CO_3 (236 mg, 1.71 mmol) was added. The mixture was stirred at 70°C for 6 h. After the reaction completion, the reaction mixture was diluted with water, extracted with ethyl acetate, the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduce pressure to give a residue. The residue was purified by prep-TLC (SiO2, Petroleum

ether/Ethyl acetate,4:1) to give the title compound (60 mg, 45% yield, 81% purity) as a yellow oil.

LRMS (m/z): 160 $[M+1]^+$

LC (2c) r.t. (min.): 1.13

b) 3-(4-(Bromomethyl)phenyl)isoxazole

To a solution of 3-(*p*-tolyl)isoxazole (0.06 g, 305 µmol) in CCl4 (4 mL) was added 1-bromopyrrolidine-2,5-dione (81.5 mg, 458 µmol) and benzoyl benzenecarboperoxoate (1.48 mg, 6.11 µmol). The mixture was stirred at 80°C for 1 h. After the reaction completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO2, Petroleum ether-EtOAc, 4:1) to give the title compound (45 mg, 50% yield, 82% purity) as off-white solid.

LRMS (m/z): 238, 240 $[M+1]^+$

LC (2b) r.t. (min.): 0.55

INTERMEDIATE 66

4-(Bromomethyl-d_2)-*N*,*N*-dimethylbenzamide

a) Methyl 4-(dimethylcarbamoyl) benzoate

Obtained as a yellow solid (68% yield, 97% purity) from 4-(methoxycarbonyl)benzoic acid and dimethylamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 208 $[M+1]^+$

LC (2c) r.t. (min.): 0.85

b) 4-(Hydroxymethyl-d_2)-*N*,*N*-dimethylbenzamide

To a solution of methyl 4-(dimethylcarbamoyl)benzoate (1 g, 4.83 mmol) in deuteriooxymethane (10 mL) was added sodium;tetradeuterioboranuide (730 mg, 19.30 mmol) at 0°C. The mixture was stirred at 0-25°C for 6 h. After the reaction completion, the reaction was filtrated and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography (SiO_2, Petroleum ether-EtOAc gradient, 100:0 rising to 0:100) to give the title compound (310 mg, 34% yield, 96% purity) as yellow oil.

LRMS (m/z): 182 $[M+1]^+$

LC (2c) r.t. (min.): 0.59

c) 4-(Bromomethyl-d_2)-*N*,*N*-dimethylbenzamide

To a solution of 4-(hydroxymethyl-d_2)-*N*,*N*-dimethylbenzamide (100 mg, 0.55 mmol) in DCM (1 mL) was added PBr_3 (74.68 mg, 275.90 µmol, 0.5 eq) at 0°C. The mixture was stirred at 0-25°C for 3 h. After the reaction completion, the reaction was concentrated under

reduced pressure to give a residue that was purified by prep-TLC (SiO2, Petroleum ether/ Ethyl acetate, 1:1) to give the title compound (90 mg, 66% yield, 99% purity) as white solid.

LRMS (m/z): 244, 246 $[M+1]^+$

LC (2c) r.t. (min.): 0.95

INTERMEDIATE 67

2'-(4-(Dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 4-((3',4'-Dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (20% yield, 58% purity) from 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-N,N-dimethylbenzamide (Intermediate 64a) and [(1-ethoxycyclopropyl)oxy](trimethyl)silane following the synthetic procedure as described for Intermediate 1a.

LRMS (m/z): 310 $[M+1]^+$

LC (4a) r.t. (min.): 0.60

b) *N*,*N*-Dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a brown gum (70% yield, 90% purity) from 4-((3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 454, 456, 458 $[M+1]^+$

LC (4a) r.t. (min.): 1.12

c) 2'-(4-(Dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a yellow oil (79% yield, 66% purity) from *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 354 $[M+1]^+$

LC (4a) r.t. (min.): 0.64

INTERMEDIATE 68

2'-((5-Bromo-3-fluoropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *N*-((5-Bromo-3-fluoropyridin-2-yl)methyl)-2-(1*H*-pyrrol-1-yl)ethan-1-amine

Obtained as a yellow powder (26% yield, 87% purity) from 5-bromo-3-fluoro-pyridine-2-carbaldehyde and 2-pyrrol-1-ylethanamine following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 298, 300 $[M+1]^+$

LC (4a) r.t. (min.): 0.51

b) 2'-((5-Bromo-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]

Obtained as a pale yellow gum (65% yield, 90% purity) from *N*-((5-bromo-3-fluoropyridin-2-yl)methyl)-2-(1*H*-pyrrol-1-yl)ethan-1-amine and cyclobutanone following the synthetic procedure as described for Intermediate 1a.

LRMS (m/z): 350, 352 $[M+1]^+$

LC (4a) r.t. (min.): 0.67

c) 2'-((5-Bromo-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

To a solution of 2'-((5-bromo-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (154 mg, 0.44 mmol) in DCM (5 mL) and 2,2,2-trichloroacetyl chloride (123 µL, 1.10 mmol) was added dropwise at 0 °C. After 5 min, *N*,*N*-diethylethanamine (153.2 µL, 1.10 mmol) was added slowly and the reaction mixture was allowed to warm to r.t. and stirred for 1h. The DCM was removed under reduced pressure and the residue was redissolved in THF (5 mL) and NaH (aq) 1M (4.4 mL, 4.4 mmol) was added. The reaction mixture was concentrated under reduced pressure and purified by reverse phase chromatography using formic acid buffer to give the title compound (173 mg, 66% yield, 100% purity) as a white powder.

LRMS (m/z): 394, 396 $[M+1]^+$

LC (4a) r.t. (min.): 0.69

d) 2'-((5-Bromo-3-fluoropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white powder (45% yield, 100% purity) from 2'-((5-bromo-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic

acid and 3-(4-(aminomethyl)phenyl)-1,1-dimethyl-urea hydrochloride following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 569, 571 $[M+1]^+$

LC (4b) r.t. (min.): 0.69

INTERMEDIATE 69

***N*-(4-aminobenzyl)-2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 6-((3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-5-fluoro-*N*,*N*-dimethylnicotinamide

Obtained as a yellow solid (48% yield, 81% purity) from 2'-((5-bromo-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 68b) following the synthetic procedure as described for Example 88.

LRMS (m/z): 343 $[M+1]^+$

LC (2b) r.t. (min.): 0.51

b) 5-Fluoro-*N*,*N*-dimethyl-6-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)nicotinamide

Obtained as a yellow solid (70% yield, 87% purity) from 6-((3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-5-fluoro-*N*,*N*-dimethylnicotinamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 488 $[M+1]^+$

LC (2b) r.t. (min.): 0.67

c) *N*-(4-aminobenzyl)-2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

To a mixture of 5-fluoro-*N*,*N*-dimethyl-6-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)nicotinamide (0.17 g, 0.28 mmol) and 4-(aminomethyl)aniline (51.1 mg, 0.42 mmol) in DMF (5 mL) was added Na2CO3 (118 mg, 1.12 mmol). The mixture was stirred at 55 °C for 12 h. After the reaction completion the reaction mixture was filtered and concentrated to give the crude title compound (130 mg), that was used directly in the next reaction step without further purification.

LRMS (m/z): 491 $[M+1]^+$

LC (2b) r.t. (min.): 0.48

INTERMEDIATE 70

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (70% yield, 93% purity) from *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 34c) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 474 $[M+1]^+$

LC (2c) r.t. (min.): 0.95

b) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a yellow solid (70% yield, 87% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 1-(1-*tert*-butoxycarbonyl-4-piperidyl)-5-methyl-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 765 $[M+1]^+$

LC (2c) r.t. (min.): 1.22

c) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (67% yield, 85% purity) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 665 $[M+1]^+$

LC (2c) r.t. (min.): 0.96

INTERMEDIATE 71

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 4-((3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (53% yield, 85% purity) from 3,5-difluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 46) and 3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 1a) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 360 $[M+1]^+$

LC (2c) r.t. (min.): 1.23

b) 3,5-Difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a yellow solid (55% yield, 90% purity) from 4-((3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 504 $[M+1]^+$

LC (2c) r.t. (min.): 1.52

c) 2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a yellow solid (56% yield, 89% purity) from 3,5-difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 444 $[M+1]^+$

LC (2c) r.t. (min.): 0.79

INTERMEDIATE 72

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 4-((3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (54% yield, 95% purity) from 3-fluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 14) and 3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-

pyrrolo[1,2-a]pyrazine] (Intermediate 1a) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 342 $[M+1]^+$

LC (2c) r.t. (min.): 1.23

b) 3-Fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a white solid (56% yield, 95% purity) from 4-((3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 486 $[M+1]^+$

LC (2c) r.t. (min.): 1.54

c) 2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a yellow solid (56% yield, 89% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 386 $[M+1]^+$

LC (2c) r.t. (min.): 0.79

INTERMEDIATE 73

***N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide**

a) *Tert*-butyl (4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)carbamate

Obtained as a yellow solid (48% yield, 92% purity) from 5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxylic acid and *tert*-butyl (4-aminobenzyl)carbamate following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 428 $[M+1]^+$

LC (2c) r.t. (min.): 1.12

b) *N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide

Obtained (230 mg) from *tert*-butyl (4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)carbamate following the synthetic procedure as described for Intermediate 41c. The crude product was used in the next step without further purification.

LRMS (m/z): 328 $[M+1]^+$

LC (2b) r.t. (min.): 0.76

INTERMEDIATE 74

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a yellow solid (83% yield, 82% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 72b) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 490.5 $[M+1]^+$

LC (2b) r.t. (min.): 0.50

INTERMEDIATE 75

4-((3,3-Difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

a) 4-((3,3-Difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow oil (38% yield, 90% purity) from 3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 37a) and 3,5-Difluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 46) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 396 $[M+1]^+$

LC (2d) r.t. (min.): 1.67

b) 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a white solid (43% yield, 95% purity) from 4-((3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 540, 542 $[M+1]^+$

LC (2c) r.t. (min.): 1.51

INTERMEDIATE 76

***N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (81% yield, 90% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 75) and 6-(aminomethyl)pyridin-3-amine (Intermediate 32a) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 545 $[M+1]^+$

LC (2c) r.t. (min.): 1.08

INTERMEDIATE 77

3-(4-(Aminomethyl)phenyl)-1,1-dimethylurea

a) *Tert*-butyl (4-(3,3-dimethylureido)benzyl)carbamate

Obtained as a brown solid (76% yield, 98% purity) from *tert*-butyl (4-aminobenzyl)carbamate following the synthetic procedure as described for Intermediate 61a.

LRMS (m/z): 238 $[M-t\text{Bu}]^+$

LC (2c) r.t. (min.): 0.98

b) 3-(4-(Aminomethyl)phenyl)-1,1-dimethylurea

To a solution of *tert*-butyl (4-(3,3-dimethylureido)benzyl)carbamate (4.1 g, 13.4 mmol) in MeOH (8.2 mL) was added HCl/MeOH (4 M, 41 mL, 163 mmol) and the reaction mixture was stirred at 25°C for 2 h. After the reaction completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give the title compound (2.7 g, purity, 79% yield, 90% purity, HCl salt) as yellow solid. The crude product was used for next step directly without purification.

LRMS (m/z): 192 $[M-H]^-$

LC (2c) r.t. (min.): 0.28

INTERMEDIATE 78

5-Methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carbonyl chloride

The mixture of 5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxylic acid (130 mg, 0.58 mmol, 1 eq) in $SOCl_2$ (2.6 mL) was stirred at 100°C for 1 h. After the reaction

completion, the reaction mixture was concentrated under reduced pressure to give the crude title compound (134 mg) which was used in next step without further purification.

LRMS (m/z): 238 $[M-Cl+OMe+H]^+$

LC (2b) r.t. (min.): 0.41

INTERMEDIATE 79

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (71% yield, 86% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 75) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 544 $[M+1]^+$

LC (2c) r.t. (min.): 1.15

INTERMEDIATE 80

4-((3,3-Difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

a) 4-((3,3-Difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

Obtained as a white solid (35% yield, 91% purity) from 3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 37a) and 3-fluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 14) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 378 $[M+1]^+$

LC (2c) r.t. (min.): 1.25

b) 4-((3,3-Difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (41% yield, 94% purity) from 4-((3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 522, 524 $[M+1]^+$

LC (2c) r.t. (min.): 1.48

INTERMEDIATE 81

***N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (72% yield, 96% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide (Intermediate 80) and 6-(aminomethyl)pyridin-3-amine (Intermediate 32a) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 527, 528 $[M+1]^+$

LC (2c) r.t. (min.): 1.05

INTERMEDIATE 82

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 4-((3',4'-Dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a white solid (36% yield, 80% purity) from 3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 34a) and 3,5-difluoro-4-formyl-*N*,*N*-dimethyl-benzamide (Intermediate 46) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 362 $[M+1]^+$

LC (2c) r.t. (min.): 1.06

b) 3,5-Difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a yellow solid (41% yield, 94% purity) 4-((3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 506, 508 $[M+1]^+$

LC (2c) r.t. (min.): 0.60

c) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (82% yield, 90% purity) from 3,5-difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 510 $[M+1]^+$

LC (2b) r.t. (min.): 0.45

INTERMEDIATE 83

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1H-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a yellow solid (51% yield, 92% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 82) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 801 $[M+1]^+$

LC (2b) r.t. (min.): 0.56

b) 2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

A solution of *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (120 mg, 0.15 mmol) was dissolved in TFA (0.2 mL) and DCM (1 mL) at 0°C. The reaction mixture was stirred at 25°C for 2 h and after the reaction completion, the reaction mixture was concentrated under reduced pressure to give the crude title compound (110 mg, TFA salt) which was used in next step without further purification.

LRMS (m/z): 702 $[M+1]^+$

LC (2b) r.t. (min.): 0.46

INTERMEDIATE 84

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (27% yield, 85% purity) from 3,5-difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 71b) and 6-(aminomethyl)pyridin-3-amine (Intermediate 32a) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 509 $[M+1]^+$

LC (2c) r.t. (min.): 1.05

b) *Tert*-butyl 4-(4-((6-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (54% yield, 85% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 800 $[M+1]^+$

LC (2c) r.t. (min.): 1.30

c) 2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (150 mg) from *tert*-butyl 4-(4-((6-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 41c. The crude product was used in the next step without further purification.

LRMS (m/z): 351 $[M/2+1]^+$

LC (2c) r.t. (min.): 1.06

INTERMEDIATE 85

***N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

a) 4-(((2-(1*H*-Imidazol-1-yl)ethyl)amino)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a pale beige oil (86% yield, 98% purity) from 3,5-difluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 46) and 2-(1*H*-imidazol-1-yl)ethan-1-amine following the synthetic procedure as described for Intermediate 63b.

LRMS (m/z): 309 $[M+1]^+$

LC (3) r.t. (min.): 0.31

b) 4-((5',6'-Dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a yellow oil (80% yield, 95% purity) from 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide and cyclobutanone following the synthetic procedure as described for Intermediate 64b.

LRMS (m/z): 361 $[M+1]^+$

LC (3) r.t. (min.): 0.95

c) *Tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

2,2,2-trichloroacetyl chloride (0.93 mL, 8.30 mmol) was added dropwise to a stirred solution of 4-((5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (1.15 g, 3.19 mmol) in DCM (26 mL) and cooled in an ice-bath. Then TEA (1.86 mL, 13.40 mmol) was added dropwise and stirring was continued in the ice bath for 3 h. After this time, *tert*-butyl (4-(aminomethyl)phenyl)carbamate (1.85 g, 8.30 mmol) and TEA (0.89 mL, 6.38 mmol) were added and the mixture was warmed to room temperature with stirring. After 72 h, the mixture was concentrated in vacuo and partitioned between 4% $NaHCO_3$ (aq.) and EtOAc. The organic layer was washed with brine, dried with MgSO4, filtrated and evaporated to give a foam. The crude product was purified by flash chromatography (SiO_2, 0-100% EtOAc in hexanes) to give the title compound (1.40 g, 69% yield, 96% purity) as a white foam.

LRMS (m/z): 609 $[M+1]^+$

LC (3) r.t. (min.): 2.00

d) *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a beige solid (98% yield, 99% purity) from *tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 509 $[M+1]^+$

LC (3) r.t. (min.): 1.49

INTERMEDIATE 86

7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

a) *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a beige solid (63% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 85) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 800 $[M+1]^+$

LC (3) r.t. (min.): 2.04

b) 7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (78% yield, 100% purity) from *tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 700 $[M+1]^+$

LC (3) r.t. (min.): 1.41

INTERMEDIATE 87

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

To a solution of 3,5-difluoro-*N*,*N*-dimethyl-4-[[6-(2,2,2-trichloroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-2-yl]methyl]benzamide (250 mg, 495 mmol, Intermediate 71b) in DMF (2.5 mL) was added TEA (400 mg, 3.96 mmol) and 4-(aminomethyl)-3-fluoro-aniline (208 mg, 1.49 mmol). The mixture was stirred at 50°C for 12 h and after the reaction completion, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc/EtOH 3:1, 100:0 rising to 1:1) to give the title compound (0.2 g, 76% yield, 90% purity 90%) as white solid.

LRMS (m/z): 526 $[M+1]^+$

LC (2c) r.t. (min.): 1.19

b) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)-3-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (80% yield, 89% purity) from *N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 817 $[M+1]^+$

LC (2c) r.t. (min.): 1.47

c) 2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (120 mg) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-

carboxamido)methyl)-3-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 54b. The crude product was used in the next step without further purification.

LRMS (m/z): 717 $[M+1]^+$

LC (2c) r.t. (min.): 1.25

INTERMEDIATE 88

7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-methoxy-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride

a) 3,5-Difluoro-*N*,*N*-dimethyl-4-((3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide

Obtained (600 mg) from 4-((5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 85b) following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification.

LRMS (m/z): 505/507 $[M+1]^+$

LC (2b) r.t. (min.): 0.61

b) 7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid

Obtained as a white solid (35% yield, 99% purity) from 3,5-difluoro-*N*,*N*-dimethyl-4-((3'-(2,2,2-trichloroacetyl)-5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 405 $[M+1]^+$

LC (2b) r.t. (min.): 0.38

c) *N*-(4-amino-2-methoxybenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (48% yield, 99% purity) from 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid and 4-(aminomethyl)-3-methoxyaniline following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 539 $[M+1]^+$

LC (2c) r.t. (min.): 1.20

d) *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)-3-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (62% yield, 99% purity) from *N*-(4-amino-2-methoxybenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 830 $[M+1]^+$

LC (2b) r.t. (min.): 0.60

e) 7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-methoxy-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride

Obtained as a white solid (98% yield, 99% purity) from *tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)-3-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 54b.

LRMS (m/z): 366 $[M/2+1]^+$

LC (2b) r.t. (min.): 0.49

INTERMEDIATE 89

***N*-(4-aminobenzyl)-7''-(4-(dimethylcarbamoyl)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide hydrochloride**

a) 4-((5'',6''-Dihydro-7''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazin]-7''-yl)methyl)-*N*,*N*-dimethylbenzamide

To a solution of 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 64a, 400 mg, 1.47 mmol) in EtOH (12 mL), spiro[3.3]heptan-2-one (263 µL, 2.20 mmol) and TFA (11 µL, 0.14 mmol) were added and the reaction mixture heated to 120°C for 8h under mw conditions. The reaction mixture was concentrated and then purified by flash chromatography (heptane/EtOAc gradient, 1:0 rising to 0:1 and then 0-30% MeOH in EtOAc) to give the title compound (300 mg, 49% yield, 88 % purity) as a yellow oil.

LRMS (m/z): 365 $[M+1]^+$

LC (4e) r.t. (min.): 2.85

b) *Tert*-butyl (4-((7''-(4-(dimethylcarbamoyl)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamido)methyl)phenyl)carbamate

Obtained as a light yellow oil (66% yield, 90% purity) from 4-((5'',6''-dihydro-7''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazin]-7''-yl)methyl)-*N*,*N*-dimethylbenzamide and *tert*-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 613 $[M+1]^+$

LC (4e) r.t. (min.): 3.92

c) *N*-(4-aminobenzyl)-7''-(4-(dimethylcarbamoyl)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide hydrochloride

Obtained as a brown solid (100% yield, 92% purity) from *tert*-butyl (4-((7''-(4-(dimethylcarbamoyl)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 54b.

LRMS (m/z): 513 $[M+1]^+$

LC (4e) r.t. (min.): 3.21

INTERMEDIATE 90

***N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride**

a) 4-((5',6'-Dihydro-7'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as an orange solid (49% yield, 95% purity) from 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 64a) and (1-ethoxycyclopropoxy)-trimethyl-silane following the synthetic procedure as described for Intermediate 89a.

LRMS (m/z): 311 $[M+1]^+$

LC (4e) r.t. (min.): 1.97

b) *Tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

Obtained as a yellow solid (43% yield, 98% purity) from 4-((5',6'-dihydro-7'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-*N*,*N*-dimethylbenzamide and *tert*-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 559 $[M+1]^+$

LC (4e) r.t. (min.): 3.25

c) *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride

Obtained as a brown solid (100% yield, 100% purity) from *tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 54b.

LRMS (m/z): 459 $[M+1]^+$

LC (4d) r.t. (min.): 1.81

INTERMEDIATE 91

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

a) 4-((8'-Bromo-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide

To a solution of *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (500 mg, 1.07 mmol, Intermediate 23b) in acetone (5 mL) was added NBS (209 mg, 1.17 mmol). The mixture was stirred at 20°C for 12 h and after the reaction completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc gradient, 5:1 rising to 1:1) to give the title compound (300 mg, 41% yield, 80% purity) as a colorless oil.

LRMS (m/z): 548, 560 $[M+1]^+$

LC (2c) r.t. (min.): 1.70

b) Methyl 8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

To a solution of 4-((8'-bromo-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide (300 mg, 438 mmol) in MeOH (3 mL) was added NaOMe (47.3 mg, 0.88 mmol). The mixture was stirred at 20°C for 12 h and after the reaction completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc gradient, 10:1 rising to 3:1) to give the title compund (150 mg, 67% yield, 90% purity) as a colorless oil.

LRMS (m/z): 460, 462 $[M+1]^+$

LC (2c) r.t. (min.): 1.45

c) Methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

To a solution of methyl 8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate (97.5 mg, 1.63 mmol) in toluene (2 mL) and water (0.5 mL) were added K_2CO_3 (135 mg, 0.98 mmol), $Pd(OAc)_2$ (7.32 mg, 32.5 μmol) and PCy_3 (18.3 mg, 65.2 μmol). The mixture was stirred at 100°C for 12 h and after the reaction completion, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the title compound (100 mg, crude) that was directly used without further purification.

LRMS (m/z): 396 $[M+1]^+$

LC (2c) r.t. (min.): 1.35

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

To a solution of methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate (100 mg, 0.25 mmol) in THF (2.4 mL) was added TMSOK (162 mg, 1.26 mmol). The mixture was stirred at 80°C for 12 h and after the reaction completion, the reaction mixture was filtered and purified by prep-HPLC (2, B from 10.00% to 40.00% in 8.00 min) to give the title compound (40 mg, 41% yield, 98% purity) as a white solid.

LRMS (m/z): 382 $[M+1]^+$

LC (2c) r.t. (min.): 0.89

INTERMEDIATE 92

4-(4-Cyclopropylpiperazin-1-yl)benzoic acid

a) Methyl 4-(4-cyclopropylpiperazin-1-yl)benzoate

Obtained as a white solid (77% yield, 91% purity) from methyl 4-(piperazin-1-yl)benzoate and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Example 122.

LRMS (m/z): 261 $[M+1]^+$

LC (2c) r.t. (min.): 1.21

b) 4-(4-Cyclopropylpiperazin-1-yl)benzoic acid

Obtained as a white solid (64% yield, 95% purity) from methyl 4-(4-cyclopropylpiperazin-1-yl)benzoate following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 247 $[M+1]^+$

LC (2c) r.t. (min.): 0.62

INTERMEDIATE 93

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) Methyl 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Obtained as a colorless oil (61% yield, 89% purity) from *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 34c) following the synthetic procedure as described for Intermediate 91b.

LRMS (m/z): 384 $[M+1]^+$

LC (2c) r.t. (min.): 1.08

b) Methyl 8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Obtained as a white solid (65% yield, 97% purity) from methyl 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 462, 464 $[M+1]^+$

LC (2c) r.t. (min.): 0.55

c) Methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

To a solution of methyl methyl 8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate (1.50 g, 3.24 mmol) in dioxane (30 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.22 g, 4.87 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (795 mg, 0.97 mmol) and Cs_2CO_3 (4.23 g, 13.0 mmol) under N_2 protection. The mixture was stirred at 100°C for 12 h and after the reaction completion the reaction mixture was concentrated under reduced pressure to the title compound (1.2 g) that was used directly without purification.

LRMS (m/z): 398 $[M+1]^+$

LC (2h) r.t. (min.): 1.18

d) 2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a white solid (35% yield, 94% purity) from methyl 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate following the synthetic procedure as described for Intermediate 91d.

LRMS (m/z): 384 $[M+1]^+$

LC (2b) r.t. (min.): 0.37

e) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (39% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 488 $[M+1]^+$

LC (2b) r.t. (min.): 0.50

INTERMEDIATE 94

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 4-((3',4'-Dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide

Obtained as a white solid (60% yield, 50% purity) from 3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine] (Intermediate 34) and 3-fluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 14) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 344 $[M+1]^+$

LC (2c) r.t. (min.): 1.04

b) 3-Fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

Obtained as a white solid (56% yield, 80% purity) from 4-((3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 489, 490 $[M+1]^+$

LC (2c) r.t. (min.): 1.33

c) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (42% yield, 97% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 87a.

LRMS (m/z): 492 $[M+1]^+$

LC (2c) r.t. (min.): 0.97

INTERMEDIATE 95

7-Fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid

a) Methyl 7-fluoroquinoline-6-carboxylate

To a solution of 6-bromo-7-fluoro-quinoline (4.00 g, 17.7 mmol, 1 eq) in MeOH (80 mL) was added $Pd(dppf)Cl_2$ (1.29 g, 1.77 mmol) and TEA (5.37 g, 53.1 mmol) under N_2 atmosphere. The suspension was degassed and purged with CO for 3 times, and stirred under CO (45 Psi) at 80°C for 12 h. After the reaction completion, the reaction mixture was

concentrated under reduced pressure to give a residue that was purified by column chromatography (SiO2, Petroleum ether/EtOAc gradient, 10:0 rising to 1:1) to give the title compound (3 g, 89%, 100% purity) as a white solid.

LRMS (m/z): 206 $[M+1]^+$

LC (2c) r.t. (min.): 0.98

b) Methyl 7-fluoro-1,2,3,4-tetrahydroquinoline-6-carboxylate

A solution of methyl 7-fluoroquinoline-6-carboxylate (3 g, 14.6 mmol) in MeOH (120 mL) was stirred at 20°C until becoming a clear solution. The fixed bed (SS, 5 mL) with granular catalyst (Ru/SiO_2, 3 g) was heated to 100°C. The H_2 back pressure regulator was adjusted to 2.5 MPa. The above solution was pumped into the fixed bed at a flow rate of 10 mL/min, and the flow rate of H_2 was 300 mL/min. The reaction mixture was collected after running 3.3 mins. After the reaction completion, the reaction mixture was concentrated under reduced pressure to give the crude title compound (2 g) as a white solid that was used for the next step without purification.

LRMS (m/z): 210 $[M+1]^+$

LC (2c) r.t. (min.): 1.13

c) Methyl 7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylate

Obtained as a white solid (59% yield, 98% purity) from methyl 7-fluoro-1,2,3,4-tetrahydroquinoline-6-carboxylate and formaldehyde following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 224 $[M+1]^+$

LC (2i) r.t. (min.): 0.50

d) 7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid

Obtained as a white solid (79% yield, 98% purity) from methyl 7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 210 $[M+1]^+$

LC (2i) r.t. (min.): 0.29

INTERMEDIATE 96

4-(3-(Methylamino)-3-oxopropyl)benzoic acid

a) Methyl 4-(3-(methylamino)-3-oxopropyl)benzoate

Obtained as a white solid (64% yield, 85% purity) from 3-(4-(methoxycarbonyl)phenyl)propanoic acid and methanamine hydrochloride following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 221 $[M+1]^+$

LC (2a) r.t. (min.): 0.33

b) 4-(3-(Methylamino)-3-oxopropyl)benzoic acid

Obtained as a white solid (51% yield, 95% purity) from methyl 4-(3-(methylamino)-3-oxopropyl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 208 $[M+1]^+$

LC (2b) r.t. (min.): 0.09

INTERMEDIATE 97

***Tert*-butyl ((4'-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-[1,1'-biphenyl]-2-yl)methyl)(methyl)carbamate**

a) 2'-(((*Tert*-butoxycarbonyl)(methyl)amino)methyl)-[1,1'-biphenyl]-4-carboxylic acid

Obtained as a yellow solid (29% yield, 80% purity) from 4-iodobenzoic acid and (2-((methylamino)methyl)phenyl)boronic acid following the synthetic procedure as described for Intermediate 93c.

LRMS (m/z): 340 $[M+1]^+$

LC (2b) r.t. (min.): 0.41

b) *Tert*-butyl ((4'-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-[1,1'-biphenyl]-2-yl)methyl)(methyl)carbamate

Obtained as a white solid (31% yield, 88% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 2'-(((tert-

butoxycarbonyl)(methyl)amino)methyl)-[1,1'-biphenyl]-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 795.5 $[M+1]^+$

LC (2c) r.t. (min.): 1.52

INTERMEDIATE 98

***N*-(4-(3-((*tert*-butyldiphenylsilyl)oxy)propanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (70% yield, 100% purity) from 4 *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 3-((tert-butyldiphenylsilyl)oxy)propanoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 783 $[M+1]^+$

LC (3) r.t. (min.): 2.35

INTERMEDIATE 99

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a yellow solid (45% yield, 90% purity) from 4 *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 763 $[M+1]^+$

LC (2b) r.t. (min.): 0.53

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (55% yield, 97% purity) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 54b.

LRMS (m/z): 664 $[M+1]^+$

LC (2a) r.t. (min.): 0.30

INTERMEDIATE 100

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of ethyl 1*H*-pyrazole-4-carboxylate (1.00 g, 7.14 mmol) in DMF (10 mL) were added Cs_2CO_3 (4.65 g, 14.3 mmol) and *tert*-butyl 4-methylsulfonyl-oxypiperidine-1-carboxylate (2.19 g, 7.85 mmol). The mixture was stirred at 120°C for 12 h and after the reaction completion, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography (SiO2, Petroleum ether/EtOAc gradient, 10:0 rising to 0:10) to give the title compound (1.20 g, 52% yield, 97% purity) as white solid.

LRMS (m/z): 268 $[M+1]^+$

LC (2c) r.t. (min.): 1.22

b) 1-(1-(*Tert*-butoxycarbonyl)piperidin-4-yl)-1*H*-pyrazole-4-carboxylic acid

To a solution of *tert*-butyl 4-(4-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (1.20 g, 3.71 mmol) in MeOH (15 mL) and H_2O (3 mL) was added KOH (833 mg, 14.8 mmol). The mixture was stirred at 20°C for 12 h and after the reaction completion, the reaction mixture was diluted with water, extracted with EtOAc and the aqueous phase was adjusted by 1 N hydrochloric acid to pH = 3. The mixture was extracted with EtOAc and the organic phase was washed with brine, dried over anhydrous sodium sulfate and filtered. The

filtrate was concentrated under reduced pressure to give the title compound (0.7 g, purity 99.7%, yield 63.8%) as white solid that was directly used in the next reaction.

LRMS (m/z): 240 $[M+1]^+$

LC (2c) r.t. (min.): 0.71

c) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (50% yield, 73% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 749.5 $[M+1]^+$

LC (2a) r.t. (min.): 0.40

d) 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (50% yield, 73% purity) from *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 649.5, 971.5 $[M+1, M+Na]^+$

LC (2a) r.t. (min.): 0.30

INTERMEDIATE 101

***N*-(4-(1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl 3-hydrazineylazetidine-1-carboxylate

To a solution of *tert*-butyl 3-iodoazetidine-1-carboxylate (2.00 g, 7.06 mmol) in EtOH (10 mL) was added NH2-NH2.H2O (3.54 g, 70.6 mmol) and the mixture was stirred at 80°C for 12 h. After the reaction completion, the reaction mixture was diluted with water, extracted with DCM and the combined organic phase was washed with brine, dried over anhydrous

sodium sulfate and filtered. The filtrate was concentrated under reduce pressure to give the crude title compound (1 g) that was used for the next step without purification.

LRMS (m/z): 228 $[M+1]^+$

LC (2c) r.t. (min.): 1.28

b) Ethyl 1-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

To a solution of *tert*-butyl 3-hydrazinoazetidine-1-carboxylate (0.90 g, 4.81 mmol) in EtOH (9 mL) was added DIEA (932 mg, 7.21 mmol) and ethyl (2E)-2-(dimethylaminomethylene)-3-oxo-butanoate (979 mg, 5.29 mmol), and the mixture was stirred at 25°C for 12 h. After the reaction completion, the reaction mixture was diluted with water, extracted with EtOAc and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduce pressure to give a residue that was purified by column chromatography (SiO2, Petroleum ether/EtOAc gradient rising from 1/0 to 3/1) to give ethyl the title compound (0.50 g, 34% yield, 86% purity) as white solid.

LRMS (m/z): 254 $[M+1]^+$

LC (2c) r.t. (min.): 1.20

c) 1-(1-(*Tert*-butoxycarbonyl)azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

Obtained as a white solid (66% yield, 76% purity) from ethyl 1-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 280 $[M+1]^+$

LC (2c) r.t. (min.): 0.66

d) *Tert*-butyl 3-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)azetidine-1-carboxylate

Obtained as a white solid (62% yield, 92% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 735 $[M+1]^+$

LC (2c) r.t. (min.): 1.31

e) *N*-(4-(1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (41% yield, 95% purity) from *tert*-butyl 3-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)azetidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 635 $[M+1]^+$

LC (2c) r.t. (min.): 1.08

INTERMEDIATE 102 and INTERMEDIATE 103

Benzyl (1*r*,3*r*)-3-cyanocyclobutane-1-carboxylate and benzyl (1*s*,3*s*)-3-cyanocyclobutane-1-carboxylate

a) Benzyl (1*s*,3*s*)-3-((methylsulfonyl)oxy)cyclobutane-1-carboxylate

To a solution of benzyl (1*s*,3*s*)-3-hydroxycyclobutane-1-carboxylate (1.00 g, 4.85 mmol) in DCM (10 mL) was added TEA (981 mg, 9.70 mmol) and MsCl (666 mg, 5.82 mmol) at 0°C. The mixture was stirred at 25°C for 2 h and after the reaction completion, the reaction mixture was quenched with water and extracted with DCM. The organic layer was concentrated under reduced pressure to give the title compound (0.9 g, 58% yield, 89% purity) as a yellow solid.

LRMS (m/z): 302 $[M+1]^+$

LC (2b) r.t. (min.): 0.52

b) Benzyl (1*r*,3*r*)-3-cyanocyclobutane-1-carboxylate and benzyl (1*s*,3*s*)-3-cyanocyclobutane-1-carboxylate

To a solution of benzyl (1*s*,3*s*)-3-((methylsulfonyl)oxy)cyclobutane-1-carboxylate (0.9 g, 2.74 mmol) in DMF (9 mL) was added NaCN (310 mg, 6.33 mmol) and 15-CROWN-5 (69.7 mg, 0.32 mmol), and the mixture was stirred at 80°C for 12 h. After the reaction completion, the reaction mixture was diluted with H_2O and then extracted with DCM. The combined organic layers were dried over Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO2, petroleum ether / EtOAc, 3: 1) to give (1*r*,3*r*)-benzyl 3-cyanocyclobutanecarboxylate (Intermediate 102, 120 mg, 18% yield, 94% purity) and (1*s*,3*s*)-benzyl 3-cyanocyclobutanecarboxylate (230 mg, 34% yield, 92% purity) both as white solid.

(1*r*,3*r*)-benzyl 3-cyanocyclobutanecarboxylate
LRMS (m/z): 233 $[M+1]^+$
LC (2c) r.t. (min.): 1.17

(1*s*,3*s*)-benzyl 3-cyanocyclobutanecarboxylate
LRMS (m/z): 233 $[M+1]^+$
LC (2c) r.t. (min.): 1.16

INTERMEDIATE 104
(1*r*,3*r*)-3-Cyanocyclobutane-1-carboxylic acid

Obtained as a white solid (48% yield, 90% purity) from (1*r*,3*r*)-benzyl 3-cyanocyclobutanecarboxylate following the synthetic procedure as described for Intermediate 23c.

INTERMEDIATE 105
(1*s*,3*s*)-3-Cyanocyclobutane-1-carboxylic acid

Obtained as a white solid (48% yield, 90% purity) from (1*s*,3*s*)-benzyl 3-cyanocyclobutanecarboxylate following the synthetic procedure as described for Intermediate 23c.

INTERMEDIATE 106
***N*-(4-(4-(azetidin-3-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide trifluoroacetate**

a) *Tert*-butyl 3-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)phenyl)azetidine-1-carboxylate
Obtained as a white solid (63% yield, 87% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(1-(tert-butoxycarbonyl)azetidin-3-yl)benzoic acid following the synthetic procedure as described for Intermediate 1e.
LRMS (m/z): 731 $[M+1]^+$
LC (2c) r.t. (min.): 1.38

b) *N*-(4-(4-(azetidin-3-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide trifluoroacetate

Obtained as a white solid (83% yield, 97% purity) from *tert*-butyl 3-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)phenyl)azetidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 631 $[M+1]^+$

LC (2c) r.t. (min.): 1.04

INTERMEDIATE 107

4-(4-Cyclobutylpiperazin-1-yl)benzoic acid

a) Methyl 4-(4-cyclobutylpiperazin-1-yl)benzoate

Obtained as a white solid (25% yield, 99% purity) from methyl 4-fluorobenzoate and 1-cyclobutylpiperazine following the synthetic procedure as described for Intermediate 15.

LRMS (m/z): 261 $[M+1]^+$

LC (4a) r.t. (min.): 0.37

b) 4-(4-Cyclobutylpiperazin-1-yl)benzoic acid

Obtained as a clear gum (63% yield, 80% purity) from methyl 4-(4-cyclobutylpiperazin-1-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

INTERMEDIATE 108

4-(1-Cyclobutylpiperidin-4-yl)benzoic acid

a) Methyl 4-(piperidin-4-yl)benzoate

4-(1-*Tert*-butoxycarbonyl-4-piperidyl)benzoic acid (2.00 g, 6.55 mmol) was dissolved in MeOH (20 mL) and then dropwise thionyl chloride (2.40 mL, 33 mmol) was added at 0 °C and the reaction mixture was heated to 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford the crude title compound as hydrochloride (1.7 g) that was directly used in the following reaction without further purification.

b) Methyl 4-(1-cyclobutylpiperidin-4-yl)benzoate

Obtained as a light yellow solid (85% yield, 96% purity) from methyl 4-(piperidin-4-yl)benzoate and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 274 $[M+1]^+$

LC (4d) r.t. (min.): 3.78

c) 4-(1-Cyclobutylpiperidin-4-yl)benzoic acid

Obtained as a beige solid (64% yield, 99% purity) from methyl 4-(1-cyclobutylpiperidin-4-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 260 $[M+1]^+$

LC (4d) r.t. (min.): 1.18

INTERMEDIATE 109

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((6-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (50% yield, 98% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1c.

LRMS (m/z): 764 $[M+1]^+$

LC (2c) r.t. (min.): 1.28

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (83% yield, 98% purity) from *tert*-butyl 4-(4-((6-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 664 $[M+1]^+$

LC (2c) r.t. (min.): 1.06

INTERMEDIATE 110

***N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) 4-(aminomethyl)-3-fluoroaniline

To a solution of 4-amino-2-fluoro-benzonitrile (0.5 g, 3.67 mmol) in MeOH (10 mL) and HCl (0.5 mL) was added Pd/C (50 mg, 10% purity) under Ar atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25°C for 12 h. After the reaction completion, the reaction mixture was filtered and concentrated to give the crude title compound (0.6 g, HCl salt) that was directly used in the following reaction without further purification.

LRMS (m/z): 124 $[M+1]^+$

LC (2c) r.t. (min.): 0.17

b) *N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (81% yield, 90% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) and 4-(aminomethyl)-3-fluoroaniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 490 $[M+1]^+$

LC (2c) r.t. (min.): 1.14

INTERMEDIATE 111

2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)-3-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (48% yield, 90% purity) from *N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 110) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 781 $[M+1]^+$

LC (2c) r.t. (min.): 1.40

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (86% yield, 93% purity) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)-3-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 41c.

LRMS (m/z): 681 $[M+1]^+$

LC (2c) r.t. (min.): 1.14

INTERMEDIATE 112

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a yellow solid (68% yield, 85% purity) from 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 71) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 508 $[M+1]^+$

LC (2c) r.t. (min.): 1.15

INTERMEDIATE 113

2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (71% yield, 82% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 112) and 1-(1-(tert-

butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 799 $[M+1]^+$

LC (2c) r.t. (min.): 1.37

b) 2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (91% yield, 92% purity) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 699 $[M+1]^+$

LC (2c) r.t. (min.): 1.11

INTERMEDIATE 114

***N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxami**

Obtained as a white solid (35% yield, 98% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid (Intermediate 64d) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 473 $[M+1]^+$

LC (2e) r.t. (min.): 3.19

INTERMEDIATE 115

1-(1-Cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

a) Ethyl 5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxylate

Obtained as a white solid (89% yield, 90% purity) from *tert*-butyl 4-(4-(ethoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 238 $[M+1]^+$

LC (2c) r.t. (min.): 0.81

b) Ethyl 1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

Obtained as a white solid (73% yield, 90% purity) from ethyl 5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxylate and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 292 $[M+1]^+$

LC (2c) r.t. (min.): 1.13

c) 1-(1-Cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

To a solution of ethyl 1-(1-cyclobutyl-4-piperidyl)-5-methyl-pyrazole-4-carboxylate (0.35 g, 1.20 mmol) in EtOH (3.5 mL) and H_2O (3.5 mL) was added NaOH (96.1 mg, 2.40 mmol) and the mixture was stirred at 40°C for 12 h. After the reaction completion, the reaction mixture was concentrated under reduced pressure to give a residue, which was diluted with water and the mixture was acidified to pH = 7-8 with aqueous HCl (1 N), and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduce pressure to give a residue, which was purified by prep-HPLC (3, B from 1.00% to 21.00% in 8.00 min) to give the title compound (200 mg, 57% yield, 90% purity) as a white solid.

LRMS (m/z): 264 $[M+1]^+$

LC (2c) r.t. (min.): 0.61

INTERMEDIATE 116

4-(3-Methoxyazetidin-1-yl)benzoic acid

a) Methyl 4-(3-methoxyazetidin-1-yl)benzoate

Obtained as a white solid (99% yield, 100% purity) from methyl 4-fluorobenzoate and 3-methoxyazetidine hydrochloride following the synthetic procedure as described for Intermediate 15.

LRMS (m/z): 221 $[M+1]^+$

LC (4a) r.t. (min.): 0.83

b) 4-(3-Methoxyazetidin-1-yl)benzoic acid

Obtained as a yellow solid (92% yield, 100% purity) from methyl 4-(3-methoxyazetidin-1-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 208 $[M+1]^+$

LC (4a) r.t. (min.): 0.64

INTERMEDIATE 117

4-(3-Methoxypyrrolidin-1-yl)benzoic acid

a) Methyl 4-(3-methoxypyrrolidin-1-yl)benzoate

To a solution of methyl 4-bromobenzoate (0.5 g, 2.33 mmol) and 3-methoxypyrrolidine (353 mg, 3.49 mmol) in DME (5 mL) were added Cs_2CO_3 (1.52 g, 4.65 mmol) and XPhos Pd G3 (197 mg, 0.23 mmol) and the mixture was stirred at 80°C for 12 h. After the reaction completion, the reaction mixture was filtered and the solution was concentrated under reduced pressure to give a residue that was purified by column chromatography (SiO2, petroleum ether/EtOAc, gradient rising from 10/1 to 1/1) to give the title compound (0.25 g, 46% yield, 86% purity) as a brown solid.

LRMS (m/z): 236 $[M+1]^+$

LC (2i) r.t. (min.): 0.55

b) 4-(3-Methoxypyrrolidin-1-yl)benzoic acid

Obtained (100 mg) from methyl 4-(3-methoxypyrrolidin-1-yl)benzoate following the synthetic procedure as described for Intermediate 23c. The crude product was used in the next step without further purification.

LRMS (m/z): 222 $[M+1]^+$

LC (2c) r.t. (min.): 0.55

INTERMEDIATE 118

7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

a) *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (65% yield, 90% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 764 $[M+1]^+$

LC (2c) r.t. (min.): 1.33

b) 7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained (920 mg) from *tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b. The crude product was used in the next step without further purification.

