TITLE OF THE INVENTION

Interleukin-17 Inhibitors

FIELD OF THE INVENTION

The present invention relates to pyridine-N oxide substituted 2-formamido (*N*-phenyl and *N*-pyridyl) acetamide compounds. The present invention also relates to processes for the preparation of said compounds, pharmaceutical compositions comprising said compounds, and use of said compounds in the treatment of conditions, diseases and disorders mediated by interleukin-17 (IL-17).

BACKGROUND OF THE INVENTION

Interleukin-17 (IL-17) family cytokines are important regulators of inflammatory responses and participate in immune responses to infections. The family consists of six members, IL-17A to IL-17F. IL-17A (frequently cited as IL-17), the prototypic member of the family, was originally identified as a cytokine produced by the subset of CD4+ T-cells that is now termed Th17 (Matsuzaki *et al Microbiol. Immunol.* 2018, 62, 1-13).

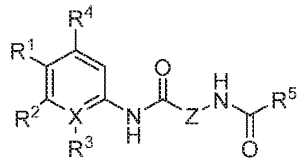
IL-17, a T-cell derived cytokine present *e.g.* in rheumatoid arthritis (RA), acts as a pro-inflammatory cytokine, particularly in conjunction with IL-1 and TNF-α (Chabaud *et al Arthritis Rheum.* 1999, 42, 963-970; Awane M *et al J. Immunol*. 1999, 162, 5337-5344). IL-17 induces MMP production and downregulates TIMP (Jovanovic *et al J. Rheumatol.* 2001, 28, 712-718), and blockage of IL-1 and IL-17 has a synergistic effect on inflammation and bone destruction *in vivo* (Chabaud *et al Arthritis Rheum* 2001, 44, 1293-1303). Inappropriate or excessive production of IL-17 is associated with the pathology of various diseases and disorders, such as rheumatoid arthritis (Witowski *et al Cell. Mol. Life Sci*. 2004, 61, 567-579), osteoarthritis, loosening of bone implants, acute transplant rejection (Antonysamy *et al J. Immunol.* 1999, 162, 577-584; Van Kooten *et al J. Am. Soc. Nephrol*. 1998, 9, 1526-1534), septicemia, septic or endotoxic shock, allergies, asthma (Molet *et al J. Allergy Clin. Immunol*. 2001, 108, 430-438), bone loss, psoriasis (Teunissen *et al J. Invest. Dermatol.* 1998, 111, 645-649), ischemia, systemic sclerosis (Kurasawa *et al Arthritis Rheum*. 2000, 43, 2455-2463), stroke, and other inflammatory disorders. Antibodies to IL-17 have been proposed for use in the treatment of IL-17 mediated diseases and disorders; see for instance, WO 95/18826 or WO 2006/013107. One of the major problems associated with such antibody-based treatments is that they require repeated subcutaneous injections. Such injections may be associated with pain, bruising of the injected area, skin irritation, or skin infection. Small molecule IL-17 modulators are described in WO2020/127685, Liu *et al Sci. Rep.* 2016, 6, 30859, WO 2013/116682 and WO2014/066726.

There is a need to provide new and/or alternative treatments for IL-17 mediated diseases and/or conditions, which may allow, for example, a different mode of administration (for example oral or topical application) and/or demonstrate improved solubility and/or exposure *in vivo*.

SUMMARY OF THE INVENTION

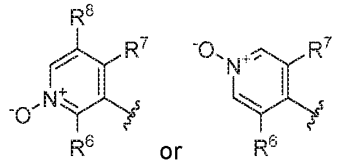
The present invention provides compounds of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein below. The compounds of formula (I) inhibit the IL-17 pathway and are therefore potentially useful in the treatment of conditions, diseases and disorders such as psorisasis, psoriatic arthritis, ankylosing spondylitis or non-radiographic axial spondyloarthritis. Inhibition of the IL-17 pathway provides new treatments and therapies for patients suffering from IL-17-related diseases/disorders. The compounds of formula (I) may be suitable for oral or topical application and may further exhibit improved solubility and/or exposure *in vivo*.

In one aspect of the present invention, a compound of formula (I) is provided,


(I),

wherein,

R^1 is


or wherein,

R^6 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^7 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^8 is selected from H, halo, C_1-C_3alkyl and hydroxymethyl;

X is C or N and when X is N, R^3 is absent;

R^2 is selected from H and F;

R^3 is selected from H, F and Cl;

R^4 is selected from H and F;

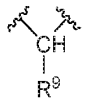
R^5 is a 5-membered heteroaryl comprising 1 or 2 heteroatoms independently selected from N, S, and O, and wherein said heteroaryl is unsubstituted or substituted with one or two groups independently selected from C_1-C_3alkyl and C_3-C_4cycloalkyl, wherein said C_1-C_3alkyl is unsubstituted

or substituted with one or more groups independently selected from F, OH, C_1-C_3alkoxy, -C(O)OH and $NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are independently selected from H and C_1-C_3alkyl;

or

R^5 is a 5-membered heteroaryl comprising one N atom wherein said 5-membered heteroaryl is fused to a 6-membered heterocycle comprising one N atom wherein said heterocycle is unsubstituted or substituted with a group selected from C_1-C_3alkyl, C_1-C_3alkoxyC_1-C_3alkyl, -C(O)C_1-C_3alkyl, C_3-C_4cycloalkyl and oxetanyl;

Z is



, wherein R^9 is selected from

(1) monocyclic C_5-C_8cycloalkyl and C_6-bicycloalkyl,

each of which is independently unsubstituted or substituted with one or more groups independently selected at each occurrence from fluoro, C_1-C_3alkyl and C_1-C_3fluoroalkyl,

and wherein said monocyclic C_5-C_8cycloalkyl is optionally fused to phenyl; wherein said phenyl is unsubstituted or substituted with one or more groups selected from halo, C_1-C_3alkyl, C_3-C_5cycloalkyl or C_1-C_3fluoroalkyl;

(2) monocyclic C_5-C_8cycloalkenyl, which is unsubstituted or substituted with one or more fluoro;

(3) C_1-C_3alkyl, which is unsubstituted or substituted with one or two phenyl groups, wherein said phenyl at each occurrence is independently unsubstituted or substituted with one or more halo;

or a pharmaceutically acceptable salt thereof.

The present invention relates to compounds of formula (I), or subformulae thereof, and pharmaceutically acceptable salts thereof, as herein defined, which are inhibitors of the IL-17 pathway. Accordingly, compounds of the present invention may therefore be potentially useful in the treatment of psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In another aspect, the invention provides a composition, in particular, a pharmaceutical composition, which comprises (e.g. a therapeutically effective amount of) a compound of formula (I), or subformulae thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

In another aspect, the invention provides a combination, in particular a pharmaceutical combination, which comprises (e.g. a therapeutically effective amount of) a compound of formula (I) or subformulae thereof, or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents.

In another aspect, the invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, for use in methods of treating, preventing, or ameliorating a condition, disease, or disorder treatable by modulating (e.g. inhibiting) IL-17 activity.

In another aspect, the invention provides a compound of formula (I), or subformulae thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of autoimmune diseases and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis and non-radiographic axial spondyloarthritis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathis arthritis, osteoarthritis, tendinopathy, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies, including eczema and dermatitis, as well as asthma; in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Grave's disease, sarcoidosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, Behcet disease, lichen planopilaris, lichen planus, hidradenitis suppurativa, acne, recurrent aphthous stomatitis, and periodontitis, pyoderma gangraenosum, and other neutrophil dermatoses, pityriasis rubra pilaris, bullous pemphigoid and ichthyosis, endometriosis, non-alcoholic steatohepatitis, interstitial lung fibrosis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), tumors, multiple sclerosis, autism, depressiona DNA, Alzheimer's disease, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

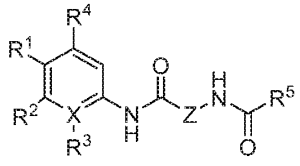
DETAILED DESCRIPTION OF THE INVENTION

Various embodiments of the invention are described herein.

The definition of the substituents applies to compounds of formulae (I), (IA) and (IB) as applicable.

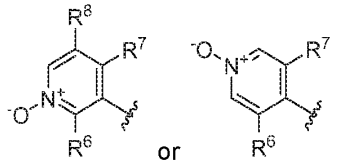
The definition of the substituents applies to the end-products as well as to the corresponding intermediates.