LRMS (m/z): 664 $[M+1]^+$

LC (2b) r.t. (min.): 1.08

INTERMEDIATE 119

4-(1-(Oxetan-3-yl)piperidin-4-yl)benzoic acid

a) Methyl 4-(1-(oxetan-3-yl)piperidin-4-yl)benzoate

Obtained as an off-white solid (93% yield, 100% purity) from methyl 4-(piperidin-4-yl)benzoate (Intermediate 108a) and oxetan-3-one following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 276 $[M+1]^+$

LC (4c) r.t. (min.): 0.89

b) 4-(1-(Oxetan-3-yl)piperidin-4-yl)benzoic acid

Obtained (1.00 g) from methyl 4-(1-(oxetan-3-yl)piperidin-4-yl)benzoate following the synthetic procedure as described for Intermediate 10b. The crude product was used in the next step without further purification.

INTERMEDIATE 120

1-(1-Cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

a) Ethyl 1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

Obtained as a yellow oil (80% yield, 90% purity) from ethyl 1-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate following the synthetic procedure as described for Example 89.

LRMS (m/z): 210 $[M+1]^+$

LC (2c) r.t. (min.): 0.72

b) Ethyl 1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

Obtained as a yellow oil (44% yield, 85% purity) from ethyl 1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 250 $[M+1]^+$

LC (2c) r.t. (min.): 1.04

c) 1-(1-Cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

Obtained as a yellow oil (47% yield, 90% purity) from ethyl 1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate following the synthetic procedure as described for Intermediate 115c.

LRMS (m/z): 222 $[M+1]^+$

LC (2c) r.t. (min.): 0.27

INTERMEDIATE 121

1-(1-Cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

a) Ethyl 1-(1-cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

Obtained as a white solid (58% yield, 98% purity) from ethyl 1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (Intermediate 120a) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 264 $[M+1]^+$

LC (2c) r.t. (min.): 1.10

b) 1-(1-Cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

Obtained as a white solid (75% yield, 90% purity) from ethyl 1-(1-cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylate following the synthetic procedure as described for Intermediate 115c.

LRMS (m/z): 236 $[M+1]^+$

LC (2c) r.t. (min.): 0.29

INTERMEDIATE 122

4-(1-(2,2-Difluoroethyl)piperidin-4-yl)benzoic acid hydrochloride

a) Methyl 4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzoate

A mixture of methyl 4-(4-piperidyl)benzoate hydrochloride (1.00 g, 3.91 mmol), 2,2-difluoroethyl trifluoromethanesulfonate (700 µL, 5.18 mmol) and potassium carbonate (3.20

g, 23 mmol) were dissolved in ACN (20 mL) and 2-methyloxolane (2 mL) and the reaction mixture was heated to 65 °C for 4 h. The reaction mixture was filtered through celite (washing with MeCN) and concentrated under reduced pressure to give the crude title compound (2.00 g) that was directly used in the following reaction without further purification.

LRMS (m/z): 284 $[M+1]^+$

LC (4c) r.t. (min.): 1.08

b) 4-(1-(2,2-Difluoroethyl)piperidin-4-yl)benzoic acid hydrochloride

Obtained as a white solid (43% yield, 80% purity) from methyl 4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 270 $[M+1]^+$

LC (4c) r.t. (min.): 0.39

INTERMEDIATE 123

***N*-((5-aminopyridin-2-yl)methyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (31% yield, 99% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid (Intermediate 64d) and 6-(aminomethyl)pyridin-3-amine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 474 $[M+1]^+$

LC (2e) r.t. (min.): 2.92

INTERMEDIATE 124

***N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a yellow solid (59% yield, 100% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 37c) and 6-(aminomethyl)pyridin-3-amine following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 509 $[M+1]^+$

LC (2e) r.t. (min.): 3.21

INTERMEDIATE 125

1-(1-Cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

a) Ethyl 1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylate

Obtained as a white solid (61% yield, 98% purity) from ethyl 5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxylate (Intermediate 115a) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 278 $[M+1]^+$

LC (2c) r.t. (min.): 1.13

b) 1-(1-Cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid

Obtained as a white solid (65% yield, 99% purity) from ethyl 1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 250 $[M+1]^+$

LC (2c) r.t. (min.): 0.63

INTERMEDIATE 126

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a yellow solid (75% yield, 98% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 37c) and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 508 $[M+1]^+$

LC (2e) r.t. (min.): 3.51

INTERMEDIATE 127

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

a) *Tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a yellow solid (61% yield, 96% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 126) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 799 $[M+1]^+$

LC (2c) r.t. (min.): 1.36

b) 2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (91% yield, 91% purity) from *tert*-butyl 4-(4-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 41c.

LRMS (m/z): 699 $[M+1]^+$

LC (2b) r.t. (min.): 0.47

INTERMEDIATE 128

5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylic acid

a) Ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylate

Obtained as a yellow oil (69% yield, 59% purity) from ethyl pyrazolo[1,5-a]pyrazine-3-carboxylate following the synthetic procedure as described for Intermediate 95b.

LRMS (m/z): 196 $[M+1]^+$

LC (2c) r.t. (min.): 0.70

b) Ethyl 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylate

Obtained as a white solid (40% yield, 54% purity) from ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylate and formaldehyde following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 210 $[M+1]^+$

LC (2c) r.t. (min.): 0.82

c) 5-Methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylic acid

Obtained (140 mg, sodium salt) from ethyl 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylate following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 182 $[M+1]^+$

LC (2g) r.t. (min.): 0.22

INTERMEDIATE 129

2-Fluoro-4-morpholinobenzoic acid

a) Methyl 2-fluoro-4-morpholinobenzoate

Morpholine (420 µL, 4.80 mmol) and methyl 4-bromo-2-fluoro-benzoate (1.00 g, 4.29 mmol) were dissolved in anhydrous 1,4-dioxane (20 mL) and cesium carbonate (4.20 g, 13 mmol) was added. The reaction mixture was degassed with nitrogen for 5 min, then XPhos (205 mg, 0.43 mmol) and $Pd(OAc)_2$ (60 mg, 0.27 mmol) were added and further degassed for 5 min. The reaction mixtrue was heated to 100 °C for 16 h and after reaction completion, the reaction mixture was filtered through celite, washed with MeCN and concentrated. The crude was purified by FCC using a Biotage Selekt (25g Sfar Duo column, eluting with 0-50% EtOAc in heptane) to give the title compound (1.05 g, 100% yield, 99% purity) as an off white solid.

LRMS (m/z): 240 $[M+1]^+$

LC (4a) r.t. (min.): 0.77

b) 2-Fluoro-4-morpholinobenzoic acid

Obtained as a pale green solid (87% yield, 100% purity) from methyl 2-fluoro-4-morpholinobenzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 226 $[M+1]^+$

LC (4a) r.t. (min.): 0.60

INTERMEDIATE 130

***N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) 4-((5,6-Dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide

Obtained as a white solid (68% yield, 96% purity) from 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 85a) and oxetan-3-one following the synthetic procedure as described for Intermediate 64b.

LRMS (m/z): 366 $[M+1]^+$

LC (2c) r.t. (min.): 0.83

b) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a white solid (67% yield, 96% purity) from 4-((5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide and *tert*-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 611 $[M+1]^+$

LC (2e) r.t. (min.): 3.64

c) *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (81% yield, 99% purity) from *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 511 $[M+1]^+$

LC (2e) r.t. (min.): 2.81

INTERMEDIATE 131

7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

a) *Tert*-butyl 4-(4-((4-((7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (65% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 130) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 802 $[M+1]^+$

LC (3) r.t. (min.): 1.88

b) 7-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (79% yield, 95% purity) from *tert*-butyl 4-(4-((4-((7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 702 $[M+1]^+$

LC (3) r.t. (min.): 1.22

INTERMEDIATE 132

***N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) 4-((5,6-Dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-*N*,*N*-dimethylbenzamide

Obtained as a yellow solid (39% yield, 92% purity) from 4-(((2-(1*H*-imidazol-1-yl)ethyl)amino)methyl)-N,N-dimethylbenzamide (Intermediate 64a) and oxetan-3-one following the synthetic procedure as described for Intermediate 64b.

LRMS (m/z): 327 $[M+1]^+$

LC (2c) r.t. (min.): 0.79

b) *N*,*N*-dimethyl-4-((3-(2,2,2-trichloroacetyl)-5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)benzamide

Obtained (1g) from 4-((5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1c. The crude product was used in the next step without further purification.

LRMS (m/z): 471, 473 $[M+1]^+$

LC (2c) r.t. (min.): 1.15

c) 7-(4-(Dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxylic acid

Obtained as a white solid (73% yield, 95% purity) from *N*,*N*-dimethyl-4-((3-(2,2,2-trichloroacetyl)-5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)benzamide following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 371 $[M+1]^+$

LC (2c) r.t. (min.): 0.66

d) *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (54% yield, 100% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxylic acid and 4-(aminomethyl)aniline following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 475 $[M+1]^+$

LC (2c) r.t. (min.): 0.92

INTERMEDIATE 133

3-(4-Cyclopropylpiperazin-1-yl)benzoic acid

a) Methyl 3-(4-cyclopropylpiperazin-1-yl)benzoate

Obtained as a yellow gum (69% yield, 98% purity) from methyl 3-bromobenzoate and 1-cyclopropylpiperazine following the synthetic procedure as described for Intermediate 129a.

LRMS (m/z): 261 $[M+1]^+$

LC (4a) r.t. (min.): 0.51

b) 3-(4-Cyclopropylpiperazin-1-yl)benzoic acid

Obtained as an off-white solid (100% yield, 98% purity) from methyl 3-(4-cyclopropylpiperazin-1-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 247 $[M+1]^+$

LC (4a) r.t. (min.): 0.40

INTERMEDIATE 134

4-(4-Methoxypiperidin-1-yl)benzoic acid

a) Methyl 4-(4-methoxypiperidin-1-yl)benzoate

Obtained as an off-white solid (30% yield, 97% purity) from methyl 4-fluorobenzoate and 4-methoxypiperidine following the synthetic procedure as described for Intermediate 15.

LRMS (m/z): 250 $[M+1]^+$

LC (4a) r.t. (min.): 0.87

b) 4-(4-Methoxypiperidin-1-yl)benzoic acid

Obtained as a white solid (60% yield, 92% purity) from methyl 4-(4-methoxypiperidin-1-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 236 $[M+1]^+$

LC (4a) r.t. (min.): 0.66

INTERMEDIATE 135

4-(3-oxomorpholino)benzoic acid

a) Methyl 4-(3-oxomorpholino)benzoate

Methyl 4-iodobenzoate (1.00 g, 3.81 mmol) was dissolved in toluene (20 mL), followed by the addition of morpholin-3-one (772 mg, 7.64 mmol), tripotassium phosphate (1.00 g, 4.71 mmol), CuI (73 mg, 0.38 mmol) and DMEDA (82 µL, 0.76 mmol). The mixture was degassed and refilled with N_2 three times and was heated to 100 °C under N_2 for 18 h, cooled, and quenched with saturated ammonium chloride solution. The reaction mixture was extracted with EtOAc, dried with Na_2SO4 and the solvent was evaporated under reduced pressure. The resulting crude was purified by silica gel column chromatography (heptane/ EtOAc, 0-100% followed by 20% MeOH in EtOAc) to give the title compound (633 mg, 71% yield, 100% purity) as an off-white solid.

LRMS (m/z): 236 $[M+1]^+$

LC (4e) r.t. (min.): 1.90

b) 4-(3-Oxomorpholino)benzoic acid

Obtained as an off-white solid (48% yield, 98% purity) from methyl 4-(3-oxomorpholino)benzoate following the synthetic procedure as described for Intermediate 23c.

LRMS (m/z): 222 $[M+1]^+$

LC (4d) r.t. (min.): 1.24

INTERMEDIATE 136

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

a) *Tert*-butyl 4-(4-((4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (56% yield, 90% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 766 $[M+1]^+$

LC (2c) r.t. (min.): 1.18

b) 7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (83% yield, 94% purity) from *tert*-butyl 4-(4-((4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 666 $[M+1]^+$

LC (2c) r.t. (min.): 0.94

INTERMEDIATE 137

***N*-(4-acetamidobenzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl 8'-bromo-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (86% yield, 96% purity) from *tert*-butyl 6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate (Intermediate 1c) following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 385 $[M\text{-}Boc+1]^+$

LC (2b) r.t. (min.): 0.82

b) 2'-(*Tert*-butyl) 6'-methyl 8'-bromo-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2',6'-dicarboxylate

Obtained as a yellow solid (82% yield, 83% purity) from *tert*-butyl 8'-bromo-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 91b.

LRMS (m/z): 343, 345 $[M\text{-}50]^+$

LC (2a) r.t. (min.): 0.66

c) 2'-(*Tert*-butyl) 6'-methyl 8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2',6'-dicarboxylate

Obtained as a white solid (43% yield, 95% purity) from 2'-(*tert*-butyl) 6'-methyl 8'-bromo-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2',6'-dicarboxylate following the synthetic procedure as described for Intermediate 91c.

LRMS (m/z): 235, 237 $[M\text{-}Boc]^+$

LC (2j) r.t. (min.): 2.95

d) 2'-(*Tert*-butoxycarbonyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a white solid (52% yield, 86% purity) from 2'-(*tert*-butyl) 6'-methyl 8'-bromo-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2',6'-dicarboxylate following the synthetic procedure as described for Intermediate 91d.

LRMS (m/z): 265, 266 $[M\text{-}55]^+$

LC (2a) r.t. (min.): 0.42

e) *Tert*-butyl 6'-((4-acetamidobenzyl)carbamoyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate

Obtained as a white solid (69% yield, 96% purity) from 2'-(*tert*-butoxycarbonyl)-8'-methyl-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 367 $[M\text{-Boc}]^+$

LC (2c) r.t. (min.): 1.28

f) *N*-(4-acetamidobenzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained (70 mg) from *tert*-butyl 6'-((4-acetamidobenzyl)carbamoyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-2'-carboxylate following the synthetic procedure as described for Intermediate 17b. The crude product was used in the next step without further purification.

LRMS (m/z): 367 $[M+1]^+$

LC (2a) r.t. (min.): 0.31

INTERMEDIATE 138

***N*-(4-aminobenzyl)-1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

a) *Tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

Obtained as an off-white solid (58% yield, 83% purity) from 4-((5',6'-dihydro-7'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazin]-7'-yl)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 64b) and tert-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 573 $[M+1]^+$

LC (4a) r.t. (min.): 0.73

b) *Tert*-butyl (4-((1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

Tert-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate (200 mg, 0.31 mmol) was dissolved in ACN (5 mL) and NCS (52 mg, 0.39 mmol) was added. The reaction mixture

was heated to 85°C for 16 h and after reaction completion the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (KP Amino column, heptane/EtOAc, gradient rising from 100:0 to 20:80) to give the title compound (150 mg, 63% yield, 80 % purity) as a clear gum.

c) *N*-(4-aminobenzyl)-1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a pale yellow solid (81% yield, 90% purity) from *tert*-butyl (4-((1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 507, 509 $[M+1]^+$

LC (4a) r.t. (min.): 0.67

INTERMEDIATE 139

***N*-(4-aminobenzyl)-1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a yellow solid (89% yield, 82% purity) from *tert*-butyl (4-((1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate (Example 263) following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 551, 553 $[M+1]^+$

LC (4c) r.t. (min.): 1.03

INTERMEDIATE 140

***N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a white solid (78% yield, 97% purity) from 4-((5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 132a) and tert-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 575 $[M+1]^+$

LC (2c) r.t. (min.): 1.18

b) *Tert*-butyl (4-((1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a white solid (52% yield, 91% purity) from *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 138b.

LRMS (m/z): 609 $[M+1]^+$

LC (2c) r.t. (min.): 1.30

c) *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (69% yield, 86% purity) from *tert*-butyl (4-((1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 509 $[M+1]^+$

LC (2c) r.t. (min.): 1.03

INTERMEDIATE 141

1-Bromo-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

a) 7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (66% yield, 80% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 546 $[M+1]^+$

LC (4a) r.t. (min.): 0.68

b) 1-Bromo-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (14% yield, 100% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 624, 626 $[M+1]^+$

LC (4c) r.t. (min.): 0.81

INTERMEDIATE 142

***N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) *Tert*-butyl (4-((1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a white solid (50% yield, 98% purity) from *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate (Intermediate 130b) following the synthetic procedure as described for Intermediate 138b.

LRMS (m/z): 645 $[M+1]^+$

LC (3) r.t. (min.): 1.95

b) *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white foam (88% yield, 92% purity) from *tert*-butyl (4-((1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 545 $[M+1]^+$

LC (3) r.t. (min.): 1.60

INTERMEDIATE 143

***N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a white solid (22% yield, 80% purity) from 4-((5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-*N*,*N*-dimethylbenzamide (Intermediate 132a) and *tert*-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 85c.

LRMS (m/z): 575.5 $[M+1]^+$

LC (2c) r.t. (min.): 1.15

b) *Tert*-butyl (4-((1-bromo-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a yellow solid (55% yield, 80% purity) from *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 653, 655 $[M+1]^+$

LC (2c) r.t. (min.): 1.28

c) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

Obtained as a yellow solid (51% yield, 90% purity) from *tert*-butyl (4-((1-bromo-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 93c.

LRMS (m/z): 589 $[M+1]^+$

LC (2c) r.t. (min.): 1.20

d) *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a beige solid (88% yield, 85% purity) from *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 489 $[M+1]^+$

LC (2c) r.t. (min.): 0.97

INTERMEDIATE 144

Lithium 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate

a) Methyl 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate

Obtained as an off white solid (74% yield, 100% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-

a]pyrazine]-3'-carboxylic acid (Intermediate 64d) and methyl 4-(aminomethyl)benzoate hydrochloride following the synthetic procedure as described for Intermediate 17a

LRMS (m/z): 516 $[M+1]^+$

LC (4a) r.t. (min.): 0.73

b) Lithium 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate

Obtained (437 mg) from methyl 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate following the synthetic procedure as described for Intermediate 10b. The product was directly used in next step without further purification.

LRMS (m/z): 502.5 $[M+1]^+$

LC (4a) r.t. (min.): 0.60

INTERMEDIATE 145

1-(1-Cyclopropylpiperidin-4-yl)-1*H*-imidazol-4-amine

a) *Tert*-butyl 4-(4-nitro-1*H*-imidazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (19% yield, 98% purity) from 4-nitro-1*H*-imidazole and *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 15.

LRMS (m/z): 297.5 $[M+1]^+$

LC (4a) r.t. (min.): 0.77

b) 4-(4-Nitro-1*H*-imidazol-1-yl)piperidine hydrochloride

Obtained (200 mg) from *tert*-butyl 4-(4-nitro-1*H*-imidazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b. The product was directly used in next step without further purification.

LRMS (m/z): 197 $[M+1]^+$

LC (4b) r.t. (min.): 0.36

c) 1-Cyclopropyl-4-(4-nitro-1*H*-imidazol-1-yl)piperidine

Obtained as a yellow gum (52% yield, 96% purity) from 4-(4-nitro-1*H*-imidazol-1-yl)piperidine hydrochloride following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 237 $[M+1]^+$

LC (4b) r.t. (min.): 0.55

d) 1-(1-Cyclopropylpiperidin-4-yl)-1*H*-imidazol-4-amine

Obtained (140 mg) from 1-cyclopropyl-4-(4-nitro-1*H*-imidazol-1-yl)piperidine following the synthetic procedure as described for Intermediate 63b. The product was directly used in next step without further purification.

INTERMEDIATE 146

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) Ethyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-3-fluoro-1*H*-pyrrole-2-carboxylate

Ethyl 3-fluoro-1*H*-pyrrole-2-carboxylate (2.40 g, 15.0 mmol), *tert*-butyl *N*-(2-bromoethyl)carbamate (5.50 g, 25.0 mmol) and potassium iodide (150 mg, 0.90 mmol) were dissolved in ACN (20 mL) and then 2-*tert*-butyl-1,1,3,3-tetramethyl-guanidine (4.00 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred for 16 h at r.t. and after the reaction completion the reaction mixture was concentrated under reduced pressure and then purified by flash chromatography (SiO_2, heptane/EtOAc gradient rising from 100:0 to 50:50) to give a residue that was further purified by reverse phase chromatography using formic acid buffer to give the title compound (2.40 g, 8.00 mmol, 52% yield, 100% purity) as a clear oil.

LRMS (m/z): 323 $[M+1]^+$

LC (4a) r.t. (min.): 0.93

b) Ethyl 1-(2-aminoethyl)-3-fluoro-1*H*-pyrrole-2-carboxylate 2,2,2-trifluoroacetate

Obtained (3.00 g) from ethyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-3-fluoro-1*H*-pyrrole-2-carboxylate following the synthetic procedure as described for Intermediate 1f. The product was directly used in next step without further purification.

c) Ethyl 7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Obtained as a pale yellow solid (74% yield, 99% purity) from ethyl 1-(2-aminoethyl)-3-fluoro-1*H*-pyrrole-2-carboxylate 2,2,2-trifluoroacetate and oxetan-3-one following the synthetic procedure as described for Intermediate 89a.

LRMS (m/z): 255 $[M+1]^+$

LC (4a) r.t. (min.): 0.51

d) Ethyl 2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate

Obtained as a clear solid (88% yield, 99% purity) from ethyl 7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 417 $[M+1]^+$

LC (4a) r.t. (min.): 0.86

e) 2'-(4-(Dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid

Obtained as a white solid (73% yield, 75% purity) from ethyl 2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylate following the synthetic procedure as described for Intermediate 115c.

LRMS (m/z): 388 $[M+1]^+$

LC (4a) r.t. (min.): 0.64

f) *Tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate

Obtained as an off-white solid (79% yield, 70% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *tert*-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 593 $[M+1]^+$

LC (4a) r.t. (min.): 0.94

g) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (80% yield, 80% purity) from *tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 492 $[M+1]^+$

LC (4a) r.t. (min.): 0.59

INTERMEDIATE 147

***N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

a) *Tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

Obtained as a yellow solid (53% yield, 90% purity) from *tert*-butyl (4-((1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate (Example 263) following the synthetic procedure as described for Intermediate 93c.

LRMS (m/z): 587.5 $[M+1]^+$

LC (2c) r.t. (min.): 1.33

b) *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a yellow solid (79% yield, 90% purity) from *tert*-butyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 487 $[M+1]^+$

LC (2c) r.t. (min.): 1.10

INTERMEDIATE 148

***N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

a) *Tert*-butyl (6-((8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamate

Obtained as a white solid (99% yield, 80% purity) from *N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 34c) and tert-butyl (6-(aminomethyl)pyridin-3-yl)carbamate following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 653, 655 $[M+1]^+$

LC (2c) r.t. (min.): 1.23

b) *Tert*-butyl (6-((2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamate

Obtained as a white solid (51% yield, 90% purity) from *tert*-butyl (6-((8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamate following the synthetic procedure as described for Intermediate 93c.

LRMS (m/z): 589 $[M+1]^+$

LC (2c) r.t. (min.): 1.19

c) *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (72% yield, 90% purity) from *tert*-butyl (6-((2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)pyridin-3-yl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 489 $[M+1]^+$

LC (2c) r.t. (min.): 0.96

INTERMEDIATE 149

4-(4-Cyclobutyl-2-oxopiperazin-1-yl)benzoic acid

a) 4-Cyclobutylpiperazin-2-one

Obtained as a colourless oil (62% yield, 95% purity) from piperazin-2-one and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 155 $[M+1]^+$

LC (4c) r.t. (min.): 0.50

b) Methyl 4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzoate

Obtained as a yellow solid (63% yield, 90% purity) from 4-cyclobutylpiperazin-2-one and methyl 4-iodobenzoate following the synthetic procedure as described for Intermediate 16.

LRMS (m/z): 289 $[M+1]^+$

LC (4a) r.t. (min.): 0.47

c) 4-(4-Cyclobutyl-2-oxopiperazin-1-yl)benzoic acid

Obtained as a white powder (13% yield, 100% purity) from methyl 4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzoate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 275 $[M+1]^+$

LC (4a) r.t. (min.): 0.34

INTERMEDIATE 150

***N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

a) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-1-iodo-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

To a solution of *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate (Intermediate 140a, 100 mg, 0.17 mmol) in ACN (2 mL) 1-iodopyrrolidine-2,5-dione (43 mg, 0.19 mmol) and silver;bis(trifluoromethylsulfonyl)azanide (7 mg, 0.02 mmol) were added, and the reaction mixture was stirred at r.t. over the weekend. After te reaction completion, the reaction mixture was concentrated under vacuum and purified prep-HPLC (5a) to give the title compound (37 mg, 29% yield, 94% purity) as an off-white solid.

LRMS (m/z): 701 $[M+1]^+$

LC (4a) r.t. (min.): 0.97

b) *Tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate

To a solution of *tert*-butyl (4-((7-(4-(dimethylcarbamoyl)benzyl)-1-iodo-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamate (150 mg, 0.20 mmol) in DMF (5 mL), methyl 2,2-difluoro-2-fluorosulfonyl-acetate (125 µL, 0.98 mmol), *N*,*N*,*N*,*N*,*N*,*N*-hexamethylphosphoric triamide (171 µL, 0.98 mmol) and copper iodide (150 mg, 0.79 mmol) were added. The reaction mixture was degassed for 5 min and then heated to 100 °C for 2h. After the reaction completion, the reaction mixture was filtered under vacuum through glass fibre filter paper, washed with EtOAc and the filtrate concentrated under vacuum. The resulting crude was purified by flash cromatography (SiO2, 0-100% EtOAc in heptanes, 0-20% MeOH in EtOAc) to give the title compound (145 mg, 82% yield, 87% purity) as a yellow solid.

LRMS (m/z): 643.5 $[M+1]^+$

LC (4a) r.t. (min.): 1.00

c) *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (100% yield, 94% purity) from methyl 4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzoate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 543 $[M+1]^+$

LC (4a) r.t. (min.): 0.66

INTERMEDIATE 151

4-(1-cyclopropylazetidin-3-yl)benzoic acid

a) *Tert*-butyl 3-(4-(ethoxycarbonyl)phenyl)azetidine-1-carboxylate

Obtained as a yellow solid (100% yield, 94% purity) from ethyl 4-bromobenzoate and *tert*-butyl 3-bromoazetidine-1-carboxylate following the synthetic procedure as described for Intermediate 40a.

LRMS (m/z): 250 $[M\text{-}tBu+H]^+$

LC (2c) r.t. (min.): 1.39

b) Ethyl 4-(azetidin-3-yl)benzoate

Obtained as a yellow oil (80% yield, 90% purity) from *tert*-butyl 3-(4-(ethoxycarbonyl)phenyl)azetidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 206 $[M+H]^+$

LC (2c) r.t. (min.): 0.76

c) Ethyl 4-(1-cyclopropylazetidin-3-yl)benzoate

Obtained as a yellow oil (42% yield, 90% purity) from ethyl 4-(azetidin-3-yl)benzoate and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 246 $[M+H]^+$

LC (2c) r.t. (min.): 1.25

d) 4-(1-Cyclopropylazetidin-3-yl)benzoic acid

Obtained as a white solid (61% yield, 90% purity) from ethyl ethyl 4-(1-cyclopropylazetidin-3-yl)benzoate following the synthetic procedure as described for Intermediate 115c.

LRMS (m/z): 218 $[M+H]^+$

LC (2c) r.t. (min.): 0.50

INTERMEDIATE 152

1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

a) *Tert*-butyl 4-(4-((4-((1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a yellow solid (49% yield, 90% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 140) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 800 $[M+1]^+$

LC (2c) r.t. (min.): 1.27

b) 1-Chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (87% yield, 90% purity) from *tert*-butyl 4-(4-((4-((1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 700.5, 702.5 $[M+1]^+$

LC (2c) r.t. (min.): 1.05

INTERMEDIATE 153

7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

a) *Tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

Obtained as a white solid (62% yield, 90% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 147) and 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 778 $[M+1]^+$

LC (2c) r.t. (min.): 1.35

b) 7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained (90 mg, HCl salt) from *tert*-butyl 4-(4-((4-((7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamoyl)-5-methyl-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the synthetic procedure as described for Intermediate 17b.

LRMS (m/z): 678 $[M+1]^+$

LC (2b) r.t. (min.): 0.48

EXAMPLES

EXAMPLE 1

***N*-(4-acetamidobenzyl)-2'-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (47% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and *N*-(4-formylphenyl)-*N*-methylacetamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 514 $[M+1]^+$

LC (1) r.t. (min.): 1.81

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.40 (t, 1H), 7.49 (d, 2H), 7.44 (d, 2H), 7.26 (d, 2H), 7.19 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.16 (t, 2H), 3.53 (s, 2H), 3.12 (s, 3H), 2.84 (t, 2H), 2.39 (q, 2H), 2.21 – 2.11 (m, 2H), 2.00 (s, 3H), 1.99 – 1.92 (m, 1H), 1.91 – 1.83 (m, 1H), 1.75 (s, 3H).

EXAMPLE 2

***N*-(4-acetamidobenzyl)-2'-(4-(isopropyl(methyl)carbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (73% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*-isopropyl-*N*-methylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 2.17

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.62 (s, 1H), 8.12 (t, 1H), 7.48 (d, 2H), 7.44 (d, 2H), 7.29 (d, 2H), 7.21 (d, 2H), 6.85 (d, 1H), 6.18 (d, 1H), 4.33 (d, 2H), 4.37 – 4.10 (m, 1H), 4.18 (t, 2H), 3.60 (s, 2H), 2.90 (t, 2H), 2.78 (s, 3H), 2.47 – 2.39 (m, 2H), 2.26 – 2.13 (m, 2H), 2.01 (s, 3H), 2.00 – 1.93 (m, 1H), 1.94 – 1.84 (m, 1H), 1.13 (d, 6H).

EXAMPLE 3

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3,5-dimethylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (33% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-N,N,2,6-tetramethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 1.80

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.49 (d, 2H), 7.19 (d, 2H), 7.06 (s, 2H), 6.87 (d, 1H), 6.19 (d, 1H), 4.31 (d, 2H), 4.14 (t, 2H), 3.44 (s, 2H), 3.00 (s, 3H), 2.82 (t, 2H), 2.69 (s, 3H), 2.40 (q, 2H), 2.20 – 2.12 (m, 2H), 2.10 (s, 6H), 2.00 (s, 3H), 1.99 – 1.92 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 4

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (35% yield, 98% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*,*N*,2-trimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 1.67

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H), 8.39 (t, 1H), 7.49 (d, 2H), 7.28 – 7.16 (m, 4H), 7.08 (d, 1H), 6.87 (d, 1H), 6.19 (d, 1H), 4.31 (d, 2H), 4.15 (t, 2H), 3.49 (s, 2H), 2.98 (s, 3H), 2.83 (t, 2H), 2.73 (s, 3H), 2.40 (q, 2H), 2.21 – 2.11 (m, 5H), 2.00 (s, 3H), 1.99 – 1.92 (m, 1H), 1.91 – 1.83 (m, 1H).

EXAMPLE 5

***N*-(4-acetamidobenzyl)-2'-((5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (47% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 6-formyl-*N*,*N*-dimethylnicotinamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 515 $[M+1]^+$

LC (1) r.t. (min.): 1.56

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H), 8.52 (d, 1H), 8.39 (t, 1H), 7.82 (dd, 1H), 7.61 (d, 1H), 7.49 (d, 2H), 7.19 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.19 (t, 2H), 3.68 (s, 2H), 2.99 (s, 3H), 2.95 – 2.87 (m, 5H), 2.39 (q, 2H), 2.22 – 2.11 (m, 2H), 2.00 (s, 3H), 1.99 – 1.91 (m, 1H), 1.91 – 1.83 (m, 1H).

EXAMPLE 6

***N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (25% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1-methyl-1*H*-imidazol-2-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 523 $[M+1]^+$

LC (1) r.t. (min.): 1.40

1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.46 (s, 1H), 8.77 (dd, 2H), 8.44 (t, 1H), 7.85 (dd, 2H), 7.70 (d, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.29 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 2.96 (s, 3H), 2.91 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.12 (m, 2H), 2.03 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H).

EXAMPLE 7

***N*-(4-acetamidobenzyl)-2'-(4-(4-methyl-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (10% yield, 97% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(4-methyl-4*H*-1,2,4-triazol-3-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 524 $[M+1]^+$

LC (1) r.t. (min.): 1.53

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.19 (s, 1H), 7.64 (d, 2H), 7.56 (s, 2H), 7.47 (d, 2H), 7.37 – 7.25 (m, 3H), 6.60 (d, 1H), 6.22 (d, 1H), 6.14 (s, 1H), 4.52 (d, 2H), 4.31 (s, 2H), 3.77 (s, 3H), 3.62 (s, 2H), 3.01 (s, 2H), 2.47 (s, 2H), 2.34 – 2.23 (m, 2H), 2.17 (s, 3H), 2.11 – 1.90 (m, 2H).

EXAMPLE 8

2'-(4-(1,3,4-Oxadiazol-2-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (46% yield, 97% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1,3,4-oxadiazol-2-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 511 $[M+1]^+$

LC (1) r.t. (min.): 1.94

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 9.32 (s, 1H), 8.40 (t, 1H), 7.98 (d, 2H), 7.63 (d, 2H), 7.49 (d, 2H), 7.20 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.31 (d, 2H), 4.17 (t, 2H), 3.63 (s, 2H), 2.86 (t, 2H), 2.41 (q, 2H), 2.23 – 2.12 (m, 2H), 2.01 (s, 3H), 2.00 – 1.93 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 9

***N*-(4-acetamidobenzyl)-2'-(4-(oxazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (18% yield, 98% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(oxazol-2-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 510 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.40 (t, 1H), 8.19 (s, 1H), 7.97 – 7.90 (m, 2H), 7.55 (d, 2H), 7.53 – 7.46 (m, 2H), 7.36 (s, 1H), 7.20 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.17 (dd, 2H), 3.59 (s, 2H), 2.85 (dd, 2H), 2.41 (dd, 2H), 2.17 (s, 2H), 2.01 (s, 3H), 1.99 – 1.93 (m, 1H), 1.93 – 1.84 (m, 1H).

EXAMPLE 10

***N*-(4-acetamidobenzyl)-2'-((1-isobutyrylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as an off white solid (65% yield, 100% purity) from *N*-(4-acetamidobenzyl)-2'-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and isobutyryl chloride following the synthetic procedure as described for Intermediate 27a.

LRMS (m/z): 520 $[M+1]^+$

LC (1) r.t. (min.): 1.66

1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, 2H), 7.28 (d, 2H), 7.18 (s, 1H), 6.54 (d, 1H), 6.13 (d, 1H), 6.05 (br t, 1H), 4.63 (br d, 1H), 4.51 (d, 2H), 4.31 (t, 2H), 3.94 (br d, 1H), 3.08 (t, 2H), 3.01 (br t, 1H), 2.80 (m, 1H), 2.54 (bd t, 1H), 2.30 (q, 2H), 2.25 – 2.19 (m, 2H), 2.18 (s, 3H), 2.07 – 1.92 (m, 2H), 1.92 – 1.76 (m, 4H), 1.12 (d, 3H), 1.11 (d, 3H), 1.09 – 0.98 (m, 3H).

EXAMPLE 11

2'-(4-(1*H*-pyrazol-1-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (36% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1*H*-

pyrazol-1-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 509 $[M+1]^+$

LC (1) r.t. (min.): 2.00

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.46 (d, 1H), 8.39 (t, 1H), 7.78 (d, 2H), 7.72 (d, 1H), 7.49 (d, 4H), 7.20 (d, 2H), 6.88 (d, 1H), 6.55 – 6.49 (m, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.16 (t, 2H), 3.55 (s, 2H), 2.85 (t, 2H), 2.42 (q, 2H), 2.22 – 2.13 (m, 2H), 2.01 (s, 3H), 2.00 – 1.93 (m, 1H), 1.92 – 1.84 (m, 1H).

EXAMPLE 12

***N*-(4-acetamidobenzyl)-2'-(4-(3-methyloxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (53% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1*H*-pyrazol-1-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 513 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.49 (d, 2H), 7.36 (d, 2H), 7.19 (dd, 4H), 6.87 (d, 1H), 6.19 (d, 1H), 4.78 (d, 2H), 4.52 (d, 2H), 4.31 (d, 2H), 4.14 (t, 2H), 3.49 (s, 2H), 2.82 (t, 2H), 2.39 (q, 2H), 2.20 – 2.12 (m, 2H), 2.01 (s, 3H), 1.99 – 1.91 (m, 1H), 1.91 – 1.80 (m, 1H), 1.61 (s, 3H).

EXAMPLE 13

Methyl 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylate

Obtained as a white solid (80% yield, 98% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1*H*-pyrazol-1-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 491 $[M+1]^+$

LC (1) r.t. (min.): 1.61

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.28 (d, 2H), 7.16 (s, 1H), 6.52 (d, 1H), 6.12 (d, 1H), 6.04 (t, 1H), 4.51 (d, 2H), 4.30 (t, 2H), 3.67 (s, 3H), 3.07 (t,

2H), 2.48 (s, 2H), 2.37 – 2.25 (m, 2H), 2.22 – 2.13 (m, 5H), 2.01 – 1.79 (m, 2H), 1.57 (s, 6H).

EXAMPLE 14

3-((6'-((4-Acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid

Obtained as a white solid (79% yield, 99% purity) from methyl 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylate following the synthetic procedure as described for Intermediate 10b.

LRMS (m/z): 477 $[M+1]^+$

LC (1) r.t. (min.): 1.27

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.63 – 11.83 (m, 1H), 9.86 (s, 1H), 8.36 (t, 1H), 7.48 (d, 2H), 7.18 (d, 2H), 6.82 (d, 1H), 6.12 (d, 1H), 4.30 (d, 2H), 4.14 (t, 2H), 2.93 (t, 2H), 2.43 (s, 2H), 2.25 (q, 2H), 2.12 – 2.03 (m, 2H), 2.00 (s, 3H), 1.96 – 1.88 (m, 1H), 1.86 (s, 6H), 1.84 – 1.73 (m, 1H).

EXAMPLE 15

***N*-(4-acetamidobenzyl)-2'-(4-(3-(dimethylamino)oxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (38% yield, 98% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(3-(dimethylamino)oxetan-3-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 542 [M+1]+

LC (1) r.t. (min.): 1.36

^{1}H NMR($CDCl_3$, 400 MHz): δ (ppm) 7.50 – 7.44 (m, 4H), 7.30 (d, 2H), 7.19 (s, 1H), 7.09 (d, 2H), 6.59 (d, 1H), 6.22 (s, 1H), 6.13 – 6.07 (m, 1H), 4.97 – 4.91 (m, 4H), 4.52 (d, 2H), 4.31 (s, 2H), 3.57 (s, 2H), 2.99 (s, 2H), 2.46 (s, 1H), 2.34 – 2.25 (m, 3H), 2.20 – 2.16 (m, 8H), 2.10 – 1.99 (m, 3H).

EXAMPLE 16

***N*-(4-acetamidobenzyl)-2'-((3-(dimethylcarbamoyl)bicyclo[1.1.1]pentan-1-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white foam (75% yield, 99% purity) from 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-*2'H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid and dimethylamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 504 $[M+1]^+$

LC (1) r.t. (min.): 1.40

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.28 (d, 2H), 7.20 (s, 1H), 6.53 (d, 1H), 6.12 (d, 1H), 6.05 (t, 1H), 4.51 (d, 2H), 4.31 (t, 2H), 3.13 – 3.04 (m, 5H), 2.92 (s, 3H), 2.49 (s, 2H), 2.37 – 2.27 (m, 2H), 2.23 – 2.14 (m, 5H), 2.07 (s, 6H), 2.01 – 1.81 (m, 2H).

EXAMPLE 17

***N*-(4-acetamidobenzyl)-2'-(4-(1-hydroxy-2-methylpropyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white foam (29% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(1-hydroxy-2-methylpropyl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 515 $[M+1]^+$

LC (1) r.t. (min.): 2.10

^{1}H NMR($CDCl_3$, 400 MHz): δ (ppm) 7.47 (d, 2H), 7.36 (d, 2H), 7.33 – 7.26 (m, 4H), 7.18 (s, 1H), 6.58 (d, 1H), 6.20 (d, 1H), 6.08 (t, 1H), 4.52 (d, 2H), 4.36 (d, 1H), 4.29 (t, 2H), 3.53 (s, 2H), 2.96 (t, 2H), 2.53 – 2.39 (m, 2H), 2.32 – 2.23 (m, 2H), 2.18 (s, 3H), 2.09 – 1.91 (m, 3H), 1.82 (s, 1H), 1.01 (d, 3H), 0.80 (d, 3H).

EXAMPLE 18

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white foam (19% yield, 92% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 3-fluoro-4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 532 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.61 (t, 1H), 7.49 (d, 2H), 7.27 (d, 2H), 7.23 (dd, 1H), 7.18 (dd, 1H), 6.85 (d, 1H), 6.25 (d, 1H), 4.44 (s, 2H), 4.27 (t, 2H), 3.64 (s, 2H), 3.09 (s, 3H), 3.05 – 3.00 (m, 2H), 3.00 (s, 3H), 2.56 – 2.44 (m, 2H), 2.32 – 2.23 (m, 2H), 2.10 (s, 3H), 2.08 – 2.00 (m, 1H), 1.99 – 1.84 (m, 1H).

EXAMPLE 19

***N*-(4-acetamidobenzyl)-2'-(2-methyl-4-(1H-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (43% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 2-methyl-4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 524 $[M+1]^+$

LC (1) r.t. (min.): 2.32

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 9.24 (s, 1H), 8.40 (t, 1H), 8.20 (s, 1H), 7.68 (d, 1H), 7.62 (dd, 1H), 7.52 (d, 1H), 7.48 (d, 2H), 7.20 (d, 2H), 6.89 (d, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 4.19 (t, 2H), 3.58 (s, 2H), 2.84 (t, 2H), 2.47 – 2.38 (m, 5H), 2.21 – 2.12 (m, 2H), 2.01 (s, 3H), 1.99 – 1.92 (m, 1H), 1.91 – 1.82 (m, 1H).

EXAMPLE 20

***N*-(4-acetamidobenzyl)-2'-(4-isobutyrylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

N-(4-acetamidobenzyl)-2'-(4-(1-hydroxy-2-methylpropyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (29 mg, 56.3 μmol) was dissolved in DCM (1 mL) under an argon atmosphere and the stirred mixture was cooled in an ice bath. Dess-Martin periodinane (29 mg, 68.3 μmol) was added to the mixture and the mixture was stirred overnight. Saturated aqueous sodium thiosulphate (0.5 mL) was added and the mixture was vigorously stirred for 15 min. The mixture was diluted with DCM and washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH-DCM gradient, 0:100 rising to 10:90) to give the title compound (20 mg, 69% yield, 97% purity) as a white foam.

LRMS (m/z): 513 $[M+1]^+$

LC (1) r.t. (min.): 2.73

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.92 (d, 2H), 7.52 – 7.44 (m, 4H), 7.30 (d, 2H), 7.14 (s, 1H), 6.58 (d, 1H), 6.20 (d, 1H), 6.07 (t, 1H), 4.52 (d, 2H), 4.30 (t, 2H), 3.60 (s, 2H), 3.57 – 3.52 (m, 1H), 2.97 (t, 2H), 2.49 – 2.41 (m, 2H), 2.30 – 2.24 (m, 2H), 2.18 (s, 3H), 2.05 – 1.93 (m, 2H), 1.22 (d, 6H).

EXAMPLE 21

***N*-(4-acetamidobenzyl)-2'-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (38% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*-methylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 500 $[M+1]^+$

LC (1) r.t. (min.): 1.59

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.44 – 8.35 (m, 2H), 7.78 (d, 2H), 7.49 (d, 2H), 7.46 (d, 2H), 7.19 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.15 (t, 2H), 3.56 (s, 2H), 2.82 (t, 2H), 2.76 (d, 3H), 2.40 (q, 2H), 2.20 – 2.11 (m, 2H), 2.01 (s, 3H), 1.99 – 1.92 (m, 1H), 1.91 – 1.81 (m, 1H).

EXAMPLE 22

***N*-((2-((3*R*,5*S*)-3,5-dimethylpiperazin-1-yl)pyrimidin-4-yl)methyl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine**

Obtained as a white solid (40% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and *N*-(4-formylphenyl)acetamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 500 $[M+1]^+$

LC (1) r.t. (min.): 1.53

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (s, 1H), 9.88 (s, 1H), 8.40 (t, 1H), 7.50 (t, 4H), 7.27 (d, 2H), 7.19 (d, 2H), 6.87 (d, 1H), 6.19 (d, 1H), 4.31 (d, 2H), 4.12 (t, 2H), 3.43 (s, 2H), 2.79 (t, 2H), 2.39 (q, 2H), 2.20 – 2.10 (m, 2H), 2.01 (s, 3H), 2.01 (s, 3H), 1.98 – 1.91 (m, 1H), 1.91 – 1.80 (m, 1H).

EXAMPLE 23

***N*-(4-acetamidobenzyl)-2'-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (8% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-(2-oxopyrrolidin-1-yl)benzaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 526 $[M+1]^+$

LC (1) r.t. (min.): 1.77

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.59 (d, 2H), 7.49 (d, 2H), 7.36 (d, 2H), 7.19 (d, 2H), 6.87 (d, 1H), 6.19 (d, 1H), 4.31 (d, 2H), 4.13 (t, 2H), 3.81 (t, 2H), 3.48 (s, 2H), 2.80 (t, 2H), 2.49 – 2.44 (m, 2H), 2.44 – 2.34 (m, 2H), 2.20 – 2.11 (m, 2H), 2.10 – 2.02 (m, 2H), 2.00 (s, 3H), 1.99 – 1.90 (m, 1H), 1.89 – 1.82 (m, 1H).