In embodiment 1, the invention therefore provides a compound of formula (I):


(I),

wherein,

R^1 is


or wherein,

R^6 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^7 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^8 is selected from H, halo, C_1-C_3alkyl and hydroxymethyl;

X is C or N and when X is N, R^3 is absent;

R^2 is selected from H and F;

R^3 is selected from H, F and Cl;

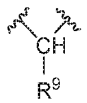
R^4 is selected from H and F;

R^5 is a 5-membered heteroaryl comprising 1 or 2 heteroatoms independently selected from N, S, and O, and wherein said heteroaryl is unsubstituted or substituted with one or two groups independently selected from C_1-C_3alkyl and C_3-C_4cycloalkyl, wherein said C_1-C_3alkyl is unsubstituted or substituted with one or more groups independently selected from F, OH, C_1-C_3alkoxy, -C(O)OH and $NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are independently selected from H and C_1-C_3alkyl;

or

R^5 is a 5-membered heteroaryl comprising one N atom wherein said 5-membered heteroaryl is fused to a 6-membered heterocycle comprising one N atom wherein said heterocycle is unsubstituted or substituted with a group selected from C_1-C_3alkyl, C_1-C_3alkoxyC_1-C_3alkyl, -C(O)C_1-C_3alkyl, C_3-C_4cycloalkyl and oxetanyl;

Z is


, wherein R^9 is selected from

(1) monocyclic C_5-C_8cycloalkyl and C_6-bicycloalkyl,

each of which is independently unsubstituted or substituted with one or more groups independently selected at each occurrence from fluoro, C_1-C_3alkyl and C_1-C_3fluoroalkyl,

and wherein said monocyclic C_5-C_8cycloalkyl is optionally fused to phenyl; wherein said phenyl is unsubstituted or substituted with one or more groups selected from halo, C_1-C_3alkyl, C_3-C_5cycloalkyl or C_1-C_3fluoroalkyl;

(2) monocyclic C_5-C_8cycloalkenyl, which is unsubstituted or substituted with one or more fluoro;

(3) C_1-C_3alkyl, which is unsubstituted or substituted with one or two phenyl groups, wherein said phenyl at each occurrence is independently unsubstituted or substituted with one or more halo;

or a pharmaceutically acceptable salt thereof.

Definitions

For the purpose of interpreting this specification, the following definitions will apply unless specified otherwise and when appropriate, terms used in the singular will also include the plural and vice versa. It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include the plural unless the context clearly dictates otherwise. Thus, for example, reference to "the compound" includes reference to one or more compounds, and so forth.

As used herein, the term "C_1-C_3alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to three carbon atoms, and which is attached to the rest of the molecule by a single bond. Examples of C_1-C_3alkyl include, but are not limited to, methyl, ethyl, *n*-propyl and 1-methylethyl (*iso*-propyl).

As used herein, the term "C_1-C_3fluoroalkyl" refers to a C_1-C_3alkyl as defined herein which is substituted with at least one fluorine atom, up to the maximum permitted number of fluorine atoms as substituent positions allow. Examples of C_1-C_3fluoroalkyl include, but are not limited to, mono-, di- and tri-fluoromethyl.

As used herein, the term "C_1-C_3alkoxy" refers to the radical -O-C_1-C_3alkyl, wherein the C_1-C_3alkyl portion is as defined herein.

As used herein, the term "C_1-C_3alkoxyC_1-C_3alkyl" refers to a C_1-C_3alkyl radical substituted by C_1-C_3alkoxy. Examples of C_1-C_3alkoxyC_1-C_3alkyl include, but are not limited to, methoxymethyl and methoxyethyl.

As used herein, the term "C_3-C_4cycloalkyl" refers to a stable, saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having three or four carbon atoms, i.e. cyclopropyl or cyclobutyl.

As used herein, the term "monocyclic C_5-C_8cycloalkyl" refers to a stable monocyclic, saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from five to eight carbon atoms. Examples of monocyclic C_5-C_8cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, the term “monocyclic C_5-C_8cycloalkenyl” refers to a stable, monocyclic, partially saturated (i.e. containing at least one double bond) hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from five to eight carbon atoms. Examples of monocyclic C_5-C_8cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term “C_6-bicycloalkyl” refers to a stable, saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having six carbon atoms and two fused rings. Examples of C_6-bicycloalkyl include bicyclo[3.1.0]hexanyl and bicyclo[2.2.0]hexanyl.

As used herein, the term “5-membered heteroaryl comprising 1 or 2 heteroatoms independently selected from N, S, and O”, refers to an aromatic ring radical of 5 ring atoms, one or two of which are selected from N, S and O and the rest are carbon. Examples include pyrazolyl (particularly pyrazol-5-yl), isoxazolyl (particularly isoxazol-4-yl), furanyl, pyrrolyl and thiazole. 5-membered heteroaryl comprising one N atom is to be construed accordingly.

As used herein, the term "Halo" refers to bromo, chloro, fluoro or iodo, preferably chloro or fluoro.

Unless specified otherwise, the term “compounds of the present invention” refers to compounds of formula (I), and subformulae thereof, such as compounds of formula (IA) or (IB), as defined herein, and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties. The term "compounds of the (present) invention" or "a compound of the (present) invention" refers to a compound as defined in any one of the embodiments mentioned below.

Various embodiments of the invention are described herein, it will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

Further enumerated embodiments:

Embodiment 2. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to embodiment 1, wherein R^6 at each occurrence is selected from H, F, Cl, methyl and difluoromethyl.

Embodiment 3. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to embodiment 1 or 2, wherein R^6 is methyl.

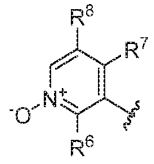
Embodiment 4. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 3, wherein R^7 at each occurrence is selected from H, F, Cl, methyl and trifluoromethyl.

Embodiment 5. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 4, wherein R^7 at each occurrence is selected from Cl, methyl and trifluoromethyl.

Embodiment 6. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 5, wherein R^8 is selected from H, chloro, methyl and hydroxymethyl.

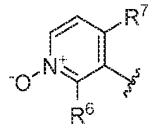
Embodiment 7. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 6, wherein R^8 is H.

Embodiment 8. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 7, wherein R^1 is



, wherein R^6, R^7 and R^8 are as defined in any one of embodiments 1 to 7.

Embodiment 9. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 8, wherein R^1 is



wherein R^6 and R^7 are as defined in any one of embodiments 1 to 5.

Embodiment 10. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 9, wherein X is C.

Embodiment 11. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 10, wherein R^3 is H.

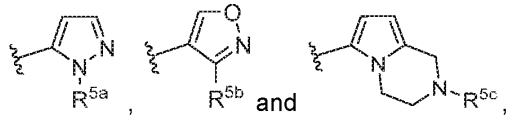
Embodiment 12. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 10, wherein R^4 is H.

Embodiment 13. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 12, wherein R^5 is a 5-membered heteroaryl comprising 1 or 2 heteroatoms independently selected from N, S, and O, at least one of which is N, and wherein said heteroaryl is unsubstituted or substituted with one group selected from C_1-C_3alkyl and C_3-C_4cycloalkyl, wherein said C_1-C_3alkyl is unsubstituted or substituted with one group selected from OH, C_1-C_3alkoxy, -C(O)OH and $NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are independently selected from H and C_1-C_3alkyl;
or
R^5 is a 5-membered heteroaryl comprising one N atom wherein said 5-membered heteroaryl is fused to a 6-membered heterocycle comprising one N atom wherein said heterocycle is unsubstituted or substituted with one group selected from C_1-C_3alkyl, C_1-C_3alkoxyC_1-C_3alkyl, -C(O)C_1-C_3alkyl, C_3-C_4cycloalkyl and oxetanyl.

Embodiment 14. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 13, wherein R^5 is selected from pyrazolyl (particularly pyrazol-5-yl), isoxazolyl (particularly isoxazol-4-yl) and 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazinyl (particularly 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-yl), wherein said pyrazole and isoxazole are each independently substituted with one group selected from C_1-C_3alkyl and C_3-C_4cycloalkyl, wherein said C_1-C_3alkyl is unsubstituted or substituted with one group selected from OH, C_1-C_3alkoxy, -C(O)OH and $NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are independently selected from H and C_1-C_3alkyl; and said 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine is unsubstituted or substituted with one group selected from C_1-C_3alkyl, C_1-C_3alkoxyC_1-C_3alkyl, -C(O)C_1-C_3alkyl, C_3-C_4cycloalkyl and oxetanyl.

Embodiment 15. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 14, wherein R^5 is selected from pyrazolyl (particularly pyrazol-5-yl), isoxazolyl (particularly isoxazol-4-yl) and 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazinyl (particularly 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl), wherein said pyrazole and isoxazole are each independently substituted with one group selected from methyl, ethyl, isopropyl, cyclopropyl and cyclobutyl, wherein said methyl and ethyl are each unsubstituted or substituted with one group selected from OH, methoxy, -C(O)OH, NH_2 and $N(CH_3)_2$; and said 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazinyl, is unsubstituted or substituted with one group selected from methyl, methoxyethyl, -C(O)CH_3), cyclopropyl and oxetanyl.

Embodiment 16. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 15, wherein R^5 is selected from



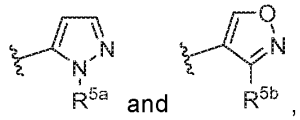
wherein

R^{5a} is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-(CH_2)_2OH$, $-(CH_2)_2OCH_3$, $-CH_2C(O)OH$ and $-(CH_2)_2N(CH_3)_2$;

R^{5b} is selected from methyl, ethyl, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2NH_2$ and $-CH_2N(CH_3)_2$; and

R^{5c} is selected from H, methyl, $-C(O)CH_3$, cyclopropyl, oxetanyl and $-(CH_2)_2OCH_3$.

Embodiment 17. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 16, wherein R^5 is selected from



wherein

R^{5a} is selected from methyl and ethyl; and

R^{5b} is selected from methyl and ethyl.

Embodiment 18. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 17, wherein R^9 is selected from,

(1) monocyclic C_5-C_7cycloalkyl and C_6-bicycloalkyl,
each of which is independently unsubstituted or substituted with one or two groups independently selected at each occurrence from fluoro, C_1-C_3alkyl and C_1-C_3fluoroalkyl,
and wherein said monocyclic C_5-C_7cycloalkyl is optionally fused to unsubstituted phenyl;

(2) monocyclic C_5-C_8cycloalkenyl, which is unsubstituted or substituted with one fluoro;

(3) methyl, which is unsubstituted or substituted with one or two phenyl groups, wherein said phenyl at each occurrence is independently unsubstituted or substituted with one chloro.

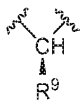
Embodiment 19. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 18, wherein R^9 is selected from cyclopentyl, cyclohexyl, cycloheptyl, 1,2,3,4-tetrahydronaphthalen-1-yl, 1,2,3,4-tetrahydronaphthalen-2-yl, bicyclo[3.1.0]hexanyl, cyclohexenyl, 2-chlorobenzyl and diphenylmethyl, wherein said cyclopentyl, cyclohexyl, cycloheptyl,

1,2,3,4-tetrahydronaphthalen-1-yl, 1,2,3,4-tetrahydronaphthalen-2-yl and bicyclo[3.1.0]hexanyl are independently unsubstituted or substituted with one or two groups independently selected at each occurrence from fluoro, methyl and trifluoromethyl, and wherein said cyclohexenyl is unsubstituted or substituted with one fluoro.

Embodiment 20. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 19, wherein R^9 is selected from cyclopentyl, cyclohexyl, cyclohexenyl and 1,2,3,4-tetrahydronaphthalen-1-yl, wherein said cyclohexyl is unsubstituted or substituted with one group selected from methyl and trifluoromethyl or substituted with two fluoro, and wherein said cyclohexenyl is substituted with one fluoro.

Embodiment 21. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 20, wherein

Z is



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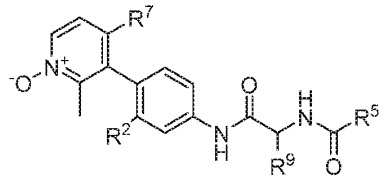
Embodiment 22. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 19, wherein the compound is of formula (IA):



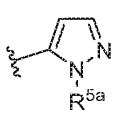
(IA),

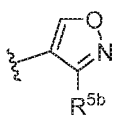
wherein,

R^7 is selected from Cl, methyl and trifluoromethyl;

R^2 is selected from H and F;

R^5 is selected from



and


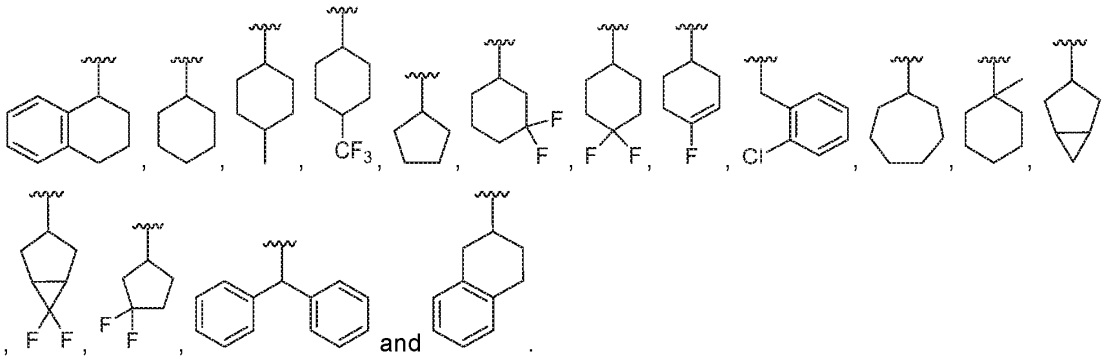
,

wherein,

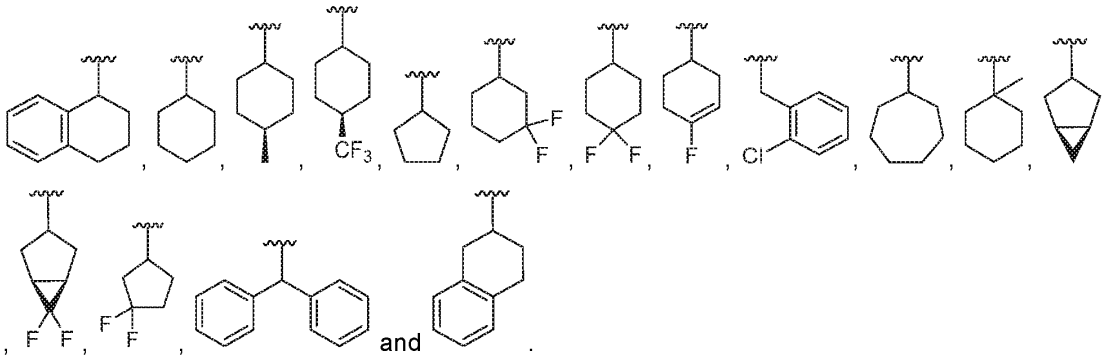
R^{5a} is selected from methyl and ethyl; and

R^{5b} is selected from methyl and ethyl;

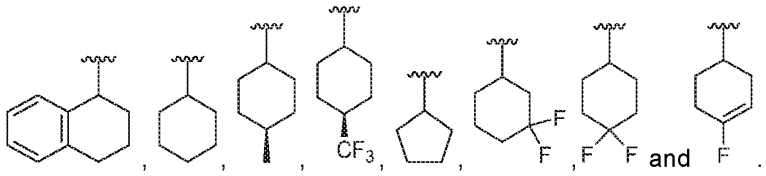
R^9 is selected from



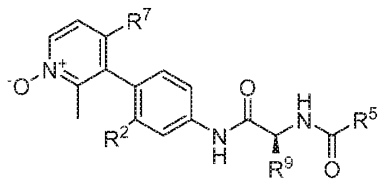
Embodiment 23. A compound, or a pharmaceutically acceptable salt thereof, according to embodiment 22, wherein R^9 is selected from



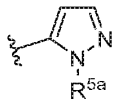
Embodiment 24. A compound, or a pharmaceutically acceptable salt thereof, according to embodiment 23, wherein R^9 is selected from



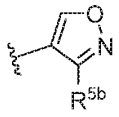
Embodiment 25. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 22 to 24, wherein the compound is of formula (IB):


(IB), wherein R^2, R^5, R^7 and R^9 are as defined in any one of embodiments 22 to 24.