EXAMPLE 24

***N*-(4-(dimethylamino)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (17% yield, 95% purity) from *N*-(4-(dimethylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 10a.

LRMS (m/z): 500 $[M+1]^+$

LC (1) r.t. (min.): 1.86

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.51 (d, 2H), 7.39 (d, 2H), 7.18 (d, 2H), 6.81 (d, 1H), 6.78 – 6.72 (m, 2H), 6.24 (d, 1H), 4.37 (s, 2H), 4.22 (t, 2H), 3.61 (s, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 2.97 (t, 2H), 2.89 (s, 6H), 2.56 – 2.44 (m, 2H), 2.32 – 2.21 (m, 2H), 2.14 – 2.01 (m, 1H), 2.00 – 1.89 (m, 1H).

EXAMPLE 25

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (52% yield, 93% purity) from *N*-(4-acetamidobenzyl)-*N*-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-

formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 10a.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 1.90

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.55 (d, 2H), 7.51 (d, 2H), 7.40 (d, 2H), 7.21 (d, 2H), 6.49 (d, 1H), 6.24 (d, 1H), 4.75 (s, 2H), 4.02 (t, 2H), 3.61 (s, 2H), 3.12 – 3.08 (m, 6H), 3.01 (s, 3H), 2.97 (t, 2H), 2.56 – 2.45 (m, 2H), 2.31 – 2.22 (m, 2H), 2.10 (s, 3H), 2.09 – 2.01 (m, 1H), 2.00 – 1.87 (m, 1H).

EXAMPLE 26

***N*-benzyl-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (29% yield, 94% purity) from *N*-benzyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 10a.

LRMS (m/z): 457 $[M+1]^+$

LC (1) r.t. (min.): 2.14

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.51 (d, 2H), 7.40 (d, 2H), 7.36 – 7.27 (m, 4H), 7.26 – 7.18 (m, 1H), 6.86 (d, 1H), 6.26 (d, 1H), 4.48 (s, 2H), 4.22 (t, 2H), 3.61 (s, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 2.98 (t, 2H), 2.57 – 2.44 (m, 2H), 2.33 – 2.22 (m, 2H), 2.14 – 2.01 (m, 1H), 2.00 – 1.88 (m, 1H).

EXAMPLE 27

***N*-((1-acetylpiperidin-4-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (9% yield, 91% purity) from *N*-((1-acetylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 10a.

LRMS (m/z): 506 $[M+1]^+$

LC (1) r.t. (min.): 1.57

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.51 (d, 2H), 7.40 (d, 2H), 6.81 (d, 1H), 6.25 (d, 1H), 4.55 – 4.48 (m, 1H), 4.20 (t, 2H), 3.96 – 3.90 (m, 1H), 3.61 (s, 2H), 3.19 (t, 2H), 3.15 – 3.05 (m, 5H), 3.01 (s, 3H), 2.97 (t, 2H), 2.62 (td, 1H), 2.56 – 2.45 (m,

2H), 2.31 – 2.23 (m, 2H), 2.09 (s, 3H), 2.08 – 2.01 (m, 1H), 2.00 – 1.89 (m, 1H), 1.89 – 1.72 (m, 2H), 1.27 – 1.04 (m, 2H).

EXAMPLE 28

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (35% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 34d) and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 516 $[M+1]^+$

LC (1) r.t. (min.): 1.91

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.90 (s, 1H), 8.50 (t, 1H), 8.36 (s, 1H), 7.51 – 7.47 (m, 3H), 7.38 (d, 2H), 7.19 (d, 2H), 6.95 (d, 1H), 6.41 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.32 (d, 2H), 4.18 (t, 2H), 3.86 (s, 2H), 2.98 (s, 3H), 2.92 (s, 3H), 2.80 (t, 2H), 2.01 (s, 3H).

EXAMPLE 29

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white foam (75% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 1.80

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.48 – 7.40 (m, 4H), 7.37 (d, 2H), 7.33 – 7.26 (m, 3H), 6.54 (d, 1H), 6.10 (t, 1H), 5.91 (d, 1H), 4.50 (d, 2H), 4.32 (t, 2H), 3.66 (s, 2H), 3.11 (s, 3H), 3.03 – 2.93 (m, 5H), 2.16 (s, 3H), 2.14 – 2.06 (m, 2H), 2.05 – 1.96 (m, 2H), 1.83 (t, 4H).

EXAMPLE 30

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (41% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 2.47

^{1}H NMR (CDCl3, 400 MHz) δ 7.67 (s, 1H), 7.44 (d, 4H), 7.38 (d, 2H), 7.25 (d, 2H), 6.56 (d, 1H), 6.23 (t, 1H), 5.95 (d, 1H), 4.49 (d, 2H), 4.25 (t, 2H), 3.68 (s, 2H), 3.12 (s, 3H), 3.05 (t, 2H), 3.01 (s, 3H), 2.21 (d, 2H), 2.14 (s, 3H), 1.85 (q, 4H), 1.65 (br t, 2H), 1.56 (br d, 2H).

EXAMPLE 31

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (37% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 550 $[M+1]^+$

LC (1) r.t. (min.): 2.58

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.48 (t, 1H), 7.49 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.20 (d, 2H), 6.88 (d, 1H), 6.12 (d, 1H), 4.31 (d, 2H), 4.22 (t, 2H), 3.58 (s, 2H), 3.06 (q, 2H), 2.99 – 2.79 (m, 10H), 2.00 (s, 3H).

EXAMPLE 32

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (37% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 2.43

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.49 (d, 2H), 7.43 (d, 2H), 7.35 (d, 2H), 7.20 (d, 2H), 6.86 (d, 1H), 6.10 (d, 1H), 4.31 (d, 2H), 4.16 (t, 2H), 3.49 (s, 2H), 3.00 – 2.87 (m, 8H), 2.22 (d, 2H), 2.07 (d, 2H), 2.01 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H).

EXAMPLE 33

***N*-(4-acetamidobenzyl)-2'-(4-(azetidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (42% yield, 100% purity) from 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzoic acid and azetidine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 526 $[M+1]^+$

LC (1) r.t. (min.): 1.80

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.39 (t, 1H), 7.57 (d, 2H), 7.49 (d, 2H), 7.45 (d, 2H), 7.19 (d, 2H), 6.87 (d, 1H), 6.19 (d, 1H), 4.34 – 4.24 (m, 4H), 4.15 (t, 2H), 4.02 (t, 2H), 3.56 (s, 2H), 2.83 (t, 2H), 2.39 (q, 2H), 2.30 – 2.21 (m, 2H), 2.21 – 2.10 (m, 2H), 2.01 (s, 3H), 1.98 – 1.91 (m, 1H), 1.91 – 1.82 (m, 1H).

EXAMPLE 34

***N*-(4-acetamidobenzyl)-2'-(4-(pyrrolidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (46% yield, 100% purity) from 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzoic acid and pyrrolidine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 540 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.52 – 7.40 (m, 6H), 7.19 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.15 (t, 2H), 3.55 (s, 2H), 3.44 (t, 2H), 3.37 (t, 2H), 2.84 (t, 2H), 2.39 (q, 2H), 2.22 – 2.10 (m, 2H), 2.00 (s, 3H), 1.99 – 1.92 (m, 1H), 1.91 – 1.75 (m, 5H).

EXAMPLE 35

***N*-(4-acetamidobenzyl)-2'-(4-(piperidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (36% yield, 99% purity) from 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzoic acid and piperidine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 523 $[M+1]^+$

LC (1) r.t. (min.): 1.40

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.63 (d, 2H), 7.52 – 7.45 (m, 4H), 7.25 – 7.17 (m, 3H), 6.95 (s, 1H), 6.88 (d, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 4.17 (t, 2H), 3.73 (s, 3H), 3.57 (s, 2H), 2.87 (t, 2H), 2.42 (q, 2H), 2.23 – 2.13 (m, 2H), 2.01 (s, 3H), 1.99 – 1.93 (m, 1H), 1.93 – 1.84 (m, 1H).

EXAMPLE 36

***N*-(4-acetamidobenzyl)-2'-(4-(morpholine-4-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (28% yield, 97% purity) from 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzoic acid and morpholine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 524 $[M+1]^+$

LC (1) r.t. (min.): 1.53

^{1}H NMR(CDCl3, 400 MHz): δ (ppm) 8.19 (s, 1H), 7.64 (d, 2H), 7.56 (s, 2H), 7.47 (d, 2H), 7.37 – 7.25 (m, 3H), 6.60 (d, 1H), 6.22 (d, 1H), 6.14 (s, 1H), 4.52 (d, 2H), 4.31 (s, 2H), 3.77 (s, 3H), 3.62 (s, 2H), 3.01 (s, 2H), 2.47 (s, 2H), 2.34 – 2.23 (m, 2H), 2.17 (s, 3H), 2.11 – 1.90 (m, 2H).

EXAMPLE 37

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (57% yield, 97% purity) from 4-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluorobenzoic acid and *N*-methylmethanamine hydrochloride following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 511 $[M+1]^+$

LC (1) r.t. (min.): 1.94

^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 9.32 (s, 1H), 8.40 (t, 1H), 7.98 (d, 2H), 7.63 (d, 2H), 7.49 (d, 2H), 7.20 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.31 (d, 2H), 4.17 (t, 2H), 3.63 (s, 2H), 2.86 (t, 2H), 2.41 (q, 2H), 2.23 – 2.12 (m, 2H), 2.01 (s, 3H), 2.00 – 1.93 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 38

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (36% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 510 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.40 (t, 1H), 8.19 (s, 1H), 7.97 – 7.90 (m, 2H), 7.55 (d, 2H), 7.53 – 7.46 (m, 2H), 7.36 (s, 1H), 7.20 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.17 (dd, 2H), 3.59 (s, 2H), 2.85 (dd, 2H), 2.41 (dd, 2H), 2.17 (s, 2H), 2.01 (s, 3H), 1.99 – 1.93 (m, 1H), 1.93 – 1.84 (m, 1H).

EXAMPLE 39

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(methylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (63% yield, 100% purity) from *tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)(methyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 520 $[M+1]^+$

LC (1) r.t. (min.): 1.66

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.28 (d, 2H), 7.18 (s, 1H), 6.54 (d, 1H), 6.13 (d, 1H), 6.05 (br t, 1H), 4.63 (br d, 1H), 4.51 (d, 2H), 4.31 (t, 2H), 3.94 (br d, 1H), 3.08 (t, 2H), 3.01 (br t, 1H), 2.80 (m, 1H), 2.54 (bd t, 1H), 2.30 (q, 2H),

2.25 – 2.19 (m, 2H), 2.18 (s, 3H), 2.07 – 1.92 (m, 2H), 1.92 – 1.76 (m, 4H), 1.12 (d, 3H), 1.11 (d, 3H), 1.09 – 0.98 (m, 3H).

EXAMPLE 40

***N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (53% yield, 100% purity) 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid *N*-(6-(aminomethyl)pyridin-3-yl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 2.17

^{1}H NMR(MeOD, 400 MHz): δ (ppm) 7.55 – 7.44 (m, 6H), 7.25 (d, 2H), 6.85 (d, 1H), 6.29 (d, 1H), 4.42 (d, 2H), 4.22 (t, 2H), 3.86 – 3.82 (m, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.90 – 2.71 (m, 2H), 2.48 – 2.34 (m, 2H), 2.09 (s, 3H), 2.07 – 1.98 (m, 1H), 1.98 – 1.89 (m, 1H).

EXAMPLE 41

***N*-(4-acetamido-3-methylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (38% yield, 97% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)-2-methylphenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 462 $[M+1]^+$

LC (1) r.t. (min.): 1.09

^{1}H NMR(CDCl3, 400 MHz): δ (ppm) 7.42 (d, 2H), 7.38 (d, 2H), 6.56 (d, 1H), 6.20 (d, 1H), 5.72 (t, 1H), 4.25 (t, 2H), 3.56 (s, 2H), 3.51 (d, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.95 (t, 2H), 2.52 – 2.40 (m, 2H), 2.33 – 2.23 (m, 2H), 2.09 – 1.88 (m, 2H), 1.69 – 1.53 (m, 8H).

EXAMPLE 42

***N*-(4-acetamido-3,5-dimethylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (54% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)-2,6-dimethylphenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 504 $[M+1]^+$

LC (1) r.t. (min.): 1.47

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.42 (d, 2H), 7.37 (d, 2H), 6.57 (d, 1H), 6.20 (d, 1H), 5.84 – 5.74 (m, 2H), 4.24 (t, 2H), 3.56 (s, 2H), 3.54 (d, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.95 (t, 2H), 2.50 – 2.41 (m, 2H), 2.32 – 2.24 (m, 2H), 2.07 – 1.99 (m, 8H), 1.93 (s, 3H).

EXAMPLE 43

***N*-(3-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (64% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-[3-(aminomethyl)phenyl]acetamide hydrochloride following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 509 $[M+1]^+$

LC (1) r.t. (min.): 2.00

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.46 (d, 1H), 8.39 (t, 1H), 7.78 (d, 2H), 7.72 (d, 1H), 7.49 (d, 4H), 7.20 (d, 2H), 6.88 (d, 1H), 6.55 – 6.49 (m, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.16 (t, 2H), 3.55 (s, 2H), 2.85 (t, 2H), 2.42 (q, 2H), 2.22 – 2.13 (m, 2H), 2.01 (s, 3H), 2.00 – 1.93 (m, 1H), 1.92 – 1.84 (m, 1H).

EXAMPLE 44

***N*-(4-acetamido-3-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (27% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)-2-fluorophenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 513 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.39 (t, 1H), 7.49 (d, 2H), 7.36 (d, 2H), 7.19 (dd, 4H), 6.87 (d, 1H), 6.19 (d, 1H), 4.78 (d, 2H), 4.52 (d, 2H), 4.31 (d, 2H), 4.14 (t, 2H), 3.49 (s, 2H), 2.82 (t, 2H), 2.39 (q, 2H), 2.20 – 2.12 (m, 2H), 2.01 (s, 3H), 1.99 – 1.91 (m, 1H), 1.91 – 1.80 (m, 1H), 1.61 (s, 3H).

EXAMPLE 45

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (87% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-[4-(aminomethyl)phenyl]-*N*-methyl-acetamide;hydrochloride following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 511 $[M+1]^+$

LC (1) r.t. (min.): 1.31

^{1}H NMR (CDCl3, 400 MHz)) δ 7.47 (s, 1H), 7.44 – 7.34 (m, 5H), 7.16 (t, 1H), 6.59 (d, 1H), 6.47 – 6.30 (m, 2H), 6.15 (d, 1H), 4.64 (d, 2H), 4.23 – 4.16 (m, 2H), 3.54 (s, 2H), 3.13 (s, 3H), 3.01 (s, 3H), 2.93 – 2.84 (m, 2H), 2.62 – 2.57 (m, 3H), 2.44 (q, 2H), 2.30 – 2.20 (m, 2H), 2.03 – 1.86 (m, 2H).

EXAMPLE 46

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((2-oxoindolin-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (46% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 5-(aminomethyl)indolin-2-one following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 491 [M+1]+

LC (1) r.t. (min.): 1.61

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.28 (d, 2H), 7.16 (s, 1H), 6.52 (d, 1H), 6.12 (d, 1H), 6.04 (t, 1H), 4.51 (d, 2H), 4.30 (t, 2H), 3.67 (s, 3H), 3.07 (t, 2H), 2.48 (s, 2H), 2.37 – 2.25 (m, 2H), 2.22 – 2.13 (m, 5H), 2.01 – 1.79 (m, 2H), 1.57 (s, 6H),

EXAMPLE 47

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((2-methyl-1*H*-benzo[d]imidazol-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (99% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and (2-methyl-1*H*-benzo[d]imidazol-5-yl)methanamine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 477 $[M+1]^+$

LC (1) r.t. (min.): 1.27

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.63 – 11.83 (m, 1H), 9.86 (s, 1H), 8.36 (t, 1H), 7.48 (d, 2H), 7.18 (d, 2H), 6.82 (d, 1H), 6.12 (d, 1H), 4.30 (d, 2H), 4.14 (t, 2H), 2.93 (t, 2H), 2.43 (s, 2H), 2.25 (q, 2H), 2.12 – 2.03 (m, 2H), 2.00 (s, 3H), 1.96 – 1.88 (m, 1H), 1.86 (s, 6H), 1.84 – 1.73 (m, 1H).

EXAMPLE 48

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (57% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 4-(aminomethyl)-*N*-methyl-benzamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 1.36

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.50 – 7.44 (m, 4H), 7.30 (d, 2H), 7.19 (s, 1H), 7.09 (d, 2H), 6.59 (d, 1H), 6.22 (s, 1H), 6.13 – 6.07 (m, 1H), 4.97 – 4.91 (m, 4H), 4.52 (d, 2H), 4.31 (s, 2H), 3.57 (s, 2H), 2.99 (s, 2H), 2.46 (s, 1H), 2.34 – 2.25 (m, 3H), 2.20 – 2.16 (m, 8H), 2.10 – 1.99 (m, 3H).

EXAMPLE 49

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((3-methyloxetan-3-yl)amino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white foam (79% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)-3-methyloxetan-3-amine following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 550 $[M+1]^+$

LC (1) r.t. (min.): 2.25

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.49 (d, 2H), 7.27 (d, 2H), 7.12 – 7.01 (m, 2H), 6.84 (d, 1H), 6.25 (d, 1H), 4.44 (d, 2H), 4.33 (t, 2H), 3.61 (s, 2H), 3.08 (s, 3H), 3.07 – 3.03 (m, 2H), 2.98 (s, 3H), 2.57 – 2.45 (m, 2H), 2.32 – 2.23 (m, 2H), 2.10 (s, 3H), 2.08 – 1.98 (m, 1H), 1.97 – 1.86 (m, 1H).

EXAMPLE 50

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (37% yield, 94% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 1-(4-(aminomethyl)phenyl)pyrrolidin-2-one following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.43 (d, 2H), 7.38 (d, 2H), 7.16 (d, 2H), 6.55 (d, 1H), 6.48 – 6.40 (m, 2H), 6.18 (d, 1H), 5.99 (t, 1H), 4.80 (d, 2H), 4.57 (d, 2H), 4.44 (d, 2H), 4.30 (t, 2H), 3.57 (s, 2H), 3.11 (br s, 3H), 3.01 – 2.94 (m, 5H), 2.52 – 2.40 (m, 2H), 2.31 – 2.22 (m, 2H), 2.09 – 1.88 (m, 2H), 1.68 (s, 3H).

EXAMPLE 51

***N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (60% yield, 99% purity) from cyclopropanecarboxylic acid and *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 504 $[M+1]^+$

LC (1) r.t. (min.): 1.40

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.28 (d, 2H), 7.20 (s, 1H), 6.53 (d, 1H), 6.12 (d, 1H), 6.05 (t, 1H), 4.51 (d, 2H), 4.31 (t, 2H), 3.13 – 3.04 (m, 5H), 2.92 (s, 3H), 2.49 (s, 2H), 2.37 – 2.27 (m, 2H), 2.23 – 2.14 (m, 5H), 2.07 (s, 6H), 2.01 – 1.81 (m, 2H).

EXAMPLE 52

***N*-((1-acetylindolin-5-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (26% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 1-(5-(aminomethyl)indolin-1-yl)ethan-1-one following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 542 $[M+1]^+$

LC (1) r.t. (min.): 2.47

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.67 (s, 1H), 7.44 (d, 4H), 7.38 (d, 2H), 7.25 (d, 2H), 6.56 (d, 1H), 6.23 (t, 1H), 5.95 (d, 1H), 4.49 (d, 2H), 4.25 (t, 2H), 3.68 (s, 2H), 3.12 (s, 3H), 3.05 (t, 2H), 3.01 (s, 3H), 2.21 (d, 2H), 2.14 (s, 3H), 1.85 (q, 4H), 1.65 (br t, 2H), 1.56 (br d, 2H).

EXAMPLE 53

***N*-(3-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (44% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(3-aminophenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 556 $[M+1]^+$

LC (1) r.t. (min.): 1.64

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 8.00 (s, 1H), 7.46 (d, 2H), 7.41 (d, 2H), 7.36 (d, 2H), 7.24 (d, 2H), 6.62 (d, 1H), 6.35 (t, 1H), 6.19 (d, 1H), 4.93 (t, 2H), 4.79 (dd, 2H), 4.49 (d, 2H), 4.25 (t, 2H), 3.86 (m, 1H), 3.55 (s, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.93 (t, 2H), 2.45 (q, 2H), 2.26 (t, 2H), 2.10 – 1.86 (m, 2H).

EXAMPLE 54

***N*-(4-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (40% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-aminophenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 577 $[M+1]^+$

LC (1) r.t. (min.): 1.87

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.40 (s, 1H), 9.09 (s, 1H), 8.74 (s, 1H), 8.47 – 8.42 (m, 1H), 8.29 (d, 1H), 7.69 (d, 2H), 7.55 (t, 1H), 7.43 (d, 2H), 7.35 (d, 2H), 7.28 (d, 2H), 6.90 (s, 1H), 6.21 (s, 1H), 4.35 (d, 2H), 4.17 (br s, 2H), 3.56 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.87 – 2.83 (m, 2H), 2.46 – 2.34 (m, 2H), 2.19 – 2.15 (m, 2H), 1.98 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 55

***N*,2'-bis(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (65% yield, 95% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and 4-(aminomethyl)-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 540 $[M+1]^+$

LC (1) r.t. (min.): 1.95

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.43 (t, 1H), 7.57 (d, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.28 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.34 (d, 2H), 4.15 (t, 2H), 3.79 (t, 2H), 3.55 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.84 (t, 2H), 2.49 – 2.33 (m, 4H), 2.17 (s, 2H), 2.04 (m, 2H), 1.99 – 1.80 (m, 2H).

EXAMPLE 56

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (81 mg, 0.12 mmol) was dissolved in MeOH (3 mL) and 10% Pd/C (77 mg, 0.36 mmol) was added under a N_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (15 PSI) at 25°C for 6 h. After reaction completion, the mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (2, B from 35.00% to 65.00% in 8.00 min) to give the title compound (16 mg, 19% yield, 98% purity) as a white solid.

LRMS (m/z): 556 $[M+1]^+$

LC (1) r.t. (min.): 1.85

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 8.66 (s, 1H), 7.59 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.33 (d, 2H), 6.61 (d, 1H), 6.24 (t, 1H), 6.20 (d, 1H), 5.13 (dd, 1H), 4.83 (q, 1H), 4.70 (q, 1H), 4.53 (d, 2H), 4.29 (t, 2H), 3.57 (s, 2H), 3.13 – 3.05 (m, 4H), 3.02 – 2.93 (m, 5H), 2.79 – 2.70 (m, 1H), 2.46 (q, 2H), 2.32 – 2.23 (m, 2H), 2.12 – 1.93 (m, 2H).

EXAMPLE 57

***Tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate**

Obtained as a white solid (89% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and tert-butyl (4-(aminomethyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 515 $[M+1]^+$

LC (1) r.t. (min.): 2.10

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.47 (d, 2H), 7.36 (d, 2H), 7.33 – 7.26 (m, 4H), 7.18 (s, 1H), 6.58 (d, 1H), 6.20 (d, 1H), 6.08 (t, 1H), 4.52 (d, 2H), 4.36 (d, 1H), 4.29 (t, 2H), 3.53 (s, 2H), 2.96 (t, 2H), 2.53 – 2.39 (m, 2H), 2.32 – 2.23 (m, 2H), 2.18 (s, 3H), 2.09 – 1.91 (m, 3H), 1.82 (s, 1H), 1.01 (d, 3H), 0.80 (d, 3H).

EXAMPLE 58

***N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (92% yield, 97% purity) from *tert*-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 472 $[M+1]^+$

LC (1) r.t. (min.): 1.35

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.43 (d, 2H), 7.38 (d, 2H), 7.15 – 7.11 (m, 2H), 6.69 – 6.64 (m, 2H), 6.55 (d, 1H), 6.18 (d, 1H), 5.99 (t, 1H), 4.44 (d, 2H), 4.29 (t, 2H), 3.66 (br s, 2H), 3.55 (s, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.96 (t, 2H), 2.45 (q, 2H), 2.31 – 2.21 (m, 2H), 2.08 – 1.88 (m, 2H).

EXAMPLE 59

***N*-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-*2'H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

N-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (20 mg, 42.4 µmol) was dissolved in DCM (1 mL) and DIEA was added (22 µL, 126 µmol). The mixture was cooled in an ice bath, cyclopropanecarbonyl chloride (4 µL, 44 µmol) was added, and the reaction mixture was stirred at 25°C for 1 h. The mixture was diluted with 4% aqueous $NaHCO_3$, extracted with DCM and the organic layer was washed with a saturated aqueous solution of K_2CO_3, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the title compound (96% yield, 97% purity) as a white solid.

LRMS (m/z): 540 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.15 (s, 1H), 8.42 (t, 1H), 7.51 (d, 2H), 7.45 (d, 2H), 7.37 – 7.33 (m, 2H), 7.20 (d, 2H), 6.89 (d, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 4.16 (t, 2H), 3.56 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.85 (t, 2H), 2.44 – 2.37 (m, 2H), 2.20 – 2.14 (m, 2H), 2.02 – 1.94 (m, 1H), 1.91 – 1.84 (m, 1H), 1.78 – 1.73 (m, 1H), 0.80 – 0.74 (m, 4H).

EXAMPLE 60

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-isopropylbenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (40% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 4-isopropylbenzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 618 $[M+1]^+$

LC (1) r.t. (min.): 2.99

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.88 (s, 1H), 7.79 (d, 2H), 7.59 (d, 2H), 7.40 (d, 2H), 7.35 (d, 2H), 7.31 (d, 4H), 6.58 (d, 1H), 6.18 (d, 1H), 6.14 (t, 1H), 4.52 (d, 2H), 4.27 (t, 2H), 3.54 (s, 2H), 3.09 (br s, 3H), 3.00 – 2.91 (m, 6H), 2.44 (q, 2H), 2.25 (t, 2H), 2.07 – 1.97 (m, 1H), 1.97 – 1.84 (m, 1H), 1.26 (d, 6H).

EXAMPLE 61

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(isonicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (48% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and isonicotinic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 577 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.46 (s, 1H), 8.77 (dd, 2H), 8.44 (t, 1H), 7.85 (dd, 2H), 7.70 (d, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.29 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 2.96 (s, 3H), 2.91 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.12 (m, 2H), 2.03 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H).

EXAMPLE 62

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-pivalamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white foam (89% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and pivaloyl chloride following the synthetic procedure as described for Example 59.

LRMS (m/z): 556 $[M+1]^+$

LC (1) r.t. (min.): 2.30

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.50 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.34 – 7.28 (m, 3H), 6.57 (d, 1H), 6.19 (d, 1H), 6.07 (t, 1H), 4.52 (d, 2H), 4.29 (t, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 3.03 – 2.92 (m, 5H), 2.50 – 2.40 (m, 2H), 2.32 – 2.22 (m, 2H), 2.06 – 1.89 (m, 2H), 1.32 (s, 9H).

EXAMPLE 63

***N*-(4-(cyclobutanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (94% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and cyclobutanecarbonyl chloride following the synthetic procedure as described for Example 59.

LRMS (m/z): 554 $[M+1]^+$

LC (1) r.t. (min.): 2.18

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.50 (d, 2H), 7.44 (d, 2H), 7.38 (d, 2H), 7.29 (d, 2H), 7.05 (s, 1H), 6.58 (d, 1H), 6.19 (d, 1H), 6.08 (t, 1H), 4.52 (d, 2H), 4.28 (t, 2H), 3.56 (s, 2H), 3.20 – 3.07 (m, 4H), 3.03 – 2.91 (m, 5H), 2.49 – 1.88 (m, 12H).

EXAMPLE 64

***N*-(4-Benzamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (58% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and benzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 576 $[M+1]^+$

LC (1) r.t. (min.): 2.23

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.22 (s, 1H), 8.45 (t, 1H), 7.97 – 7.90 (m, 2H), 7.70 (d, 2H), 7.62 – 7.54 (m, 1H), 7.54 – 7.47 (m, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.26 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.35 (d, 2H), 4.17 (t, 2H), 3.55 (s, 2H), 2.96 (s, 3H), 2.90 (s, 3H), 2.84 (t, 2H), 2.46 – 2.34 (m, 2H), 2.23 – 2.12 (m, 2H), 2.02 – 1.92 (m, 1H), 1.92 – 1.83 (m, 1H).

EXAMPLE 65

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (53% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and oxetane-3-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 556 $[M+1]^+$

LC (1) r.t. (min.): 1.64

^{1}H NMR (CDCl3, 400 MHz) δ 8.00 (s, 1H), 7.46 (d, 2H), 7.41 (d, 2H), 7.36 (d, 2H), 7.24 (d, 2H), 6.62 (d, 1H), 6.35 (t, 1H), 6.19 (d, 1H), 4.93 (t, 2H), 4.79 (dd, 2H), 4.49 (d, 2H), 4.25 (t, 2H), 3.86 (m, 1H), 3.55 (s, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.93 (t, 2H), 2.45 (q, 2H), 2.26 (t, 2H), 2.10 – 1.86 (m, 2H).

EXAMPLE 66

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(nicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (51% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and nicotinic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 577 $[M+1]^+$

LC (1) r.t. (min.): 1.87

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.40 (s, 1H), 9.09 (s, 1H), 8.74 (s, 1H), 8.47 – 8.42 (m, 1H), 8.29 (d, 1H), 7.69 (d, 2H), 7.55 (t, 1H), 7.43 (d, 2H), 7.35 (d, 2H), 7.28 (d, 2H), 6.90 (s, 1H), 6.21 (s, 1H), 4.35 (d, 2H), 4.17 (br s, 2H), 3.56 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.87 – 2.83 (m, 2H), 2.46 – 2.34 (m, 2H), 2.19 – 2.15 (m, 2H), 1.98 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 67

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-2-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (86% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and oxetane-2-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 556 $[M+1]^+$

LC (1) r.t. (min.): 1.85

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 8.66 (s, 1H), 7.59 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.33 (d, 2H), 6.61 (d, 1H), 6.24 (t, 1H), 6.20 (d, 1H), 5.13 (dd, 1H), 4.83 (q, 1H), 4.70 (q, 1H), 4.53 (d, 2H), 4.29 (t, 2H), 3.57 (s, 2H), 3.13 – 3.05 (m, 4H), 3.02 – 2.93 (m, 5H), 2.79 – 2.70 (m, 1H), 2.46 (q, 2H), 2.32 – 2.23 (m, 2H), 2.12 – 1.93 (m, 2H).

EXAMPLE 68

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(tetrahydro-2H-pyran-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

N-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (40 mg, 84.8 μmol) and 4-(tetrahydro-2*H*-pyran-4-yl)benzoic acid (35 mg, 0.17 mmol) were dissolved in DMF (0.8 mL), and BOP reagent (113 mg, 254 μmol,) and TEA (70 μL, 0.51 mmol) were added at 0°C. The mixture was stirred at 25°C for 12 h. After reaction completion, the mixture was purified directly by prep-HPLC (2, B from 40.00% to 70.00% in 8.00 min) to give the title compound (28 mg, 24% yield, 96% purity) as a white solid.

LRMS (m/z): 660 $[M+1]^+$

LC (1) r.t. (min.): 2.56

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.44 (t, 1H), 7.88 (d, 2H), 7.69 (d, 2H), 7.44 (d, 2H), 7.40 (d, 2H), 7.34 (d, 2H), 7.26 (d, 2H), 6.89 (d, 1H), 6.21 (d, 1H), 4.35 (d, 2H), 4.16 (t, 2H), 3.99 – 3.92 (m, 2H), 3.56 (s, 2H), 3.49 – 3.38 (m, 2H), 2.96 (s, 3H), 2.90 (s, 3H), 2.87 – 2.82 (m, 3H), 2.46 – 2.34 (m, 2H), 2.21 – 2.12 (m, 2H), 2.02 – 1.93 (m, 1H), 1.92 – 1.82 (m, 1H), 1.74 – 1.65 (m, 4H).

EXAMPLE 69

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

N-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (40 mg, 65.1 μmol) was dissolved in dry pyridine (0.5 mL) and *N*,*N*-dimethylcarbamoyl chloride (7.2 μL, 78.2 μmol) was added. The resulting red reaction mixture was stirred at r.t. for 7 h. After reaction completion, the mixture was diluted with 4% aqueous NaHCO3, extracted with EtOAc, and the organic phase was washed with 1M aqueous NH_4Cl. The aqueous phases were combined and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by reverse phase chromatography using formic acid buffer to give the title compound (18 mg, 51% yield, 99% purity) as a white solid after freeze drying.

LRMS (m/z): 543 $[M+1]^+$

LC (1) r.t. (min.): 1.83

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.43 (d, 2H), 7.39 – 7.33 (m, 4H), 7.26 (d, 2H), 6.57 (d, 1H), 6.31 (s, 1H), 6.19 (d, 1H), 6.06 (t, 1H), 4.50 (d, 2H), 4.29 (t, 2H), 3.55 (s, 2H), 3.11 (s, 3H), 3.03 (s, 6H), 3.01 – 2.93 (m, 5H), 2.50 – 2.39 (m, 2H), 2.31 – 2.22 (m, 2H), 2.07 – 1.91 (m, 2H).

EXAMPLE 70

***N*-(4-(bicyclo[1.1.1]pentane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (81% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and bicyclo[1.1.1]pentane-1-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 566 $[M+1]^+$

LC (1) r.t. (min.): 2.27

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.54 – 7.42 (m, 4H), 7.39 (d, 2H), 7.29 (d, 2H), 7.15 (s, 1H), 6.59 (d, 1H), 6.22 (d, 1H), 6.11 (t, 1H), 4.52 (d, 2H), 4.30 (t, 2H), 3.57 (s, 2H), 3.10 (s, 3H), 3.07 – 2.93 (m, 5H), 2.54 (s, 1H), 2.33 – 2.21 (m, 2H), 2.15 (s, 6H), 2.11 – 1.90 (m, 4H).

EXAMPLE 71

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(pyridin-2-ylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

N-[(4-aminophenyl)methyl]-2-[[4-(dimethylcarbamoyl) phenyl]methyl] spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxamide (80 mg, 0.17 mmol) and 2-bromopyridine (19 μL, 0.20 mmol) were dissolved in 2-methyl-2-butanol (1 mL), and Cs_2CO_3 (111 mg, 0.34 mmol) and BrettPhos Pd G3 (16 mg, 17 μmol) were added under argon. The mixture was stirred at 90°C for 12 h. After reaction completion, the mixture was filtered and the filtrate was purified by prep-HPLC (2, B from 40.00% to 70.00% in 8.00 min) to give the title compound (25 mg, 27% yield, 98% purity) as a white solid.

LRMS (m/z): 549 $[M+1]^+$

LC (1) r.t. (min.): 1.76

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.93 (s, 1H), 8.37 (t, 1H), 8.11 (d, 1H), 7.58 (d, 2H), 7.54 – 7.49 (m, 1H), 7.44 (d, 2H), 7.34 (d, 2H), 7.18 (d, 2H), 6.88 (d, 1H), 6.79 (d, 1H), 6.73 – 6.65 (m, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.17 (t, 2H), 3.56

(s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.10 (m, 2H), 2.05 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H).

EXAMPLE 72

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (49% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 635 $[M+1]^+$

LC (1) r.t. (min.): 1.58

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.70 (s, 1H), 8.41 (t, 1H), 8.15 (s, 1H), 7.62 (d, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.23 (d, 2H), 6.89 (d, 1H), 6.20 (d, 1H), 4.34 (d, 2H), 4.16 (t, 2H), 4.11 (t, 2H), 3.82 (s, 2H), 3.56 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.84 (q, 4H), 2.43 – 2.34 (m, 5H), 2.22 – 2.12 (m, 2H), 2.03 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H)

EXAMPLE 73

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-6-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

N-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (50 mg, 106 μmo) and 1-methylindoline-6-carboxylic acid (47 mg, 265 μmol) were dissolved in THF (1 mL) and DIEA (55 μL, 0.32 mmol) and bromo(tripyrrolidin-1-yl)phosphonium hexafluorophosphate (74 mg, 0.16 mmol) were added. The mixture was stirred at 20°C for 12 h, and, after reaction completion, the mixture was filtered and purified by prep-HPLC (2, B from 31.00% to 56.00% in 8.00 min) to give the title compound (5.3 mg, 7% yield, 97% purity) as a white solid.

LRMS (m/z): 631 $[M+1]^+$

LC (1) r.t. (min.): 2.47

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.75 (s, 1H), 7.60 (d, 2H), 7.41 (d, 2H), 7.36 (d, 2H), 7.32 (d, 2H), 7.11 (d, 1H), 7.07 (d, 1H), 6.93 (s, 1H), 6.57 (d, 1H), 6.19 (d, 1H), 6.11 – 6.02 (m, 1H), 4.53 (d, 2H), 4.28 (t, 2H), 3.55 (s, 2H), 3.37 (t, 2H), 3.09

(s, 3H), 3.04 – 2.90 (m, 7H), 2.80 (s, 3H), 2.51 – 2.36 (m, 2H), 2.32 – 2.20 (m, 2H), 2.08 – 1.97 (m, 1H), 1.97 – 1.86 (m, 1H).

EXAMPLE 74

***N*-(4-(3,3-dimethylbutanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (41% yield, 100% purity) *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 3,3-dimethylbutanoyl chloride following the synthetic procedure as described for Intermediate 27a.

LRMS (m/z): 570 $[M+1]^+$

LC (1) r.t. (min.): 2.56

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.72 (s, 1H), 8.39 (t, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 7.34 (d, 2H), 7.19 (d, 2H), 6.87 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.15 (t, 2H), 3.55 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.84 (t, 2H), 2.39 (q, 2H), 2.23 – 2.09 (m, 4H), 2.02 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H), 1.00 (s, 9H).

EXAMPLE 75

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(picolinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (45% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and 3,3-dimethylbutanoyl chloride and picolinic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 577 $[M+1]^+$

LC (1) r.t. (min.): 2.37

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.58 (s, 1H), 8.73 (d, 1H), 8.44 (t, 1H), 8.14 (d, 1H), 8.06 (td, 1H), 7.83 (d, 2H), 7.66 (ddd, 1H), 7.44 (d, 2H), 7.34 (d, 2H), 7.28 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 2.96 (br s, 3H), 2.91 (br s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.12 (m, 2H), 2.03 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H).

EXAMPLE 76

***N*-((5-benzamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (48% yield, 98% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and benzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 577 $[M+1]^+$

LC (1) r.t. (min.): 2.16

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 8.68 (d, 1H), 8.18 (dd, 1H), 7.91 – 7.85 (m, 3H), 7.57 (t, 1H), 7.50 (t, 2H), 7.44 – 7.31 (m, 5H), 6.89 (t, 1H), 6.70 (d, 1H), 6.21 (d, 1H), 4.65 (d, 2H), 4.27 (t, 2H), 3.54 (s, 2H), 3.09 (s, 3H), 3.03 – 2.88 (m, 5H), 2.52 – 2.36 (m, 2H), 2.31 – 2.21 (m, 2H), 2.09 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H).

EXAMPLE 77

***N*-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (76% yield, 97% purity) from *tert*-butyl (3-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)bicyclo[1.1.1]pentan-1-yl)carbamate (Intermediate 43) following the synthetic procedure as described for Intermediate 1f.

LRMS (m/z): 462 $[M+1]^+$

LC (1) r.t. (min.): 1.09

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.42 (d, 2H), 7.38 (d, 2H), 6.56 (d, 1H), 6.20 (d, 1H), 5.72 (t, 1H), 4.25 (t, 2H), 3.56 (s, 2H), 3.51 (d, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.95 (t, 2H), 2.52 – 2.40 (m, 2H), 2.33 – 2.23 (m, 2H), 2.09 – 1.88 (m, 2H), 1.69 – 1.53 (m, 8H).

EXAMPLE 78

***N*-((3-acetamidobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (quantitative yield, 100% purity) *N*-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and acetyl chloride following the synthetic procedure as described for Intermediate 27a.

LRMS (m/z): 504 $[M+1]^+$

LC (1) r.t. (min.): 1.47

^{1}H NMR (CDCl3, 400 MHz): δ (ppm) 7.42 (d, 2H), 7.37 (d, 2H), 6.57 (d, 1H), 6.20 (d, 1H), 5.84 – 5.74 (m, 2H), 4.24 (t, 2H), 3.56 (s, 2H), 3.54 (d, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.95 (t, 2H), 2.50 – 2.41 (m, 2H), 2.32 – 2.24 (m, 2H), 2.07 – 1.99 (m, 8H), 1.93 (s, 3H).

EXAMPLE 79

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (26% yield, 92% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 532 $[M+1]^+$

LC (1) r.t. (min.): 2.36

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.45 (t, 1H), 7.49 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.19 (d, 2H), 6.76 (s, 1H), 4.30 (d, 2H), 4.14 (t, 2H), 3.61 (s, 2H), 2.96 (s, 3H), 2.91 (s, 3H), 2.81 (t, 2H), 2.44 – 2.34 (m, 4H), 2.05 – 1.95 (m, 4H), 1.92 – 1.81 (m, 1H).

EXAMPLE 80

***N*-(4-acetamidobenzyl)-2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide**

Obtained as a white solid (17% yield, 81% purity) from 2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 502 $[M+1]^+$

LC (1) r.t. (min.): 1.59

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.50 (s, 1H), 7.64 – 7.51 (m, 2H), 7.53 – 7.37 (m, 2H), 7.48 (d, 2H), 7.17 (d, 2H), 6.89 (s, 1H), 6.16 (s, 1H), 4.69 (s, 1H), 4.47 – 3.96 (m, 5H), 3.07 – 2.83 (m, 8H), 2.00 (s, 3H), 1.70 (s, 6H).

EXAMPLE 81

***N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

To a solution of 3,5-difluoro-4-formyl-*N*,*N*-dimethyl-benzamide (90 mg, 0.42 mmol, Intermediate 46) and *N*-[(5-acetamido2-pyridyl)methyl]spiro[3,4-dihydro-2*H*-pyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxamide (50 mg, 0.14 mmol, Intermediate 47) in DMF (1 mL) and AcOH (0.2 mL) was added trimethoxymethane (15 mg, 0.14 mmol). The mixture was stirred at 20°C for 30 min, $NaBH(OAc)_3$ (60 mg, 0.28 mmol) was added and the mixture was stirred again at 20°C for 11.5 h. After the reaction completion, the mixture was purified directly by prep-HPLC (2, B from 20.00% to 50.00% in 8.00 min, Flow rate: 50 mL/min) to give the title compound (25 mg, 33% yield, 100% purity) as a white solid.

LRMS (m/z): 551 $[M+1]^+$

LC (1) r.t. (min.): 1.94

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.60 (d, 1H), 8.17 (d, 1H), 7.73 – 7.57 (m, 1H), 7.35 (d, 1H), 7.00 – 6.93 (m, 3H), 6.73 (d, 1H), 6.22 (d, 1H), 4.66 (d, 2H), 4.41 (m, 2H), 3.58 (s, 2H), 3.12 – 3.07 (m, 5H), 2.99 (s, 3H), 2.51 (m, 2H), 2.33 – 2.25 (m, 2H), 2.23 (s, 3H), 2.11 – 1.86 (m, 2H).

EXAMPLE 82

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-methylbenzyl)-3',4'-dihydro-2'*NaB*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

N-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (52 mg, 0.15 mmol, Intermediate 1f) and 4-formyl-*N*,*N*,3-trimethyl-benzamide (85 mg, 0.44 mmol, Intermediate 48) were dissolved in DMF (3 mL) and TEA (37 mg, 0.37 mmol) and AcOH (27 mg, 0.44 mmol) were added. After stirring at 20°C for 1 h, $NaBH(OAc)_3$ (157 mg, 0.74 mmol) was added and the mixture was stirred at 100°C for 3 h. After the reaction completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue that was purified by prep-HPLC (2, B from 25.00% to 55.00% in 8.00min, Flow rate: 50.00 mL/min) to give the title compound (26 mg, 34% yield, 100% purity) as a white solid.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 2.11

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.39 (d, 1H), 7.32 – 7.26 (m, 3H), 7.22 (s, 1H), 7.18 (d, 1H), 6.59 (d, 1H), 6.20 (d, 1H), 6.11 (s, 1H), 4.52 (d, 2H),

4.30 (t, 2H), 3.55 (s, 2H), 3.10 (s, 3H), 2.99 (s, 3H), 2.94 (t, 2H), 2.53 – 2.42 (m, 2H), 2.41 (s, 3H), 2.32 – 2.21 (m, 2H), 2.17 (s, 3H), 2.09 – 1.97 (m, 1H), 1.98 – 1.86 (m, 1H).

EXAMPLE 83

***N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1H-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (19% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide acid (Intermediate 1f) and 4-(5-methyl-1*H*-1,2,4-triazol-1-yl)benzaldehyde (Intermediate 49) following the synthetic procedure as described for Example 82.