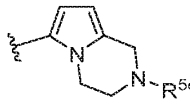
Embodiment 26. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 25, wherein R^5 is


, wherein R^{5a} is selected from methyl and ethyl.

Embodiment 27. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 25, wherein R^5 is


, wherein R^{5b} is selected from methyl and ethyl.

Embodiment 28. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 25, wherein R^5 is


, wherein R^{5c} is selected from H, methyl, $-C(O)CH_3$, cyclopropyl, oxetan-3-yl and $-(CH_2)_2OCH_3$.

Embodiment 29. A compound, or a pharmaceutically acceptable salt thereof, according to embodiment 1, wherein the compound is selected from the exemplified compounds herein described.

Embodiment 30. A compound, or a pharmaceutically acceptable salt thereof, according to embodiment 1, wherein the compound is selected from:
2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide;
4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide;

2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-2-(4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide;
4-chloro-3-(4-(2-(3-ethylisoxazole-4-carboxamido)-2-(4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide;
3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
4-chloro-3-(4-(2-(3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide;
3-(4-(2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-(4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-(2-(3-ethylisoxazole-4-carboxamido)-2-(4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-(2-(3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
3-(4-(2-(3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide; or
3-(4-(2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

Embodiment 31. A compound, or a pharmaceutically acceptable salt thereof, according to embodiment 1, wherein the compound is selected from:

2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide;
4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide;
2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide;
4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide;
(S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;

4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide;
3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;
3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide; or
3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

Embodiment 32. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide.

Embodiment 33. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide.

Embodiment 34. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide.

Embodiment 35. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide.

Embodiment 36. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is (S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide.

Embodiment 37. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide.

Embodiment 38. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

Embodiment 39. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

Embodiment 40. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide.

Embodiment 41. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide.

Embodiment 42. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide.

Embodiment 43. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is 3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide, 3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide or 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

Embodiment 44. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43, and a pharmaceutically acceptable carrier.

Embodiment 45. A combination comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43, and one or more therapeutically active agents.

Embodiment 46. A combination comprising a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to embodiment 45, wherein said one or more therapeutically active agents are independently selected from a disease-modifying antirheumatic drug (DMARD); vitamin D derivatives; steroids; retinoids; JAK / TYK inhibitors; salicyclic acid; coal tar; anthralin; a calcineurin inhibitor; a modulator of lymphocyte recirculation; a mTOR inhibitor; an ascomycin having immuno-suppressive properties; immunosuppressive compounds; adhesion molecule inhibitors; a chemotherapeutic agent; UV therapy agent; an anti tumor necrosis factor (TNF) agent; T-cell signal inhibitors; blockers of pro-inflammatory cytokines; chemokines blokers; pyrimidine synthesis inhibitors; antimalarials; lymphocytes interacting compounds; sphingosine-1-phosphate (S1P) inhibitors; nonsteroidal anti-inflammatory drugs ("NSAIDs"); an anti-infectious agent; or a acetylsalicylic acid drugs (ASA) including aspirin.

Embodiment 47. A method of modulating IL-17 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43.

Embodiment 48. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43, for use as a medicament, in particular for treating, or preventing an IL-17 mediated disease or condition.

Embodiment 49. A compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43, for use in the treatment, or prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis and non-radiographic axial spondyloarthritis, Reiter syndrome, reactive

arthritis, psoriatic arthritis, and enterophathis arthritis, osteoarthritis, tendinopathy, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies, including eczema and dermatitis, as well as asthma; in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Grave's disease, sarcoidosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, Behcet disease, lichen planopilaris, lichen planus, hidradenitis suppurativa, acne, recurrent aphthous stomatitis, and periodontitis, pyoderma gangraenosum, and other neutrophil dermatoses, pityriasis rubra pilaris, bullous pemphigoid and ichthyosis, endometriosis, non-alcoholic steatohepatitis, interstitial lung fibrosis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), tumors, multiple sclerosis, autism, depressiona DNA, Alzheimer's disease, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

Embodiment 50. A method of treating, or preventing an IL-17 mediated disease or condition selected from autoimmune diseases and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis and non-radiographic axial spondyloarthritis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathis arthritis, osteoarthritis, tendinopathy, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies, including eczema and dermatitis, as well as asthma; in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Grave's disease, sarcoidosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior),

keratoconjunctivitis sicca and vernal keratoconjunctivitis, Behcet disease, lichen planopilaris, lichen planus, hidradenitis suppurativa, acne, recurrent aphthous stomatitis, and periodontitis, pyoderma gangraenosum, and other neutrophil dermatoses, pityriasis rubra pilaris, bullous pemphigoid and ichthyosis, endometriosis, non-alcoholic steatohepatitis, interstitial lung fibrosis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), tumors, multiple sclerosis, autism, depressiona DNA, Alzheimer's disease, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia, wherein the method comprises administering to the subject a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 1 to 43.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers, or as mixtures thereof, for example as pure optical isomers, or as stereoisomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible stereoisomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- stereoisomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be (E) or (Z) configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms "salt" or "salts" refer to an acid addition or base addition salt of a compound of the invention. "Salts" include in particular "pharmaceutically acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

In another aspect, the present invention provides compounds according to any one of embodiments 1 to 43, in acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate trifenatate, trifluoroacetate or xinafoate salt form.

In another aspect, the present invention provides compounds according to any one of embodiments 1 to 43, in sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, copper, isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine or tromethamine salt form.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Isotopes that can be incorporated into compounds of the invention include, for example, isotopes of hydrogen.

Further, incorporation of certain isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index or tolerability. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). Deuterium substituents may be incorporated into the R^9 groups of the compounds of the present invention, for example, when R^9 is a C_5-C_8cycloalkyl group as defined herein, e.g. a

cyclopentyl, cyclohexyl or cycloheptyl group of the compounds of the present invention. The concentration of deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted as being deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). It should be understood that the term “isotopic enrichment factor” can be applied to any isotope in the same manner as described for deuterium.

Other examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, and chlorine, such as ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, and ^{36}Cl. Accordingly, it should be understood that the invention includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

PHARMACEUTICAL COMPOSITION

As used herein, the term “pharmaceutical composition” refers to a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, in a form suitable for oral or parenteral administration.

As used herein, the term "pharmaceutically acceptable carrier" refers to a substance useful in the preparation or use of a pharmaceutical composition and includes, for example, suitable diluents, solvents, dispersion media, surfactants, antioxidants, preservatives, isotonic agents, buffering agents, emulsifiers, absorption delaying agents, salts, drug stabilizers, binders, excipients,

disintegration agents, lubricants, wetting agents, sweetening agents, flavoring agents, dyes, and combinations thereof, as would be known to those skilled in the art (see, for example, Remington The Science and Practice of Pharmacy, 22nd Ed. Pharmaceutical Press, 2013, pp. 1049-1070).

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by IL-17, or (ii) associated with IL-17 activity, or (iii) characterized by activity (normal or abnormal) of IL-17; or (2) reduce or inhibit the activity of IL-17; or (3) reduce or inhibit the expression of IL-17. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective in at least partially reducing or inhibiting the activity of IL-17; or at least partially reducing or inhibiting the expression of IL-17.

As used herein, the term “subject” refers to primates (*e.g.*, humans, male or female), dogs, rabbits, guinea pigs, pigs, rats and mice. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter or biomarker associated with the disease or disorder, including those which may not be discernible to the patient.

As used herein, the term “prevent”, “preventing” or “prevention” of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically, or in quality of life from such treatment.

As used herein, the term “a”, “an”, “the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, stereoisomers, diastereomers, optical isomers (antipodes), racemates, atropisomers or mixtures thereof. For example, the compound of Example 2 herein may exist in substantially the pure form of one of the two atropisomer forms or mixtures of the two forms, thus the name 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide used herein includes the pure atropisomer forms (Ra) or (Sa) and mixtures thereof. The two atropisomeric forms are referred to herein as (Ra) or (Sa) forms indicating the stereochemical configuration about the single bond of restricted rotation connecting the substituted phenyl and pyridyl rings.

Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, atropisomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic compound may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved

by chiral chromatography, e.g., high performance liquid chromatography (HPLC) using a chiral adsorbent.