LRMS (m/z): 524 $[M+1]^+$

LC (1) r.t. (min.): 1.74

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.40 (t, 1H), 8.01 (s, 1H), 7.61 – 7.47 (m, 6H), 7.21 (d, 2H), 6.89 (d, 1H), 6.22 (d, 1H), 4.32 (d, 2H), 4.19 (t, 2H), 3.62 (s, 2H), 2.89 (t, 2H), 2.47 (s, 3H), 2.46 – 2.36 (m, 2H), 2.24 – 2.14 (m, 2H), 2.01 (s, 3H), 2.00 – 1.82 (m, 2H).

EXAMPLE 84

***N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (36% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide acid (Intermediate 1f) and 4-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzaldehyde (Intermediate 50) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 524 $[M+1]^+$

LC (1) r.t. (min.): 1.68

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 (s, 1H), 7.65 (d, 2H), 7.55 (d, 2H), 7.47 (d, 2H), 7.30 (d, 2H), 7.18 – 7.15 (m, 1H), 6.59 (d, 1H), 6.21 (d, 1H), 6.09 (d, 1H), 4.53 (d, 2H), 4.31 (t, 2H), 4.01 (s, 3H), 3.62 (s, 2H), 3.00 (t, 2H), 2.54 – 2.41 (m, 2H), 2.35 – 2.23 (m, 2H), 2.18 (s, 3H), 2.08 – 1.89 (m, 2H).

EXAMPLE 85

***N*-(4-acetamidobenzyl)-2'-(2-chloro-4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (39% yield, 99% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide acid (Intermediate 1f) and 3-chloro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 51) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 548 $[M+1]^+$

LC (1) r.t. (min.): 2.34

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.67 (d, 1H), 7.46 (d, 2H), 7.42 (s, 1H), 7.30 (m, 3H), 7.18 (s, 1H), 6.58 (d, 1H), 6.21 (d, 1H), 6.08 (t, 1H), 4.53 (d, 2H), 4.37 (t, 2H), 3.71 (s, 2H), 3.11 (s, 3H), 3.05 – 2.95 (m, 5H), 2.54 – 2.42 (m, 2H), 2.33 – 2.24 (m, 2H), 2.18 (s, 3H), 2.08 – 1.88 (m, 2H).

EXAMPLE 86

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (43% yield, 93% purity) from *N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 52d) and 3,5-difluoro-4-formyl-*N*,*N*-dimethylbenzamide (Intermediate 47) following the synthetic procedure as described for Example 81.

LRMS (m/z): 550 $[M+1]^+$

LC (1) r.t. (min.): 2.11

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.70 (d, 2H), 7.34 (d, 2H), 6.96 (d, 2H), 6.66 (d, 1H), 6.43 (t, 1H), 6.40 – 6.32 (m, 1H), 6.21 (d, 1H), 4.58 (d, 2H), 4.41 (t, 2H), 3.58 (broad s, 2H), 3.13 – 3.02 (m, 5H), 2.99 (s, 3H), 2.98 (s, 3H), 2.51 (q, 2H), 2.28 (broad t, 2H), 2.09 – 1.87 (m, 2H).

EXAMPLE 87

***N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1*H*-pyrazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (45% yield, 100% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide acid (Intermediate 1f) and 4-(5-methyl-1*H*-pyrazol-1-yl)benzaldehyde (Intermediate 53) following the synthetic procedure as described for Example 82.

LRMS (m/z): 523 $[M+1]^+$

LC (1) r.t. (min.): 2.23

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.40 (t, 1H), 7.56 – 7.43 (m, 7H), 7.21 (d, 2H), 6.89 (d, 1H), 6.29 – 6.25 (m, 1H), 6.22 (d, 1H), 4.32 (d, 2H), 4.19 (t, 2H), 3.60 (s, 2H), 2.89 (t, 2H), 2.47 – 2.37 (m, 2H), 2.33 (s, 3H), 2.24 – 2.14 (m, 2H), 2.02 (s, 3H), 2.00 – 1.82 (m, 2H).

EXAMPLE 88

2'-((3-Chloro-5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Well A of a COware apparatus was charged with 2'-((5-bromo-3-chloropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 54, 37 mg, 0.05 mmol), *N*-methylmethanamine hydrochloride (16 mg, 0.20 mmol), Xantphos (3.2 mg, 0.005 mmol), Na_2CO_3 (14.6 mg, 0.14 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) and 1,4-dioxane (1 mL). Well B was charged with toluene (1 mL), formic acid (10.4 μL, 0.28 mmol) and MsCl (21.3 μL, 0.28 mmol). The reaction mixture in well A was degassed by sparging with N_2 for 5 minutes before triethylamine (76.6 μL, 0.55 mmol) was added dropwise to well B. The reaction was heated to 100 °C for 2 h. The reaction mixture was filtered under vacuum and the filtrated concentrated under vacuum. The crude was purified by prep-HPLC (5c followed by 5a) to give the title compound (4.8 mg,15% yield 100% purity) as a white powder.

LRMS (m/z): 578, 580 $[M+1]^+$

LC (4d) r.t. (min.): 1.85

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.55 (d, 1H), 8.40 (t, 1H), 8.23 (s, 1H), 8.01 (d, 1H), 7.43 – 7.37 (m, 2H), 7.19 – 7.13 (m, 2H), 6.89 (d, 1H), 6.22 (d, 1H), 4.32 (d, 2H), 4.27 (t, 2H), 3.70 (s, 2H), 3.03 – 2.90 (m, 14H), 2.49 – 2.39 (m, 2H), 2.24 – 2.15 (m, 2H), 2.02 – 1.94 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 89

***N*-(4-(1*H*-imidazol-2-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 56b, 29 mg, 0.04 mmol) was dissolved in DCM (1 mL) and TFA

(68 μL, 0.88 mmol) was added. The mixture was stirred at r.t. for 72 h and then concentrated in vacuo. A solution of ammonia in MeOH (7M, 2.00 mL) was added and the solution was stirred for 30 min and then concentrated in vacuo. The residue was purified by reverse phase chromatography to give the title compound (6.9 mg, 30% yield, 100% purity) as a white solid.

LRMS (m/z): 523 $[M+1]^+$

LC (3) r.t. (min.): 1.05

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.69 (d, 2H), 7.40 (d, 2H), 7.36 (d, 2H), 7.22 (d, 2H), 7.09 (s, 2H), 6.80 – 6.70 (m, 2H), 6.21 (d, 1H), 4.51 (d, 2H), 4.24 (t, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.92 (t, 2H), 2.51 – 2.43 (m, 2H), 2.32 – 2.24 (m, 2H), 2.10 – 1.90 (m, 2H).

EXAMPLE 90

***N*-(4-(4*H*-1,2,4-triazol-3-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (64% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-((2-(trimethylsilyl)ethoxy)methyl)-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 57b) following the synthetic procedure as described for Example 89.

LRMS (m/z): 524 $[M+1]^+$

LC (3) r.t. (min.): 1.18

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.17 (s, 1H), 8.00 – 7.95 (m, 2H), 7.45 – 7.34 (m, 6H), 6.65 (d, 1H), 6.33 (t, 1H), 6.21 (d, 1H), 4.61 (d, 2H), 4.28 (t, 2H), 3.57 (s, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.95 (t, 2H), 2.51 – 2.43 (m, 2H), 2.30 – 2.24 (m, 2H), 2.05 – 1.92 (m, 2H).

EXAMPLE 91

2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((1-(methylcarbamoyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

2-[[4-(Dimethylcarbamoyl)phenyl]methyl]-*N*-(4-piperidylmethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxamide (77.5 mg, 0.16 mmol) was dissolved in DCM (2 mL) and *N*-methylimidazole-1-carboxamide (22 mg, 0.18 mmol) and TEA (25 μL, 0.18 mmol) were added to the initial solution and the mixture was allowed to stir at r.t. Two further additions of *N*-methylimidazole-1-carboxamide (9 mg each, 0.14

mmol) and TEA (25 μL, 0.18 mmol) were performed to achieve reaction completion. Then, the mixture was concentrated under reduced pressure and the residue was purified by reverse phase chromatography to give the title compound (63 mg, 73% yield, 100% purity).

LRMS (m/z): 521 $[M+1]^+$

LC (1) r.t. (min.): 1.57

^{1}H NMR ($CDCl_3$, 400 MHz,): δ (ppm) 7.40 (AB quartet, 4H), 6.57 (d, 1H), 6.20 (d, 1H), 5.93 (s, 1H), 5.12 (broad t, 1H), 4.44 – 4.35 (m, 1H), 4.25 (t, 2H), 3.95 (broad d, 2H), 3.56 (s, 2H), 3.27 (t, 2H), 3.11 (broad s, 3H), 2.99 (broad s, 3H), 2.95 (t, 2H), 2.80 (d, 3H), 2.75 (broad d, 2H), 2.46 (broad q, 2H), 2.27 (broad t, 2H), 2.10 – 1.99 (m, 3H), 1.97 (m, 1H), 1.75 (broad d, 2H).

EXAMPLE 92

***N*-((4-acetamidophenyl)methyl-d2)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (52% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) and 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(piperidin-4-ylmethyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 516 $[M+1]^+$

LC (1) r.t. (min.): 2.11

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.39 (s, 1H), 7.50 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.21 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.16 (t, 2H), 3.56 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.85 (t, 2H), 2.47 – 2.34 (m, 2H), 2.23 – 2.12 (m, 2H), 2.01 (s, 3H), 2.01 – 1.92 (m, 1H), 1.93 – 1.82 (m, 1H)

EXAMPLE 93

***N*-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-*2'H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (37% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c) and 4-(aminomethyl)benzamide following the synthetic procedure as described for Intermediate 54c.

LRMS (m/z): 500 $[M+1]^+$

LC (1) r.t. (min.): 1.95

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.51 (t, J = 6.1 Hz, 1H), 7.92 (br. s, 1H), 7.86 – 7.79 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 – 7.33 (m, 4H), 7.30 (br. s, 1H), 6.92 (d, J = 3.9 Hz, 1H), 6.23 (d, J = 4.0 Hz, 1H), 4.43 (d, J = 6.1 Hz, 2H), 4.17 (t, J = 5.8 Hz, 2H), 3.57 (s, 2H), 3.04 – 2.89 (m, 6H), 2.89 – 2.83 (m, 2H), 2.47 – 2.37 (m, 2H), 2.25 – 2.13 (m, 2H), 2.05 – 1.82 (m, 2H).

EXAMPLE 94

***N*-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-*2'H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

To a solution of 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 23c, 100 mg, 0.27 mmol) and NMI (98 µL, 1.23 mmol) in CAN anhydrous (0.60 mL) was added isopropyl (4-(aminomethyl)phenyl)carbamate hydrochloride (Intermediate 60, 77 mg, 0.31 mmol). A solution of bis(dimethylamino)methylidenechloranium;hexafluorophosphate (92 mg, 0.33 mmol) in ACN-anhydrous (0.60 mL) was then added dropwise at room temperature. The mixture was stirred at r.t. for 3h. The mixture was diluted with water and extracted with EtOAc. Organics were combined and evaporated to give a crude that was purified by reverse phase chromatography to give the title compound (95 mg, 0.17 mmol, 63% yield, 98% purity) as a cream solid.

LRMS (m/z): 558 $[M+1]^+$

LC (1) r.t. (min.): 2.39

^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.47 (s, 1H), 8.39 (s, 1H), 7.45 (d, 2H), 7.41 – 7.33 (m, 4H), 7.19 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.88 (h, 1H), 4.31 (d, 2H), 4.24 – 4.11 (m, 2H), 3.56 (s, 2H), 3.03 – 2.89 (m, 6H), 2.89 – 2.80 (m, 2H), 2.47 – 2.35 (m, 2H), 2.25 – 2.13 (m, 2H), 2.01 – 1.84 (m, 2H), 1.26 – 1.23 (m, 6H).

EXAMPLE 95

2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (43% yield, 100% purity) from 3-(6-(aminomethyl)pyridin-3-yl)-1,1-dimethylurea (Intermediate 61) and 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 62) following the synthetic procedure as described for Intermediate 1e

LRMS (m/z): 603 $[M+1]^+$

LC (1) r.t. (min.): 2.54

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.48 (s, 1H), 8.39 (t, 1H), 7.59 (t, 1H), 7.38 (d, 2H), 7.22 (d, 2H), 7.16 (d, 2H), 6.89 (d, 1H), 6.21 (d, 1H), 4.31 (d, 2H), 4.21 (t, 2H), 3.63 – 3.56 (m, 6H), 3.44 – 3.37 (m, 4H), 2.97 (s, 3H), 2.93 – 2.86 (m, 5H), 2.40 (q, 2H), 2.22 – 2.13 (m, 2H), 2.05 – 1.92 (m, 1H), 1.92 – 1.80 (m, 1H)

EXAMPLE 96

***N*-(4-acetamidobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (55% yield, 100% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid (Intermediate 63) and *N*-(4-(aminomethyl)phenyl)acetamide following the synthetic procedure as described for Intermediate 1e

LRMS (m/z): 529 $[M+1]^+$

LC (1) r.t. (min.): 2.63

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.57 (bs, 1H), 7.49 – 7.36 (m, 6H), 7.30 (d, 2H), 7.13 (s, 1H), 4.51 (d, 2H), 4.33 (t, 2H), 3.64 (s, 2H), 3.11 (s, 3H), 3.00 (s, 3H), 2.89 (t, 2H), 2.53 – 2.45 (m, 7H), 2.17 (s, 3H), 2.16 – 1.94 (m, 2H).

EXAMPLE 97

7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(methylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (67% yield, 100% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxylic acid (Intermediate 63) 4-(aminomethyl)-*N*-methylbenzamide following the synthetic procedure as described for Intermediate 1e

LRMS (m/z): 529 $[M+1]^+$

LC (1) r.t. (min.): 2.57

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (d, 2H), 7.66 (s, 1H), 7.47 – 7.37 (m, 6H), 6.08 (s, 1H), 4.60 (d, 2H), 4.32 (t, 2H), 3.65 (s, 2H), 3.11 (s, 3H), 3.06 – 2.95 (m, 6H), 2.89 (t, 2H), 2.57 – 2.49 (m, 4H), 2.48 (s, 3H), 2.21 – 1.95 (m, 2H).

EXAMPLE 98

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (62% yield, 99% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 64) following the synthetic procedure as described for Intermediate 21

LRMS (m/z): 732 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.69 (s, 1H), 8.06 (d, 1H), 7.66 (d, 2H), 7.44 (dd, 2H), 7.36 (t, 2H), 7.26 (d, 1H), 7.23 – 7.16 (m, 2H), 5.06 (s, 1H), 4.62 (s, 1H), 4.20 – 4.11 (m, 2H), 4.07 – 4.02 (m, 1H), 3.59 (s, 1H), 3.52 (s, 1H), 3.29 (s, 1H), 3.02 – 2.83 (m, 12H), 2.78 – 2.69 (m, 1H), 2.55 – 2.52 (m, 3H), 2.48 – 2.37 (m, 2H), 2.25 – 2.14 (m, 2H), 2.09 – 1.72 (m, 12H), 1.68 – 1.56 (m, 2H).

EXAMPLE 99

***N*-(4-acetamidobenzyl)-2'-(4-(isoxazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

N-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 1f, 40 mg, 0.11 mmol) and 3-[4-(bromomethyl)phenyl]isoxazole (Intermediate 65, 44 mg, 148 μmol) were dissolved in ACN (1 mL) and DIEA (44.0 mg, 0.34 mmol) was added. The mixture was stirred at 60°C for 2 h. After the reaction completion, the mixture was purified directly by prep-HPLC (2, B from 35.00% to 70.00% in 8.00 min) to give the title compound (26.5 mg, yield 46%, 100% purity) as white solid.

LRMS (m/z): 510 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.99 (d, 1H), 8.41 (t, 1H), 7.86 (d, 2H), 7.54 (d, 2H), 7.50 (d, 2H), 7.21 (d, 2H), 7.14 (d, 1H), 6.89 (d, 1H), 6.22 (d, 1H), 4.32 (d, 2H), 4.18 (t, 2H), 3.60 (s, 2H), 2.86 (t, 2H), 2.43 (q, 2H), 2.24 – 2.13 (m, 2H), 2.02 (s, 3H), 2.01 – 1.93 (m, 1H), 1.90 (s, 1H).

EXAMPLE 100

***N*-(4-acetamidobenzyl)-2'-((4-(dimethylcarbamoyl)phenyl)methyl-*d*2)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide.**

Obtained as a white solid (45% yield, 98% purity) from *N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 1f) and 4-(bromomethyl-d_2)-*N*,*N*-dimethylbenzamide (Intermediate 66) following the synthetic procedure as described for Example 99.

LRMS (m/z): 526 $[M+1]^+$

LC (1) r.t. (min.): 2.10

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.88 (s, 1H), 8.40 (t, 1H), 7.50 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.20 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 4.16 (t, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.13 (m, 2H), 2.01 (s, 3H), 2.03 – 1.93 (m, 1H), 1.93 – 1.84 (m, 1H).

EXAMPLE 101

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a light orange powder (15% yield, 97% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 67) and *N*-(4-(aminomethyl)phenyl)acetamide hydrochloride following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 500.5 $[M+1]^+$

LC (4e) r.t. (min.): 2.62

1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.46 (dd, 2H), 7.39 – 7.32 (m, 4H), 7.28 (d, 2H), 6.52 (brs, 1H), 6.10 (s, 1H), 5.59 (brs, 1H), 4.52 (d, J = 5.5 Hz, 2H), 4.43 (brs, 2H), 3.81 (s, 2H), 3.19 (brs, 2H), 3.11 (s, 3H), 2.98 (s, 3H), 2.17 (s, 3H), 1.14 (brs, 2H), 1.00 (brs, 2H).

EXAMPLE 102

2'-((5-(Dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (17% yield, 100% purity) from 2'-((5-bromo-3-fluoropyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-

pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 68) and dimethylamine hydrochloride following the synthetic procedure as described for Example 88.

LRMS (m/z): 562 $[M+1]^+$

LC (1) r.t. (min.): 2.42

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.44 (s, 1H), 8.39 (t, 1H), 8.22 (s, 1H), 7.81 (dd, 1H), 7.42 – 7.37 (m, 2H), 7.18 – 7.11 (m, 2H), 6.89 (d, 1H), 6.22 (d, 1H), 4.32 (d, 2H), 4.28 – 4.21 (m, 2H), 3.67 – 3.63 (m, 2H), 3.03 – 2.89 (m, 12H), 2.71 – 2.65 (m, 2H), 2.42 – 2.36 (m, 2H), 2.23 – 2.15 (m, 2H), 1.99 – 1.93 (m, 1H), 1.91 – 1.84 (m, 1H).

EXAMPLE 103

2'-((5-(Dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

To a solution of *N*-(4-aminobenzyl)-2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 69, 0.13 g, 0.27 mmol) in THF (5 mL) was added 4-morpholinobenzoic acid (54.9 mg, 0.27 mmol) and DMC·HCl (89.6 mg, 0.53 mmol) and DIEA (171 mg, 1.32 mmol, 230.79 µL). The mixture was stirred at 20 °C for 4 h. After the reaction completion the reaction mixture was concentrated to give the residue that was purified by prep-HPLC (1b, B from 10.00% to 40.00% in 8.00 min) to give the title compound (73 mg, 40.52% yield, 100% purity) as a white solid.

LRMS (m/z): 680 $[M+1]^+$

LC (1) r.t. (min.): 2.34

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.93 (s, 1H), 8.47 – 8.41 (m, 2H), 7.88 (d, 2H), 7.81 (dd, 1H), 7.70 (d, 2H), 7.25 (d, 2H), 7.02 (d, 2H), 6.90 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.25 (t, 2H), 3.78 – 3.71 (m, 4H), 3.65 (s, 2H), 3.28 – 3.21 (m, 4H), 3.00 (s, 3H), 2.98 – 2.90 (m, 5H), 2.39 (q, 2H), 2.23 – 2.14 (m, 2H), 2.04 – 1.92 (m, 1H), 1.92 – 1.80 (m, 1H).

EXAMPLE 104

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (65% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 719 $[M+1]^+$

LC (1) r.t. (min.): 2.28

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.50 (t, 1H), 8.06 (s, 1H), 7.61 (d, 2H), 7.49 (d, 2H), 7.38 (d, 2H), 7.22 (d, 2H), 6.96 (d, 1H), 6.42 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.35 (d, 2H), 4.22 – 4.10 (m, 3H), 3.86 (s, 2H), 2.97 (s, 3H), 2.93 (s, 3H), 2.87 (d, 2H), 2.81 (t, 2H), 2.76 – 2.67 (m, 1H), 2.53 (s, 3H), 2.03 – 1.92 (m, 4H), 1.91 – 1.71 (m, 6H), 1.63 (d, 2H).

EXAMPLE 105

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (33% yield, 91% purity) from 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 71) and 3-(6-(aminomethyl)pyridin-3-yl)-1,1-dimethylurea (Intermediate 61) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 580 $[M+1]^+$

LC (1) r.t. (min.): 2.50

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.56 (d, 1H), 8.48 (t, 1H), 8.43 (s, 1H), 7.81 (dd, 1H), 7.21 – 7.13 (m, 3H), 6.93 (d, 1H), 6.23 (d, 1H), 4.40 (d, 2H), 4.23 (t, 2H), 3.53 (s, 2H), 2.97 (s, 3H), 2.95 – 2.87 (m, 11H), 2.45 – 2.33 (m, 2H), 2.24 – 2.15 (m, 2H), 2.03 – 1.92 (m, 1H), 1.87 (s, 1H).

EXAMPLE 106

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (43% yield, 93% purity) from 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 72) and 3-(6-(aminomethyl)pyridin-3-yl)-1,1-dimethylurea (Intermediate 61) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 562 $[M+1]^+$

LC (1) r.t. (min.): 2.23

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.56 (d, 1H), 8.48 (t, 1H), 8.43 (s, 1H), 7.81 (dd, 1H), 7.59 (t, 1H), 7.22 (d, 2H), 7.18 (d, 1H), 6.93 (d, 1H), 6.23 (d, 1H), 4.40 (d, 2H), 4.20 (t, 2H), 3.58 (s, 2H), 2.97 (s, 3H), 2.95 – 2.88 (m, 11H), 2.45 – 2.34 (m, 2H), 2.24 – 2.13 (m, 2H), 2.04 – 1.92 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 107

***N*-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (25% yield, 96% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 72b) and 4-(aminomethyl)benzamide following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 518 $[M+1]^+$

LC (1) r.t. (min.): 2.13

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.53 (t, 1H), 7.92 (s, 1H), 7.82 (d, 2H), 7.58 (t, 1H), 7.35 (d, 2H), 7.31 (s, 1H), 7.22 (d, 2H), 6.92 (d, 1H), 6.23 (d, 1H), 4.43 (d, 2H), 4.20 (t, 2H), 3.58 (s, 2H), 2.97 (s, 3H), 2.93 – 2.88 (m, 5H), 2.40 (q, 2H), 2.23 – 2.12 (m, 2H), 2.03 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H).

EXAMPLE 108

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (38% yield, 94% purity) from 3-fluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 72) and *N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide (Intermediate 73) following the synthetic procedure as described for Example 103.

LRMS (m/z): 695 $[M+1]^+$

LC (1) r.t. (min.): 1.75

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.43 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.58 (d, 1H), 7.27 – 7.19 (m, 4H), 6.90 (d, 1H), 6.22 (d, 1H), 4.35 (d, 2H), 4.21 (t, 2H), 4.18 – 4.08 (m, 1H), 3.58 (s, 2H), 2.97 (s, 3H), 2.88 (d, 7H), 2.54 (s, 3H), 2.40 (q, 2H), 2.24 – 2.14 (m, 5H), 2.08 – 2.00 (m, 4H), 2.00 – 1.91 (m, 1H), 1.92 – 1.83 (m, 1H), 1.80 – 1.74 (m, 2H).

EXAMPLE 109

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (31% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 74) and oxetane-3-carboxylic acid following the synthetic procedure as described for Example 103.

LRMS (m/z): 574 $[M+1]^+$

LC (1) r.t. (min.): 1.90

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (s, 1H), 8.42 (t, 1H), 7.58 (t, 1H), 7.54 (d, 2H), 7.26 – 7.19 (m, 4H), 6.89 (d, 1H), 6.21 (d, 1H), 4.68 (d, 4H), 4.33 (d, 2H), 4.21 (t, 2H), 3.93 (p, 1H), 3.58 (s, 2H), 2.97 (s, 3H), 2.93 – 2.89 (m, 5H), 2.40 (q, 2H), 2.23 – 2.12 (m, 2H), 2.04 – 1.92 (m, 1H), 1.92 – 1.80 (m, 1H).

EXAMPLE 110

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (45% yield, 100% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 75) and 4-(aminomethyl)-N-methylbenzamide following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 586 $[M+1]^+$

LC (1) r.t. (min.): 2.85

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.59 (t, 1H), 8.37 (q, 1H), 7.78 (d, 2H), 7.36 (d, 2H), 7.19 (d, 2H), 6.92 (d, 1H), 6.15 (d, 1H), 4.44 (d, 2H), 4.30 (t, 2H), 3.58 (s, 2H), 3.09 – 2.86 (m, 12H), 2.77 (d, 3H).

EXAMPLE 111

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (51% yield, 98% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 75) and 3-(6-(aminomethyl)pyridin-3-yl)-1,1-dimethylurea (Intermediate 61) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 616 $[M+1]^+$

LC (1) r.t. (min.): 2.69

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.60 – 8.53 (m, 2H), 8.44 (s, 1H), 7.81 (dd, 1H), 7.24 – 7.12 (m, 3H), 6.93 (d, 1H), 6.15 (d, 1H), 4.41 (d, 2H), 4.30 (t, 2H), 3.58 (s, 2H), 3.07 – 2.86 (m, 18H).

EXAMPLE 112

***N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (52% yield, 100% purity) *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 76) following the synthetic procedure as described for Intermediate 18a.

LRMS (m/z): 587 $[M+1]^+$

LC (1) r.t. (min.): 2.75

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.10 (s, 1H), 8.64 (d, 1H), 8.58 (t, 1H), 7.94 (dd, 1H), 7.25 (d, 1H), 7.19 (d, 2H), 6.94 (d, 1H), 6.15 (d, 1H), 4.43 (d, 2H), 4.30 (t, 2H), 3.58 (s, 2H), 3.09 – 2.89 (m, 9H), 2.90 (s, 3H), 2.05 (s, 3H).

EXAMPLE 113

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (41% yield, 100% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 75) and 3-(4-(aminomethyl)phenyl)-1,1-dimethylurea (Intermediate 77) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 615 $[M+1]^+$

LC (1) r.t. (min.): 3.06

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.47 (t, 1H), 8.22 (s, 1H), 7.38 (d, 2H), 7.19 (d, 2H), 7.14 (d, 2H), 6.89 (d, 1H), 6.13 (d, 1H), 4.34 – 4.28 (m, 4H), 3.57 (s, 2H), 3.05 – 2.86 (m, 12H), 2.90 (s, 6H).

EXAMPLE 114

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

To a solution of *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

(Intermediate 79, 150 mg, 0.28 mmol) in DCM (1.5 mL) were added TEA (140 mg, 1.38 mmol) and 5-methyl-1-(1-methyl-4-piperidyl)pyrazole-4-carbonyl chloride (Intermediate 78, 133 mg, 0.55 mmol) at 0°C and the mixture was stirred at 25°C for 2 h. After the reaction completion, the mixture was concentrated and purified by prep-HPLC (1b, B from 10.00% to 40.00% in 8.00 min) to give the title compound (76 mg, 33% yield, 98% purity) as a white solid.

LRMS (m/z): 749 $[M+1]^+$

LC (1) r.t. (min.): 2.91

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.76 (s, 1H), 7.58 – 7.51 (m, 3H), 7.31 (d, 2H), 6.98 (d, 2H), 6.55 (d, 1H), 6.18 – 6.13 (m, 2H), 4.53 (d, 2H), 4.47 (t, 2H), 4.19 – 4.10 (m, 1H), 3.63 (s, 2H), 3.23 – 2.86 (m, 14H), 2.61 (s, 3H), 2.45 (s, 3H), 2.50 – 2.26 (m, 6H).

EXAMPLE 115

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (49% yield, 96% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide (Intermediate 80) and 3-(6-(aminomethyl)pyridin-3-yl)-1,1-dimethylurea (Intermediate 61) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 598 $[M+1]^+$

LC (1) r.t. (min.): 2.68

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.58 – 8.51 (m, 2H), 8.43 (s, 1H), 7.81 (dd, 1H), 7.59 (t, 1H), 7.27 – 7.21 (m, 2H), 7.19 (d, 1H), 6.94 (d, 1H), 6.14 (d, 1H), 4.41 (d, 2H), 4.28 (t, 2H), 3.61 (s, 2H), 3.12 – 2.86 (m, 18H).

EXAMPLE 116

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (55% yield, 100% purity) from 4-((3,3-difluoro-6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-3-fluoro-*N*,*N*-dimethylbenzamide (Intermediate 80) and 3-(4-(aminomethyl)phenyl)-1,1-dimethylurea (Intermediate 77) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 597 $[M+1]^+$

LC (1) r.t. (min.): 3.05

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.46 (t, 1H), 8.22 (s, 1H), 7.60 (t, 1H), 7.39 (d, 2H), 7.27 – 7.20 (m, 2H), 7.15 (d, 2H), 6.89 (d, 1H), 6.13 (d, 1H), 4.35 – 4.24 (m, 4H), 3.61 (s, 2H), 3.13 – 2.88 (m, 18H).

EXAMPLE 117

***N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (44% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 81) and cyclopropanecarboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 595 $[M+1]^+$

LC (1) r.t. (min.): 2.84

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.36 (s, 1H), 8.67 (d, 1H), 8.58 (t, 1H), 7.95 (dd, 1H), 7.59 (t, 1H), 7.28 – 7.20 (m, 3H), 6.94 (d, 1H), 6.15 (d, 1H), 4.43 (d, 2H), 4.27 (t, 2H), 3.61 (s, 2H), 3.12 – 2.86 (m, 12H), 1.78 (p, 1H), 0.84 – 0.78 (m, 4H).

EXAMPLE 118

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-*N*-((5-(1-methyl-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (44% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 81) and 1-methyl-1H-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 635 $[M+1]^+$

LC (1) r.t. (min.): 2.83

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.98 (s, 1H), 8.79 (d, 1H), 8.59 (t, 1H), 8.31 (s, 1H), 8.05 (dd, 1H), 8.01 (s, 1H), 7.60 (t, 1H), 7.29 (d, 1H), 7.26 – 7.20 (m, 2H), 6.95 (d, 1H), 6.15 (d, 1H), 4.45 (d, 2H), 4.28 (t, 2H), 3.89 (s, 3H), 3.62 (s, 2H), 3.14 – 2.85 (m, 12H).

EXAMPLE 119

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-*N*-((5-(1-methyl-1*H*-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (54% yield, 97% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 81) and 1-methyl-1H-imidazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 635 $[M+1]^+$

LC (1) r.t. (min.): 2.83

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.05 (s, 1H), 8.90 (d, 1H), 8.58 (t, 1H), 8.16 (dd, 1H), 7.82 (d, 1H), 7.78 (d, 1H), 7.60 (t, 1H), 7.30 – 7.20 (m, 3H), 6.95 (d, 1H), 6.15 (d, 1H), 4.44 (d, 2H), 4.28 (t, 2H), 3.73 (s, 3H), 3.61 (s, 2H), 3.13 – 2.88 (m, 12H).

EXAMPLE 120

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (23% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 82) following the synthetic procedure as described for Intermediate 61a.

LRMS (m/z): 581 $[M+1]^+$

LC (1) r.t. (min.): 2.63

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.46 (t, 1H), 8.21 (s, 1H), 7.38 (d, 2H), 7.20 (d, 2H), 7.13 (d, 2H), 6.94 (d, 1H), 6.41 (d, 1H), 4.91 (d, 2H), 4.65 (d, 2H), 4.30 (d, 2H), 4.19 (t, 2H), 3.81 (s, 2H), 2.98 (s, 3H), 2.92 – 2.86 (m, 11H).

EXAMPLE 121

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (36% yield, 100% purity) from 3,5-difluoro-*N*,*N*-dimethyl-4-((6'-(2,2,2-trichloroacetyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide (Intermediate 82b) and *N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide (Intermediate 73) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 715 $[M+1]^+$

LC (1) r.t. (min.): 2.22

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.66 (s, 1H), 8.52 (t, 1H), 8.07 (s, 1H), 7.61 (d, 2H), 7.25 – 7.17 (m, 4H), 6.95 (d, 1H), 6.42 (d, 1H), 4.91 (d, 2H), 4.65 (d, 2H), 4.34 (d, 2H), 4.20 (t, 2H), 4.17 – 4.09 (m, 1H), 3.80 (s, 2H), 2.97 (s, 3H), 2.93 – 2.83 (m, 7H), 2.53 (s, 3H), 2.20 (s, 3H), 2.10 – 1.96 (m, 4H), 1.82 – 1.70 (m, 2H).

EXAMPLE 122

***N*-(4-(1-(1-Cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

To a solution of 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 83 TFA salt, 110 mg, 0.14 mmol) in MeOH (1.1 mL) was added TEA (27.3 mg, 0.27 mmol), followed by AcOH (24.3 mg, 0.41 mmol) and (1-ethoxycyclopropoxy)-trimethyl-silane (94.1 mg, 0.54 mmol) and the mixture was stirred at 25°C for 1 h. Then NaBH3CN (25.5 mg, 0.41 mmol) was added and the mixture was stirred at 60°C for 11 h. After the reaction completion, the mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (1b, B from 15.00% to 45.00% in 8.00 min) to give the title compound (15 mg, 14% yield, 100% purity) as a white solid.

LRMS (m/z): 741 $[M+1]^+$

LC (1) r.t. (min.): 1.91

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.53 (d, 2H), 7.41 (s, 1H), 7.30 (d, 2H), 7.00 (d, 2H), 6.60 (d, 1H), 6.43 (d, 1H), 6.08 (t, 1H), 5.11 (d, 2H), 4.80 (d, 2H), 4.52 (d, 2H), 4.37 (t, 2H), 4.20 – 4.01 (m, 1H), 3.93 (s, 2H), 3.30 – 3.15 (m, 2H), 3.11 (s, 3H), 3.01 (s, 3H), 2.94 (t, 2H), 2.62 (s, 3H), 2.49 – 2.31 (m, 2H), 2.31 – 2.12 (m, 2H), 1.96 – 1.67 (m, 3H), 0.63 – 0.35 (m, 4H).

EXAMPLE 123

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (47% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 82) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 699 $[M+1]^+$

LC (1) r.t. (min.): 2.68

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 (d, 2H), 7.78 (s, 1H), 7.59 (d, 2H), 7.31 (d, 2H), 7.00 (d, 2H), 6.94 (d, 2H), 6.62 (d, 1H), 6.43 (d, 1H), 6.14 (t, 1H), 5.12 (d, 2H), 4.80 (d, 2H), 4.52 (d, 2H), 4.38 (t, 2H), 3.93 (s, 2H), 3.91 – 3.85 (m, 4H), 3.32 – 3.25 (m, 4H), 3.11 (s, 3H), 3.00 (s, 3H), 2.96 (t, 2H).

EXAMPLE 124

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (47% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 84) following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 714 $[M+1]^+$

LC (1) r.t. (min.): 1.77

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.63 (d, 1H), 8.06 (dd, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 7.28 (d, 1H), 6.99 – 6.92 (m, 3H), 6.70 (d, 1H), 6.20 (d, 1H), 4.63 (d, 2H), 4.40 (t, 2H), 4.09 – 3.97 (m, 1H), 3.56 (s, 2H), 3.09 (s, 3H), 3.07 – 3.01 (m, 4H), 2.98 (s, 3H), 2.61 (s, 3H), 2.49 (q, 2H), 2.32 (s, 3H), 2.36 – 2.22 (m, 5H), 2.16 – 2.06 (m, 2H), 2.06 – 1.95 (m, 1H), 1.95 – 1.85 (m, 2H).

EXAMPLE 125

7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (44% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 85) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 698 $[M+1]^+$

LC (3) r.t. (min.): 1.85

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H), 7.71 (s, 1H), 7.65 – 7.57 (m, 3H), 7.35 (d, 2H), 7.09 (s, 1H), 7.02 – 6.95 (m, 2H), 6.93 (d, 2H), 4.57 (d, 2H), 4.49 (t,

2H), 3.90 – 3.83 (m, 4H), 3.56 (s, 2H), 3.31 – 3.24 (m, 4H), 3.10 (s, 3H), 3.05 (t, 2H), 2.99 (s, 3H), 2.58 – 2.48 (m, 2H), 2.31 – 2.23 (m, 2H), 2.09 – 1.95 (m, 2H).

EXAMPLE 126

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (53% yield, 100% purity) 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 86) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 754 $[M+1]^+$

LC (1) r.t. (min.): 2.14

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.61 (t, 1H), 7.53 (d, 2H), 7.40 (s, 1H), 7.33 (d, 2H), 7.08 (s, 1H), 6.98 (d, 2H), 4.55 (d, 2H), 4.48 (t, 2H), 4.09 – 4.01 (m, 1H), 3.56 (s, 2H), 3.10 (s, 3H), 3.08 – 3.01 (m, 4H), 2.99 (s, 3H), 2.82 – 2.73 (m, 1H), 2.61 (s, 3H), 2.58 – 2.48 (m, 2H), 2.32 – 2.21 (m, 4H), 2.10 – 1.66 (m, 12H).

EXAMPLE 127

***N*-(4-(1-(1-Cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (52% yield, 100% purity) 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 86) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 740 $[M+1]^+$

LC (1) r.t. (min.): 2.11

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.61 (t, 1H), 7.53 (d, 2H), 7.41 (s, 1H), 7.33 (d, 2H), 7.08 (s, 1H), 7.01 – 6.95 (m, 2H), 4.55 (d, 2H), 4.48 (t, 2H), 4.11 – 4.02 (m, 1H), 3.56 (s, 2H), 3.22 – 3.15 (m, 2H), 3.10 (s, 3H), 3.05 (t, 2H), 2.99

(s, 3H), 2.62 (s, 3H), 2.58 – 2.48 (m, 2H), 2.41 – 2.31 (m, 2H), 2.31 – 2.14 (m, 4H), 2.11 – 1.64 (m, 5H), 0.51 – 0.38 (m, 4H).

EXAMPLE 128

7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as an off-white solid (86% yield, 97% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 85) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 595 $[M+1]^+$

LC (1) r.t. (min.): 2.41

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.62 (t, 1H), 7.49 (d, 2H), 7.43 – 7.36 (m, 1H), 7.30 (d, 2H), 7.08 (s, 1H), 7.03 – 6.93 (m, 2H), 4.91 – 4.68 (m, 1H), 4.54 (d, 2H), 4.48 (t, 2H), 3.56 (s, 2H), 3.10 (s, 3H), 3.05 (t, 2H), 2.99 (s, 3H), 2.53 (dt, 2H), 2.32 – 2.21 (m, 2H), 2.11 – 1.94 (m, 1H), 1.85 – 1.71 (m, 1H), 1.31 – 1.17 (m, 2H), 0.90 – 0.77 (m, 1H).

EXAMPLE 129

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (59% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 87) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 731 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.77 (s, 1H), 7.70 (s, 1H), 7.64 (dd, 1H), 7.31 (t, 1H), 7.08 (dd, 1H), 6.95 (d, 2H), 6.59 (d, 1H), 6.25 – 6.16 (m, 2H), 4.55 (d, 2H),

4.39 (t, 2H), 4.11 – 3.99 (m, 1H), 3.56 (s, 2H), 3.09 (s, 3H), 3.07 – 3.01 (m, 4H), 2.98 (s, 3H), 2.61 (s, 3H), 2.49 (q, 2H), 2.35 (s, 3H), 2.33 – 2.21 (m, 4H), 2.21 – 2.09 (m, 2H), 2.06 – 1.86 (m, 4H).

EXAMPLE 130

7'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-methoxy-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (66% yield, 100% purity) from 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(2-methoxy-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride (Intermediate 88) and formaldehyde following the synthetic procedure as described for Example 122.

LRMS (m/z): 744 $[M+1]^+$

LC (1) r.t. (min.): 2.35

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.66 (s, 1H), 8.50 (t, 1H), 8.08 (s, 1H), 7.47 (d, 1H), 7.26 – 7.15 (m, 4H), 7.10 (d, 1H), 4.36 (d, 2H), 4.30 (t, 2H), 4.20 – 4.08 (m, 1H), 3.82 (s, 3H), 3.53 (s, 2H), 2.97 (s, 3H), 2.93 (t, 2H), 2.90 (s, 3H), 2.88 – 2.84 (m, 2H), 2.55 (s, 3H), 2.40 (q, 2H), 2.26 – 2.16 (m, 5H), 2.08 – 1.96 (m, 5H), 1.94 – 1.84 (m, 1H), 1.82 – 1.72 (m, 2H).

EXAMPLE 131

7''-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide

Obtained as a white solid (20% yield, 100% purity) from *N*-(4-aminobenzyl)-7''-(4-(dimethylcarbamoyl)benzyl)-6'',7''-dihydro-5''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide hydrochloride (Intermediate 89) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 702 $[M+1]^+$

LC (1) r.t. (min.): 3.04

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.94 (s, 1H), 8.84 (t, 1H), 7.92 – 7.86 (m, 2H), 7.72 – 7.67 (m, 2H), 7.44 (d, 2H), 7.35 (d, 2H), 7.28 (d, 2H), 7.02 (d, 2H), 6.97

(s, 1H), 4.38 (d, 2H), 4.24 (t, 2H), 3.78 – 3.73 (m, 4H), 3.48 (s, 2H), 3.27 – 3.24 (m, 4H), 3.03 – 2.89 (m, 6H), 2.88 (t, 2H), 2.47 – 2.42 (m, 2H), 2.38 – 2.32 (m, 2H), 2.16 (t, 2H), 2.10 – 2.04 (m, 2H), 1.87 – 1.78 (m, 2H).

EXAMPLE 132

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (17% yield, 99% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide hydrochloride (Intermediate 90) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 648 $[M+1]^+$

LC (1) r.t. (min.): 2.60

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.93 (s, 1H), 8.83 (t, 1H), 7.91 – 7.86 (m, 2H), 7.71 – 7.67 (m, 2H), 7.39 (d, 2H), 7.33 (d, 2H), 7.30 – 7.25 (m, 2H), 7.05 – 6.99 (m, 2H), 6.73 (s, 1H), 4.45 – 4.40 (m, 2H), 4.38 (d, 2H), 3.79 – 3.71 (m, 6H), 3.25 (dd, 4H), 3.13 – 3.06 (m, 2H), 2.99 – 2.87 (m, 6H), 1.17 – 1.12 (m, 2H), 1.06 – 1.01 (m, 2H).

EXAMPLE 133

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (27% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxylic acid (Intermediate 91) and *N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide (Intermediate 73) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 691 $[M+1]^+$

LC (1) r.t. (min.): 1.65

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.74 (s, 1H), 7.53 (d, 2H), 7.46 (d, 2H), 7.43 – 7.37 (m, 3H), 7.30 (d, 2H), 6.37 (s, 1H), 6.00 (t, 1H), 4.51 (d, 2H), 4.28 (t, 2H), 4.16 – 3.97 (m, 1H), 3.72 (s, 2H), 3.19 – 2.95 (m, 8H), 2.88 (t, 2H), 2.68 – 2.55 (m,

5H), 2.55 – 2.41 (m, 3H), 2.41 – 2.22 (m, 7H), 2.22 – 2.06 (m, 3H), 2.07 – 1.95 (m, 2H), 1.95 – 1.80 (m, 1H).

EXAMPLE 134

_N_-(4-(4-(4-Cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'_H_-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (33% yield, 99% purity) from _N_-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'_H_-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 93) and 4-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 92) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 716 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.90 (s, 1H), 8.42 (t, 1H), 7.85 (d, 2H), 7.68 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.22 (d, 2H), 6.99 (d, 2H), 6.77 (s, 1H), 4.92 (d, 2H), 4.86 (d, 2H), 4.33 (d, 2H), 4.15 (t, 2H), 3.96 (s, 2H), 3.28 – 3.21 (m, 4H), 2.98 (s, 3H), 2.93 (s, 3H), 2.73 (t, 2H), 2.70 – 2.63 (m, 4H), 2.38 (s, 3H), 1.70 – 1.62 (m, 1H), 0.49 – 0.39 (m, 2H), 0.39 – 0.31 (m, 2H).

EXAMPLE 135

2'-(4-(Dimethylcarbamoyl)-2-fluorobenzyl)-_N_-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'_H_-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (42% yield, 100% purity) from _N_-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'_H_-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 94) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 681 $[M+1]^+$

LC (1) r.t. (min.): 2.47

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H), 7.77 (s, 1H), 7.63 – 7.55 (m, 3H), 7.31 (d, 2H), 7.21 (dd, 1H), 7.14 (dd, 1H), 6.92 (d, 2H), 6.64 (d, 1H), 6.44 (d, 1H), 6.15 (t, 1H), 5.02 (d, 2H), 4.82 (d, 2H), 4.53 (d, 2H), 4.37 (t, 2H), 4.01 (s, 2H), 3.91 – 3.84 (m, 4H), 3.31 – 3.25 (m, 4H), 3.11 (s, 3H), 3.01 (s, 3H), 2.91 (t, 2H).

EXAMPLE 136

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (36% yield, 97% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid (Intermediate 95) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 2.96

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.22 (s, 1H), 7.48 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.29 (d, 2H), 6.57 (d, 1H), 6.20 (d, 1H), 6.06 (t, 1H), 4.52 (d, 2H), 4.29 (t, 2H), 3.76 – 3.69 (m, 2H), 3.56 (s, 2H), 3.45 (s, 3H), 3.11 (s, 3H), 3.04 – 2.94 (m, 5H), 2.67 – 2.60 (m, 2H), 2.51 – 2.40 (m, 2H), 2.31 – 2.22 (m, 2H), 2.11 – 1.95 (m, 2H).

EXAMPLE 137

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-methoxypropanamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (49% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 3-methoxypropanoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 558 $[M+1]^+$

LC (1) r.t. (min.): 1.76

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.22 (s, 1H), 7.48 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.29 (d, 2H), 6.57 (d, 1H), 6.20 (d, 1H), 6.06 (t, 1H), 4.52 (d, 2H), 4.29 (t, 2H), 3.76 – 3.69 (m, 2H), 3.56 (s, 2H), 3.45 (s, 3H), 3.11 (s, 3H), 3.04 – 2.94 (m, 5H), 2.67 – 2.60 (m, 2H), 2.51 – 2.40 (m, 2H), 2.31 – 2.22 (m, 2H), 2.11 – 1.95 (m, 2H).

EXAMPLE 138

***N*-(4-(2-Cyclopropylacetamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (72% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 2-cyclopropylacetic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 554 $[M+1]^+$

LC (1) r.t. (min.): 2.16

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.62 (s, 1H), 7.51 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.31 (d, 2H), 6.58 (d, 1H), 6.20 (d, 1H), 6.07 (t, 1H), 4.53 (d, 2H), 4.29 (t, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 3.04 – 2.92 (m, 5H), 2.50 – 2.42 (m, 2H), 2.33 (d, 2H), 2.31 – 2.23 (m, 2H), 2.05 – 1.94 (m, 2H), 1.11 – 1.05 (m, 1H), 0.74 – 0.68 (m, 2H), 0.33 – 0.27 (m, 2H).

EXAMPLE 139

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((1*R*,2*R*)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (47% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*R*,2*R*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 558 $[M+1]^+$

LC (3) r.t. (min.): 1.31

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 (d, 2H), 7.43 (d, 3H), 7.38 (d, 3H), 7.29 (d, 2H), 6.58 (d, 1H), 6.20 (d, 1H), 6.09 (t, 1H), 4.91 – 4.68 (m, 1H), 4.52 (d, 2H), 4.28 (t, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 3.02 – 2.94 (m, 5H), 2.50 – 2.41 (m, 2H), 2.30 – 2.23 (m, 2H), 2.03 – 1.87 (m, 2H), 1.82 – 1.74 (m, 2H), 1.27 – 1.19 (m, 1H).

EXAMPLE 140

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methyl-1H-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (72% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1-methyl-1*H*-imidazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 580 $[M+1]^+$

LC (1) r.t. (min.): 1.84

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.95 (s, 1H), 7.71 – 7.65 (m, 2H), 7.62 (d, 1H), 7.46 – 7.41 (m, 3H), 7.38 (d, 2H), 7.33 (d, 2H), 6.58 (d, 1H), 6.20 (d, 1H), 6.08 (t, 1H), 4.54 (d, 2H), 4.30 (t, 2H), 3.77 (s, 3H), 3.56 (s, 2H), 3.11 (s, 3H), 3.02 – 2.92 (m, 5H), 2.50 – 2.42 (m, 2H), 2.30 – 2.24 (m, 2H), 2.10 – 1.93 (m, 2H).

EXAMPLE 141

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-(methylamino)-3-oxopropyl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (47% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(3-(methylamino)-3-oxopropyl)benzoic acid (Intermediate 96) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 661 $[M+1]^+$

LC (1) r.t. (min.): 1.94

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.45 (t, 1H), 7.86 (d, 2H), 7.77 (q, 1H), 7.70 (d, 2H), 7.45 (d, 2H), 7.39 – 7.30 (m, 4H), 7.27 (d, 2H), 6.90 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.18 (t, 2H), 3.57 (s, 2H), 2.97 (s, 3H), 2.94 – 2.82 (m, 7H), 2.55 (d, 3H), 2.47 – 2.35 (m, 4H), 2.24 – 2.12 (m, 2H), 2.04 – 1.92 (m, 1H), 1.91 – 1.84 (m, 1H).

EXAMPLE 142

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (62% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 580 $[M+1]^+$

LC (1) r.t. (min.): 1.75

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.93 (s, 1H), 7.83 (s, 1H), 7.56 (d, 2H), 7.46 – 7.36 (m, 4H), 7.33 (d, 2H), 6.59 (d, 1H), 6.20 (d, 1H), 6.10 (t, 1H), 4.54 (d, 2H), 4.29 (t, 2H), 3.96 (s, 3H), 3.56 (s, 2H), 3.10 (s, 3H), 3.06 – 2.89 (m, 5H), 2.50 – 2.41 (m, 2H), 2.31 – 2.23 (m, 2H), 2.08 – 1.92 (m, 2H).

EXAMPLE 143

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methyl-1*H*-pyrazole-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (68% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1-methyl-1*H*-pyrazole-3-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 580 $[M+1]^+$

LC (1) r.t. (min.): 1.91

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.68 (s, 1H), 7.69 – 7.65 (m, 2H), 7.46 – 7.36 (m, 5H), 7.33 (d, 2H), 6.88 (d, 1H), 6.59 (d, 1H), 6.20 (d, 1H), 6.08 (t, 1H), 4.54 (d, 2H), 4.30 (t, 2H), 3.97 (s, 3H), 3.57 (s, 2H), 3.11 (s, 3H), 3.03 – 2.94 (m, 5H), 2.50 – 2.42 (m, 2H), 2.27 (t, 2H), 2.07 – 1.92 (m, 2H).

EXAMPLE 144

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (30% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 558 $[M+1]^+$

LC (1) r.t. (min.): 1.88

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 (d, 2H), 7.43 (d, 2H), 7.38 (d, 3H), 7.30 (d, 2H), 6.58 (d, 1H), 6.20 (d, 1H), 6.08 (t, 1H), 4.91 – 4.68 (m, 1H), 4.52 (d, 2H), 4.29 (t, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 3.03 – 2.94 (m, 5H), 2.49 – 2.41 (m, 2H), 2.30 – 2.24 (m, 2H), 2.09 – 1.74 (m, 4H), 1.27 – 1.19 (m, 1H).

EXAMPLE 145

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(2'-((methylamino)methyl)-[1,1'-biphenyl]-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (23% yield, 96% purity) from *tert*-butyl ((4'-((4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamoyl)-[1,1'-biphenyl]-2-yl)methyl)(methyl)carbamate (Intermediate 97) following the synthetic procedure as described for Intermediate 41c.

LRMS (m/z): 695 $[M+1]^+$

LC (1) r.t. (min.): 2.18

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.43 (s, 1H), 7.91 (d, 2H), 7.65 (d, 2H), 7.58 (d, 1H), 7.46 – 7.29 (m, 12H), 6.65 (d, 1H), 6.26 (d, 1H), 6.21 (d, 1H), 4.54 (d, 2H), 4.28 (t, 2H), 3.83 (s, 2H), 3.56 (s, 2H), 3.11 (s, 3H), 3.02 – 2.94 (m, 5H), 2.49 – 2.40 (m, 2H), 2.33 (s, 3H), 2.30 – 2.22 (m, 2H), 2.11 – 1.98 (m, 1H), 1.99 – 1.88 (m, 1H).

EXAMPLE 146

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-hydroxypropanamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

TBAF (1M in THF, 0.054 mL, 0.054 mmol) was added to a stirred solution of *N*-(4-(3-((*tert*-butyldiphenylsilyl)oxy)propanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 98, 35 mg, 45 μmol) in dry THF (1 mL). After 2 h, water was added and the mixture was extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by reverse phase chromatography to give the title compound (11 mg, 45% yield, 100% purity) as a white solid.

LRMS (m/z): 544 $[M+1]^+$

LC (1) r.t. (min.): 1.59

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (s, 1H), 7.48 (d, 2H), 7.43 (d, 2H), 7.38 (d, 2H), 7.30 (d, 2H), 6.58 (d, 1H), 6.20 (d, 1H), 6.09 (t, 1H), 4.52 (d, 2H), 4.28 (t, 2H), 3.99 (t, 2H), 3.56 (s, 2H), 3.11 (br s, 3H), 3.07 – 2.89 (m, 5H), 2.67 – 2.59 (m, 2H), 2.51 – 2.40 (m, 2H), 2.32 – 2.20 (m, 2H), 2.07 – 1.89 (m, 2H), 1.00 (t, 1H).

EXAMPLE 147

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (35% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 677 $[M+1]^+$

LC (1) r.t. (min.): 1.53

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.66 (s, 1H), 8.44 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.23 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 4.19 – 4.15 (m, 3H), 3.56 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.87 – 2.83 (m, 4H), 2.54 (s, 3H), 2.41 (q, 2H), 2.24 – 2.12 (m, 5H), 2.08 – 1.93 (m, 5H), 1.93 – 1.82 (m, 1H), 1.80 – 1.70 (m, 2H).

EXAMPLE 148

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-(1-ethylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (51% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and acetaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 691 $[M+1]^+$

LC (1) r.t. (min.): 1.69

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.42 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.23 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 4.21 – 4.14 (m, 3H), 3.57 (s, 2H), 3.01 – 2.90 (m, 8H), 2.86 (t, 2H), 2.54 (s, 3H), 2.47 – 2.31 (m, 4H), 2.22 – 2.14 (m, 2H), 2.09 – 1.93 (m, 5H), 1.93 – 1.83 (m, 1H), 1.82 – 1.76 (m, 2H), 1.01 (t, 3H).

EXAMPLE 149

***N*-(4-(1-(1-Cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (47% yield, 97% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 703 $[M+1]^+$

LC (1) r.t. (min.): 1.74

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.99 (s, 1H), 7.58 (d, 2H), 7.51 (d, 2H), 7.40 (d, 2H), 7.31 (d, 2H), 6.86 (d, 1H), 6.26 (d, 1H), 4.47 (s, 2H), 4.33 – 4.24 (m, 1H), 4.23 (t, 2H), 3.62 (s, 2H), 3.22 – 3.14 (m, 2H), 3.10 (s, 3H), 3.03 – 2.95 (m, 5H), 2.60 (s, 3H), 2.57 – 2.41 (m, 4H), 2.33 – 2.24 (m, 2H), 2.23 – 2.01 (m, 3H), 2.01 – 1.84 (m, 3H), 1.80 – 1.70 (m, 1H), 0.56 – 0.42 (m, 4H)

EXAMPLE 150

***N*-(4-(1-(1-Cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (44% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 717 $[M+1]^+$

LC (1) r.t. (min.): 1.63

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.42 (t, 1H), 8.06 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.23 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 4.21 – 4.13 (m, 3H), 3.57 (s, 2H), 3.01 – 2.82 (m, 10H), 2.77 – 2.67 (m, 2H), 2.53 (s, 3H), 2.41 (q, 2H), 2.24 – 2.12 (m, 2H), 1.97 (t, 5H), 1.92 – 1.72 (m, 6H), 1.63 (d, 2H).

EXAMPLE 151

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(1-(oxetan-3-yl)piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (52% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and oxetan-3-one following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 719 $[M+1]^+$

LC (1) r.t. (min.): 1.85

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.82 – 7.78 (m, 2H), 7.52 (d, 2H), 7.40 (d, 2H), 7.36 (d, 2H), 7.28 (d, 2H), 6.60 (d, 1H), 6.24 (t, 1H), 6.18 (d, 1H), 4.70 – 4.59 (m, 4H), 4.50 (d, 2H), 4.27 (t, 2H), 4.13 – 3.99 (m, 1H), 3.57 – 3.50 (m, 3H), 3.10 (s, 3H), 2.98 (s, 3H), 2.94 (t, 2H), 2.88 (d, 2H), 2.60 (s, 3H), 2.44 (q, 2H), 2.37 – 2.18 (m, 4H), 2.08 – 1.87 (m, 6H).

EXAMPLE 152

***N*-(4-(1-(1-(2,2-Difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

To a solution of 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide hydrochloride (Intermediate 99·HCl, 0.16 g, 0.23 mmol) and 2,2-difluoroethyl trifluoromethanesulfonate (73.5 mg, 0.34 mmol) in MeCN (1.6 mL) was added TEA (93 mg, 0.92 mmol). The mixture was stirred at 25°C for 12 h and after the reaction completion, the reaction mixture was purified by prep-HPLC (2, B from 40.00% to 75.00% in 8.00 min) to give the title compound (0.074 g, 44% yield, 98 %purity) as a white solid.

LRMS (m/z): 727 $[M+1]^+$

LC (1) r.t. (min.): 1.85

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.42 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.23 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 6.15 (dt, 1H), 4.34 (d, 2H), 4.24 – 4.15 (m, 3H), 3.57 (s, 2H), 3.04 – 2.94 (m, 5H), 2.92 (s, 3H), 2.85 (t, 2H), 2.77 (td, 2H), 2.54 (s, 3H), 2.41 (dd, 4H), 2.22 – 2.13 (m, 2H), 2.09 – 1.93 (m, 3H), 1.93 – 1.84 (m, 1H), 1.83 – 1.75 (m, 2H).

EXAMPLE 153

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (43% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 99) and 1-fluoro-2-iodoethane following the synthetic procedure as described for Example 152.

LRMS (m/z): 709 $[M+1]^+$

LC (1) r.t. (min.): 1.55

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.42 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.24 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.55 (dt, 2H), 4.34 (dd, 2H), 4.23 – 4.14 (m, 3H), 3.57 (s, 2H), 3.03 – 2.94 (m, 5H), 2.91 (s,

3H), 2.85 (t, 2H), 2.66 (dt, 2H), 2.54 (s, 3H), 2.41 (q, 2H), 2.26 – 2.13 (m, 4H), 2.09 – 1.84 (m, 4H), 1.83 – 1.76 (m, 2H).

EXAMPLE 154

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (82% yield, 99% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 100) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 1.59

EXAMPLE 155

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(1-methylazetidin-3-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (12% yield, 87% purity) from *N*-(4-(1-(azetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 101) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 649 $[M+1]^+$

LC (1) r.t. (min.): 1.61

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.69 (s, 1H), 8.42 (t, 1H), 8.14 (s, 1H), 7.62 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.24 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.97 (p, 1H), 4.35 (d, 2H), 4.17 (t, 2H), 3.72 (t, 2H), 3.57 (s, 2H), 3.38 (t, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.86 (t, 2H), 2.48 (s, 3H), 2.46 – 2.34 (m, 2H), 2.31 (s, 3H), 2.23 – 2.13 (m, 2H), 2.05 – 1.81 (m, 2H).

EXAMPLE 156

***N*-(4-(1,5-dimethyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (62% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1,5-dimethyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 594 $[M+1]^+$

LC (1) r.t. (min.): 2.07

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.55 (d, 2H), 7.47 – 7.41 (m, 3H), 7.38 (d, 2H), 7.32 (d, 2H), 6.59 (d, 1H), 6.21 (d, 1H), 6.10 (t, 1H), 4.53 (d, 2H), 4.36 – 4.26 (m, 2H), 3.83 (s, 3H), 3.58 (s, 2H), 3.11 (s, 3H), 3.05 – 2.94 (m, 5H), 2.60 (s, 3H), 2.56 – 2.40 (m, 2H), 2.33 – 2.23 (m, 2H), 2.10 – 1.90 (m, 2H).

EXAMPLE 157

***N*-(4-(1*H*-pyrazole-3-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (18% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 1*H*-pyrazole-3-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 564 $[M+1]^+$

LC (4d) r.t. (min.): 2.78

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 13.40 (s, 1H), 9.99 (s, 1H), 8.43 (t, 1H), 7.86 (s, 1H), 7.73 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.25 (d, 2H), 6.90 (d, 1H), 6.78 (s, 1H), 6.21 (d, 1H), 4.35 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 2.99 – 2.89 (m, 6H), 2.85 (t, 2H), 2.46 – 2.34 (m, 2H), 2.26 – 2.13 (m, 2H), 2.04 – 1.93 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 158

***N*-(4-((1*r*,3*r*)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (53% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*r*,3*r*)-3-cyanocyclobutane-1-carboxylic acid (Intermediate 104) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 579 $[M+1]^+$

LC (1) r.t. (min.): 2.23

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47 (d, 2H), 7.42 (d, 2H), 7.38 (d, 2H), 7.29 (d, 3H), 6.59 (d, 1H), 6.20 (d, 1H), 6.16 – 6.11 (m, 1H), 4.52 (d, 2H), 4.27 (t, 2H), 3.56 (s, 2H), 3.36 – 3.26 (m, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.95 (t, 2H), 2.86 – 2.74 (m, 2H), 2.67 – 2.55 (m, 2H), 2.51 – 2.40 (m, 2H), 2.31 – 2.22 (m, 2H), 2.10 – 1.88 (m, 2H).

EXAMPLE 159

***N*-(4-((1*s*,3*s*)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (51% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*s*,3*s*)-3-cyanocyclobutane-1-carboxylic acid (Intermediate 105) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 579 $[M+1]^+$

LC (1) r.t. (min.): 2.15

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46 (d, 2H), 7.42 (d, 2H), 7.37 (d, 2H), 7.29 (d, 2H), 7.21 – 7.10 (m, 1H), 6.59 (d, 1H), 6.20 (d, 1H), 6.15 – 6.09 (m, 1H), 4.52 (d, 2H), 4.27 (t, 2H), 3.56 (s, 2H), 3.07 (dt, 8H), 2.96 (t, 2H), 2.86 – 2.75 (m, 2H), 2.66 – 2.56 (m, 2H), 2.46 (q, 2H), 2.31 – 2.22 (m, 2H), 2.11 – 1.88 (m, 2H).

EXAMPLE 160

(1*R*,4*R*)-*N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxamide

Obtained as a white solid (40% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 597 $[M+1]^+$

LC (1) r.t. (min.): 1.96

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.38 (t, 1H), 8.27 (s, 1H), 7.45 (d, 2H), 7.42 (d, 2H), 7.35 (d, 2H), 7.15 (d, 2H), 6.89 (d, 1H), 6.20 (d, 1H), 4.67 (s, 1H), 4.60 (s, 1H), 4.31 (d, 2H), 4.17 (t, 2H), 3.71 (s, 2H), 3.56 (s, 2H), 3.38 (d, 1H), 3.29 (d, 1H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.45 – 2.35 (m, 2H), 2.22 – 2.12 (m, 2H), 2.04 – 1.84 (m, 2H), 1.85 – 1.73 (m, 2H).

EXAMPLE 161

(1*R*,5*S*)-*N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide

Obtained as a white solid (39% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 611 $[M+1]^+$

LC (1) r.t. (min.): 2.20

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.55 (s, 1H), 8.38 (t, 1H), 7.44 (t, 4H), 7.35 (d, 2H), 7.16 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.34 – 4.27 (m, 4H), 4.17 (t, 2H), 3.62 – 3.49 (m, 6H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.46 – 2.35 (m, 2H), 2.16 (d, 2H), 2.04 – 1.75 (m, 6H).

EXAMPLE 162

***N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.4]octane-6-carboxamide**

Trichloromethyl carbonochloridate (25.0 µL, 0.21 mmol) was dissolved in DCM (2 mL) and then *N*-[(4-aminophenyl)methyl]-2-[[4-(dimethylcarbamoyl)phenyl]methyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,1'-cyclobutane]-6-carboxamide (Intermediate 41a, 70.0 mg, 0.15 mmol) dissolved in DCM (2 mL) and *N*,*N*-diethylethanamine (62.0 µL, 0.44 mmol) was added and the reaction mixture was stirred for 5 min. Then 2-oxa-6-azaspiro[3.4]octane (40.0 µL, 0.38 mmol) in DCM (2 mL) was added and the reaction mixture was stirred for 2 h. After the reaction completion, the reaction mixture was concentrated and purified by prep-HPLC (5b) to give the title compound (42.5 mg, 47% yield, 98% purity) as a white solid

LRMS (m/z): 611 $[M+1]^+$

LC (1) r.t. (min.): 2.04

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.38 (t, 1H), 8.11 (s, 1H), 7.49 – 7.41 (m, 4H), 7.35 (d, 2H), 7.14 (d, 2H), 6.89 (d, 1H), 6.20 (d, 1H), 4.54 (d, 2H), 4.48 (d, 2H), 4.31 (d, 2H), 4.17 (t, 2H), 3.61 (s, 2H), 3.56 (s, 2H), 3.37 (t, 2H), 3.00 – 2.89 (m, 6H), 2.85 (t, 2H), 2.44 – 2.35 (m, 2H), 2.22 – 2.11 (m, 4H), 2.05 – 1.94 (m, 1H), 1.92 – 1.82 (m, 1H).

EXAMPLE 163

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-methylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (20% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and methylamine hydrochloride following the synthetic procedure as described for Example 162.

LRMS (m/z): 527 $[M+1]^+$

LC (4e) r.t. (min.): 2.66

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.48 (s, 1H), 8.37 (t, 1H), 7.45 (d, 2H), 7.35 (d, 2H), 7.32 (d, 2H), 7.14 (d, 2H), 6.88 (d, 1H), 6.20 (d,1H), 6.10 – 5.92 (m, 1H), 4.29 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 2.99 – 2.90 (m, 6H), 2.85 (t, 2H), 2.62 (d, 3H), 2.45 – 2.37 (m, 2H), 2.17 (ddd, 2H), 2.04 – 1.93 (m, 1H), 1.91 – 1.84 m, 1H).

EXAMPLE 164

***N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide**

Obtained as a white solid (52% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 2-oxa-7-azaspiro[3.5]nonane following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 625 $[M+1]^+$

LC (1) r.t. (min.): 2.30

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43 (d, 2H), 7.38 (d, 2H), 7.30 (d, 2H), 7.26 (d, 2H), 6.57 (d, 1H), 6.38 (s, 1H), 6.19 (d, 1H), 6.06 (t, 1H), 4.50 (d, 2H), 4.47 (s, 4H), 4.28 (t, 2H), 3.56 (s, 2H), 3.43 – 3.37 (m, 4H), 3.11 (s, 3H), 3.03 – 2.93 (m, 5H), 2.50 – 2.40 (m, 2H), 2.32 – 2.23 (m, 2H), 1.95 – 2.08 (m, 2H), 1.94 – 1.89 (m, 4H).

EXAMPLE 165

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(tetrahydrofuran-2-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (52% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and tetrahydrofuran-2-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 570 $[M+1]^+$

LC (1) r.t. (min.): 1.89

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.61 (s, 1H), 8.41 (t, 1H), 7.60 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.22 (d, 2H), 6.89 (d, 1H), 6.21 (d, 1H), 4.40 – 4.30 (m, 3H), 4.16 (t, 2H), 3.97 (q, 1H), 3.82 (q, 1H), 3.56 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.11 (m, 3H), 2.03 – 1.90 (m, 2H), 1.90 – 1.79 (m, 3H).

EXAMPLE 166 and EXAMPLE 167

(*S*)-2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide and (*R*)-2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Example 56, 20 mg) were purified by chiral prep-HPLC (6, heptane/ EtOH + 0.2% DEA, 70:30) to give a first eluting peak (28.0 min) that was arbitraly asigned as (*S*)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (5.4 mg, 87% purity, chiral purity >99:1) as a white sticky solid and a second eluting peak (34.4 min) that was arbitraly asigned as (*R*)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (7.6 mg, 84% purity, chiral purity 99.5:2.5 of a second eluting peak (34.4 min) were obtained with a chiral purity of 99.5:2.5) as a white sticky solid.

(*S*)-enantiomer

LRMS (m/z): 673 $[M+1]^+$

LC (1) r.t. (min.): 1.69

(*R*)-enantiomer

LRMS (m/z): 673 $[M+1]^+$

LC (1) r.t. (min.): 1.79

EXAMPLE 168

***N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)morpholine-4-carboxamide**

Obtained as a white solid (56% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and morpholine-4-carbonyl chloride following the synthetic procedure as described for Example 69.

LRMS (m/z): 585 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43 (d, 2H), 7.38 (d, 2H), 7.33 (d, 2H), 7.26 (d, 2H), 6.57 (d, 1H), 6.31 (s, 1H), 6.19 (d, 1H), 6.05 (d, 1H), 4.51 (d, 2H), 4.29 (t, 2H), 3.78 – 3.72 (m, 4H), 3.56 (s, 2H), 3.51 – 3.45 (m, 4H), 3.11 (s, 3H), 3.04 – 2.93 (m, 5H), 2.50 – 2.41 (m, 2H), 2.31 – 2.23 (m, 2H), 2.07 – 1.93 (m, 2H).

EXAMPLE 169

***N*-(4-(cyclohexanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (61% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and cyclohexanecarboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 582 $[M+1]^+$

LC (1) r.t. (min.): 2.48

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.74 (s, 1H), 8.40 (t, 1H), 7.52 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.19 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.31 (d, 2H), 4.16 (t, 2H), 3.56 (s, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.45 – 2.35 (m, 2H), 2.35 – 2.25 (m, 1H), 2.23 – 2.13 (m, 2H), 2.04 – 1.93 (m, 1H), 1.89 (s, 1H), 1.81 – 1.70 (m, 4H), 1.68 – 1.61 (m, 1H), 1.46 – 1.32 (m, 2H), 1.32 – 1.12 (m, 3H).

EXAMPLE 170

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(pyrrolidine-1-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (56% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and pyrrolidine-1-carbonyl chloride following the synthetic procedure as described for Example 69.

LRMS (m/z): 569 $[M+1]^+$

LC (1) r.t. (min.): 1.90

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47 – 7.34 (m, 4H),7.28 – 7.22 (m, 4H), 6.57 (d, 1H), 6.19 (d, 1H), 6.15 (s, 1H), 6.03 (t, 1H), 4.50 (d, 2H), 4.29 (t, 2H), 3.56 (s, 2H), 3.50 – 3.43 (m, 4H), 3.16 – 3.06 (m, 3H), 3.03 – 2.92 (m, 5H), 2.50 – 2.39 (m, 2H), 2.32 – 2.22 (m, 2H), 2.08 – 1.91 (m, 6H).

EXAMPLE 171

***N*-(4-(azetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (40% yield, 95% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and azetidine following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 555 $[M+1]^+$

LC (1) r.t. (min.): 1.84

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.37 (t, 1H), 8.29 (s, 1H), 7.43 (dd, 4H), 7.35 (d, 2H), 7.14 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.30 (d, 2H), 4.17 (t, 2H), 3.92 (t, 4H), 3.56 (s, 2H), 3.01 – 2.88 (m, 6H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.11 (m, 4H), 2.03 – 1.93 (m, 1H), 1.93 – 1.81 (m, 1H).

EXAMPLE 172

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-ethyl-3-methylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (87% yield, 97% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and *N*-methylethanamine following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 557 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.38 (t, 1H), 8.16 (s, 1H), 7.45 (d, 2H), 7.37 (dd, 4H), 7.14 (d, 2H), 6.88 (d, 1H), 6.21 (d, 1H), 4.31 (d, 2H), 4.17 (t, 2H), 3.56 (s, 2H), 3.01 – 2.81 (m, 10H), 2.41 (q, 2H), 2.22 – 2.12 (m, 2H), 2.05 – 1.93 (m, 1H), 1.93 – 1.81 (m, 1H), 1.05 (t, 3H).

EXAMPLE 173

***N*-(4-(3-cyanoazetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (46% yield, 95% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and azetidine-3-carbonitrile hydrochloride following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 580 $[M+1]^+$

LC (1) r.t. (min.): 1.68

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.59 (s, 1H), 8.38 (t, 1H), 7.45 (d, 2H), 7.40 (d, 2H), 7.35 (d, 2H), 7.17 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.31 (d, 2H), 4.22 (t, 2H), 4.17 (t, 2H), 4.06 (dd, 2H), 3.79 – 3.67 (m, 1H), 3.56 (s, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.13 (m, 2H), 2.03 – 1.81 (m, 2H).

EXAMPLE 174

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-methoxyazetidine-1-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (42% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 3-methoxyazetidine hydrochloride following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 585 $[M+1]^+$

LC (1) r.t. (min.): 1.75

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.41 (s, 1H), 8.37 (t, 1H), 7.45 (d, 2H), 7.41 (d, 2H), 7.35 (d, 2H), 7.15 (d, 2H), 6.88 (d, 1H), 6.20 (d, 1H), 4.30 (d, 2H), 4.20 – 4.13 (m, 3H), 4.10 (dd, 2H), 3.73 (dd, 2H), 3.56 (s, 2H), 3.21 (s, 3H), 2.97 (s, 3H), 2.92 (s, 3H), 2.85 (t, 2H), 2.40 (q, 2H), 2.22 – 2.13 (m, 2H), 2.04 – 1.81 (m, 2H).

EXAMPLE 175

2'-(4-(d¡Dimethylcarbamoyl)benzyl)-*N*-(4-((1s,3s)-3-methoxycyclobutane-1-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (16% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and (1*s*,3*s*)-3-methoxycyclobutane-1-carboxylic acid following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 584 $[M+1]^+$

LC (1) r.t. (min.): 1.89

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.55 (s, 1H), 7.47 (d, 2H), 7.44 – 7.34 (m, 4H), 7.24 (d, 2H), 6.59 (d, 1H), 6.21 – 6.16 (m, 2H), 4.50 (d, 2H), 4.27 (t, 2H), 3.88 – 3.76 (m, 1H), 3.55 (s, 2H), 3.25 (s, 3H), 3.11 (s, 3H), 3.01 – 2.92 (m, 5H), 2.71 – 2.58 (m, 1H), 2.56 – 2.41 (m, 4H), 2.32 – 2.22 (m, 4H), 2.09 – 1.86 (m, 2H).

EXAMPLE 176

Isobutyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate

Obtained as a off-white solid (18% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and isobutyl carbonochloridate following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 572 $[M+1]^+$

LC (1) r.t. (min.): 2.50

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.53 (d, 2H), 7.44 – 7.38 (m, 4H), 7.27 (d, 2H), 6.87 (d, 1H), 6.28 (d, 1H), 5.51 (s, 1H), 4.45 (s, 2H), 4.24 (t, 2H), 3.92 (d, 2H), 3.64 (s, 2H), 3.12 (s, 3H), 3.07 – 2.97 (m, 5H), 2.58 – 2.46 (m, 2H), 2.35 – 2.25 (m, 2H), 2.11 - 2.05 (m, 1H), 2.00 – 1.95 (m, 2H), 1.00 (d, 6H).

EXAMPLE 177

***N*-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide**

Obtained as a white solid (36% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 2-oxa-6-azaspiro[3.3]heptane following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 597 $[M+1]^+$

LC (1) r.t. (min.): 1.72

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.29 (m, 6H), 7.23 (d, 2H), 6.59 (d, 1H), 6.23 (s, 1H), 6.21 – 6.14 (m, 2H), 4.78 (s, 4H), 4.49 (d, 2H), 4.27 (t, 2H), 4.17 (s, 4H), 3.55 (s, 2H), 3.11 (s, 3H), 2.98 (s, 2H), 2.95 (t, 2H), 2.52 – 2.39 (m, 2H), 2.31 – 2.21 (m, 2H), 2.08 – 1.89 (m, 2H).

EXAMPLE 178

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (38% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-

a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 661 $[M+1]^+$

LC (1) r.t. (min.): 2.41

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.93 (s, 1H), 8.43 (t, 1H), 7.88 (d, 2H), 7.69 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.25 (d, 2H), 7.02 (d, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.35 (d, 2H), 4.18 (t, 2H), 3.78 – 3.71 (m, 4H), 3.57 (s, 2H), 3.28 – 3.21 (m, 4H), 2.97 (s, 3H), 2.92 (s, 3H), 2.86 (t, 2H), 2.41 (q, 2H), 2.22 – 2.13 (m, 2H), 2.04 – 1.84 (m, 2H).

EXAMPLE 179

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a off-white solid (23% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 674 $[M+1]^+$

LC (1) r.t. (min.): 1.64

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.91 (s, 1H), 8.43 (t, 1H), 7.90 – 7.84 (m, 2H), 7.73 – 7.67 (m, 2H), 7.48 – 7.43 (m, 2H), 7.39 – 7.34 (m, 2H), 7.29 – 7.22 (m, 2H), 7.04 – 6.98 (m, 2H), 6.91 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.18 (t, 2H), 3.57 (s, 2H), 3.29 (t, 4H), 3.02 – 2.89 (m, 6H), 2.87 (t, 2H), 2.45 (t, 4H), 2.43 – 2.36 (m, 2H), 2.23 (s, 3H), 2.22 – 2.15 (m, 2H), 2.01 – 1.86 (m, 2H).

EXAMPLE 180

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylazetidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a off-white solid (41% yield, 95% purity) from *N*-(4-(4-(azetidin-3-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 106 TFA salt) and formaldehyde following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 645 $[M+1]^+$

LC (1) r.t. (min.): 1.64

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.15 (s, 1H), 8.43 (t, 1H), 7.92 (d, 2H), 7.70 (d, 2H), 7.48 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.27 (d, 2H), 6.90 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.18 (t, 2H), 3.73 – 3.64 (m, 3H), 3.57 (s, 2H), 3.19 (s, 2H), 3.01 – 2.89 (m, 6H), 2.86 (t, 2H), 2.46 – 2.36 (m, 2H), 2.32 (s, 3H), 2.23 – 2.13 (m, 2H), 2.05 – 1.93 (m, 1H), 1.93 – 1.82 (m, 1H).

EXAMPLE 181

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (32% yield, 85% purity) from *N*-(4-(4-bromobenzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 39c) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following the synthetic procedure as described for Intermediate 39d.

LRMS (m/z): 671 $[M+1]^+$

LC (1) r.t. (min.): 1.61

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.18 (s, 1H), 8.44 (t, 1H), 7.93 (d, 2H), 7.71 (d, 2H), 7.54 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.27 (d, 2H), 6.91 (d, 1H), 6.38 – 6.32 (m, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.18 (t, 2H), 3.57 (s, 2H), 3.27 – 3.22 (m, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.86 (t, 2H), 2.49 – 2.46 (m, 2H), 2.45 – 2.37 (m, 2H), 2.36 (s, 3H), 2.34 – 2.27 (m, 2H), 2.23 – 2.12 (m, 2H), 2.05 – 1.93 (m, 1H), 1.93 – 1.81 (m, 1H).

EXAMPLE 182

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (44% yield, 95% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(1-methylpiperidin-4-yl)benzoic acid hydrochloride following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 673 $[M+1]^+$

LC (1) r.t. (min.): 1.59

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.44 (t, 1H), 7.87 (d, 2H), 7.70 (d, 2H), 7.45 (d, 2H), 7.39 (d, 2H), 7.35 (d, 2H), 7.26 (d, 2H), 6.90 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.17 (t, 2H), 3.57 (s, 2H), 3.02 – 2.83 (m, 10H), 2.58 – 2.51 (m, 1H), 2.41 (q, 2H), 2.26 – 2.13 (m, 5H), 2.04 – 1.83 (m, 4H), 1.80 – 1.61 (m, 4H).

EXAMPLE 183

***N*-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as an off-white solid (26% yield, 91% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(4-cyclobutylpiperazin-1-yl)benzoic acid (Intermediate 107) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 714 $[M+1]^+$

LC (1) r.t. (min.): 1.67

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.91 (s, 1H), 8.43 (t, 1H), 7.90 – 7.85 (m, 2H), 7.73 – 7.64 (m, 2H), 7.49 – 7.44 (m, 2H), 7.39 – 7.34 (m, 2H), 7.28 – 7.22 (m, 2H), 7.03 – 6.98 (m, 2H), 6.91 (d, 1H), 6.22 (d, 1H), 4.36 (d, 2H), 4.18 (t, 2H), 3.57 (s, 2H), 3.28 (t, 4H), 3.02 – 2.90 (m, 6H), 2.86 (t, 2H), 2.74 (p, 1H), 2.47 – 2.35 (m, 6H), 2.24 – 2.15 (m, 2H), 2.05 – 1.96 (m, 3H), 1.93 – 1.77 (m, 3H), 1.72 – 1.61 (m, 2H).

EXAMPLE 184

***N*-(4-(4-(1-cyclobutylpiperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a yellow solid (19% yield, 92% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 41a) and 4-(1-cyclobutylpiperidin-4-yl)benzoic acid (Intermediate 108) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 713 $[M+1]^+$

LC (1) r.t. (min.): 2.26

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.43 (t, 1H), 7.92 – 7.83 (m, 2H), 7.76 – 7.66 (m, 2H), 7.45 (d, 2H), 7.42 – 7.32 (m, 4H), 7.31 – 7.23 (m, 2H), 6.90 (d, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 4.17 (t, 2H), 3.57 (s, 2H), 3.02 – 2.91 (m,

6H), 2.90 – 2.83 (m, 4H), 2.74 – 2.68 (m, 1H), 2.59 – 2.54 (m, 1H), 2.45 – 2.36 (m, 2H), 2.23 – 2.13 (m, 2H), 2.05 – 1.93 (m, 3H), 1.93 – 1.71 (m, 7H), 1.71 – 1.57 (m, 4H).

EXAMPLE 185

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (36% yield, 97% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and dimethylcarbamic chloride following the synthetic procedure as described for Example 69.

LRMS (m/z): 544 $[M+1]^+$

LC (1) r.t. (min.): 1.57

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.56 (d, 1H), 8.48 (t, 1H), 8.44 (s, 1H), 7.81 (dd, 1H), 7.45 (d, 2H), 7.35 (d, 2H), 7.18 (d, 1H), 6.93 (d, 1H), 6.22 (d, 1H), 4.40 (d, 2H), 4.16 (t, 2H), 3.57 (s, 2H), 3.02 – 2.90 (m, 12H), 2.85 (t, 2H), 2.41 (q, 2H), 2.24 – 2.13 (m, 2H), 2.05 – 1.82 (m, 2H).

EXAMPLE 186

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (49% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 675 $[M+1]^+$

LC (1) r.t. (min.): 1.73

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.18 (s, 1H), 8.85 (d, 1H), 8.63 – 8.48 (m, 1H), 8.12 (dd, 1H), 7.94 (d, 2H), 7.59 – 7.42 (m, 2H), 7.40 – 7.35 (m, 2H), 7.30 (d, 1H), 7.11 (d, 2H), 6.96 (s, 1H), 6.35 – 6.16 (m, 1H), 4.45 (d, 2H), 4.32 – 4.12 (m, 2H), 4.12 – 3.90 (m, 2H), 3.72 – 3.48 (m, 2H), 3.47 – 3.07 (m, 6H), 2.97 (s, 3H), 2.91 (s, 3H), 2.86 – 2.82 (m, 5H), 2.62 – 2.37 (m, 2H), 2.27 – 2.10 (m, 2H), 2.04 – 1.95 (m, 1H), 1.94 – 1.82 (m, 1H).

EXAMPLE 187

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (48% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 662 $[M+1]^+$

LC (1) r.t. (min.): 2.47

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.12 (s, 1H), 8.84 (d, 1H), 8.52 (t, 1H), 8.11 (dd, 1H), 7.90 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.29 (d, 1H), 7.03 (d, 2H), 6.95 (d, 1H), 6.23 (d, 1H), 4.45 (d, 2H), 4.17 (t, 2H), 3.78 – 3.71 (m, 4H), 3.57 (s, 2H), 3.29 – 3.23 (m, 4H), 2.97 (s, 3H), 2.91 (s, 3H), 2.86 (t, 2H), 2.41 (q, 2H), 2.24 – 2.14 (m, 2H), 2.05 – 1.94 (m, 1H), 1.93 – 1.82 (m, 1H).

EXAMPLE 188

***N*-((5-(4-(1-cyclobutylpiperidin-4-yl)benzamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (26% yield, 98% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and 4-(1-cyclobutylpiperidin-4-yl)benzoic acid (Intermediate 108) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 714 $[M+1]^+$

LC (1) r.t. (min.): 1.92

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.63 (s, 1H), 8.31 (s, 1H), 8.09 (d, 1H), 7.76 (d, 2H), 7.42 – 7.13 (m, 7H), 6.93 (s, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 4.56 (s, 2H), 4.18 (s, 2H), 3.46 (s, 2H), 3.02 (s, 3H), 2.98 – 2.94 (m, 2H), 2.91 (s, 3H), 2.88 – 2.84 (m, 2H), 2.74 – 2.63 (m, 1H), 2.58 – 2.45 (m, 1H), 2.42 – 2.29 (m, 2H), 2.19 (s, 2H), 2.11 – 1.53 (m, 14H).

EXAMPLE 189

***N*-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (34% yield, 96% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((5-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 109) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 704 $[M+1]^+$

LC (1) r.t. (min.): 1.87

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.84 (s, 1H), 8.77 (d, 1H), 8.51 (t, 1H), 8.08 (s, 1H), 8.03 (dd, 1H), 7.45 (d, 2H), 7.35 (d, 2H), 7.28 (d, 1H), 6.94 (d, 1H), 6.23 (d, 1H), 4.44 (d, 2H), 4.26 – 4.13 (m, 3H), 3.57 (s, 2H), 3.06 – 2.99 (m, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.86 (t, 2H), 2.55 (s, 3H), 2.47 – 2.29 (m, 4H), 2.23 – 2.14 (m, 2H), 2.04 – 1.83 (m, 4H), 1.82 – 1.75 (m, 2H), 1.69 – 1.60 (m, 1H), 0.47 – 0.39 (m, 2H), 0.34 – 0.29 (m, 2H).

EXAMPLE 190

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (14% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 32) and 5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 1.77

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.63 (d, 1H), 8.09 (dd, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.45 – 7.34 (m, 4H), 7.31 (d, 1H), 6.93 (t, 1H), 6.71 (d, 1H), 6.21 (d, 1H), 4.64 (d, 2H), 4.27 (t, 2H), 4.07 (s, 1H), 3.55 (s, 2H), 3.11 (s, 3H), 3.07 (s, 2H), 2.99 (s, 3H), 2.96 (t, 2H), 2.62 (s, 3H), 2.51 – 2.11 (m, 11H), 2.10 – 1.83 (m, 4H).

EXAMPLE 191

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(2-fluoro-4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (46% yield, 97% purity) from *N*-(4-amino-2-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 110) and 4-(1-methylpiperidin-4-yl)benzoic acid hydrochloride following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 691 $[M+1]^+$

LC (1) r.t. (min.): 1.72

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.96 (s, 1H), 7.81 (d, 2H), 7.72 (dd, 1H), 7.44 – 7.31 (m, 7H), 7.16 (dd, 1H), 6.61 (d, 1H), 6.25 – 6.17 (m, 2H), 4.57 (d, 2H), 4.26 (t, 2H), 3.54 (s, 2H), 3.11 (s, 3H), 3.05 – 2.97 (m, 5H), 2.94 (t, 2H), 2.62 – 2.51 (m, 1H), 2.44 (q, 2H), 2.35 (s, 3H), 2.31 – 2.22 (m, 2H), 2.16 – 1.98 (m, 3H), 1.98 – 1.89 (m, 1H), 1.89 – 1.81 (m, 4H).

EXAMPLE 192

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (48% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(2-fluoro-4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 111) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 695 $[M+1]^+$

LC (1) r.t. (min.): 1.61

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (s, 1H), 7.73 (s, 1H), 7.62 (dd, 1H), 7.43 – 7.34 (m, 4H), 7.31 (t, 1H), 7.09 (dd, 1H), 6.60 (d, 1H), 6.23 (t, 1H), 6.19 (d, 1H), 4.54 (d, 2H), 4.25 (t, 2H), 4.09 – 3.98 (m, 1H), 3.53 (s, 2H), 3.10 (s, 3H), 3.05 – 2.96 (m, 5H), 2.93 (t, 2H), 2.61 (s, 3H), 2.44 (q, 2H), 2.33 (s, 3H), 2.36 – 2.20 (m, 4H), 2.18 – 1.83 (m, 6H).

EXAMPLE 193

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (63% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 112) and oxetane-3-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 592 $[M+1]^+$

LC (1) r.t. (min.): 2.18

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (s, 1H), 8.43 (t, 1H), 7.54 (d, 2H), 7.23 (d, 2H), 7.17 (d, 2H), 6.89 (d, 1H), 6.22 (d, 1H), 4.73 – 4.65 (m, 4H), 4.33 (d, 2H), 4.23 (t, 2H), 3.93 (p, 1H), 3.53 (s, 2H), 2.97 (s, 3H), 2.95 – 2.88 (m, 5H), 2.39 (q, 2H), 2.18 (m, 2H), 2.04 – 1.90 (m, 1H), 1.91 – 1.76 (m, 1H).