METHOD OF SYNTHESIZING THE COMPOUNDS OF THE INVENTION

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

The compounds of the present application can be prepared by those skilled in the art of organic synthesis using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled chemist in light of the teachings herein.

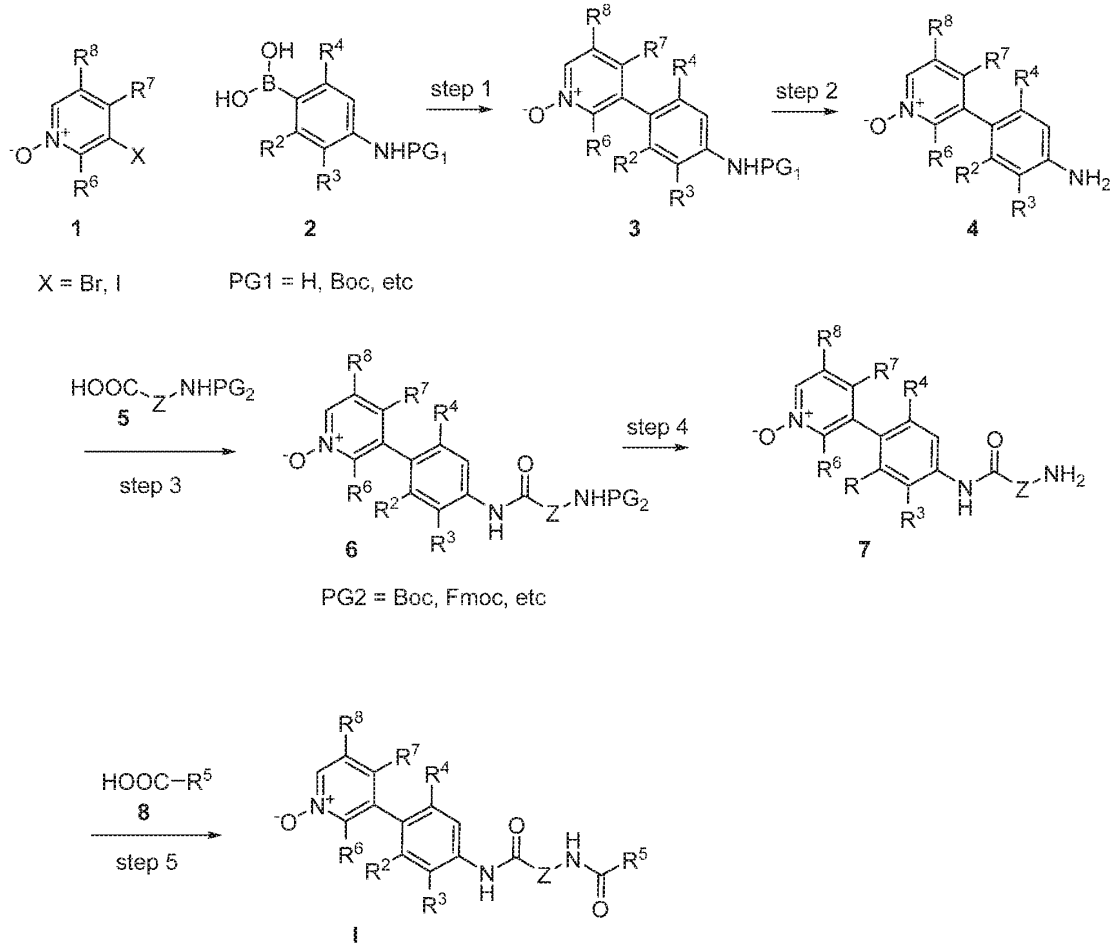
The compounds of Formula (I) may be prepared by methods as set forth in the following synthetic reaction schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis as described for example in Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999 or Protecting Groups, 3rd edition, Thieme, Stuttgart, 2004. Protective groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

Those skilled in the art will recognize if a stereocentre exists in the compounds disclosed herein. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

Compounds of the present disclosure can be synthesized by following the steps outlined in Schemes 1, 2 and 3. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

In the following general methods, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Z are as previously defined in the above embodiments, or limited to designations in the Schemes. PG1 and PG2 are suitable protecting groups. Unless otherwise stated, starting materials are either commercially available or are prepared by known methods.

Reaction Scheme 1



Scheme 1

Step 1 involves the Suzuki-coupling of compounds **1** and **2** as shown in Scheme 1 in a suitable solvent such as dioxane in the presence of suitable catalysts such as Pd(dppf)Cl_2-DCM complex or other Pd-containing catalysts and in the presence of a suitable base, such as aqueous Na_2CO_3, at suitable temperatures, such as 100 °C.

In step 2 a suitable protecting group PG1, (*e.g.* PG1 = Boc) is removed. This involves reacting **3** with suitable reagent, e.g. HCl or TFA in a suitable solvent, *e.g.* dioxane at suitable temperatures, such as room temperature. Alternative conditions and protecting groups (*e.g.* PG1 = Fmoc) are described in the literature (*e.g.* T. W. Green and P. G. M. Wuts (2014) Protective Groups in Organic Synthesis, 5th edition, John Wiley & Sons.

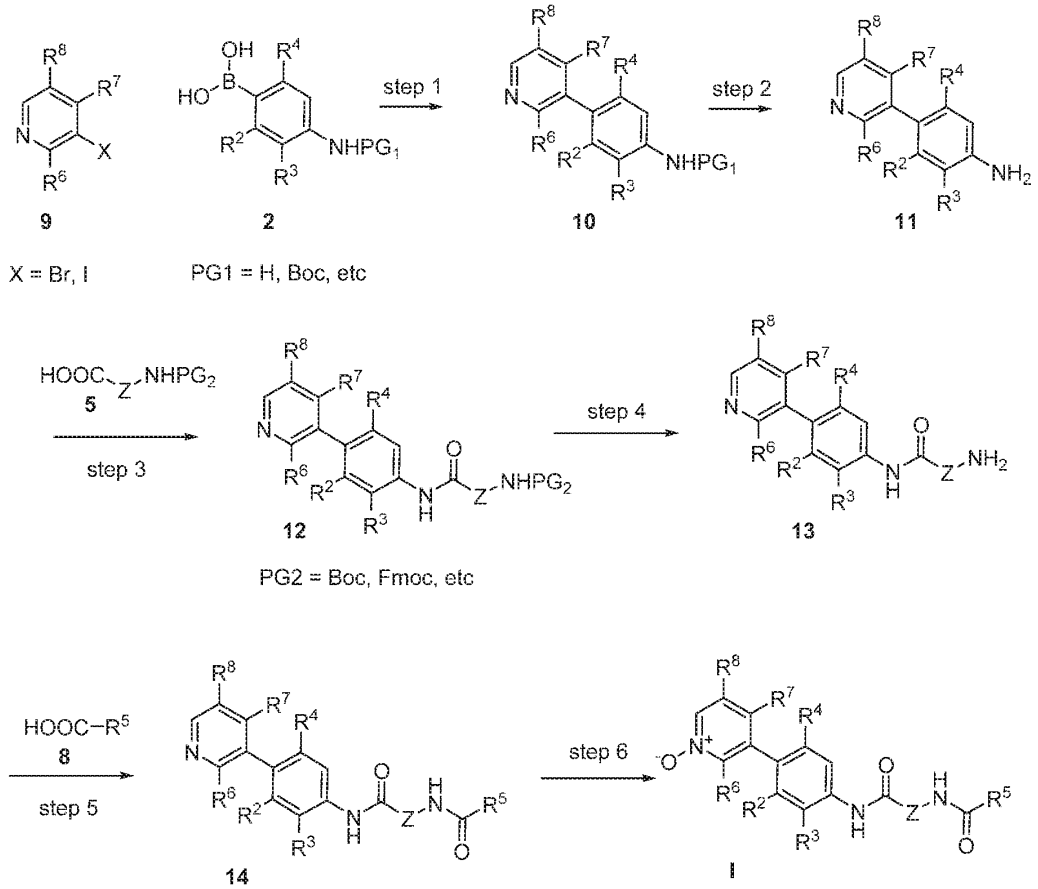
Step 3 involves coupling of **4** with a suitable protected amino acid **5** (e.g. PG2 = Boc or Cbz or Fmoc) in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature.

Step 4 involves removal of the protecting group PG2 from compoud **6**, by a method similar to that of step 2.

Step 5 involves coupling of **7** with a suitable acid in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature, leading to compound **I**.

This synthesis route can also be applied for the synthesis of 4-substituted pyridine-N-oxides.

Reaction scheme 2



Scheme 2

Step 1 involves the Suzuki-coupling of compound **2** with a substituted pyridine **9** as shown in Scheme 2, in a suitable solvent such as dioxane in the presence of suitable catalysts such as Pd(dppf)Cl_2-DCM complex or other Pd-containing catalysts and in the presence of a suitable base, such as aqueous Na_2CO_3, at suitable temperatures, such as 100 °C.

In step 2, a suitable protecting group PG1, (*e.g.* PG1 = Boc) is removed. This involves reacting **10** with suitable reagent, e.g. HCl or TFA in a suitable solvent, *e.g.* dioxane at suitable temperatures, such as room temperature. Alternative conditions and protecting groups (*e.g.* PG1 = Fmoc) are described in the literature (*e.g.* T. W. Green and P. G. M. Wuts (2014) Protective Groups in Organic Synthesis, 5th edition, John Wiley & Sons.

Step 3 involves coupling of **11** with a suitable protected amino acid **5** (e.g. PG2 = Boc or Cbz or Fmoc) in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature.

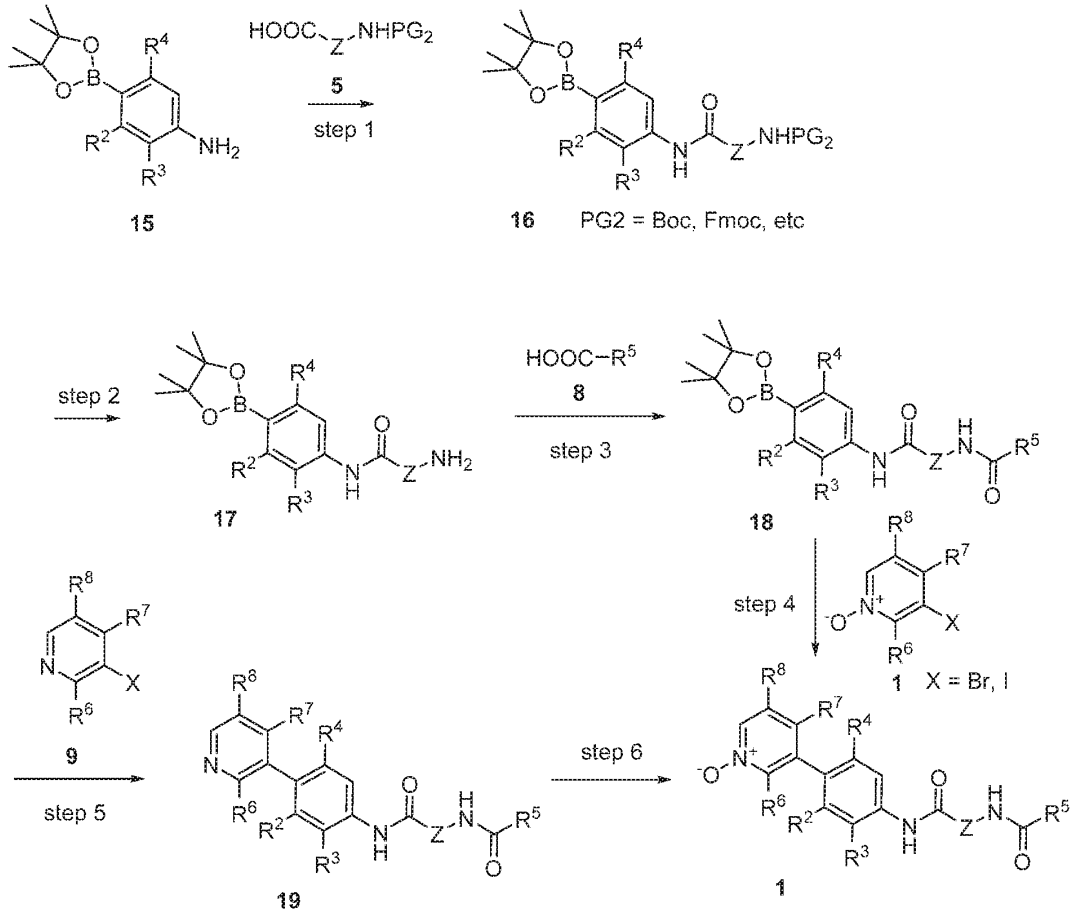
Step 4 involves removal of the protecting group PG2 from compoud **12**, by a method similar to that of step 2.

Step 5 involves coupling of **13** with a suitable acid **8** in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature.

Step 6 involves oxidation of the pyridine 14 to the pyridine-N-oxide with a suitable oxidant (e.g. mCPBA) in a suitable solvent (e.g. DCM), at suitable temperatures, such as RT, leading to compound **I.**

This synthesis route can also be applied for the synthesis of 4-substituted pyridine-N-oxides.

Reaction scheme 3



Scheme 3

Step 1 involves coupling of a suitable boronic ester **15** with a suitable protected amino acid **5** (e.g. PG2 = Boc or Cbz or Fmoc) in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature.

In step 2, a suitable protecting group PG1, (*e.g.* PG1 = Boc) is removed. This involves reacting **16** with suitable reagent, e.g. HCl or TFA in a suitable solvent, *e.g.* dioxane at suitable temperatures, such as room temperature. Alternative conditions and protecting groups (*e.g.* PG1 = Fmoc) are described in the literature (*e.g.* T. W. Green and P. G. M. Wuts (2014) Protective Groups in Organic Synthesis, 5th edition, John Wiley & Sons.

Step 3 involves coupling of **17** with a suitable acid **8** in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable amide coupling reagent, for example ®T3P or HATU, and a suitable base, such as DIPEA, at a suitable temperature, such as room temperature.

Step 4 involves Suzuki-coupling of of 18 with a suitable substituted pyridine-N-oxide, in a suitable solvent such as dioxane in the presence of suitable catalysts such as Pd(dppf)Cl_2-DCM complex or other Pd-containing catalysts and in the presence of a suitable base, such as aqueous Na_2CO_3, at suitable temperatures, such as 100 °C, leading to compund **I.**

Alternatively, compound can be prepared from compound **18** by a 2-step procedure involving a Suzuki coupling of **18** with a suitable substituted pyridine **9** (step 5), followed by N-oxidation of pyridine **14** to the pyridine-N-oxide with a suitable oxidant (e.g. mCPBA) in a suitable solvent (e.g. DCM), at suitable temperatures, such as RT (step 6) , leading to compound **I**.

This synthesis route can also be applied for the synthesis of 4-substituted pyridine-N-oxides.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure material. Compounds of the invention and intermediates can also be converted into each other according to methods generally known to those skilled in the art.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (*e.g.* by injection, infusion, transdermal or topical administration), and rectal administration. Topical administration may also pertain to inhalation or intranasal application. For topical administration the pharmaceutical compositions of the present invention can be made up, for example, as creams, ointments or gels. The pharmaceutical compositions of the present invention can be made up in a solid form (including, without limitation, capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including, without limitation, solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavors and sweeteners.

METHOD OF USE OF THE INVENTION

The compounds of formulae (I), (IA) or (IB) in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example IL-17 modulating properties, for example as indicated in *in vitro* tests as provided in the next sections, and are therefore indicated for therapy or for use as research chemicals, *e.g.* as tool compounds.