EXAMPLE 194

2'-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (37% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 113) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 713 $[M+1]^+$

LC (1) r.t. (min.): 2.46

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.43 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.23 (d, 2H), 7.18 (d, 2H), 6.90 (d, 1H), 6.22 (d, 1H), 4.35 (d, 2H), 4.24 (t, 2H), 4.19 – 4.09 (m, 1H), 3.53 (s, 2H), 2.97 (s, 3H), 2.94 – 2.88 (m, 5H), 2.86 (d, 2H), 2.54 (s, 3H), 2.45 – 2.34 (m, 2H), 2.25 – 2.13 (m, 5H), 2.10 – 1.92 (m, 5H), 1.92 – 1.81 (m, 1H), 1.81 – 1.71 (m, 2H).

EXAMPLE 195

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (36% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 115) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 718 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.73 (s, 1H), 7.63 (t, 1H), 7.53 (d, 2H), 7.47 (s, 1H), 7.43 – 7.36 (m, 4H), 7.32 (d, 2H), 7.08 (s, 1H), 4.54 (d, 2H), 4.33 (t, 2H), 4.12 – 3.97 (m, 1H), 3.54 (s, 2H), 3.11 (s, 3H), 3.08 – 2.97 (m, 5H), 2.95 (t, 2H), 2.82 – 2.71 (m, 1H), 2.61 (s, 3H), 2.53 – 2.42 (m, 2H), 2.33 – 2.18 (m, 4H), 2.05 (s, 4H), 1.89 (s, 8H).

EXAMPLE 196

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (42% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 662 $[M+1]^+$

LC (1) r.t. (min.): 3.11

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H), 7.76 (s, 1H), 7.64 (t, 1H), 7.60 (d, 2H), 7.45 – 7.36 (m, 4H), 7.34 (d, 2H), 7.08 (s, 1H), 6.92 (d, 2H), 4.56 (d, 2H), 4.34 (t, 2H), 3.90 – 3.84 (m, 4H), 3.54 (s, 2H), 3.31 – 3.24 (m, 4H), 3.11 (s, 3H), 3.02 – 2.92 (m, 5H), 2.48 (q, 2H), 2.31 – 2.21 (m, 2H), 2.12 – 1.91 (m, 2H).

EXAMPLE 197

***N*-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (15% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(4-cyclobutylpiperazin-1-yl)benzoic acid (Intermediate 107) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 715 $[M+1]^+$

LC (1) r.t. (min.): 2.51

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.91 (s, 1H), 8.87 (t, 1H), 7.91 – 7.84 (m, 2H), 7.72 – 7.68 (m, 2H), 7.50 – 7.43 (m, 2H), 7.39 – 7.34 (m, 2H), 7.31 – 7.25 (m, 2H), 7.20 (s, 1H), 7.03 – 6.97 (m, 2H), 4.38 (d, 2H), 4.26 (t, 2H), 3.56 (s, 2H), 3.31 – 3.24 (m, 4H), 3.02 – 2.90 (m, 6H), 2.88 (t, 2H), 2.79 – 2.69 (m, 1H), 2.47 – 2.39 (m, 2H), 2.39 – 2.35 (m, 4H), 2.25 – 2.16 (m, 2H), 2.08 – 1.95 (m, 3H), 1.95 – 1.77 (m, 3H), 1.72 – 1.60 (m, 2H).

EXAMPLE 198

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(6-morpholinonicotinamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (10% yield, 99% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 6-morpholinonicotinic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 664 $[M+1]^+$

LC (4e) r.t. (min.): 2.88

^{1}H NMR (MeOD, 500 MHz): δ (ppm) 8.74 (d, J = 2.5 Hz, 1H), 8.11 (dd, J = 9.0, 2.6 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.57 – 7.51 (m, 2H), 7.45 – 7.41 (m, 2H), 7.41 – 7.36 (m, 2H), 7.23 (s, 1H), 6.88 (d, J = 9.1 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.58 – 4.53 (m, 2H), 4.39 – 4.31 (m, 2H), 3.83 – 3.79 (m, 3H), 3.70 – 3.63 (m, 5H), 3.15 – 3.09 (m, 3H), 3.05 – 3.00 (m, 4H), 2.60 – 2.52 (m, 2H), 2.35 – 2.28 (m, 2H), 2.16 – 2.09 (m, 1H), 2.08 – 2.00 (m, 1H).

EXAMPLE 199

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-morpholinobenzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide formate

Obtained as a white solid (41% yield, 99% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 3-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 662 $[M+1]^+$

LC (1) r.t. (min.): 2.63

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.88 (t, 1H), 8.13 (s, 1H), 7.68 (d, 2H), 7.49 – 7.42 (m, 3H), 7.36 (dd, 4H), 7.29 (d, 2H), 7.20 (s, 1H), 7.15 (dd, 1H), 4.38 (d, 2H), 4.24 (d, 2H), 3.76 (t, 4H), 3.56 (s, 2H), 3.18 (t, 4H), 3.04 – 2.82 (m, 8H), 2.46 – 2.38 (m, 2H), 2.23 – 2.13 (m, 2H), 2.08 – 1.97 (m, 1H), 1.96 – 1.80 (m, 1H).

EXAMPLE 200

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (53% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(1-methylpiperidin-4-yl)benzoic acid hydrochloride following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 674 $[M+1]^+$

LC (1) r.t. (min.): 1.91

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.90 (t, 1H), 7.87 (d, 2H), 7.69 (d, 2H), 7.46 (d, 2H), 7.39 (d, 2H), 7.35 (d, 2H), 7.29 (d, 2H), 7.19 (s, 1H), 4.38 (d, 2H), 4.25 (t, 2H), 3.55 (s, 2H), 2.97 (s, 3H), 2.93 – 2.83 (m, 7H), 2.55 (d, 1H), 2.42 (q, 2H), 2.19 (s, 5H), 2.08 – 1.84 (m, 4H), 1.79 – 1.62 (m, 4H).

EXAMPLE 201

***N*-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as an off-white solid (48% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 92) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 701 $[M+1]^+$

LC (1) r.t. (min.): 1.95

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.91 (s, 1H), 8.86 (t, 1H), 7.89 – 7.81 (m, 2H), 7.72 – 7.66 (m, 2H), 7.50 – 7.45 (m, 2H), 7.38 – 7.34 (m, 2H), 7.30 – 7.25 (m, 2H), 7.20 (s, 1H), 7.03 – 6.97 (m, 2H), 4.38 (d, 2H), 4.25 (t, 2H), 3.55 (s, 2H), 3.26 – 3.23 (m, 4H), 3.01 – 2.90 (m, 6H), 2.90 – 2.86 (m, 2H), 2.69 – 2.65 (m, 4H), 2.48 – 2.38 (m, 2H), 2.25 – 2.16 (m, 2H), 2.07 – 1.99 (m, 1H), 1.93 – 1.87 (m, 1H), 1.69 – 1.63 (m, 1H), 0.48 – 0.43 (m, 2H), 0.38 – 0.33 (m, 2H).

EXAMPLE 202

***N*1-(4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)-*N*^{2},*N*^{2}-dimethyloxalamide**

Obtained as a white solid (55% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 2-(dimethylamino)-2-oxo-acetic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 572 $[M+1]^+$

LC (1) r.t. (min.): 2.05

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.65 (s, 1H), 8.88 (t, 1H), 7.60 – 7.54 (m, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.32 (m, 2H), 7.32 – 7.26 (m, 2H), 7.19 (s, 1H), 4.36 (d, 2H), 4.23 (t, 2H), 3.55 (s, 2H), 3.02 (s, 3H), 3.00 – 2.89 (m, 11H), 2.46 – 2.36 (m, 2H), 2.24 – 2.15 (m, 2H), 2.09 – 1.83 (m, 2H).

EXAMPLE 203

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (43% yield, 99% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 662 $[M+1]^+$

LC (1) r.t. (min.): 2.64

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.87 (s, 1H), 8.86 (t, 1H), 7.88 – 7.83 (m, 2H), 7.71 – 7.63 (m, 2H), 7.50 – 7.44 (m, 2H), 7.39 – 7.33 (m, 2H), 7.30 – 7.24 (m, 2H), 7.20 (s, 1H), 6.52 – 6.45 (m, 2H), 4.41 – 4.33 (m, 3H), 4.28 – 4.22 (m, 2H), 4.18 – 4.10 (m, 2H), 3.73 – 3.70 (m, 2H), 3.55 (s, 2H), 3.26 (s, 3H), 2.99 – 2.90 (m, 6H), 2.90 – 2.86 (m, 2H), 2.47 – 2.38 (m, 2H), 2.23 – 2.16 (m, 2H), 2.06 – 1.98 (m, 1H), 1.95 – 1.86 (m, 1H).

EXAMPLE 204

Isobutyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate

N-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114, 60 mg, 0.13 mmol) was dissolved in pyridine (1 mL) and isobutyl carbonochloridate (16.5 µL, 0.13 mmol) was added. The RM was stirred at r.t. for 1h and after reaction completion, the reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (5c) to give the title compound (40.5 mg, 55% yield, 99% purity) as an off white solid.

LRMS (m/z): 573 $[M+1]^+$

LC (1) r.t. (min.): 2.86

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.54 (s, 1H), 8.82 (t, 1H), 7.48 – 7.44 (m, 2H), 7.42 – 7.33 (m, 4H), 7.26 – 7.20 (m, 2H), 7.19 (s, 1H), 4.34 (d, 2H), 4.24 (t, 2H), 3.85 (d, 2H), 3.55 (s, 2H), 3.02 – 2.84 (m, 8H), 2.48 – 2.36 (m, 2H), 2.26 – 2.16 (m, 2H), 2.08 – 1.97 (m, 1H), 1.96 – 1.84 (m, 2H), 0.93 (d, 6H).

EXAMPLE 205

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(2-morpholinopyrimidine-5-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (47% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 2-morpholinopyrimidine-5-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 664 $[M+1]^+$

LC (1) r.t. (min.): 2.45

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.09 (s, 1H), 8.91 (s, 2H), 8.88 (t,1H), 7.68 – 7.62 (m, 2H), 7.49 – 7.44 (m, 2H), 7.38 – 7.34 (m, 2H), 7.32 – 7.27 (m, 2H), 7.20 (s, 1H), 4.39 (d, 2H), 4.25 (t, 2H), 3.85 – 3.80 (m, 4H), 3.71 – 3.65 (m, 4H), 3.56 (s, 2H), 3.00 – 2.83 (m, 8H), 2.47 – 2.37 (m, 2H), 2.25 – 2.14 (m, 2H), 2.06 – 1.98 (m, 1H), 1.96 – 1.85 (m, 1H).

EXAMPLE 206

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxypyrrolidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (42% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(3-methoxypyrrolidin-1-yl)benzoic acid (Intermediate 117) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 676 $[M+1]^+$

LC (1) r.t. (min.): 2.76

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.77 (d, 2H), 7.74 – 7.63 (m, 2H), 7.60 (d, 2H), 7.49 – 7.37 (m, 4H), 7.34 (d, 2H), 7.16 – 7.05 (m, 1H), 6.57 (d, 2H), 4.56 (d, 2H), 4.43 – 4.27 (m, 2H), 4.13 (m, 1H), 3.59 – 3.39 (m, 6H), 3.38 (s, 3H), 3.12 (s, 3H), 3.05 – 2.92 (m, 5H), 2.57 – 2.38 (m, 2H), 2.32 – 1.93 (m, 6H).

EXAMPLE 207

***N*-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (31% yield, 100% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 118) and 2,2-difluoroethyl trifluoromethanesulfonate following the synthetic procedure as described for Example 152.

LRMS (m/z): 728 $[M+1]^+$

LC (1) r.t. (min.): 2.12

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.85 (t, 1H), 8.07 (s, 1H), 7.61 (d, 2H), 7.46 (d, 2H), 7.35 (d, 2H), 7.26 (d, 2H), 7.19 (s, 1H), 6.15 (tt, 1H), 4.36 (d, 2H), 4.24 (t, 2H), 4.23 – 4.14 (m, 1H), 3.55 (s, 2H), 3.04 – 2.95 (m, 5H), 2.91 (s, 3H), 2.87 (t, 2H), 2.78 (td, 2H), 2.54 (s, 3H), 2.47 – 2.33 (m, 4H), 2.24 – 2.15 (m, 2H), 2.09 – 1.97 (m, 3H), 1.96 – 1.84 (m, 1H), 1.83 – 1.75 (m, 2H).

EXAMPLE 208

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as an off-white solid (40% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(1-(oxetan-3-yl)piperidin-4-yl)benzoic acid (Intermediate 119) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 716 $[M+1]^+$

LC (1) r.t. (min.): 1.90

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.87 (t, 1H), 7.93 – 7.84 (m, 2H), 7.75 – 7.62 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.25 (m, 2H), 7.19 (s, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.38 (d, 2H), 4.25 (t, 2H), 3.55 (s, 2H), 3.47 – 3.36 (m, 1H), 3.00 – 2.90 (m, 6H), 2.89 – 2.85 (m, 2H), 2.85 – 2.77 (m, 2H), 2.66 – 2.53 (m, 1H), 2.42 (dt, 2H), 2.23 – 2.13 (m, 2H), 2.09 – 1.96 (m, 1H), 1.94 – 1.83 (m, 3H), 1.81 – 1.64 (m, 4H).

EXAMPLE 209

***N*-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a yellow oil (80% yield, 93% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 118) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 704 $[M+1]^+$

LC (1) r.t. (min.): 1.88

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.86 (t, 1H), 8.05 (s, 1H), 7.61 (d, 2H), 7.46 (d, 2H), 7.35 (d, 2H), 7.26 (d, 2H), 7.19 (s, 1H), 4.36 (d, 2H), 4.24 (t, 2H), 4.21 – 4.15 (m, 1H), 3.55 (s, 2H), 3.06 – 2.99 (m, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.87 (t, 2H), 2.54 (s, 3H), 2.47 – 2.29 (m, 4H), 2.24 – 2.15 (m, 2H), 2.08 – 1.86 (m, 4H), 1.82 – 1.74 (m, 2H), 1.68 – 1.61 (m, 1H), 0.43 (d, 2H), 0.32 (d, 2H).

EXAMPLE 210

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (57% yield, 100% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 599 $[M+1]^+$

LC (1) r.t. (min.): 2.32

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.19 (s, 1H), 8.85 (t, 1H), 7.52 (d, 2H), 7.45 (d, 2H), 7.35 (d, 2H), 7.25 (d, 2H), 7.19 (s, 1H), 4.90 (dtd, 1H), 4.35 (d, 2H), 4.24 (t, 2H), 3.55 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.87 (t, 2H), 2.41 (q, 2H), 2.23 – 2.15 (m, 2H), 1.99 (m, 3H), 1.61 (dtd, 1H), 1.11 (ddt, 1H).

EXAMPLE 211

***N*-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (40% yield, 89% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 120) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 676 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (s, 1H), 7.62 (t, 1H), 7.54 (d, 2H), 7.50 (s, 1H), 7.44 – 7.35 (m, 4H), 7.32 (d, 2H), 7.08 (s, 1H), 4.94 – 4.85 (m, 1H), 4.54 (d, 2H), 4.33 (t, 2H), 3.86 (t, 2H), 3.78 (t, 2H), 3.54 (s, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 2.95 (t, 2H), 2.55 (d, 3H), 2.48 (q, 2H), 2.30 – 2.21 (m, 2H), 2.12 – 1.93 (m, 3H), 0.48 – 0.40 (m, 4H).

EXAMPLE 212

***N*-(4-(1-(1-cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (44% yield, 89% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 1-(1-cyclobutylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 121) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 690 $[M+1]^+$

LC (1) r.t. (min.): 2.04

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (s, 1H), 7.61 (t, 1H), 7.54 (d, 2H), 7.47 (s, 1H), 7.45 – 7.35 (m, 4H), 7.32 (d, 2H), 7.08 (s, 1H), 4.93 (p, 1H), 4.55 (d, 2H), 4.34 (t, 2H), 3.76 (t, 2H), 3.61 (t, 2H), 3.54 (s, 2H), 3.33 – 3.24 (m, 1H), 3.11 (s, 3H), 2.99 (s, 3H), 2.96 (t, 2H), 2.56 (s, 3H), 2.48 (q, 2H), 2.30 – 2.21 (m, 2H), 2.13 – 1.84 (m, 6H), 1.84 – 1.64 (m, 2H).

EXAMPLE 213

***N*-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (53% yield, 93% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 114) and 4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzoic acid hydrochloride (Intermediate 122) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 724 $[M+1]^+$

LC (1) r.t. (min.): 2.27

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 10.13 (s, 1H), 8.87 (t, 1H), 7.93 – 7.79 (m, 2H), 7.76 – 7.61 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.37 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 2H), 7.19 (s, 1H), 6.15 (tt, 1H), 4.38 (d, 2H), 4.25 (t, 2H), 3.55 (s, 2H), 3.02 (d, 2H), 2.99 – 2.90 (m, 6H), 2.87 (t, 2H), 2.76 (td, 2H), 2.58 (td, 1H), 2.42 (dt, 2H), 2.28 (td, 2H), 2.24 – 2.14 (m, 2H), 2.06 – 1.97 (m, 1H), 1.94 – 1.84 (m, 1H), 1.79 – 1.63 (m, 4H).

EXAMPLE 214

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (39% yield, 96% purity) from *N*-((5-aminopyridin-2-yl)methyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-*5'H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 123) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 676 $[M+1]^+$

LC (1) r.t. (min.): 1.64

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.90 (t, 1H), 8.84 (d, 1H), 8.12 (dd, 1H), 7.89 (d, 2H), 7.46 (d, 2H), 7.35 (d, 2H), 7.31 (d, 1H), 7.23 (s, 1H), 7.02 (d, 2H), 4.50 (d, 2H), 4.25 (t, 2H), 3.56 (s, 2H), 3.33 – 3.26 (m, 4H), 2.97 (s, 3H), 2.93 – 2.84 (m, 5H), 2.50 – 2.36 (m, 6H), 2.28 – 2.15 (m, 5H), 2.12 – 1.97 (m, 1H), 1.98 – 1.82 (m, 1H).

EXAMPLE 215

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (11% yield, 98% purity) from *N*-((5-aminopyridin-2-yl)methyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-*5'H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 123) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 2.92

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.15 (s, 1H), 8.88 (t, 1H), 8.85 (d, 1H), 8.13 (dd, 1H), 7.94 – 7.89 (m, 2H), 7.49 – 7.45 (m, 2H), 7.39 – 7.35 (m, 2H), 7.32 (d, 1H), 7.23 (s, 1H), 7.07 – 7.02 (m, 2H), 4.51 (d, 2H), 4.26 (t, 2H), 3.79 – 3.72 (m, 4H), 3.57 (s, 2H), 3.29 – 3.25 (m, 4H), 3.01 – 2.91 (m, 6H), 2.89 (t, 2H), 2.47 – 2.40 (m, 2H), 2.25 – 2.19 (m, 2H), 2.08 – 2.00 (m, 1H), 1.96 – 1.88 (m, 1H).

EXAMPLE 216

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (28% yield, 98% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 711 $[M+1]^+$

LC (1) r.t. (min.): 2.58

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.10 (s, 1H), 8.84 (d, 1H), 8.59 (t, 1H), 8.11 (dd, 1H), 7.88 (d, 2H), 7.46 (d, 2H), 7.36 (d, 2H), 7.29 (d, 1H), 7.02 (d, 2H), 6.95 (d, 1H), 6.15 (d, 1H), 4.45 (d, 2H), 4.24 (t, 2H), 3.61 (s, 2H), 3.31 – 3.26 (m, 4H), 3.12 – 3.00 (m, 2H), 2.99 – 2.84 (m, 10H), 2.48 – 2.41 (m, 4H), 2.22 (s, 3H).

EXAMPLE 217

***N*-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (40% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 125) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 740 $[M+1]^+$

LC (1) r.t. (min.): 2.60

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.84 (s, 1H), 8.77 (d, 1H), 8.58 (t, 1H), 8.08 (s, 1H), 8.04 (dd, 1H), 7.46 (d, 2H), 7.36 (d, 2H), 7.28 (d, 1H), 6.95 (d, 1H), 6.15 (d, 1H), 4.44 (d, 2H), 4.27 – 4.16 (m, 3H), 3.60 (s, 2H), 3.15 – 2.84 (m, 14H), 2.55 (s, 3H), 2.39 – 2.29 (m, 2H), 2.01 – 1.89 (m, 2H), 1.78 (d, 2H), 1.69 – 1.61 (m, 1H), 0.47 – 0.40 (m, 2H), 0.34 – 0.28 (m, 2H).

EXAMPLE 218

***N*-((5-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (41% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid (Intermediate 115) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 754 $[M+1]^+$

LC (1) r.t. (min.): 2.61

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.85 (s, 1H), 8.77 (d, 1H), 8.58 (t, 1H), 8.09 (s, 1H), 8.04 (dd, 1H), 7.46 (d, 2H), 7.36 (d, 2H), 7.28 (d, 1H), 6.95 (d, 1H), 6.15 (d, 1H), 4.44 (d, 2H), 4.23 (t, 2H), 4.21 – 4.11 (m, 1H), 3.60 (s, 2H), 3.08 (q, 2H), 2.99 – 2.83 (m, 12H), 2.78 – 2.67 (m, 1H), 2.55 (s, 3H), 2.05 – 1.92 (m, 4H), 1.92 – 1.75 (m, 6H), 1.68 – 1.57 (m, 2H).

EXAMPLE 219

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-((5-(1-methyl-1*H*-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (33% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 1-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 617 $[M+1]^+$

LC (1) r.t. (min.): 2.80

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.65 (s, 1H), 8.13 (d, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.44 – 7.36 (m, 4H), 7.32 (d, 1H), 7.00 (t, 1H), 6.71 (d, 1H), 6.18 (d, 1H), 4.65 (d, 2H), 4.32 (t, 2H), 3.97 (s, 3H), 3.61 (s, 2H), 3.21 – 2.89 (m, 12H).

EXAMPLE 220

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-((5-(1-methyl-1*H*-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihdro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (53% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 1-methyl-1*H*-pyrazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 617 $[M+1]^+$

LC (1) r.t. (min.): 2.78

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.00 (s, 1H), 8.77 (d, 1H), 8.23 (dd, 1H), 7.63 (s, 1H), 7.46 – 7.36 (m, 5H), 7.34 (d, 1H), 7.00 (t, 1H), 6.71 (d, 1H), 6.18 (d, 1H), 4.66 (d, 2H), 4.33 (t, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 3.18 – 2.88 (m, 12H).

EXAMPLE 221

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (39% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 124) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 698 $[M+1]^+$

LC (1) r.t. (min.): 3.02

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.12 (s, 1H), 8.84 (d, 1H), 8.58 (t, 1H), 8.11 (dd, 1H), 7.91 (d, 2H), 7.46 (d, 2H), 7.36 (d, 2H), 7.29 (d, 1H), 7.03 (d, 2H), 6.95 (d, 1H), 6.15 (d, 1H), 4.45 (d, 2H), 4.23 (t, 2H), 3.78 – 3.71 (m, 4H), 3.61 (s, 2H), 3.28 – 3.24 (m, 4H), 3.08 (q, 2H), 2.99 – 2.89 (m, 10H).

EXAMPLE 222

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(1-methyl-1*H*-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (38% yield, 92% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 126) and 1-methyl-1H-imidazole-4-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 619 $[M+1]^+$

LC (1) r.t. (min.): 2.86

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.95 (s, 1H), 7.67 (d, 2H), 7.61 (d, 1H), 7.46 – 7.36 (m, 5H), 7.32 (d, 2H), 6.18 – 6.10 (m, 2H), 4.53 (d, 2H), 4.35 (t, 2H), 3.77 (s, 3H), 3.62 (s, 2H), 3.11 (s, 3H), 3.07 – 2.85 (m, 10H).

EXAMPLE 223

***N*-(4-(Cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (46% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-

pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 126) and cyclopropanecarboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 576 $[M+1]^+$

LC (1) r.t. (min.): 3.00

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.55 – 7.36 (m, 7H), 7.28 (d, 2H), 6.57 (d, 1H), 6.19 – 6.14 (m, 2H), 4.51 (d, 2H), 4.34 (t, 2H), 3.62 (s, 2H), 3.12 (s, 3H), 3.07 – 2.89 (m, 9H), 1.55 – 1.44 (m, 1H), 1.12 – 1.04 (m, 2H), 0.89 – 0.79 (m, 2H).

EXAMPLE 224

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (68% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 126) and dimethylcarbamic chloride following the synthetic procedure as described for Example 69.

LRMS (m/z): 579 $[M+1]^+$

LC (1) r.t. (min.): 3.04

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.45 (t, 1H), 8.22 (s, 1H), 7.46 (d, 2H), 7.42 – 7.33 (m, 4H), 7.15 (d, 2H), 6.89 (d, 1H), 6.12 (d, 1H), 4.31 (d, 2H), 4.24 (t, 2H), 3.60 (s, 2H), 3.11 – 3.00 (m, 2H), 3.00 – 2.85 (m, 16H).

EXAMPLE 225

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (68% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 127) and formaldehyde following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 713 $[M+1]^+$

LC (1) r.t. (min.): 2.74

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.50 (t, 1H), 8.07 (s, 1H), 7.62 (d, 2H), 7.46 (d, 2H), 7.36 (d, 2H), 7.24 (d, 2H), 6.90 (d, 1H), 6.13 (d, 1H), 4.35 (d, 2H), 4.24 (t, 2H), 4.20 – 4.04 (m, 1H), 3.60 (s, 2H), 3.15 – 3.00 (m, 2H), 3.00 – 2.82 (m, 12H), 2.54 (s, 3H), 2.20 (s, 3H), 2.10 – 1.95 (m, 4H), 1.82 – 1.72 (m, 2H).

EXAMPLE 226

2'-(4-(Dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (41% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 126) and 4-(1-methylpiperidin-4-yl)benzoic acid hydrochloride following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 709 $[M+1]^+$

LC (1) r.t. (min.): 2.26

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.52 (t, 1H), 7.87 (d, 2H), 7.70 (d, 2H), 7.46 (d, 2H), 7.39 (d, 2H), 7.36 (d, 2H), 7.27 (d, 2H), 6.91 (d, 1H), 6.13 (d, 1H), 4.36 (d, 2H), 4.24 (t, 2H), 3.60 (s, 2H), 3.11 – 3.00 (m, 2H), 2.99 – 2.83 (m, 12H), 2.58 – 2.52 (m, 1H), 2.19 (s, 3H), 2.01 – 1.92 (m, 2H), 1.79 – 1.64 (m, 4H).

EXAMPLE 227

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (62% yield, 100% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 127) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 753 $[M+1]^+$

LC (1) r.t. (min.): 2.49

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.73 (s, 1H), 7.54 (d, 2H), 7.45 – 7.36 (m, 5H), 7.31 (d, 2H), 6.56 (d, 1H), 6.16 (d, 1H), 6.11 (t, 1H), 4.53 (d, 2H), 4.34 (t, 2H), 4.11 – 3.95 (m, 1H), 3.62 (s, 2H), 3.19 – 2.85 (m, 14H), 2.85 – 2.72 (m, 1H), 2.61 (s, 3H), 2.37 – 2.19 (m, 2H), 2.14 – 2.00 (m, 2H), 1.98 – 1.80 (m, 5H), 1.79 – 1.60 (m, 3H).

EXAMPLE 228

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (49% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 2.45

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.94 (s, 1H), 8.53 (t, 1H), 7.93 – 7.86 (m, 2H), 7.74 – 7.67 (m, 2H), 7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.28 – 7.23 (m, 2H), 7.06 – 7.00 (m, 2H), 6.97 (d, 1H), 6.43 (d, 1H), 4.90 (d, 2H), 4.66 (d, 2H), 4.36 (d, 2H), 4.20 (t, 2H), 3.87 (s, 2H), 3.77 – 3.74 (m, 4H), 3.26 – 3.24 (m, 4H), 3.01 – 2.91 (m, 6H), 2.82 (t, 2H).

EXAMPLE 229

***N*-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as an off-white solid (10% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 92) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 702 $[M+1]^+$

LC (1) r.t. (min.): 1.93

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.91 (s, 1H), 8.52 (t, 1H), 7.90 – 7.81 (m, 2H), 7.72 – 7.66 (m, 2H), 7.53 – 7.47 (m, 2H), 7.42 – 7.35 (m, 2H), 7.27 – 7.21 (m, 2H), 7.03 – 6.94 (m, 3H), 6.42 (d, 1H), 4.90 (d, 2H), 4.66 (d, 2H), 4.36 (d, 2H), 4.19 (t, J = 5.7 Hz, 2H), 3.87 (s, 2H), 3.27 – 3.22 (m, 4H), 3.04 – 2.89 (m, 6H), 2.86 – 2.78 (m, 2H), 2.74 – 2.62 (m, 4H), 1.71 – 1.61 (m, 1H), 0.48 – 0.42 (m, 2H), 0.39 – 0.33 (m, 2H).

EXAMPLE 230

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (16% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(1-methylpiperidin-4-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 675 $[M+1]^+$

LC (1) r.t. (min.): 1.84

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.53 (t, 1H), 7.91 – 7.85 (m, 2H), 7.73 – 7.65 (m, 2H), 7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 4H), 7.29 – 7.23 (m, 2H), 6.96 (d, 1H), 6.43 (d, 1H), 4.90 (d, 2H), 4.66 (d, 2H), 4.36 (d, 2H), 4.24 – 4.16 (m, 2H), 3.87 (s, 2H), 3.51 – 3.50 (m, 1H), 3.00 – 2.92 (m, 6H), 2.90 – 2.86 (m, 2H), 2.85 – 2.80 (m, 2H), 2.20 (s, 3H), 2.04 – 1.92 (m, 2H), 1.80 – 1.65 (m, 4H).

EXAMPLE 231

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (4% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 677 $[M+1]^+$

LC (4e) r.t. (min.): 1.69

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.91 (s, 1H), 8.52 (t, 1H), 7.88 – 7.84 (m, 2H), 7.72 – 7.66 (m, 2H), 7.53 – 7.48 (m, 2H), 7.41 – 7.37 (m, 2H), 7.27 – 7.23 (m, 2H), 7.03 – 6.99 (m, 2H), 6.97 (d, 1H), 6.43 (d, 1H), 4.90 (d, 2H), 4.66 (d, 2H), 4.36 (d, 2H), 4.20 (t, 2H), 3.87 (s, 2H), 3.31 – 3.26 (m, 4H), 3.00 – 2.92 (m, 6H), 2.82 (t, 2H), 2.48 – 2.42 (m, 4H), 2.23 (s, 3H).

EXAMPLE 232

***N*-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as an off-white solid (21% yield, 96% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(4-cyclobutylpiperazin-1-yl)benzoic acid (Intermediate 107) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 716 $[M+1]^+$

LC (1) r.t. (min.): 1.87

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.90 (s, 1H), 8.51 (t, 1H), 7.86 (d, 2H), 7.69 (d, 2H), 7.49 (d, 2H), 7.44 – 7.34 (m, 2H), 7.29 – 7.20 (m, 2H), 7.01 – 6.97 (m, 2H), 6.96 (d, 1H), 6.42 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.35 (d, 2H), 4.20 (t, 2H), 3.86 (s, 2H), 3.26 (t, 4H), 3.01 – 2.89 (m, 6H), 2.82 (t, 2H), 2.76 – 2.68 (m, 1H), 2.37 (t, 4H), 2.05 – 1.92 (m, 2H), 1.88 – 1.75 (m, 2H), 1.71 – 1.59 (m, 2H).

EXAMPLE 233

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (59% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 2-fluoro-4-morpholinobenzoic acid (Intermediate 129) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 681 $[M+1]^+$

LC (1) r.t. (min.): 2.52

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (d, 1H), 8.51 (t, 1H), 7.67 – 7.60 (m, 2H), 7.60 – 7.54 (m, 1H), 7.49 (d, 2H), 7.42 – 7.33 (m, 2H), 7.30 – 7.13 (m, 2H), 6.96 (d, 1H), 6.89 – 6.73 (m, 2H), 6.42 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.35 (d, 2H), 4.20 – 4.08 (m, 2H), 3.86 (s, 2H), 3.76 – 3.68 (m, 4H), 3.25 (t, 4H), 2.95 (d, 6H), 2.81 (t, 2H).

EXAMPLE 234

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (18% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 2.68

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.86 (s, 1H), 8.51 (t, 1H), 7.89 – 7.81 (m, 2H), 7.72 – 7.64 (m, 2H), 7.54 – 7.48 (m, 2H), 7.43 – 7.35 (m, 2H), 7.28 – 7.20 (m, 2H), 6.97 (d, 1H), 6.52 – 6.46 (m, 2H), 6.43 (d, 1H), 4.90 (d, 2H), 4.66 (d, 2H), 4.40 – 4.31 (m, 3H), 4.20 (t, 2H), 4.17 – 4.10 (m, 2H), 3.87 (s, 2H), 3.76 – 3.66 (m, 2H), 3.27 (s, 3H), 3.05 – 2.92 (m, 6H), 2.82 (t, 2H).

EXAMPLE 235

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (58% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(1-(oxetan-3-yl)piperidin-4-yl)benzoic acid (Intermediate 129) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 717 $[M+1]^+$

LC (1) r.t. (min.): 1.98

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.52 (t, 1H), 7.92 – 7.83 (m, 2H), 7.72 – 7.65 (m, 2H), 7.54 – 7.46 (m, 2H), 7.43 – 7.34 (m, 4H), 7.30 – 7.21 (m, 2H), 6.96 (d, 1H), 6.42 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.55 (t, 2H), 4.45 (t, 2H), 4.36 (d, 2H), 4.20 (t, 2H), 3.86 (s, 2H), 3.47 – 3.36 (m, 1H), 2.95 (d, 6H), 2.86 – 2.75 (m, 4H), 2.60 (tt, 1H), 1.92 – 1.82 (m, 2H), 1.82 – 1.62 (m, 4H).

EXAMPLE 236

***N*-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (36% yield, 86% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 120) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 677 $[M+1]^+$

LC (1) r.t. (min.): 1.92

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.69 (s, 1H), 8.50 (t, 1H), 8.15 (s, 1H), 7.62 (d, 2H), 7.49 (d, 2H), 7.38 (d, 2H), 7.23 (d, 2H), 6.96 (d, 1H), 6.42 (d, 1H), 5.03 – 4.92 (m, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.35 (d, 2H), 4.19 (t, 2H), 3.86 (s, 2H), 3.71 (t, 2H), 3.57 (t, 2H), 2.97 (s, 3H), 2.93 (s, 3H), 2.82 (d, 2H), 2.48 (s, 3H), 2.04 – 1.88 (m, 1H), 0.46 – 0.32 (m, 2H), 0.32 – 0.21 (m, 2H).

EXAMPLE 237

***N*-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as an off-white solid (58% yield, 98% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzoic acid (Intermediate 122) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 725 $[M+1]^+$

LC (1) r.t. (min.): 2.17

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 10.13 (s, 1H), 8.51 (t, 1H), 7.98 – 7.78 (m, 2H), 7.76 – 7.64 (m, 2H), 7.57 – 7.45 (m, 2H), 7.45 – 7.35 (m, 4H), 7.30 – 7.17 (m, 2H), 6.96 (d, 1H), 6.42 (d, 1H), 6.15 (tt, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.36 (d, 2H), 4.19 (t, 2H), 3.86 (s, 2H), 3.04 – 2.99 (m, 2H), 2.99 – 2.91 (m, 6H), 2.81 (t, 2H), 2.76 (td, 2H), 2.58 (ddt, 1H), 2.28 (td, 2H), 1.80 – 1.61 (m, 4H).

EXAMPLE 238

***N*-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (57% yield, 98% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 705 $[M+1]^+$

LC (1) r.t. (min.): 1.81

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.53 (d, 2H), 7.47 (d, 2H), 7.44 – 7.38 (m, 3H), 7.30 (d, 2H), 6.62 (d, 1H), 6.44 (d, 1H), 6.09 (t, 1H), 5.00 (d, 2H), 4.80 (d, 2H), 4.53 (d, 2H), 4.33 (t, 2H), 4.16 – 4.00 (m, 1H), 3.94 (s, 2H), 3.24 – 3.15 (m, 2H), 3.12 (s, 3H), 3.01 (s, 3H), 2.87 (t, 2H), 2.62 (s, 3H), 2.35 (t, 2H), 2.29 – 2.13 (m, 2H), 1.85 (d, 2H), 1.72 – 1.63 (m, 1H), 0.51 – 0.39 (m, 4H).

EXAMPLE 239

7-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a pale yellow foam (21% yield, 95% purity) from 4-((5,6-dihydro-7*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetan]-7-yl)methyl)-3,5-difluoro-*N*,*N*-dimethylbenzamide (Intermediate 130a) and 3-(4-(aminomethyl)phenyl)-1,1-dimethylurea hydrochloride (Intermediate 54b) following the synthetic procedure as described for Intermediate 69c.

LRMS (m/z): 582 $[M+1]^+$

LC (1) r.t. (min.): 1.46

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.55 (s, 1H), 7.34 (d, 2H), 7.30 (s, 1H), 7.26 – 7.23 (m, 2H), 7.04 – 6.99 (m, 2H), 6.28 (s, 1H), 5.13 (d, 2H), 4.78 (d, 2H), 4.51 (d, 2H), 4.44 (t, 2H), 3.91 (s, 2H), 3.11 (br s, 3H), 3.03 (s, 6H), 3.01 (br s, 3H), 2.94 (t, 2H).

EXAMPLE 240

7-(4-(Dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (46% yield, 97% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 130) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 700 $[M+1]^+$

LC (1) r.t. (min.): 2.37

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H), 7.72 (s, 1H), 7.65 (t, 1H), 7.59 (d, 2H), 7.35 – 7.29 (m, 3H), 7.05 – 6.99 (m, 2H), 6.92 (d, 2H), 5.13 (d, 2H), 4.79 (d, 2H), 4.55 (d, 2H), 4.45 (t, 2H), 3.91 (s, 2H), 3.89 – 3.82 (m, 4H), 3.31 – 3.24 (m, 4H), 3.11 (s, 3H), 3.01 (s, 3H), 2.95 (t, 2H).

EXAMPLE 241

***N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (59% yield, 99% purity) from 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 131) and cyclobutanone following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 756 $[M+1]^+$

LC (3) r.t. (min.): 1.37

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.58 (t, 1H), 7.53 (d, 2H), 7.38 (s, 1H), 7.31 (t, 3H), 7.05 – 6.98 (m, 2H), 5.13 (d, 2H), 4.79 (d, 2H), 4.54 (d, 2H), 4.44 (t, 2H), 4.04 (s, 1H), 3.91 (s, 2H), 3.11 (s, 3H), 3.08 – 2.98 (m, 5H), 2.95 (t, 2H), 2.80 – 2.74 (m, 1H), 2.61 (s, 3H), 2.31 – 2.21 (m, 2H), 2.09 – 1.64 (m, 10H).

EXAMPLE 242

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (31% yield, 97% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxylic acid (Intermediate 132c) and *N*-(4-(aminomethyl)phenyl)-5-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazole-4-carboxamide (Intermediate 73) following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 680 $[M+1]^+$

LC (1) r.t. (min.): 1.97

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.65 (s, 1H), 8.94 (t, 1H), 8.07 (s, 1H), 7.61 (d, 2H), 7.50 (d, 2H), 7.41 – 7.34 (m, 3H), 7.25 (d, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.36 (d, 2H), 4.26 (t, 2H), 4.21 – 4.06 (m, 1H), 3.81 (s, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.87 – 2.80 (m, 4H), 2.54 (s, 3H), 2.20 (s, 3H), 2.10 – 1.99 (m, 4H), 1.83 – 1.71 (m, 2H).

EXAMPLE 243

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (31% yield, 94% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(4-methylpiperazin-1-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 677 $[M+1]^+$

LC (1) r.t. (min.): 1.70

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.90 (s, 1H), 8.94 (t, 1H), 7.86 (d, 2H), 7.68 (d, 2H), 7.50 (d, 2H), 7.39 – 7.34 (m, 3H), 7.26 (d, 2H), 7.00 (d, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.37 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.30 – 3.25 (m, 4H), 2.97 (s, 3H), 2.92 (s, 3H), 2.84 (t, 2H), 2.48 – 2.41 (m, 4H), 2.22 (s, 3H).

EXAMPLE 244

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (66% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 664 $[M+1]^+$

LC (1) r.t. (min.): 3.37

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.93 (s, 1H), 8.94 (t, 1H), 7.88 (d, 2H), 7.75 – 7.63 (m, 2H), 7.50 (d, 2H), 7.42 – 7.33 (m, 3H), 7.26 (d, 2H), 7.01 (d, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.37 (d, 2H), 4.26 (t, 2H), 3.81 (s, 2H), 3.74 (t, 4H), 3.24 (t, 4H), 3.00 – 2.90 (m, 6H), 2.84 (t, 2H).

EXAMPLE 245

***N*-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as an off-white solid (66% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 92) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 703 $[M+1]^+$

LC (1) r.t. (min.): 1.85

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.90 (s, 1H), 8.94 (t, 1H), 7.85 (d, 2H), 7.67 (d, 2H), 7.50 (d, 2H), 7.44 – 7.33 (m, 3H), 7.26 (d, 2H), 6.99 (d, 2H),4.89 (d, 2H), 4.67 (d, 2H), 4.37 (d, 2H), 4.26 (t, 2H), 3.81 (s, 2H), 3.24 (t, 4H), 3.04 – 2.88 (m, 6H), 2.84 (t, 2H), 2.66 (t, 4H), 1.69 – 1.56 (m, 1H), 0.52 – 0.39 (m, 2H), 0.39 – 0.15 (m, 2H).

EXAMPLE 246

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (60% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(1-methylpiperidin-4-yl)benzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 676 $[M+1]^+$

LC (1) r.t. (min.): 1.80

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H), 8.95 (t, 1H), 7.87 (d, 2H), 7.68 (d, 2H), 7.50 (d, 2H), 7.43 – 7.34 (m, 5H), 7.28 (d, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.38 (d, 2H), 4.26 (t, 2H), 3.81 (s, 2H), 3.00 – 2.91 (m, 6H), 2.90 – 2.86 (m, 2H), 2.84 (t, 2H), 2.58 – 2.53 (m, 1H), 2.20 (s, 3H), 2.05 – 1.94 (m, 2H), 1.79 – 1.65 (m, 4H).

EXAMPLE 247

***N*-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as an off-white solid (34% yield, 98% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(4-cyclobutylpiperazin-1-yl)benzoic acid (Intermediate 107) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 717 $[M+1]^+$

LC (1) r.t. (min.): 1.79

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.90 (s, 1H), 8.94 (t, 1H), 7.91 – 7.73 (m, 2H), 7.68 (dd, 2H), 7.54 – 7.46 (m, 2H), 7.43 – 7.34 (m, 3H), 7.26 (d, 2H), 6.99 (d, 2H), 4.89 (d, 2H), 4.68 (d, 2H), 4.37 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.27 (t, 4H), 3.02 – 2.88 (m, 6H), 2.85 (t, 2H), 2.73 (p, 1H), 2.37 (t, 4H), 2.07 – 1.93 (m, 2H), 1.89 – 1.76 (m, 2H), 1.71 – 1.58 (m, 2H).

EXAMPLE 248

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (70% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 3-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 664 $[M+1]^+$

LC (1) r.t. (min.): 2.34

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 10.12 (s, 1H), 8.95 (t, 1H), 7.68 (d, 2H), 7.50 (d, 2H), 7.44 (d, 1H), 7.40 – 7.33 (m, 5H), 7.29 (d, 2H), 7.15 (dt, 1H), 4.89 (d, 2H), 4.68 (d, 2H), 4.38 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.76 (t, 4H), 3.18 (t, 4H), 3.02 – 2.88 (m, 6H), 2.84 (t, 2H).

EXAMPLE 249

***N*-(4-(3-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as an off-white solid (55% yield, 97% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 3-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 133) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 703 $[M+1]^+$

LC (1) r.t. (min.): 1.82

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.11 (s, 1H), 8.95 (t, 1H), 7.71 – 7.61 (m, 2H), 7.50 (d, 2H), 7.44 – 7.41 (m, 1H), 7.40 – 7.36 (m, 3H), 7.36 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.17 – 7.07 (m, 1H), 4.89 (d, 2H), 4.68 (d, 2H), 4.38 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.17 (dd, 4H), 2.95 (d, 6H), 2.84 (t, 2H), 2.69 (t, 4H), 1.66 (tt, 1H), 0.51 – 0.42 (m, 2H), 0.37 – 0.29 (m, 2H).

EXAMPLE 250

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (78% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-

3-carboxamide (Intermediate 132) and 2-fluoro-4-morpholinobenzoic acid (Intermediate 129) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 682 $[M+1]^+$

LC (1) r.t. (min.): 2.44

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (d, 1H), 8.94 (t, 1H), 7.67 – 7.61 (m, 2H), 7.59 – 7.51 (m, 1H), 7.50 (d, 2H), 7.41 – 7.31 (m, 3H), 7.26 (d, 2H), 6.95 – 6.63 (m, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.37 (d, 2H), 4.26 (t, 2H), 3.81 (s, 2H), 3.73 (t, 4H), 3.25 (t, 4H), 3.00 – 2.91 (m, 6H), 2.84 (t, 2H).

EXAMPLE 251

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (42% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 664 $[M+1]^+$

LC (1) r.t. (min.): 2.63

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.87 (s, 1H), 8.94 (t, 1H), 7.87 – 7.81 (m, 2H), 7.71 – 7.64 (m, 2H), 7.53 – 7.48 (m, 2H), 7.41 – 7.36 (m, 3H), 7.29 – 7.23 (m, 2H), 6.51 – 6.46 (m, 2H), 4.90 (d, 2H), 4.68 (d, 2H), 4.40 – 4.33 (m, 3H), 4.27 (t, 2H), 4.17 – 4.10 (m, 2H), 3.81 (s, 2H), 3.74 – 3.69 (m, 2H), 3.26 (s, 3H), 3.03 – 2.90 (m, 6H), 2.85 (t, J = 5.7 Hz, 2H).

EXAMPLE 252

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(4-methoxypiperidin-1-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (40% yield, 96% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(4-methoxypiperidin-1-yl)benzoic acid (Intermediate 134) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 692 $[M+1]^+$

LC (1) r.t. (min.): 2.55

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.88 (s, 1H), 8.94 (t, 1H), 7.89 – 7.79 (m, 2H), 7.71 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 7.31 – 7.19 (m, 2H), 7.05 – 6.90 (m, 2H), 4.89 (d, 2H), 4.68 (d, 2H), 4.37 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.65 (dt, 2H), 3.43 – 3.37 (m, 1H), 3.27 (s, 3H), 3.05 (ddd, 2H), 2.95 (d, 6H), 2.85 (t, 2H), 1.96 – 1.78 (m, 2H), 1.49 (dtd, 2H).

EXAMPLE 253

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-oxomorpholino)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a beige solid (63% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(3-oxomorpholino)benzoic acid (Intermediate 135) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 2.24

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.23 (s, 1H), 8.96 (t, 1H), 8.01 – 7.96 (m, 2H), 7.73 – 7.65 (m, 2H), 7.62 – 7.54 (m, 2H), 7.53 – 7.45 (m, 2H), 7.41 – 7.35 (m, 3H), 7.32 – 7.26 (m, 2H), 4.89 (d, 2H), 4.68 (d, 2H), 4.38 (d, 2H), 4.30 – 4.22 (m, 4H), 4.00 (dd, 2H), 3.84 – 3.77 (m, 4H), 3.05 – 2.89 (m, 6H), 2.88 – 2.81 (m, 2H).

EXAMPLE 254

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-5-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (60% yield, 97% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 1-methylindoline-5-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 634 $[M+1]^+$

LC (1) r.t. (min.): 2.73

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.78 (s, 1H), 8.93 (t, 1H), 7.73 (dd, 1H), 7.69 – 7.65 (m, 3H), 7.53 – 7.45 (m, 2H), 7.41 – 7.33 (m, 3H), 7.29 – 7.17 (m, 2H), 6.52 (d, 1H), 4.89 (d, 2H), 4.67 (d, 2H), 4.36 (d, 2H), 4.27 (t, 2H), 3.81 (s, 2H), 3.40 (t, 2H), 3.02 – 2.90 (m, 8H), 2.84 (t, 2H), 2.79 (s, 3H).

EXAMPLE 255

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (60% yield, 99% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(1-(oxetan-3-yl)piperidin-4-yl)benzoic acid (Intermediate 129) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 718 $[M+1]^+$

LC (1) r.t. (min.): 1.89

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.13 (s, 1H), 8.95 (t, 1H), 7.94 – 7.74 (m, 2H), 7.76 – 7.59 (m, 2H), 7.50 (d, 2H), 7.44 – 7.33 (m, 5H), 7.32 – 7.21 (m, 2H), 4.89 (d, 2H), 4.67 (d, 2H), 4.55 (t, 2H), 4.45 (t, 2H), 4.38 (d, 2H), 4.26 (t, 2H), 3.81 (s, 2H), 3.45 – 3.37 (m, 1H), 2.95 (d, 6H), 2.88 – 2.77 (m, 4H), 2.64 – 2.55 (m, 1H), 1.88 (dd, 2H), 1.82 – 1.60 (m, 4H).

EXAMPLE 256

***N*-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as an off-white solid (67% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzoic acid (Intermediate 122) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 726 $[M+1]^+$

LC (1) r.t. (min.): 2.07

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 10.14 (s, 1H), 8.87 (t, 1H), 7.93 – 7.84 (m, 2H), 7.75 – 7.62 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.25 (m, 2H), 7.19 (s, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.38 (d, 2H), 4.25 (t, 2H), 3.55 (s, 2H), 3.47 – 3.36 (m, 1H), 3.00 – 2.90 (m, 6H), 2.89 – 2.85 (m, 2H), 2.85 – 2.77 (m, 2H), 2.66 – 2.53 (m, 1H), 2.42 (dt, 2H), 2.23 – 2.13 (m, 2H), 2.09 – 1.96 (m, 1H), 1.94 – 1.83 (m, 3H), 1.81 – 1.64 (m, 4H).

EXAMPLE 257

***N*-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (41% yield, 89% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 132) and 1-(1-cyclopropylazetidin-3-yl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (Intermediate 120) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 1.81

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.79 (s, 1H), 7.62 (t, 1H), 7.54 (d, 2H), 7.49 – 7.38 (m, 5H), 7.34 – 7.28 (m, 3H), 5.02 (d, 2H), 4.94 – 4.84 (m, 1H), 4.79 (d, 2H), 4.54 (d, 2H), 4.39 (t, 2H), 3.92 (s, 2H), 3.85 (t, 2H), 3.77 (t, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.87 (t, 2H), 2.55 (s, 3H), 2.07 – 2.01 (m, 1H), 0.48 – 0.39 (m, 4H).

EXAMPLE 258

***N*-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (62% yield, 99% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 136) and 2,2-difluoroethyl trifluoromethanesulfonate following the synthetic procedure as described for Example 152.

LRMS (m/z): 730 $[M+1]^+$

LC (1) r.t. (min.): 1.92

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.64 (s, 1H), 8.93 (t, 1H), 8.07 (s, 1H), 7.61 (d, 2H), 7.50 (d, 2H), 7.41 – 7.34 (m, 3H), 7.25 (d, 2H), 6.15 (tt, 1H), 4.89 (d, 2H), 4.67 (d, 2H), 4.36 (d, 2H), 4.26 (t, 2H), 4.24 – 4.14 (m, 1H), 3.81 (s, 2H), 3.04 – 2.95 (m, 5H), 2.92 (s, 3H), 2.88 – 2.71 (m, 4H), 2.54 (s, 3H), 2.38 (d, 2H), 2.10 – 1.96 (m, 2H), 1.84 – 1.73 (m, 2H).

EXAMPLE 259

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (61% yield, 99% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 136) and 1-fluoro-2-iodoethane following the synthetic procedure as described for Example 152.

LRMS (m/z): 712 $[M+1]^+$

LC (1) r.t. (min.): 1.69

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.73 (s, 1H), 7.60 (t, 1H), 7.54 (d, 2H), 7.48 – 7.39 (m, 5H), 7.34 – 7.28 (m, 3H), 5.02 (d, 2H), 4.79 (d, 2H), 4.68 – 4.64 (m, 1H), 4.57 – 4.51 (m, 3H), 4.40 (t, 2H), 4.13 – 4.00 (m, 1H), 3.92 (s, 2H), 3.12 (bs, 5H), 3.01 (s, 3H), 2.87 (t, 2H), 2.77 (dbs, 2H), 2.62 (s, 3H), 2.39 – 2.23 (m, 4H), 1.87 (s, 2H).

EXAMPLE 260

***N*-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (40% yield, 97% purity) from 7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 136) and (1-ethoxycyclopropoxy)trimethylsilane following the synthetic procedure as described for Intermediate 34a.

LRMS (m/z): 706 $[M+1]^+$

LC (1) r.t. (min.): 1.71

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (s, 1H), 7.62 (t, 1H), 7.53 (d, 2H), 7.48 – 7.38 (m, 5H), 7.33 – 7.27 (m, 3H), 5.02 (d, 2H), 4.79 (d, 2H), 4.53 (d, 2H), 4.39 (t, 2H), 4.14 – 4.01 (m, 1H), 3.92 (s, 2H), 3.26 – 3.16 (m, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.87 (t, 2H), 2.61 (s, 3H), 2.43 – 2.29 (m, 2H), 2.27 – 2.15 (m, 2H), 1.93 – 1.78 (m, 2H), 1.74 – 1.65 (m, 1H), 0.58 – 0.38 (m, 4H).

EXAMPLE 261

***N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (22% yield, 97% purity) from *N*-(4-acetamidobenzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 137) and 4-formyl-*N*,*N*-dimethylbenzamide following the synthetic procedure as described for Intermediate 21.

LRMS (m/z): 528 $[M+1]^+$

LC (1) r.t. (min.): 1.77

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.87 (s, 1H), 8.30 (t, 1H), 7.49 (d, 2H), 7.47 (d, 2H), 7.37 (d, 2H), 7.18 (d, 2H), 6.68 (s, 1H), 4.29 (d, 2H), 4.12 (t, 2H), 3.72 (s, 2H), 2.97 (s, 3H), 2.92 (s, 3H), 2.79 – 2.73 (m, 2H), 2.46 (m, 4H), 2.29 (s, 3H), 2.09 – 1.91 (m, 2H), 2.01 (s, 3H).

EXAMPLE 262

1'-Chloro-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as an off-white solido (46% yield, 100% purity) from *N*-(4-aminobenzyl)-1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 138) following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 578 $[M+1]^+$

LC (1) r.t. (min.): 2.75

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.95 (t, 1H), 8.22 (s, 1H), 7.48 (d, 2H), 7.41 – 7.33 (m, 4H), 7.16 (d, 2H), 4.36 – 4.14 (m, 4H), 3.66 (s, 2H), 2.97 (s, 3H), 2.94 – 2.89 (m, 9H), 2.83 (t, 2H), 2.68 – 2.54 (m, 2H), 2.48 – 2.38 (m, 2H), 2.20 – 2.10 (m, 1H), 2.01 – 1.80 (m, 1H).

EXAMPLE 263

***Tert*-butyl (4-((1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate**

Obtained as an off-white solid (41% yield, 100% purity) from *N*-(4-aminobenzyl)-1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-

a]pyrazine]-3'-carboxamide (Intermediate 138a) following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 651 $[M+1]^+$

LC (1) r.t. (min.): 3.40

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.26 (s, 1H), 8.95 (t, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.34 (m, 4H), 7.21 – 7.17 (m, 2H), 4.34 – 4.23 (m, 4H), 3.68 (s, 2H), 3.01 – 2.89 (m, 6H), 2.84 (t, 2H), 2.71– 2.65 (m, 2H), 2.48 – 2.38 (m, 2H), 2.20 – 2.12 (m, 1H), 2.03 – 1.93 (m, 1H), 1.46 (s, 9H).

EXAMPLE 264

1'-Bromo-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (59% yield, 100% purity) from *N*-(4-aminobenzyl)-1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 139) following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 622 $[M+1]^+$

LC (1) r.t. (min.): 2.82

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.94 (t, 1H), 8.22 (s, 1H), 7.48 (d, 2H), 7.40 – 7.34 (m, 4H), 7.16 (d, 2H), 4.33 – 4.22 (m, 4H), 3.68 (s, 2H), 2.97 (s, 3H), 2.90 (s, 9H), 2.84 (t, 2H), 2.72 – 2.58 (m, 2H), 2.41 (q, 2H), 2.22 – 2.11 (m, 1H), 1.97 (tt, 1H).

EXAMPLE 265

1-Chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (62% yield, 100% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 140) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 595 $[M+1]^+$

LC (1) r.t. (min.): 2.44

^{1}H NMR (MeOD, 400 MHz): δ (ppm) 7.59 (d, 2H), 7.52 (d, 2H), 7.44 (d, 2H), 7.29 (d, 2H), 5.25 (d, 2H), 4.98 (d, 2H), 4.93 – 4.89 (m, 0.5H), 4.76 – 4.71 (m, 0.5H), 4.46

(s, 2H), 4.34 (t, 2H), 4.11 (s, 2H), 3.11 (s, 3H), 3.02 (s, 3H), 2.89 (t, 2H), 1.96 (m, 1H), 1.81 – 1.66 (m, 1H), 1.22 – 1.07 (m, 1H).

EXAMPLE 266

1-Chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (38% yield, 94% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 140) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 698 $[M+1]^+$

LC (1) r.t. (min.): 2.63

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 (d, 2H), 7.70 (s, 1H), 7.60 (d, 2H), 7.50 – 7.40 (m, 5H), 7.31 (d, 2H), 6.95 (d, 2H), 5.30 (d, 2H), 4.93 (d, 2H), 4.52 (d, 2H), 4.42 (t, 2H), 4.12 (s, 2H), 3.92 – 3.85 (m, 4H), 3.33 – 3.26 (m, 4H), 3.13 (s, 3H), 3.01 (s, 3H), 2.85 (t, 2H).

EXAMPLE 267

1-Chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (38% yield, 98% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 140) following the synthetic procedure as described for Example 69.

LRMS (m/z): 580, 582 $[M+1]^+$

LC (1) r.t. (min.): 2.38

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.03 (t, 1H), 8.21 (s, 1H), 7.56 – 7.48 (m, 2H), 7.43 – 7.30 (m, 4H), 7.18 – 7.08 (m, 2H), 5.04 (d, 2H), 4.84 (d, 2H), 4.42 – 4.23 (m, 4H), 3.94 (s, 2H),2.98 (s, 3H), 2.92 (s, 3H), 2.90 (s, 6H), 2.82 (t, 2H).

EXAMPLE 268

1-Chloro-*N*-(3-chloro-4-(3,3-dimethylureido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (19% yield, 95% purity) from 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Example 267) following the synthetic procedure as described for Intermediate 138b.

LRMS (m/z): 614, 616, 618 $[M+1]^+$

LC (1) r.t. (min.): 2.69

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.19 (t, 1H), 7.83 (s, 1H), 7.53 – 7.50 (m, 2H), 7.48 (d, 1H), 7.40 – 7.37 (m, 2H), 7.36 (d, 1H), 7.19 (dd, 1H), 5.04 (d, 2H), 4.84 (d, 2H), 4.33 (d, 2H), 4.28 (t, 2H), 3.94 (s, 2H), 2.98 (s, 3H), 2.92 (s, 9H), 2.82 (t, 2H).

EXAMPLE 269

1-Cyclopropyl-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a brown solid (25% yield, 99% purity) from 1-bromo-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 141) and cyclopropylboronic acid following the synthetic procedure as described for Intermediate 93c.

LRMS (m/z): 586 $[M+1]^+$

LC (4e) r.t. (min.): 2.56

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.51 (t, 1H), 8.23 (s, 1H), 7.58 – 7.43 (m, 2H), 7.44 – 7.30 (m, 4H), 7.18 – 7.04 (m, 2H), 5.08 – 4.93 (m, 4H), 4.31 (d, 2H), 4.23 (t, 2H), 3.96 (s, 2H), 2.96 (d, 6H), 2.91 (s, 6H), 2.78 (t, 2H), 2.34 (td, 1H), 0.98 – 0.94 (m, 2H), 0.94 – 0.89 (m, 2H).

EXAMPLE 270

1-Chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (17% yield, 98% purity) from 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Example 239) following the synthetic procedure as described for Intermediate 138b.

LRMS (m/z): 616 $[M+1]^+$

LC (1) r.t. (min.): 2.44

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.03 (t, 1H), 8.21 (s, 1H), 7.36 (d, 2H), 7.22 (d, 2H), 7.14 (d, 2H), 5.04 (d, 2H), 4.90 (d, 2H), 4.32 – 4.26 (m, 4H), 3.92 (s, 2H), 2.98 (s, 3H), 2.94 – 2.86 (m, 11H).

EXAMPLE 271

1-Chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (94% yield, 92% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 142) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 1e.

LRMS (m/z): 631 $[M+1]^+$

LC (1) r.t. (min.): 2.51

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 (t, 3H), 7.37 (s, 1H), 7.26 (s, 2H), 7.08 – 6.99 (m, 2H), 5.29 (d, 2H), 5.07 (d, 2H), 4.93 – 4.66 (m, 1H), 4.49 (d, 2H), 4.41 (t, 2H), 4.11 (s, 2H), 3.12 (s, 3H), 3.02 (s, 3H), 2.93 – 2.86 (m, 2H), 2.80 (s, 2H), 1.93 – 1.72 (m, 1H).

EXAMPLE 272

7-(4-(Dimethylcarbamoyl)benzyl)-1-methyl-*N*-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (43% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-

oxetane]-3-carboxamide (Intermediate 143) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 2.49

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H), 7.74 (s, 1H), 7.70 – 7.61 (m, 1H), 7.59 (d, 2H), 7.44 (q, 4H), 7.32 (d, 2H), 6.92 (d, 2H), 5.04 (d, 2H), 4.96 (d, 2H), 4.53 (d, 2H), 4.38 (t, 2H), 4.00 (s, 2H), 3.91 – 3.84 (m, 4H), 3.31 – 3.25 (m, 4H), 3.12 (s, 3H), 3.01 (s, 3H), 2.81 (t, 2H), 2.58 (s, 3H).

EXAMPLE 273

***N*-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (46% yield, 99% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 143) and 4-(4-cyclopropylpiperazin-1-yl)benzoic acid (Intermediate 92) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 717 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.89 (s, 1H), 8.83 (t, 1H), 7.85 (d, 2H), 7.67 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.24 (d, 2H), 6.99 (d, 2H), 4.94 (d, 2H), 4.81 (d, 2H), 4.34 (d, 2H), 4.24 (d, 2H), 3.91 (s, 2H), 3.28 – 3.21 (m, 4H), 2.97 (s, 3H), 2.93 (s, 3H), 2.76 (d, 2H), 2.69 – 2.64 (m, 4H), 2.50 (s, 3H), 1.70 – 1.59 (m, 1H), 0.47 – 0.42 (m, 2H), 0.38 – 0.33 (m, 2H).

EXAMPLE 274

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (59% yield, 99% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 143) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 575 $[M+1]^+$

LC (1) r.t. (min.): 2.13

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 – 7.58 (m, 1H), 7.51 – 7.39 (m, 7H), 7.28 (d, 2H), 5.03 (d, 2H), 4.95 (d, 2H), 4.76 (dm, 1H), 4.51 (d, 2H), 4.37 (t, 2H), 4.00 (s, 2H), 3.12 (s, 3H), 3.01 (s, 3H), 2.81 (t, 2H), 2.58 (s, 3H), 1.93 – 1.71 (m, 2H), 1.28 – 1.15 (m, 1H).

EXAMPLE 275

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((4-morpholinophenyl)carbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a yellow oil (44% yield, 100% purity) from lithium 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate (Intermediate 144) and 4-morpholinoaniline following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 662 $[M+1]^+$

LC (1) r.t. (min.): 2.95

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 10.00 (s, 1H), 9.02 (t, 1H), 7.88 (d, 2H), 7.61 (d, 2H), 7.50 – 7.40 (m, 4H), 7.39 – 7.30 (m, 2H), 7.21 (s, 1H), 6.97 – 6.85 (m, 2H), 4.47 (d, 2H), 4.23 (t, 2H), 3.73 (t, 4H), 3.55 (s, 2H), 3.06 (t, 4H), 2.98 – 2.90 (m, 6H), 2.87 (t, 2H), 2.46 – 2.37 (m, 2H), 2.25 – 2.15 (m, 2H), 2.09 – 1.97 (m, 1H), 1.94 – 1.83 (m,1H).

EXAMPLE 276

***N*-(4-((1-(1-cyclopropylpiperidin-4-yl)-1*H*-imidazol-4-yl)carbamoyl)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as an off-white solid (3% yield, 98% purity) from lithium 4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)benzoate (Intermediate 144) and 1-(1-cyclopropylpiperidin-4-yl)-1*H*-imidazol-4-amine (Intermediate 145) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 691 $[M+1]^+$

LC (4e) r.t. (min.): 2.92

^{1}H NMR (MeOD, 500 MHz): δ (ppm) 7.94 – 7.88 (m, 2H), 7.58 (s, 1H), 7.54 – 7.46 (m, 5H), 7.43 – 7.37 (m, 2H), 7.22 (s, 1H), 4.62 (s, 2H), 4.31 (t, 2H), 4.13 (tt, 1H), 3.63 (s, 2H), 3.21 – 3.15 (m, 2H), 3.10 (s, 3H), 3.04 – 2.97 (m, 5H), 2.55 (dt, 2H),

2.44 (td, 2H), 2.34 – 2.25 (m, 2H), 2.15 – 2.05 (m, 3H), 2.04 – 1.91 (m, 3H), 1.73 (tt, 1H), 0.53 (td, 2H), 0.49 – 0.40 (m, H).

EXAMPLE 277

2'-(4-(Dimethylcarbamoyl)benzyl)-7'-fluoro-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (50% yield, 95% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 146) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 681 $[M+1]^+$

LC (1) r.t. (min.): 2.75

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.92 (s, 1H), 7.96 – 7.91 (m, 1H), 7.90 – 7.85 (m, 2H), 7.75 – 7.62 (m, 2H), 7.54 – 7.44 (m, 2H), 7.43 – 7.32 (m, 2H), 7.32 – 7.18 (m, 2H), 7.09 – 6.96 (m, 2H), 6.42 (s, 1H), 4.87 (d, 2H), 4.64 (d, 2H), 4.38 (d, 2H), 4.06 (t, 2H), 3.86 (s, 2H), 3.81 – 3.64 (m, 4H), 3.28 – 3.19 (m, 4H), 3.02 – 2.90 (m, 6H), 2.86 – 2.80 (m, 2H).

EXAMPLE 278

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (50% yield, 100% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 146) following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 563 $[M+1]^+$

LC (1) r.t. (min.): 2.36

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.21 (s, 1H), 7.87 (td, 1H), 7.54 – 7.44 (m, 2H), 7.42 – 7.32 (m, 4H), 7.23 – 7.03 (m, 2H), 6.41 (s, 1H), 4.86 (d, 2H), 4.63 (d, 2H), 4.33 (d, 2H), 4.06 (dd, 2H), 3.85 (s, 2H), 2.97 (s, 3H), 2.94 – 2.87 (m, 9H), 2.83 (dd, 2H).

EXAMPLE 279

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-((5-(4-(3-methoxyazetidin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as white solid (45% yield, 100% purity) from *N*-((5-aminopyridin-2-yl)methyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-*5'H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 123) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 663 $[M+1]^+$

LC (1) r.t. (min.): 2.46

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.07 (s, 1H), 8.88 (t, 1H), 8.83 (d, 1H), 8.11 (dd, 1H), 7.87 (d, 2H), 7.46 (d, 2H), 7.36 (d, 2H), 7.30 (d, 1H), 7.22 (s, 1H), 6.49 (d, 2H), 4.49 (d, 2H), 4.39 – 4.32 (m, 1H), 4.25 (t, 2H), 4.17 – 4.11 (m, 2H), 3.72 (dd, 2H), 3.56 (s, 2H), 3.26 (s, 3H), 2.97 (s, 3H), 2.91 (s, 3H), 2.88 (t, 2H), 2.46 – 2.39 (m, 2H), 2.24 – 2.18 (m, 2H), 2.08 – 1.99 (m, 1H), 1.95 – 1.87 (m, 1H).

EXAMPLE 280

1'-Chloro-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as white solid (45% yield, 100% purity) from *N*-(4-aminobenzyl)-1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 138) and 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylic acid (Intermediate 128) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 670 $[M+1]^+$

LC (1) r.t. (min.): 2.50

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.72 (s, 1H), 9.02 (t, 1H), 8.16 (s, 1H), 7.62 (d, 2H), 7.48 (d, 2H), 7.37 (d, 2H), 7.25 (d, 2H), 4.34 (d, 2H), 4.27 (t, 2H), 4.12 (t, 2H), 3.82 (s, 2H), 3.66 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.84 (t, 4H), 2.65 – 2.57 (m, 2H), 2.46 – 2.38 (m, 5H), 2.19 – 2.10 (m, 1H), 2.00 – 1.90 (m, 1H).

EXAMPLE 281

7'-(4-(Dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (98% yield, 98% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 147) and 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylic acid (Intermediate 128) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 650 $[M+1]^+$

LC (1) r.t. (min.): 1.91

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.71 (s, 1H), 8.74 (t, 1H), 8.16 (s, 1H), 7.62 (d, 2H), 7.48 (d, 2H), 7.36 (d, 2H), 7.25 (d, 2H), 4.34 (d, 2H), 4.22 (t, 2H), 4.12 (t, 2H), 3.82 (s, 2H), 3.65 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.84 (t, 2H), 2.81 (t, 2H), 2.47 – 2.41 (m, 4H), 2.43 (s, 3H), 2.41 (s, 3H), 2.08 – 1.94 (m, 2H).

EXAMPLE 282

7'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

Obtained as a white solid (37% yield, 99% purity) from *N*-(4-aminobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 147) and (1*S*,2*S*)-2-fluorocyclopropane-1-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 573 $[M+1]^+$

LC (1) r.t. (min.): 2.28

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.19 (s, 1H), 8.72 (t, 1H), 7.51 (d, 2H), 7.48 (d, 2H), 7.36 (d, 2H), 7.23 (d, 2H), 4.90 (dtd, 1H), 4.32 (d, 2H), 4.21 (t, 2H), 3.64 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H), 2.80 (t, 2H), 2.46 – 2.41 (m, 4H), 2.42 (s, 3H), 2.09 – 1.93 (m, 3H), 1.66 – 1.56 (m, 1H), 1.15 – 1.07 (m, 1H).

EXAMPLE 283

2'-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-5-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an off-white solid (51% yield, 97% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 70a) and 1-methylindoline-5-carboxylic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 633 $[M+1]^+$

LC (1) r.t. (min.): 2.60

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.78 (s, 1H), 8.50 (t, 1H), 7.73 (dd, 1H), 7.70 – 7.64 (m, 3H), 7.52 – 7.47 (m, 2H), 7.41 – 7.35 (m, 2H), 7.22 (d, 2H), 6.96 (d, 1H), 6.52 (d, 1H), 6.42 (d, 1H), 4.89 (d, 2H), 4.65 (d, 2H), 4.35 (d, 2H), 4.20 (t, 2H), 3.86 (s, 2H), 3.40 (t, 2H), 2.99 – 2.91 (m, 8H), 2.82 (t, 2H), 2.79 (s, 3H).

EXAMPLE 284

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-*N*-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (44% yield, 99% purity) from *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 93) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 677 $[M+1]^+$

LC (1) r.t. (min.): 2.60

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.92 (s, 1H), 8.42 (t, 1H), 7.88 (d, 2H), 7.68 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.22 (d, 2H), 7.02 (d, 2H), 6.77 (s, 1H), 4.92 (d, 2H), 4.86 (d, 2H), 4.33 (d, 2H), 4.15 (t, 2H), 3.96 (s, 2H), 3.77 – 3.72 (m, 4H), 3.26 – 3.23 (m, 4H), 2.98 (s, 3H), 2.93 (s, 3H), 2.73 (t, 2H), 2.38 (s, 3H).

EXAMPLE 285

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-*N*-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a white solid (21% yield, 97% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 148) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 2.40

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.12 (s, 1H), 8.83 (d, 1H), 8.50 (t, 1H), 8.09 (dd, 1H), 7.90 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.25 (d, 1H), 7.03 (d, 2H), 6.82 (s, 1H), 4.92 (d, 2H), 4.87 (d, 2H), 4.42 (d, 2H), 4.15 (t, 2H), 3.97 (s, 2H), 3.77 – 3.70 (m, 4H), 3.28 – 3.24 (m, 4H), 2.98 (s, 3H), 2.92 (s, 3H), 2.74 (t, 2H), 2.39 (s, 3H).

EXAMPLE 286

***N*-(4-(4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

Obtained as a white solid (9% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 148) and 4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzoic acid (Intermediate 149) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 744.8 $[M+1]^+$

LC (4D) r.t. (min.): 2.11

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.22 (s, 1H), 8.43 (t, 1H), 7.99 – 7.95 (m, 2H), 7.74 – 7.67 (m, 2H), 7.55 – 7.49 (m, 4H), 7.43 – 7.36 (m, 2H), 7.29 – 7.22 (m, 2H), 6.78 (s, 1H), 4.95 – 4.91 (m, 2H), 4.90 – 4.85 (m, 2H), 4.37 – 4.32 (m, 2H), 4.19 – 4.14 (m, 2H), 3.97 (s, 2H), 3.75 – 3.70 (m, 2H), 3.09 (s, 2H), 3.00 – 2.86 (m, 7H), 2.77 – 2.73 (m, 2H), 2.72 – 2.68 (m, 2H), 2.39 (s, 3H), 2.06 – 1.99 (m, 2H), 1.89 – 1.82 (m, 2H), 1.72 – 1.64 (m, 2H).

EXAMPLE 287

2'-(4-(Dimethylcarbamoyl)benzyl)-8'-methyl-*N*-(4-(4-(3-oxomorpholino)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as a yellow solid (41% yield, 99% purity) from *N*-((5-aminopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Intermediate 148) and 4-(3-oxomorpholino)benzoic acid (Intermediate 135) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 691 $[M+1]^+$

LC (1) r.t. (min.): 2.33

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.22 (s, 1H), 8.43 (t, 1H), 8.00 – 7.96 (m, 2H), 7.69 (d, 2H), 7.58 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.25 (d, 2H), 6.78 (s, 1H), 4.92 (d, 2H), 4.86 (d, 2H), 4.34 (d, 2H), 4.24 (s, 2H), 4.15 (t, 2H), 4.00 (dd, 2H), 3.96 (s, 2H), 3.83 – 3.79 (m, 2H), 2.98 (s, 3H), 2.93 (s, 3H), 2.73 (t, 2H), 2.38 (s, 3H).

EXAMPLE 288

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-morpholinobenzamido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (30% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 150) and 4-morpholinobenzoic acid following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 732 $[M+1]^+$

LC (1) r.t. (min.): 2.74

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.94 (s, 1H), 9.12 (t, 1H), 7.92 – 7.86 (m, 2H), 7.73 – 7.66 (m, 2H), 7.57 – 7.50 (m, 2H), 7.43 – 7.37 (m, 2H), 7.31 – 7.24 (m, 2H), 7.06 – 7.00 (m, 2H), 4.90 – 4.84 (m, 2H), 4.81 – 4.76 (m, 2H), 4.42 – 4.32 (m, 4H), 3.84 (s, 2H), 3.79 – 3.72 (m, 4H), 3.29 – 3.21 (m, 4H), 3.03 – 2.87 (m, 8H).

EXAMPLE 289

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as an off-white solid (30% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 150) following the synthetic procedure as described for Intermediate 54a.

LRMS (m/z): 614 $[M+1]^+$

LC (1) r.t. (min.): 2.40

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 9.06 (t, 1H), 8.23 (s, 1H), 7.58 – 7.50 (m, 2H), 7.43 – 7.35 (m, 4H), 7.22 – 7.13 (m, 2H), 4.89 – 4.83 (m, 2H), 4.82 – 4.75 (m, 2H), 4.40 – 4.31 (m, 4H), 3.84 (s, 2H), 3.04 – 2.84 (m, 14H).

EXAMPLE 290

7-(4-(Dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (32% yield, 97% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 143) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 678 $[M+1]^+$

LC (1) r.t. (min.): 2.58

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.85 (s, 1H), 8.83 (t, 1H), 7.84 (d, 2H), 7.66 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.24 (d, 2H), 6.47 (d, 2H), 4.94 (d, 2H), 4.81 (d, 2H), 4.38 – 4.32 (m, 3H), 4.24 (t, 2H), 4.15 – 4.10 (m, 2H), 3.91 (s, 2H), 3.70 (dd, 2H), 3.25 (s, 3H), 2.98 (s, 3H), 2.92 (s, 3H), 2.76 (t, 2H), 2.50 (s, 3H).

EXAMPLE 291

***N*-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (44% yield, 98% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-

oxetane]-3-carboxamide (Intermediate 143) and 4-(4-cyclobutylpiperazin-1-yl)benzoic acid (Intermediate 107) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 731 $[M+1]^+$

LC (1) r.t. (min.): 1.96

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.93 (s, 1H), 8.84 (t, 1H), 7.88 (d, 2H), 7.67 (d, 2H), 7.51 (d, 3H), 7.38 (d, 2H), 7.25 (d, 2H), 7.09 – 6.98 (m, 2H), 4.94 (d, 2H), 4.81 (d, 2H), 4.34 (d, 2H), 4.23 (t, 3H), 3.91 (s, 2H), 3.64 – 2.83 (br s, 9H), 2.98 (s, 3H), 2.92 (s, 3H), 2.76 (d, 3H), 2.25 – 1.90 (m, 4H), 1.80 – 1.63 (m, 2H).

EXAMPLE 292

***N*-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as a white solid (39% yield, 97% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 143) and 2,2-difluoroethyl trifluoromethanesulfonate following the synthetic procedure as described for Example 152.

LRMS (m/z): 744 $[M+1]^+$

LC (1) r.t. (min.): 2.08

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.65 (s, 1H), 8.83 (t, 1H), 8.07 (s, 1H), 7.60 (d, 2H), 7.51 (d, 2H), 7.39 (d, 2H), 7.23 (d, 2H), 6.15 (tt, 1H), 4.94 (d, 2H), 4.81 (d, 2H), 4.34 (d, 2H), 4.23 (t, 2H), 4.22 – 4.15 (m, 1H), 3.91 (s, 2H), 3.31 (s, 3H), 3.02 – 2.96 (m, 5H), 2.92 (s, 3H), 2.82 – 2.73 (m, 4H), 2.54 (s, 3H), 2.40 – 2.33 (m, 2H), 2.02 (qd, 2H), 1.81 – 1.76 (m, 2H).

EXAMPLE 293

***N*-(4-(4-(1-cyclopropylazetidin-3-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide**

Obtained as an off-white solid (39% yield, 100% purity) from *N*-(4-aminobenzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 143) and 4-(1-cyclopropylazetidin-3-yl)benzoic acid (Intermediate 151) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 688 $[M+1]^+$

LC (1) r.t. (min.): 1.90

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 10.16 (s, 1H), 8.86 (t, 1H), 7.91 (d, 2H), 7.68 (d, 2H), 7.51 (d, 2H), 7.47 (d, 2H), 7.39 (d, 2H), 7.27 (d, 2H), 4.94 (d, 2H), 4.81 (d, 2H), 4.35 (d, 2H), 4.24 (t, 2H), 3.91 (s, 2H), 3.69 – 3.59 (m, 3H), 3.31 (s, 3H), 3.24 (t, 2H), 2.98 (s, 3H), 2.92 (s, 3H), 2.76 (t, 2H), 1.96 – 1.90 (m, 1H), 0.38 – 0.32 (m, 2H), 0.27 – 0.22 (m, 2H).

EXAMPLE 294

1-Chloro-*N*-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a yellow solid (36% yield, 99% purity) from 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 152) and 2,2-difluoroethyl trifluoromethanesulfonate following the synthetic procedure as described for Example 152.

LRMS (m/z): 764 $[M+1]^+$

LC (1) r.t. (min.): 2.24

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.65 (s, 1H), 9.10 (t, 1H), 8.07 (s, 1H), 7.60 (d, 2H), 7.52 (d, 2H), 7.39 (d, 2H), 7.24 (d, 2H), 6.15 (tt, 1H), 5.04 (d, 2H), 4.85 (d, 2H), 4.33 (d, 2H), 4.28 (t, 2H), 4.23 – 4.15 (m, 1H), 3.95 (s, 2H), 3.02 – 2.96 (m, 5H), 2.92 (s, 3H), 2.82 (t, 2H), 2.77 (td, 2H), 2.54 (s, 3H), 2.40 – 2.33 (m, 2H), 2.02 (qd, 2H), 1.81 – 1.76 (m, 2H).

EXAMPLE 295

1-Chloro-7-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

Obtained as a white solid (30% yield, 97% purity) from *N*-(4-aminobenzyl)-1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5*H*-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide (Intermediate 140) and 4-(3-methoxyazetidin-1-yl)benzoic acid (Intermediate 116) following the synthetic procedure as described for Intermediate 17a.

LRMS (m/z): 698 $[M+1]^+$

LC (1) r.t. (min.): 2.72

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.86 (s, 1H), 9.10 (t, 1H), 7.84 (d, 2H), 7.66 (d, 2H), 7.52 (d, 2H), 7.39 (d, 2H), 7.24 (d, 2H), 6.47 (d, 2H), 5.04 (d, 2H), 4.85 (d, 2H), 4.37 – 4.32 (m, 3H), 4.29 (t, 2H), 4.15 – 4.10 (m, 2H), 3.95 (s, 2H), 3.70 (dd, 2H), 3.25 (s, 3H), 2.98 (s, 3H), 2.92 (s, 3H), 2.82 (t, 2H).

EXAMPLE 296

***N*-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

Obtained as a white solid (46% yield, 98% purity) from 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(5-methyl-1-(piperidin-4-yl)-1*H*-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide (Intermediate 153) and 2,2-difluoroethyl trifluoromethanesulfonate following the synthetic procedure as described for Example 152.

LRMS (m/z): 742 $[M+1]^+$

LC (1) r.t. (min.): 2.29

^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 9.65 (s, 1H), 8.73 (t, 1H), 8.07 (s, 1H), 7.60 (d, 2H), 7.48 (d, 2H), 7.36 (d, 2H), 7.24 (d, 2H), 6.15 (tt, 1H), 4.33 (d, 2H), 4.24 – 4.16 (m, 3H), 3.65 (s, 2H), 3.03 – 2.95 (m, 5H), 2.91 (s, 3H), 2.83 – 2.73 (m, 4H), 2.54 (s, 3H), 2.47 – 2.41 (m, 4H), 2.42 (s, 3H), 2.40 – 2.34 (m, 2H), 2.09 – 1.94 (m, 4H), 1.82 – 1.76 (m, 2H).

EXAMPLE 297

8'-Bromo-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Obtained as an clear gum (57% yield, 95% purity) from 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide (Example 278) following the synthetic procedure as described for Intermediate 91a.

LRMS (m/z): 641, 643 $[M+1]^+$

LC (4e) r.t. (min.): 2.81

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.28 – 8.20 (m, 2H), 7.55 – 7.49 (m, 2H), 7.43 – 7.36 (m, 4H), 7.18 – 7.11 (m, 2H), 5.12 (d, 2H), 4.85 (d, 2H), 4.34 (d, 2H), 4.10 – 4.05 (m, 2H), 4.02 (s, 2H), 3.03 – 2.87 (m, 12H), 2.84 – 2.79 (m, 2H).

EXAMPLE 298

***N*-(4-acetamidobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide**

EXAMPLE 299

***N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide**

EXAMPLE 300

2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

EXAMPLE 301

7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

EXAMPLE 302

N-(4-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 303

N-(4-(4-(2-oxa-6-azaspiro[3.4]octan-6-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 304

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 305

2'-((5-(dimethylcarbamoyl)-3-methylpyridin-2-yl)methyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

EXAMPLE 306

7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

EXAMPLE 307

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 308

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 309

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methyl-4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 310

N-(4-(4-(dimethylamino)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 311

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 312

(R)-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methylmorpholino)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 313

(S)-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methylmorpholino)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 314

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(morpholinomethyl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 315

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-morpholinopicolinamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 316

N-(4-(benzo[d][1,3]dioxole-5-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 317

N-(4-(2,2-difluorobenzo[d][1,3]dioxole-5-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

EXAMPLE 318

N,N-dimethyl-4-((6'-(1-(4-(methylcarbamoyl)benzyl)-1H-1,2,3-triazol-4-yl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide

EXAMPLE 319

N-(4-(4-(4-cyclopropylpiperazin-1-yl)-2-fluorobenzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

EXAMPLE 320

2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

EXAMPLE 321

2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

EXAMPLE 322

7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,2-a]pyrazine]-3'-carboxamide

PROTAC EXAMPLES

PROTAC EXAMPLE 1

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 2

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 3

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide

PROTAC EXAMPLE 4

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 5

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 6

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((S)-15-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-16,16-dimethyl-13-oxo-4,7,10-trioxa-14-azaheptadecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 7

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 8

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 9

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 10

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 11

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 12

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 13

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 14

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 15

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 16

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 17

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide

PROTAC EXAMPLE 18

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 19

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 20

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14-tetraoxa-2-azaheptadecan-17-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 21

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 22

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 23

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide

PROTAC EXAMPLE 24

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 25

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 26

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 27

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N10-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide

PROTAC EXAMPLE 28

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 29

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 30

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide

PROTAC EXAMPLE 31

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 32

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15,18-hexaoxahenicosan-21-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 33

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxapentadecan-

15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 34

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide

PROTAC EXAMPLE 35

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 36

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide

PROTAC EXAMPLE 37

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide

PROTAC EXAMPLE 38

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 39

rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 40

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 41

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 42

N15-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12-trioxa-3-azapentadecanediamide

PROTAC EXAMPLE 43

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 44

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 45

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 46

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N11-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide

PROTAC EXAMPLE 47

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 48

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 49

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 50

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide

PROTAC EXAMPLE 51

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 52

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide

PROTAC EXAMPLE 53

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 54

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 55

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 56

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 57

N21-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12,15,18-pentaoxa-3-azahenicosanediamide

PROTAC EXAMPLE 58

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 59

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide

PROTAC EXAMPLE 60

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 61

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(7-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 62

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 63

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 64

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 65

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 66

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 67

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 68

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 69

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 70

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11-trioxa-2-azatetradecan-14-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 71

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 72

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 73

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 74

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14,17-pentaoxa-2-azaicosan-20-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 75

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 76

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 77

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15-pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 78

rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 79

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 80

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-

yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 81

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 82

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide

PROTAC EXAMPLE 83

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N12-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)dodecanediamide

PROTAC EXAMPLE 84

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 85

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 86

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

PROTAC EXAMPLE 87

N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide

PROTAC EXAMPLE 88

2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

Biological Activity

STAT6 activity in HEK-Blue™ IL-4/IL-13 cells was investigated. HEK-Blue™ IL-4/IL-13 cells (InvivoGen) are specifically designed to monitor the activation of the STAT6 induced by IL-4 or IL-13. These cells co-express the *alkaline phosphatase* (*SEAP*) gene under the control of the IFN-β minimal promoter fused to four STAT6 binding sites and the human *STAT6* gene. Treatment with IL-4 induces the STAT6-dependent expression of SEAP. SEAP protein is secreted to the supernatant and SEAP activity can be detected using the QUANTI-Blue™ Solution.

15,000 HEK-Blue™ IL-4/IL-13 were seeded in 40 µl of assay media (DMEM/Glutamax, 10% FBS w/o antibiotics) onto 384-well white plates, clear bottom and incubated over/night (O/N) at 37°C and 5% CO_2. Test compounds were prepared 200x in DMSO 100% and added to plates at different concentrations (final DMSO concentration of 0.5%) for 3 h before adding 0.06 ng/ml of IL-4 overnight (O/N) at 37°C and 5% CO_2. SEAP activity in the supernatants were assessed with the QUANTI-Blue™ Solution and the half maximal inhibitory concentration (IC_{50}) for each compound was calculated.

The results are shown in Table 1.

Table 1: Biological activity results. A ≤ 10 nM; 10 < B ≤ 100 nM; 100 < C ≤ 1000 nM; D > 1000 nM.

Example	IC_{50} (nM)
1	B
2	B
4	D
5	C
6	B
7	B
8	C
9	C
11	B
12	D
13	D
17	D
18	B
19	B
20	D
21	C
22	C
23	B
28	C
29	B
30	B
31	B
32	B
33	C
34	C
35	C
36	C
37	A
38	B
40	B
41	D
43	D
44	C
46	C
47	C
51	B
56	A
57	B
58	C

59	B
62	C
63	B
64	A
65	B
66	B
67	B
68	A
69	B
70	B
71	C
79	B
81	B
82	B
83	B
84	B
85	B
86	B
87	B
88	B
89	B
90	B
92	B
93	B
94	B
95	B
96	B
97	B
98	B
99	B
100	B
101	B
102	B
103	A
104	B
105	A
106	B
107	B
108	A
109	B
110	B
111	B

112	B
113	A
114	A
115	B
116	B
117	B
118	B
119	B
120	B
121	A
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
131	A
132	A
133	A
134	A
135	A
136	B
137	B
138	B
139	B
140	B
141	A
142	B
143	B
144	A
145	A
146	B
147	A
148	A
149	A
150	A
151	A
152	A
153	A

154	A
155	A
156	B
157	B
158	B
159	B
160	B
161	B
162	B
163	B
164	B
165	B
166	A
167	A
168	B
169	B
170	B
171	B
172	B
173	B
174	A
175	B
176	B
177	B
178	A
179	A
180	A
181	A
182	A
183	A
184	A
185	B
186	A
187	A
188	B
189	A
190	B
191	A
192	A
193	B
194	A
195	A

196	A
197	A
198	B
199	A
200	A
201	A
202	B
203	A
204	B
205	B
206	A
207	A
208	A
209	A
210	B
211	A
212	A
213	A
214	A
215	A
216	A
217	B
218	B
219	B
220	B
221	A
222	B
223	B
224	B
225	A
226	A
227	A
228	A
229	A
230	A
231	A
232	A
233	B
234	A
235	A
236	A
237	A

238	A
239	B
240	A
241	A
242	B
243	A
244	A
245	A
246	A
247	A
248	B
249	B
250	A
251	A
252	A
253	B
254	A
255	A
256	A
257	A
258	A
259	A
260	A
261	B
262	A
263	B
264	A
265	B
266	A
267	B
268	B
269	B
270	A
271	A
272	A
273	A
274	A
275	B
276	B
277	B
278	B
279	A

280	A
281	A
282	A
283	A
284	A
285	A
286	A
287	A
288	A
289	B
290	A
291	A
292	A
293	A
294	A
295	A
296	A
297	A
298	B
299	B
300	B
301	A
302	A
303	A
304	B
305	B
306	B
307	A
308	A
309	A
310	A
311	A
312	A
313	A
314	A
315	B
316	B
317	B
318	B
319	A
320	B
321	B

322	A

These results show that the compounds are effective inhibitors of STAT6.