Compounds of the invention may be useful in the treatment, or prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis and non-radiographic axial spondyloarthritis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathis arthritis, osteoarthritis, tendinopathy, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies, including eczema and dermatitis, as well as asthma; in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Grave's disease, sarcoidosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, Behcet disease, lichen planopilaris, lichen planus, hidradenitis suppurativa, acne, recurrent aphthous stomatitis, and periodontitis, pyoderma gangraenosum, and other neutrophil dermatoses, pityriasis rubra pilaris, bullous pemphigoid and ichthyosis, endometriosis, non-alcoholic steatohepatitis, interstitial lung fibrosis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), tumors, multiple sclerosis, autism, depressiona DNA, Alzheimer's disease,

inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

Thus, as a further aspect, the present invention provides the use of a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, in therapy. In a further embodiment, the therapy is treatment of a disease, disorder or condition which may be treated by inhibition of IL-17. In another embodiment, the disease is selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Thus, as a further aspect, the present invention provides a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for use in therapy. In a further embodiment, the therapy is selected from a disease which may be treated by inhibition of IL-17. In another embodiment, the disease is selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In another aspect, the invention provides a method of treating, or preventing a disease which is treated by inhibiting IL-17 comprising administration of a therapeutically effective amount of a compound of any one of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof. In a further embodiment, the disease is selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Thus, as a further aspect, the present invention provides the use of a compound of any one of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament. In a further embodiment, the medicament is for treatment, or prevention of a disease, which may be treated by inhibition of IL-17. In another embodiment, the disease is selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided, 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a

disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided (S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the

treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

In one embodiment of the present invention, there is provided 3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide, 3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide or 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment, or prevention of a disease selected from the afore-mentioned list, suitably from psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1 - 1000 mg of active ingredient(s) for a subject of about 50 - 70 kg, or about 1 - 500 mg or about 1 - 250 mg or about 1 - 150 mg or about 0.5 - 100 mg, or about 1 - 50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable using *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range

depending on the route of administration, between about 0.1 - 500 mg/kg, or between about 1 - 100 mg/kg.

COMBINATION PRODUCT AND COMBINATION THERAPY OF THE INVENTION

"Combination" refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present invention and a combination partner (*e.g.* another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow for the combination partners to have a cooperative, *e.g.* synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (*e.g.* powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (*e.g.* a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term "fixed combination" means that the therapeutic agents, *e.g.* a compound of the present invention and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the therapeutic agents, *e.g.* a compound of the present invention and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.* the administration of three or more therapeutic agents.

The term "pharmaceutical combination" as used herein refers to either a fixed combination in one dosage unit form, or non-fixed combination or a kit of parts for the combined administration where two or more therapeutic agents may be administered independently at the same time or separately within time intervals, especially where these time intervals allow for the combination partners to have a cooperative, *e.g.* synergistic effect.

The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (*e.g.* tablets,

capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

The compounds of the present invention may be administered either simultaneously with, or before, or after, one or more other therapeutic agent. The compounds of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the invention.

Thus, in another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising (e.g. a therapeutically effective amount of) a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, and one or more other therapeutically active agents.

In one embodiment, the invention provides a product comprising a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy.

In one embodiment, the therapy is the treatment, or prevention of a disease or condition mediated by IL-17. Products provided as a combined preparation include a composition comprising a compound of formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, and the other therapeutic agent(s) together in the same pharmaceutical composition, or a compound of formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical combination comprising a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, and another therapeutic agent(s). Optionally, the pharmaceutical combination may comprise a pharmaceutically acceptable carrier, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit comprises means for separately retaining said compositions,

such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for treating, or preventing a disease or condition mediated by IL-17, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating, or preventing a disease or condition mediated by IL-17 wherein the medicament is administered with a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for use in a method of treating, or preventing a disease or condition mediated by IL-17, wherein the compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating, or preventing a disease or condition mediated by IL-17, wherein the other therapeutic agent is prepared for administration with a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof. The invention also provides a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for use in a method of treating, or preventing a disease or condition mediated by IL-17, wherein the compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of

treating, or preventing a disease or condition mediated by IL-17, wherein the other therapeutic agent is administered with a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of any one of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof, for treating, or preventing a disease or condition mediated by IL-17, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by IL-17, wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I), (IA) or (IB) (in particular according to any one of embodiments 1 to 43), or a pharmaceutically acceptable salt thereof.

In one embodiment, the other therapeutic agent is a therapeutic agent useful in the treatment of a respiratory disorder and/or a therapeutic agent that is useful in the treatment of inflammation and disorders with an inflammatory component (anti-inflammatory drugs).

In one embodiment, the other therapeutic agent useful in the combination therapy is selected from a disease-modifying antirheumatic drug (DMARD); vitamin D derivatives; steroids; retinoids; JAK / TYK inhibitors; salicyclic acid; coal tar; anthralin; a calcineurin inhibitor; a modulator of lymphocyte recirculation; a mTOR inhibitor; an ascomycin having immuno-suppressive properties; immunosuppressive compounds; adhesion molecule inhibitors; a chemotherapeutic agent; UV therapy agent; an anti tumor necrosis factor (TNF) agent; T-cell signal inhibitors; blockers of pro-inflammatory cytokines; chemokines blokers; pyrimidine synthesis inhibitors; antimalarials; lymphocytes interacting compounds; sphingosine-1-phosphate (S1P) inhibitors; nonsteroidal anti-inflammatory drugs ("NSAIDs"); an anti-infectious agent; or a acetylsalicylic acid drugs (ASA) including aspirin.

Suitable disease-modifying antirheumatic drugs (DMARDs) for use in the combination include, but are not limited to, gold salts, sulphasalazine, antimalarias, methotrexate, D-penicillamine, azathioprine, mycophenolic acid, cyclosporine A, tacrolimus, sirolimus, minocycline, leflunomide, glococorticoids.

Suitable JAK / TYK inhibitors for use in the combination include, but are not limited to, pan JAK inhibitors or more specific JAK / TYK2 inhibitors such as tofacitinib, baricitinib; JAK inhibitors such as Ruxolitinib.

Suitable calcineurin inhibitors for use in the combination include, but are not limited to, cyclosporin A, FK 506, or FKBP12.

Suitable modulator of lymphocyte recirculation for use in the combination include, but are not limited to, FTY720, or FTY720 analogs.

Suitable mTOR inhibitor for use in the combination include, but are not limited to, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin (everolimus, WO2005/052187), sirolimus, temsirolimus (CCI779), ABT578, AP23573, or TAFA-93.

Suitable ascomycin having immuno-suppressive properties for use in the combination include, but are not limited to ABT-281, ASM981, corticosteroids, cyclophosphamide, azathioprene, methotrexate, leflunomide, mizoribine, mycophenolic acid, mycophenolate mofetil, or 15-deoxyspergualine.

Suitable immunosuppressive compounds for use in the combination include, but are not limited to, a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; corticosteroids; azathioprin; methotrexate; cyclosporine; retinoids; phosphodiesterase type 4 (PDE4) inhibitors such as apremilast.

Suitable adhesion molecule inhibitors for use in the combination include, but are not limited to, LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists, or VLA-4 antagonists.

Suitable chemotherapeutic agent for use in the combination include, but are not limited to, paclitaxel, gemcitabine, cisplatinum, doxorubicin, or 5-fluorouracil.

Suitable UV therapy agent for use in the combination include, but are not limited to, sunlight; or Laser.

Suitable anti-TNF agents for use in the combination include, but are not limited to, monoclonal antibodies to TNF, e.g. infliximab, adalimumab, CDP870; or receptor constructs to TNF-RI or TNF-RII, e.g. Etanercept, PEG-TNF-RI; or TNF-alpha blockers such as adalimumab, infliximab, golimumab.

Suitable T-cell signal inhibitors for use in the combination include, but are not limited to, abatacept, intergrin blockers such as vedolizumab.

Suitable blockers of proinflammatory cytokines for use in the combination include, but are not limited to, IL-1 blockers such as canckinumab; IL-1 trap such as AAL160, ACZ 885; IL-6 blockers; IL-1 receptor blockers such as anakinra; IL-12 inhibitors such as ustekinumab; IL-23 inhibitors such as risankizumab; IL-17 inhibitors such as secukinumab or ixekizumab; or IL17R blockers, such as brodalumab.

Suitable chemokines blockers for use in the combination include, but are not limited to, e.g inhibitors or activators of proteases, e.g. metalloproteases; anti-IL-15 antibodies; anti-IL-6 antibodies such as tocilizumab; or anti-CD20 or anti-CD40 antibodies such as rituximab, iscalimab.

Suitable pyrimidine synthesis inhibitors for use in the combination include, but are not limietd to, leflunomide.

Suitable antimalarials for use in the combination include, but are not limietd to, chloroquin; or hydroxachloroquine

Suitable lymphocytes interacting compounds for use in the combination include, but are not limited to, D-penicillamine.

Suitable sphingosine-1-phosphate (S1P) inhibitors for use in the combination include, but are not limited to, minocycline; or tretracycline.