For the PROTAC examples, degradation activity was measured as follows. 5,000 Normal Human Epithelial Keratinocytes (NHEK, Lonza) were plated in 20µl of complete KGM media (Lonza) onto 384 well culture-treated plates, and cells were incubated overnight at 37ºC and 5% CO2. The day after, stock solutions and serial dilutions of compounds were prepared in DMSO 100%. Then, compound solutions were diluted 40 times in complete KGM media, and 5µl of this intermediate solution was added over the 20µl of NHEK, having 0,5% DMSO final in the assay. NHEK were treated with compounds for 17h at 37ºC and 5% CO2. After the treatment, total STAT6 levels were measured by THUNDER™ Total STAT6 TR-FRET Cell Signaling Assay Kit (Bioauxilium), following the instructions of the manufacturer.

The results are shown in Table 2.

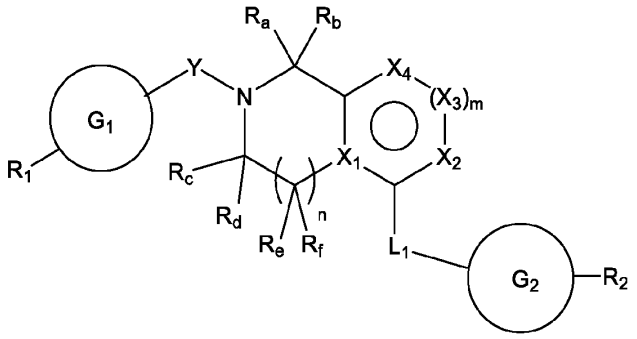
Table 2: Degradation activity results. A > 25% at 370 nM, B > 25% at 1500 nM, C < 25% at 1500 nM.

PROTAC Example No.	**Degradation activity**
3	A
4	C
6	C
7	C
8	C
9	B
10	C
11	C
13	A
14	B
18	C
19	C
21	A
29	B
31	B
34	B
35	C
38	C
39	A
40	C

41	C
42	C
43	C
44	C
45	A
46	A
47	C
48	C
53	C
54	B
55	C
57	C
61	C
63	C
69	C
71	C
72	C
73	A
74	C
77	C
78	B
79	C
80	B
81	C
83	A
84	C
85	A
86	C

CLAIMS

1. A heterocyclic compound, which heterocyclic compound is a compound of formula (I') or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof, for use as a medicament



(I')

wherein

- R_1 is C_1-C_6 haloalkyl, −L'−Z, −L'−C(O)R^y, −L'−C(O)N$R^i R^y$, −L'−C(O)OH, −L'−C(O)OR^y, −L'−NR^iC(O)R^y, −L'−SO_2N$R^i R^y$, or −L'−Het, wherein

  Het is 4- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−N$R^i R^{ii}$, and said heteroaryl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−N$R^i R^{ii}$;

  Z is selected from −OR^i, −N$R^i R^y$ and −SR^i;

  R^y is C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl, 3- to 7-membered carbocyclyl, 5- to 7-membered heteroaryl or 4- to 7-membered heterocyclyl, wherein said carbocyclyl and heterocyclyl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−N$R^i R^{ii}$, and said phenyl and heteroaryl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L'−OR^i and −L'−N$R^i R^{ii}$;

R^i and R^{ii} are the same or different and are selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

L' is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene;

- R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−Z', −L"−C(O)R^z, −L"−C(O)OR^z, −L"−C(O)$NR^{iii}R^z$, −L"−C(O)NH_2, −L"−NR^{iii}C(O)R^z, −L"−NR^{iii}C(O)OR^z, −L"−NR^{iii}C(O)$NR^{iv}R^z$, −L"−NR^{iii}C(O)C(O)$NR^{iv}R^z$, −L"−$NR^{iii}SO_2R^z$, −L"−(4- to 10-membered heterocyclyl), or −L"−(5- to 7-membered heteroaryl), wherein said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii} and −L"−$NR^{iii}R^{iv}$, and wherein said heteroaryl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii} and −L"−$NR^{iii}R^{iv}$; wherein

Z' is selected from −OH, −OR^{iii}, −NH_2, −$NR^{iii}R^z$ and −SR^{iii};

R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, −Q"−Z', −A−A', −Q'−A−A', or −A−Q"−A, wherein

A is phenyl, 3- to 7-membered carbocyclyl, 5- to 7-membered heteroaryl or 4- to 10-membered heterocyclyl, wherein said carbocyclyl and heterocyclyl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii}, −L"−$NR^{iii}R^{iv}$, and −L"−C(O)$NR^{iii}R^{iv}$, and said phenyl and heteroaryl are unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, −L"−OR^{iii}, −L"−$NR^{iii}R^{iv}$, −L"−C(O)$NR^{iii}R^{iv}$;

A' is hydrogen, phenyl or 4- to 8-membered heterocyclyl, wherein said phenyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 7-membered carbocyclyl, 4- to 7-membered heterocyclyl, −L"−OR^{iii}, and −L"−$NR^{iii}R^{iv}$, and said heterocyclyl is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 7-membered carbocyclyl, 4- to 7-membered heterocyclyl, −L"−OR^{iii}, −L"−$NR^{iii}R^{iv}$;

Q' is C_1-C_6 alkylene, C_1-C_6 haloalkylene, or −Q"−O−L"−;

Q'' is C_1-C_6 alkylene or C_1-C_6 haloalkylene;

L'' is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene;

R^{iii} and R^{iv} are the same or different and are selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety; and

- G_1 and G_2 are the same or different and are selected from phenyl, naphthyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 10-membered carbocyclyl, wherein said heterocyclyl and carbocyclyl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, oxo, and $-L^G-OR^G$, and wherein said phenyl, naphthyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and $-L^G-OR^G$, wherein

  L^G is a direct bond, C_1-C_6 alkylene or C_1-C_6 haloalkylene; and

  R^G is selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

- Y is methylene or $-C(O)-$, wherein said methylene is unsubstituted or substituted by C_1-C_4 alkyl, C_1-$_4$ haloalkyl, halogen or hydroxy;

- X_1 is C or N; m is 0 or 1; X_2, and X_3 are the same or different and are selected from N, NR' and CR'', and X_4 is selected from N, NR' and CR'''; provided that when m is 0, either (a) at least one of X_2 and X_4 is NR', and X_1 is C, or (b) X_2 is selected from N and CR'' and X_4 is selected from N and CR''', and X_1 is N; and when m is 1, X_1 is C, X_2 and X_3 are the same or different and are selected from N and CR'', and X_4 is selected from N and CR'''; wherein R' is hydrogen or C_1-C_4 alkyl, R'' is hydrogen, C_1-C_4 alkyl or halogen, and R''' is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, cyano or 3- to 5-membered carbocyclyl;

- L_1 is $-C(O)NR^v-Q-$, $-L_1'-NR^v-Q-$, or $-Het'-Q-$, wherein

  Q is a direct bond, linear or branched C_1-C_6 alkylene, or linear or branched C_1-C_6 haloalkylene, wherein said alkylene and haloalkylene are unsubstituted or substituted by a hydroxy group;

  L_1' is a direct bond, linear or branched C_1-C_2 alkylene, linear or branched C_1-C_2 haloalkylene or 4- to 6-membered heterocyclylene;

  Het' is a 4- to 6-membered heterocyclylene group or a 5- to 6-membered heteroarylene group, which group is unsubstituted or substituted by one, two or three C_1-C_3 alkyl groups which are the same or different; and

  R^v is hydrogen or C_1-C_3 alkyl;

- R_a and R_b are the same or different and are selected from C_1-C_4 alkyl or C_1-C_4 haloalkyl; or R_a and R_b together with the carbon to which they are attached form a 3- to 7-membered carbocyclyl moiety or 4- to 7-membered heterocyclyl moiety, which moiety is unsubstituted or substituted by one, two or three substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl;
- R_c and R_d are the same or different and are selected from hydrogen and C_1-C_4 alkyl, or R_c and R_d together are oxo;
- R_e and R_f are the same or different and are selected from hydrogen, halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- n is 0 or 1.

2. A heterocyclic compound for use according to claim 1, wherein the heterocyclic compound is a compound of formula (I') or a pharmaceutically acceptable salt, or a solvate, or a tautomer, or a stereoisomer thereof.

3. A heterocyclic compound for use according to claim 1 or claim 2, wherein R_1 is $-C_1$-C_4 haloalkyl, $-SR^i$, $-(C_1$-C_4 alkylene$)-OR^i$, $-C(O)R^y$, $-C(O)NR^iR^y$, $-C(O)OH$, $-C(O)OR^y$, $-NR^iC(O)R^y$, $-SO_2NR^iR^y$, or $-$Het.

4. A heterocyclic compound for use according to any one of the preceding claims, wherein Het is 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein said heterocyclyl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from oxo, C_1-C_4 alkyl, and $-N(C_1$-C_4 alkyl$)_2$, and said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_4 alkyl.

5. A heterocyclic compound for use according to any one of the preceding claims, wherein Het is 4- to 5-membered heterocyclyl which is unsubstituted or substituted by one oxo group, one C_1-C_3 alkyl group or one $-N(C_1$-C_3 alkyl$)_2$ group, or which is substituted by one oxo group and one C_1-C_3 alkyl group; or a 5-membered heteroaryl group which is unsubstituted or substituted with one or two C_1-C_3 alkyl.

6. A heterocyclic compound for use according to any one of the preceding claims, wherein R^y is C_1-C_4 alkyl, 3- to 7-membered cycloalkyl or 4- to 7-membered heterocyclyl,

wherein said cycloalkyl and heterocyclyl are unsubstituted or substituted by one C_1-C_4 alkyl group.

7. A heterocyclic compound for use according to any one of the preceding claims, wherein R^y is C_1-C_3 alkyl, or unsubstituted 4- to 6-membered heterocyclyl.

8. A heterocyclic compound for use according to any one of the preceding claims, wherein R^i is selected from hydrogen and C_1-C_4 alkyl.

9. A heterocyclic compound for use according to any one of the preceding claims, wherein R_1 is $-C(O)NR^i(C_1$-C_3 alkyl).

10. A heterocyclic compound for use according to any one of the preceding claims, wherein R_1 is $-C(O)N(CH_3)_2$.

11. A heterocyclic compound for use according to any one of the preceding claims, wherein R_2 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-Z'$, $-C(O)R^z$, $-C(O)OR^z$, $-C(O)NR^{iii}R^z$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)OR^z$, $-NR^{iii}C(O)NR^{iv}R^z$, $-NR^{iii}C(O)C(O)NR^{iv}R^z$, $-NR^{iii}SO_2R^z$, $-$(4- to 7-membered heterocyclyl) which is unsubstituted or substituted by one oxo group, or $-$(5- to 7-membered heteroaryl) which is unsubstituted or substituted with one C_1-C_3 alkyl group; or R_2 is $-L_2$-LBM, wherein L_2 is a linker and LBM is a ligase binding moiety.

12. A heterocyclic compound for use according to any one of the preceding claims, wherein R_2 is hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, $-Z'$, $-C(O)(C_1$-C_3 alkyl), $-C(O)O(C_1$-C_4 alkyl), $-C(O)NR^{iii}(C_1$-C_3 alkyl), $-C(O)NR^{iii}(-A-A')$, $-C(O)NH_2$, $-NR^{iii}C(O)R^z$, $-NR^{iii}C(O)O(C_1$-C_4 alkyl), $-NR^{iii}C(O)O(-A-A')$, $-NR^{iii}C(O)NR^{iv}(C_1$-C_3 alkyl), $-NR^{iii}C(O)C(O)NR^{iv}(C_1$-$C_3$ alkyl), $-NHSO_2(C_1$-C_3 alkyl), 5-membered heterocyclyl which is unsubstituted or substituted with one oxo group, or 5-membered heteroaryl which is unsubstituted or substituted with one C_1-C_3 alkyl group.

13. A heterocyclic compound for use according to any one of the preceding claims, wherein Z' is selected from $-OH$, $-O(C_1$-C_3 alkyl), $-NH_2$, $-NR^{iii}(C_1$-C_3 alkyl), $-NR^{iii}(C_1$-C_3 haloalkyl), a $-NH-$(5- to 6-membered heteroaryl) group which is unsubstituted, and a

−NH−(4- to 6-membered heterocyclyl) group which is unsubstituted or substituted with one C_1-C_3 alkyl group, or one C_1-C_3 alkyl group and one oxo group.

14. A heterocyclic compound for use according to any one of the preceding claims, wherein R^z is C_1-C_6 alkyl, C_1-C_6 haloalkyl, −(C_1-C_3 alkylene)−Z', −A−A', −(C_1-C_3 alkylene)−A−A', −(C_1-C_3 alkylene−O−C_1-C_3 alkylene)−A−A', or −A−(C_1-C_3 alkylene)−A, wherein

A is a phenyl moiety which is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, −N(C_1-C_3 alkyl)$_2$, and −(C_1-C_3 alkylene)−C(O)NR^{iii}(C_1-C_3 alkyl), a 3- to 7-membered cycloalkyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from C_1-C_3 alkyl, halogen, cyano, and $-OR^{iii}$, a 5- to 7-membered heteroaryl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl, or a 4- to 10-membered heterocyclyl moiety which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, cyano, C_1-C_3 alkyl, and oxo; and

A' is hydrogen, a phenyl moiety which moiety is unsubstituted or substituted with −(C_1-C_3 alkylene)−$NR^{iii}R^{iv}$, or a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$.

15. A heterocyclic compound for use according to any one of the preceding claims, wherein R^z is phenyl−A' wherein said phenyl is unsubstituted or substituted with one substituent selected from C_1-C_3 alkyl, halogen, −N(C_1-C_3 alkyl)$_2$, and −(C_1-C_3 alkylene)−C(O)NR^{iii}(C_1-C_3 alkyl), or (5- to 6-membered heteroaryl)−A' wherein said heteroaryl is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and C_1-C_3 alkyl, wherein A' is a 4- to 8-membered heterocyclyl moiety which moiety is unsubstituted or substituted by one substituent selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, oxo, 3- to 5-membered carbocyclyl, 4- to 5-membered heterocyclyl, and $-OR^{iii}$.

16. A heterocyclic compound for use according to any one of the preceding claims, wherein R^z is (unsubstituted phenyl)−A', or (pyrazolyl)−A' wherein said pyrazolyl is substituted with one methyl group, and wherein A' is piperidinyl which is substituted with

one substituent selected from cyclobutyl and $-CH_2CHF_2$, or azetidinyl which is substituted with one methoxy group, or unsubstituted morpholinyl.

17. A heterocyclic compound for use according to any one of the preceding claims, wherein R^{iii} is selected from hydrogen and C_1-C_4 alkyl.

18. A heterocyclic compound for use according to any one of the preceding claims, wherein G_1 is selected from a phenyl moiety, a 5- to 7-membered heterocyclyl moiety, a 5- to 7-membered heteroaryl moiety, or a 5- to 7-membered cycloalkyl moiety, which moiety is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl.

19. A heterocyclic compound for use according to any one of the preceding claims, wherein G_1 is phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and C_1-C_3 alkyl.

20. A heterocyclic compound for use according to any one of the preceding claims, wherein G_2 is selected from phenyl, 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 4- to 7-membered cycloalkyl, wherein said heterocyclyl and cycloalkyl are unsubstituted or substituted by one substituent selected from C_1-C_4 alkyl, $-(C_1$-C_4 alkylene)$-OH$ and oxo, and wherein said phenyl and heteroaryl are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, $-O-(C_1$-C_4 alkyl), C_1-C_4 alkyl and C_1-C_4 haloalkyl.

21. A heterocyclic compound for use according to any one of the preceding claims, wherein G_2 is phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from halogen, $-O-(C_1$-C_3 alkyl) and C_1-C_3 alkyl.

22. A heterocyclic compound for use according to any one of the preceding claims, wherein Y is methylene.

23. A heterocyclic compound for use according to any one of the preceding claims, wherein m is 0.

24. A heterocyclic compound for use according to claim 23, wherein X_1 is N, X_2 is N or CR", and X_4 is CR'".

25. A heterocyclic compound for use according to claim 24, wherein: (a) m is 0, X_1 is N, X_2 is CH and X_4 is CH; or (b) m is 0, X_1 is N, X_2 is N and X_4 is CH or $C(CH_3)$.

26. A heterocyclic compound for use according to any one of the preceding claims, wherein L_1 is $-C(O)NR^v-Q-$, –(4-membered heterocyclylene)$-NR^v-Q-$, $-NR^v-Q-$ or –(5-membered heteroarylene)$-Q-$, wherein Q is a direct bond, or unsubstituted C_1-C_2 alkylene, and R^v is hydrogen or C_1-C_3 alkyl.

27. A heterocyclic compound for use according to any one of the preceding claims, wherein L_1 is $-C(O)NR^v-Q-$, wherein Q is methylene and R^v is hydrogen.

28. A heterocyclic compound for use according to any one of the preceding claims, wherein R_a and R_b are the same or different and are C_1-C_3 alkyl, or R_a and R_b together with the carbon to which they are attached form an unsubstituted 4- to 6-membered heterocyclyl, or a 3- to 7-membered cycloalkyl which is unsubstituted or substituted by one or two substituents selected from fluorine and C_1-C_3 alkyl.

29. A heterocyclic compound for use according to any one of the preceding claims, wherein R_a and R_b together with the carbon to which they are attached form an unsubstituted 4-membered heterocyclyl, or an unsubstituted 4-membered cycloalkyl.

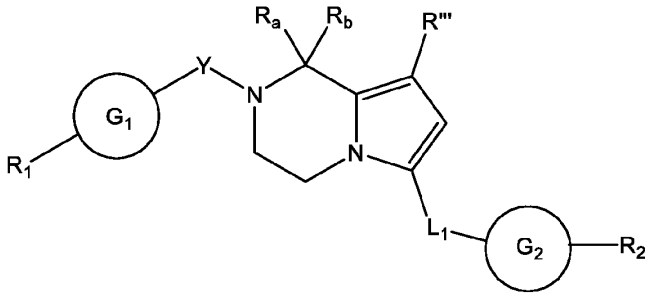
30. A heterocyclic compound for use according to any one of the preceding claims, wherein R_c and R_d are hydrogen.

31. A heterocyclic compound for use according to any one of the preceding claims, wherein R_e and R_f are hydrogen.

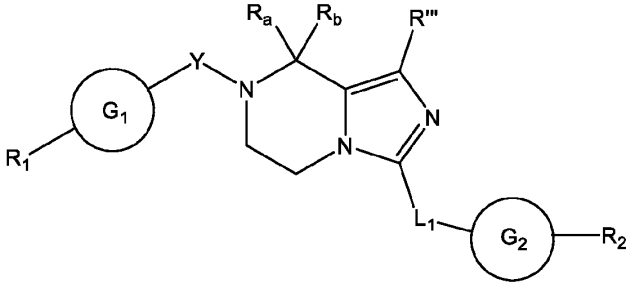
32. A heterocyclic compound for use according to any one of the preceding claims, wherein n is 1.

33. A heterocyclic compound for use according to any one of the preceding claims, wherein R_1, G_1, G_2, Y, X_1, X_2, X_3, X_4, L_1, R_a, R_b, R_c, R_d, R_e, R_f, m and n are as defined in any one of the preceding claims, and R_2 is $-L_2$-LBM.

34. A heterocyclic compound for use according to any one of the preceding claims which is a compound of formula (I'iii(a)) or (I'iii(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iii(a))



(I'iii(b))

wherein

- R_1 is CF_2CH_3, $-SCH_3$, C4 alkylene–OH, $-C(O)R^y$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)N(CH_3)(C_3$ alkyl), $-C(O)N(CH_2CH_3)_2$, $-C(O)OH$, $-C(O)OCH_3$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-SO_2NH(CH_3)$, or unsubstituted pyrrolidinone, or an oxetanyl moiety which is unsubstituted or substituted by one methyl group or one $-N(CH_3)_2$ group, or a triazolyl moiety which is unsubstituted, substituted with one methyl group, or substituted with one oxo group and one methyl group, or an imidazolyl moiety which is unsubstituted, substituted with one or two methyl groups, or substituted with one oxo group and one methyl group, or a pyrazolyl moiety which is unsubstituted or substituted by one methyl group, or

unsubstituted oxadiazolyl, or an oxazolyl moiety which is unsubstituted or substituted by one methyl group, or a furanyl moiety which is substituted with two methyl groups, or unsubstituted tetrahydrofuranyl, or unsubstituted tetrazolyl, wherein

R^y is methyl, ethyl, i-propyl, unsubstituted azetidinyl, unsubstituted pyrrolidinyl, unsubstituted piperidinyl, or unsubstituted morpholinyl;

- R_2 is hydrogen, methyl, $-CH_2F$, $-Z'$, $-C(O)CH_3$, $-C(O)O(tert\text{-butyl})$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH(-A-A')$, $-C(O)NH_2$, $-N(CH_3)C(O)CH_3$, $-NHC(O)R^z$, $-NHC(O)O(C_3\text{-}C_4$ alkyl), $-NHC(O)O$(unsubstituted phenyl), $-NHC(O)N(CH_3)_2$, $-NHC(O)N(CH_3)(CH_2CH_3)$, $-NHC(O)NH(CH_3)$, $-NHC(O)C(O)N(CH_3)_2$, $-NHSO_2(CH_3)$, unsubstituted pyrrolidinone, unsubstituted dihydrotriazolone, unsubstituted oxadiazolone, imidazolyl which is unsubstituted or substituted with one methyl group, triazolyl which is unsubstituted or substituted with one methyl group, or unsubstituted tetrazolyl, wherein

  Z' is $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-NHCH_2CF_3$, a $-NH-$pyridinyl group which is unsubstituted, a $-NH-$oxetanyl group which is unsubstituted or substituted with one methyl group, or a $-NH-$(unsubstituted pyrimidinone) group;

  R^z is methyl, *tert*-butyl, *iso*-butyl, $-CH_2-$(*tert*-butyl), cyclopropyl which is unsubstituted or substituted with one halogen group, cyclobutyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, oxadiazolyl which is substituted with one methyl group, unsubstituted thiazolyl, benzodioxazolyl which is unsubstituted or substituted with one or two halogen groups, oxetanyl which is unsubstituted or substituted with one methyl group, azetidinyl which is unsubstituted or substituted with one cyano group or one methoxy group, unsubstituted pyrrolidinyl, pyrimidinonyl which is unsubstituted or substituted with one methyl group, indolinyl which is unsubstituted or substituted with one methyl group, morpholinyl which is unsubstituted or substituted with one methyl group, piperidinyl which is unsubstituted or substituted with one methyl group, piperazinyl which is unsubstituted or substituted with one methyl group, tetrahydroquinoline which is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen and methyl, unsubstituted tetrahydrofuranyl, unsubstituted tetrahydropyranyl, tetrahydropyrazolo[1,5-a]pyrazinyl which is unsubstituted or substituted with one methyl group, tetrahydro-1H,3H-5l2-furo[3,4-c]pyrrole which is substituted with one or two methyl groups, unsubstituted oxa-

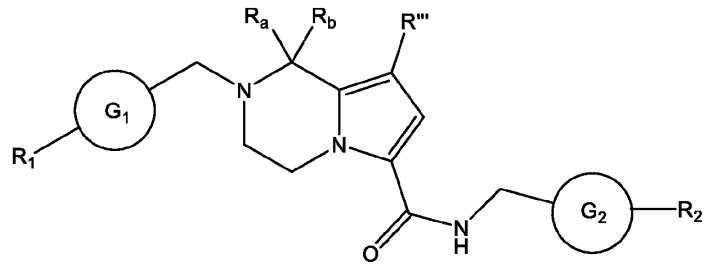
azaspiroheptane, unsubstituted oxa-azaspirooctane, unsubstituted oxa-azaspirononane, unsubstituted oxa-azabicycloheptane, unsubstituted oxa-azabicyclooctane, or phenyl−A' wherein said phenyl is unsubstituted or substituted with one substituent selected from methyl, propyl, halogen, $-N(CH_3)_2$, and –(ethylene)−C(O)NH(CH_3), or (imidazolyl)−A' wherein said imidazolyl is unsubstituted or substituted with one methyl group, or (pyrazolyl)−A' wherein said pyrazolyl is unsubstituted or substituted with one or two methyl groups, or (pyridinyl)−A' wherein said pyridinyl is unsubstituted or substituted with one C_1-C_3 alkyl group or one halogen group, or (pyrimidinyl)−A' wherein said pyrimidinyl is unsubstituted or substituted with one methyl group, wherein

A' is hydrogen, phenyl which is substituted with $-(CH_2)-NH(CH_3)$, azetidinyl which is substituted with one substituent selected from methyl, methoxy, cyclopropyl, and cyclobutyl, piperidinyl which is substituted with one substituent selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH_2CH_2F$, $-CH_2CHF_2$, methoxy, and oxetanyl, morpholinyl which is unsubstituted or substituted with one methyl group or one oxo group, piperazinyl which is substituted with one substituent selected from methyl, cyclopropyl, and cyclobutyl, tetrahydropyridinyl which is substituted with one methyl group, pyrrolidinyl which is substituted with one methoxy group, or unsubstituted oxazaspiroheptane, unsubstituted oxazaspirooctane, or unsubstituted tetrahydropyranyl;

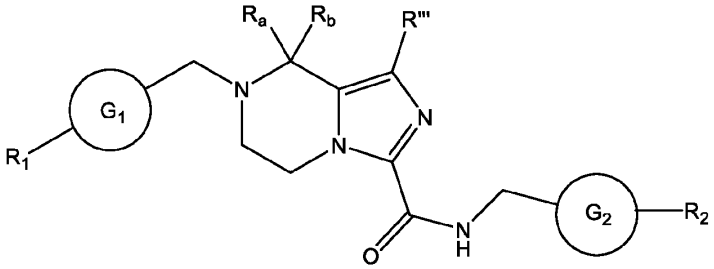
- G_1 is unsubstituted piperidinyl, unsubstituted bicyclo[1.1.1]pentyl, unsubstituted cyclohexyl, unsubstituted pyrimidinyl, pyridinyl which is unsubstituted or substituted with one methyl group, one fluorine group, or one chlorine group, or phenyl which is unsubstituted or substituted with one or two substituents which are the same or different and are selected from fluorine, chlorine and methyl;
- G_2 is unsubstituted piperidinyl, unsubstituted benzimidazolyl, unsubstituted pyrrolidinyl, unsubstituted tetrahydropyranyl, unsubstituted bicyclo[1.1.1]pentyl, cyclohexyl which is unsubstituted or substituted with one hydroxy group, unsubstituted indolinyl, unsubstituted oxoindolinyl, unsubstituted benzoxazolonyl, unsubstituted dihydroquinolinonyl, pyridinyl which is unsubstituted or substituted with one chlorine group, unsubstituted pyrimidinyl, unsubstituted indolyl, unsubstituted oxazolyl, unsubstituted thiazolyl, or phenyl which is unsubstituted or substituted with one or two substituents selected from fluorine, chlorine, methoxy and methyl;

- Y is methylene or −C(O)−;
- R''' is hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl, cyano, or cyclopropyl;
- L_1 is −C(O)NR^v−Q−, –(oxetanylene)−NR^v−Q−, or –(triazolylene)−Q−, wherein Q is a direct bond or methylene, and R^v is hydrogen or methyl;
- R_a is methyl and R_b is methyl; or R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl, unsubstituted tetrahydrofuranyl, unsubstituted cyclopropyl, unsubstituted cyclopentyl, unsubstituted cyclohexyl, or a cyclobutyl group which is unsubstituted or substituted with one or two substituents selected from fluorine and methyl.

35. A heterocyclic compound for use according to any one of the preceding claims which is a compound of formula (I'iv(a)) or (I'iv(b)) or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



(I'iv(a))



(I'iv(b))

wherein

- R_1 is −C(O)$N(CH_3)_2$;
- R_2 is −NHC(O)(−A−A'), wherein A is unsubstituted phenyl or pyrazolyl which is substituted with one methyl group, and A' is piperidinyl which is substituted with one

substituent selected from cyclobutyl and $-CH_2CHF_2$, or azetidinyl which is substituted with one methoxy group, or unsubstituted morpholinyl;

- G_1 is unsubstituted phenyl;
- G_2 is unsubstituted phenyl;
- R''' is hydrogen or methyl; and

R_a and R_b together with the carbon to which they are attached form unsubstituted oxetanyl or unsubstituted cyclobutyl.

36. A heterocyclic compound for use according to any one of the preceding claims, wherein the heterocyclic compound has an IC_{50} of no more than 10,000 nM against STAT6.

37. A heterocyclic compound for use according to any one of the preceding claims, wherein the heterocyclic compound is one of:

- *N*-(4-acetamidobenzyl)-2'-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(isopropyl(methyl)carbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3,5-dimethylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-3-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-imidazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(4-methyl-4*H*-1,2,4-triazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(1,3,4-oxadiazol-2-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(oxazol-2-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((1-isobutyrylpiperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- 2'-(4-(1*H*-pyrazol-1-yl)benzyl)-*N*-(4-acetamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-methyloxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- Methyl 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylate;
- 3-((6'-((4-acetamidobenzyl)carbamoyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid;
- *N*-(4-acetamidobenzyl)-2'-(4-(3-(dimethylamino)oxetan-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-((3-(dimethylcarbamoyl)bicyclo[1.1.1]pentan-1-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(1-hydroxy-2-methylpropyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(2-methyl-4-(1*H*-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-isobutyrylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((2-((3R,5S)-3,5-Dimethylpiperazin-1-yl)pyrimidin-4-yl)methyl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine
- *N*-(4-acetamidobenzyl)-2'-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(dimethylamino)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-benzyl-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylpiperidin-4-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-dimethyl-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(azetidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(pyrrolidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(piperidine-1-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(morpholine-4-carbonyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-methylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- *N*-(4-acetamido-3,5-dimethylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamido-3-fluorobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(*N*-methylacetamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-oxoindolin-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((2-methyl-1*H*-benzo[d]imidazol-5-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-((3-methyloxetan-3-yl)amino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(2-oxopyrrolidin-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((1-acetylindolin-5-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(3-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidophenyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*,2'-bis(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- Tert-butyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate;
- *N*-(4-aminobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-isopropylbenzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(isonicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-pivalamidobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(cyclobutanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-benzamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(nicotinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(oxetane-2-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(4-(tetrahydro-2*H*-pyran-4-yl)benzamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(bicyclo[1.1.1]pentane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(pyridin-2-ylamino)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;

- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(1-methylindoline-6-carboxamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-(3,3-dimethylbutanamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-(4-(picolinamido)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((5-benzamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-((3-acetamidobicyclo[1.1.1]pentan-1-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide;
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide; and
- *N*-(4-acetamidobenzyl)-2-(4-(dimethylcarbamoyl)benzyl)-1,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxamide.
- *N*-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)-2-methylbenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1*H*-1,2,4-triazol-1-yl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(2-chloro-4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-*N*-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide

- *N*-(4-acetamidobenzyl)-2'-(4-(5-methyl-1*H*-pyrazol-1-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-((3-chloro-5-(dimethylcarbamoyl)pyridin-2-yl)methyl)-*N*-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- *N*-(4-(1*H*-imidazol-2-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-(4*H*-1,2,4-triazol-3-yl)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-*N*-((1-(methylcarbamoyl)piperidin-4-yl)methyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-((4-acetamidophenyl)methyl-d2)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- *N*-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- isopropyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate
- *N*-(4-((2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamido)methyl)phenyl)morpholine-4-carboxamide
- *N*-(4-acetamidobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-*N*-(4-(methylcarbamoyl)benzyl)-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide
- *N*-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1*H*-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-*N*-methyl-6',7'-dihydro-5'*H*-spiro[cyclobutane-1,8'-imidazo[1,5-*a*]pyrazine]-3'-carboxamide
- *N*-(4-acetamidobenzyl)-2'-(4-(isoxazol-3-yl)benzyl)-3',4'-dihydro-2'*H*-spiro[cyclobutane-1,1'-pyrrolo[1,2-*a*]pyrazine]-6'-carboxamide
- N-(4-acetamidobenzyl)-2'-((4-(dimethylcarbamoyl)phenyl)methyl-d2)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-N-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-((5-(dimethylcarbamoyl)-3-fluoropyridin-2-yl)methyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-carbamoylbenzyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-N-(4-(methylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-acetamidopyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3,3-difluoro-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-N-((5-(1-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-3,3-difluoro-N-((5-(1-methyl-1H-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7''-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6'',7''-dihydro-5''H-dispiro[cyclobutane-1,1'-cyclobutane-3',8''-imidazo[1,5-a]pyrazine]-3''-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclopropane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-fluoro-1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methoxypropanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(2-cyclopropylacetamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1R,2R)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-(methylamino)-3-oxopropyl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2'-((methylamino)methyl)-[1,1'-biphenyl]-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-hydroxypropanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-ethylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-(oxetan-3-yl)piperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylazetidin-3-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N-(4-(1,5-dimethyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1H-pyrazole-3-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((1r,3r)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((1s,3s)-3-cyanocyclobutane-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- (1R,4R)-N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxamide
- (1R,5S)-N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.4]octane-6-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(tetrahydrofuran-2-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- (S)-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- (R)-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)morpholine-4-carboxamide
- N-(4-(cyclohexanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(pyrrolidine-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(azetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-ethyl-3-methylureido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(3-cyanoazetidine-1-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methoxyazetidine-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1s,3s)-3-methoxycyclobutane-1-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- isobutyl (4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)carbamate
- N-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylazetidin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(1-cyclobutylpiperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(3,3-dimethylureido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(4-(1-cyclobutylpiperidin-4-yl)benzamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(2-fluoro-4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(2-fluoro-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(oxetane-3-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-morpholinonicotinamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N1-(4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)-N2,N2-dimethyloxalamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- isobutyl (4-((7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-morpholinopyrimidine-5-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxypyrrolidin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 4-((7'-(4-acetamidobenzyl)-6'-oxo-3',4',6',7',8',9'-hexahydro-2'H-spiro[cyclobutane-1,1'-pyrido[4',3':4,5]pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)-N,N-dimethylbenzamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(4-(4-methylpiperazin-1-yl)benzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-((5-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(1-methyl-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(1-methyl-1H-imidazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(1-methyl-1H-imidazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(cyclopropanecarboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- N-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2-fluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclobutylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-methylpiperidin-4-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(3-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide

- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-fluoro-4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methoxypiperidin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-oxomorpholino)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(1-(oxetan-3-yl)piperidin-4-yl)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(1-(2,2-difluoroethyl)piperidin-4-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(1-(1-cyclobutylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(1-(2-fluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-acetamidobenzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- tert-butyl (4-((1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamido)methyl)phenyl)carbamate
- 1'-bromo-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-N-(3-chloro-4-(3,3-dimethylureido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(3-chloro-4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-cyclopropylazetidin-3-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N2,N2-dimethyloxalamide
- 7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-N-(4-(4-morpholinobenzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(2-methoxy-4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(1-(1-cyclopropylpiperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((4-morpholinophenyl)carbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-((1-(1-cyclopropylpiperidin-4-yl)-1H-imidazol-4-yl)carbamoyl)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-((5-(4-(3-methoxyazetidin-1-yl)benzamido)pyridin-2-yl)methyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 1'-chloro-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-N-(4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((1S,2S)-2-fluorocyclopropane-1-carboxamido)benzyl)-1'-methyl-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-((5-(4-morpholinobenzamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N-(4-(4-(4-cyclobutyl-2-oxopiperazin-1-yl)benzamido)benzyl)-2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-8'-methyl-N-(4-(4-(3-oxomorpholino)benzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-(trifluoromethyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(4-cyclobutylpiperazin-1-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(1-cyclopropylazetidin-3-yl)benzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 1-chloro-7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methoxyazetidin-1-yl)benzamido)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-1'-methyl-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 8'-bromo-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-7'-fluoro-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N-(4-acetamidobenzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-((5-(cyclopropanecarboxamido)pyridin-2-yl)methyl)-2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-3,3-difluoro-N-((5-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)methyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- N-(4-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(2-oxa-6-azaspiro[3.4]octan-6-yl)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methyl-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 2'-((5-(dimethylcarbamoyl)-3-methylpyridin-2-yl)methyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3,3-dimethylureido)benzyl)-1-methyl-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-methylpiperazin-1-yl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide

- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-methyl-4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(4-(dimethylamino)benzamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-methylindoline-5-carboxamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- (R)-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methylmorpholino)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- (S)-7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-methylmorpholino)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(morpholinomethyl)benzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-morpholinopicolinamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(benzo[d][1,3]dioxole-5-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N-(4-(2,2-difluorobenzo[d][1,3]dioxole-5-carboxamido)benzyl)-7'-(4-(dimethylcarbamoyl)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,5-a]pyrazine]-3'-carboxamide
- N,N-dimethyl-4-((6'-(1-(4-(methylcarbamoyl)benzyl)-1H-1,2,3-triazol-4-yl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazin]-2'-yl)methyl)benzamide
- N-(4-(4-(4-cyclopropylpiperazin-1-yl)-2-fluorobenzamido)benzyl)-7-(4-(dimethylcarbamoyl)benzyl)-6,7-dihydro-5H-spiro[imidazo[1,5-a]pyrazine-8,3'-oxetane]-3-carboxamide
- 2'-(4-(dimethylcarbamoyl)-2,6-difluorobenzyl)-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-7'-fluoro-N-(4-(4-morpholinobenzamido)benzyl)-3',4'-dihydro-2'H-spiro[oxetane-3,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 7'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-morpholinobenzamido)benzyl)-6',7'-dihydro-5'H-spiro[cyclobutane-1,8'-imidazo[1,2-a]pyrazine]-3'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-((S)-15-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-16,16-dimethyl-13-oxo-4,7,10-trioxa-14-azaheptadecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-

2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14-tetraoxa-2-azaheptadecan-17-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N10-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N5-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(9-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)nonanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15,18-hexaoxahenicosan-21-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxapentadecan-15-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N9-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N4-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N15-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12-trioxa-3-azapentadecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(4-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-

dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N11-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(10-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)decanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N6-((S)-1-((2S,4R)-4-

hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N21-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6,9,12,15,18-pentaoxa-3-azahenicosanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperazin-1-yl)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(7-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)acetamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11-trioxa-2-azatetradecan-14-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-

2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(7-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)amino)heptanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenyl)-1-oxo-5,8,11,14,17-pentaoxa-2-azaicosan-20-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(1-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12,15-pentaoxaoctadecan-18-amido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- rac-2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(((2R,4S)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-

2-yl)amino)-6-oxohexyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(2-(2-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperazin-1-yl)propanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N12-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)dodecanediamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(11-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)undecanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(4-(2-(((2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzamido)pentanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide
- N1-(4-((2'-(4-(dimethylcarbamoyl)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamido)methyl)phenyl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide

- 2'-(4-(dimethylcarbamoyl)benzyl)-N-(4-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamido)benzyl)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-pyrrolo[1,2-a]pyrazine]-6'-carboxamide

38. A pharmaceutical composition comprising a heterocyclic compound as defined in any one of the preceding claims, and a pharmaceutically acceptable carrier or diluent.

39. A pharmaceutical composition according to claim 38, for use as a medicament.

40. A heterocyclic compound for use according to any one of claims 1 to 37, or the composition for use of claim 39, wherein the heterocyclic compound or composition is for use in a method of treating a condition or disease selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas, preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

41. Use of a heterocyclic compound as defined in any one of claims 1 to 37, or the composition as defined in claim 38, in the manufacture of a medicament for treating a condition or disease selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic

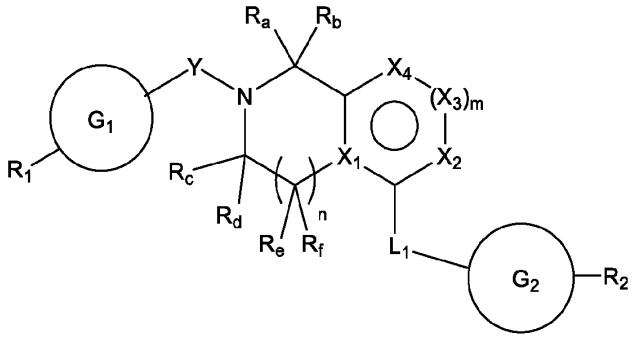
esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas, preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

42. A method of treating a condition or disease selected from atopic dermatitis, eczema, nummular eczema, allergic contact dermatitis, chronic hand eczema, hand and foot dermatitis, bullous pemphigoid, chronic spontaneous urticaria, cholinergic urticaria, chronic cold-induced urticaria, prurigo nodularis, chronic pruritus, Netherton syndrome, alopecia areata, lichen sclerosus, asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic chronic sinusitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, eosinophilic gastritis, ulcerative colitis, chronic hepatic pruritus, food allergies, atopic keratoconjunctivitis, localized scleroderma, fibrotic diseases, keloids, systemic sclerosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, eosinophilic fasciitis, eosinophilic otitis media, solid tumors and hematological cancers including cutaneous cell lymphoma (CTCL), Sezary syndrome (SS), Hodgkin lymphomas, primary mediastinal and primary central nervous system lymphoma, follicular and T cell lymphomas, in a subject, the method comprising administering to said subject a therapeutically effective amount of a heterocyclic compound as defined in any one of claims 1 to 37, or the composition of claim 38, preferably, the condition or disease is selected from atopic dermatitis, asthma, chronic spontaneous urticaria and purigo nodularis.

43. A compound which compound is

(a) a heterocyclic compound of formula (I'), wherein R_1, R_2, G_1, G_2, Y, X_1, X_2, X_3, X_4, L_1, R_a, R_b, R_c, R_d, R_e, R_f, m and n are as defined in any one of claims 1 to 37; or

(b) a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative of said heterocyclic compound,



(I')

provided that said compound is not:

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[[5-Fluoro-2-(2,2,2-trifluoroethoxy)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[5-fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[[4-(trifluoromethyl)-2-pyrimidinyl]amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-hydroxypropyl)-2,5-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(4-Ethoxy-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(3,3,3-trifluoropropyl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, hydrate (1:1);

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, with 2-propanol (1:1);

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[3-[(4,6-Dimethyl-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

Methanone, [3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]-, acetate (1:1);

[3-[(2-Ethoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, [3-[(2,5-difluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2R,5S)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]-, *relative stereochemistry*;

Bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4- c]pyrazol-5(1H)-yl]methanone; or

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-2-methyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone.

44. A compound according to claim 43, wherein said heterocyclic compound is other than:

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[[5-Fluoro-2-(2,2,2-trifluoroethoxy)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[5-fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[[4-(trifluoromethyl)-2-pyrimidinyl]amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-6,6-dimethyl-3-[(4-methyl-2-pyrimidinyl)amino]pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-hydroxypropyl)-2,5-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl] methanone;

[3-[(5-Fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[2-(Ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(2-methoxyethyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(4-Ethoxy-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(5-Fluoro-2-methoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[[5-Fluoro-2-(methoxymethyl)-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5S)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-5-(2-hydroxyethyl)-2,4-dimethyl-1-piperazinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethyl-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][1-(3,3,3-trifluoropropyl)-4-piperidinyl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(3,3,3-trifluoropropyl)-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, hydrate (1:1);

Methanone, bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]-, with 2-propanol (1:1);

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[(2S,5R)-2,5-Dimethyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(2-ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl]methanone;

[3-[(4,6-Dimethyl-2-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

[4,6-Dihydro-3-[(4-methoxy-2-pyrimidinyl)amino]-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone;

Methanone, [3-[[2-(ethylamino)-5-fluoro-4-pyrimidinyl]amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4- c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]-, acetate (1:1);

[3-[(2-Ethoxy-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S,5R)-4-(3-methoxypropyl)-2,5-dimethyl-1-piperazinyl]methanone;

[2,5-Dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl][3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl]methanone;

Methanone, [3-[(2,5-difluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethyl pyrrolo[3,4-c]pyrazol-5(1H)-yl][(2R,5S)-2,5-dimethyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1-piperazinyl]-, *relative stereochemistry*;

Bis[3-[(5-fluoro-2-methyl-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo [3,4- c]pyrazol-5(1H)-yl]methanone; or

[3-[(2-Ethoxy-5-fluoro-4-pyrimidinyl)amino]-4,6-dihydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H)-yl][(2S)-2-methyl-4-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-1-piperazinyl]methanone.