Suitable NSAIDs for use in the combination include, but are not limited to, Aceclofenac, acemetacin, acetylsalicylic acid, alclofenac, alminoprofen, amfenac, Ampiroxicam, Antolmetinguacil, Anirolac, antrafenine, azapropazone, benorylate, Bermoprofen, bindarit, bromfenac, bucloxic acid, Bucolom, Bufexamac, Bumadizon, butibufen, Butixirat, Carbasalatcalcium, carprofen, choline magnesium trisalicylate, celecoxib, Cinmetacin, Cinnoxicam, clidanac Clobuzarit Deboxamet, dexibuprofen, Dexketoprofen, diclofenac, diflunisal, droxicam, Eltenac, Enfenaminsaure, Etersalat, etodolac, etofenamate, etoricoxib, Feclobuzon, felbinac, fenbufen, fenclofenac, fenoprofen, fentiazac, Fepradinol, Feprazon, Flobufen, floctafenine, flufenamic acid, flufenisal, Flunoxaprofen, flurbiprofen, Flurbiprofenaxetil, Furofenac, Furprofen, Glucametacin, ibufenac, ibuprofen, Indobufen, indomethacin, Indometacinfarnesil, indoprofen, Isoxepac, Isoxicam, ketoprofen, ketorolac, lobenzarit, Lonazolac, lornoxicam, Loxoprofen, lumiracoxib, meclofenamic, Meclofen, mefenamic acid, meloxicam, mesalazine, Miro Profen, Mofezolac, nabumetone, naproxen, niflumic acid, olsalazine, oxaprozin, Oxipinac, oxyphenbutazone, parecoxib, phenylbutazone, Pelubiprofen, Pimeprofen, Pirazolac, Priroxicam, pirprofen, Pranoprofen, Prifelon, Prinomod, Proglumetacin, Proquazon, Protizininsaure, rofecoxib, Romazarit, salicylamide, salicylic acid, Salmi Stein, Salnacedin, salsalate, sulindac, sudoxicam, suprofen, Talniflumate, tenidap, Tenosal, tenoxicam, tepoxalin, tiaprofenic acid, Taramid, Tilnoprofenarbamel, timegadine, Tinoridin, Tiopinac, tolfenamic acid, tolmetin, Ufenamat, valdecoxib, Ximoprofen, zaltoprofen, Zoliprofen and combinations thereof.

Suitable acetylsalicylic acid drugs (ASA) for use in the combination include, but are not limited to, 5-ASA derivatives, such as sulfasalazine.

EXAMPLES

The disclosure is further illustrated by the following examples and synthetic methods, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

The compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples. All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesise the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. In all of the methods it is understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (2014) Protective Groups in Organic Synthesis, 5th edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

The chemical names were generated using ChemDraw Professional v17.1.0.105 from PerkinElmer.

Temperatures are given in degrees Celsius. As used herein, unless specified otherwise, the term “room temperature” or “ambient temperature” means a temperature of from 15°C to 30°C, such as of from 20°C to 30°C, such as of from 20°C to 25°C. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20 - 133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

ABBREVIATIONS

Abbreviations used in the following examples and elsewhere herein are:

AC	Active control
aq.	Aqueous
AcOH	Acetic acid
BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC	tertiary butyloxycarbonyl
BP reaction	Gene integration reaction between the attB and the attP sites of a Gateway® Cloning gene vector
br.	Broad
Cbz	Carboxybenzyl
d	doublet
dd	doublet of doublets

DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DME	1,4-dimethoxyethane
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediamine tetraacetic acid
EtOAc	ethyl acetate
EtOH	ethanol
eq	Equivalent(s)
FRET	Fluorescence Resonance energy transfer
GC-MS	Gas chromatography and mass spectrometry
h	hour(s)
HATU	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
HV	high vacuum
Hyflo	Celite® Hyflo Super-cel®, filter aid – SiO_2
Hz	Hertz
IPA	isopropanol
IR	Infrared
IC_{50}	Half maximal inhibitory concentration
J	Coupling constant
L/mL/µL	Liter/ milliliter / microliter
LC-MS	liquid chromatography and mass spectrometry
LDA	lithium diisopropylamide
LR reaction	Gene recombination reaction between attL and attR sites of a gene vector
M/mM/µM/nM/pM	Molar / millimolar / micromolar / nanomolar / picomolar
MeOH	methanol
mCPBA	meta-chloroperoxybenzoic acid
MS	mass spectrometry
m	multiplet
mg/µg	milligram/microgram
min	minutes

mL	milliliter
mmol	millimol
m/z	mass to charge ratio
NC	Neutral control
NHDF	Normal human dermal fibroblasts
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
n.t.	not tested
ON	over night
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
pDESTRS5a	Gateway® Cloning vector
pDON201	Gateway® Cloning entry vector
$Pd(dppf)Cl_2 \cdot DCM$	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
PEI	polyethyleneimine
PG	Protecting group
ppm	parts per million
Prep HPLC	Preparatory HPLC
pRS5a	Mammalian expression vector
rac	racemic
Rt	retention time
RT	room temperature
Rpm	Rotation per minutes
s	singlet
sat.	saturated
SDS-PAGE	Sodium dodecyl sulfate - Polyacrylamide gel electrophoresis
SFC	Supercritical fluid chromatography
t	triplet
T3P	Propylphosphonic anhydride
TBME	methyl tert-butyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	Tetramethylsilane
TNF-α	Tumor necrosis factor alpha

TRIS	2-amino-2-hydroxymethyl-1,3-propanediol
Tween 20	Polysorbate 20
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos-Pd-G2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

General Conditions:

NMR: Measurements were performed on a Bruker 600 MHz or a Bruker 400 MHz NMR spectrometerusing or not tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ-values) are reported in ppm downfield from tetramethylsilane (TMS), spectra splitting 5 patterns are designated as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), triplet (t),
triplet of doublets (td), quartet (q), quartet of doublets (qd), quintet (quint), septet (sep), multiplet, unresolved or overlapping signals (m), broad signal (br). Deuterated solvents are given in parentheses and have a chemical shifts of dimethyl sulfoxide (δ 2.50 ppm), methanol (δ 3.31 ppm), chloroform (δ 7.26 ppm), or other solvent as indicated in NMR spectral data.

Column Chromatography was performed on an ISCO CombiFlash Rf 200i system equipped with a Photodiode Array Detector and using ISCO Redisep cartridges. Columns and separation conditions are indicated in brackets in the experimental part.

Supercritical Fluid Chromatography (SFC) purifications and chiral separation were performed on a *Waters Preparative SFC-100-MS* system equipped with a *Waters 2998 Photodiode Array Detector* and a *Waters MS Single Quadrupole Detector*. Columns and separation conditions are indicated in brackets in the experimental part.

Prep-HPLC were performed either on a *Gilson* prep-HPLC system equipped with a *model 322* pump, a *model 155* UV-VIS detector and a *model 215* liquid handler or on a *Waters* prep-HPLC system equipped with a UV detector *Waters 2487 Dual & Adsorbance Detector* and an MS detector *Waters MicromassZQ*. Columns and separation conditions are indicated in brackets in the experimental part.

Mass Spectrometry was performed with LC-MS, SFC-MS, or GC-MS systems using electrospray, chemical and electron impact ionization methods from a range of instruments of the following configurations: Agilent 1100 HPLC systems with an Agilent 6110 Mass Spectrometer. $[MH]^+$ refers to protonated molecular ion of the chemical species.

MS Methods:

Method 1

Column: Acquity UPLC HSS T3, 1.8 µm, 2.1 x 50 mm

Column Temperature:60°C

Eluents A: water + 0.05% FA +3.75 mM AA, B: acetonitrile + 0.04% FA

Flow Rate 1.0 mL/min

Gradient from 5 to 98% B in 1.4 min

Method 2

Column: Acquity UPLC BEH C18, 1.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 0.05% FA +3.75 mM AA, B: isopropanol + 0.05% FA

Flow Rate 0.6 mL/min

Gradient from 5 to 98% B in 1.7 min

Method 3

Column: Acquity UPLC BEH C18, 1.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 4.76% IPA +0.05% FA +3.75 mM AA, B: isopropanol + 0.05% FA

Flow Rate 0.6 mL/min

Gradient from 1 to 98% B in 1.7 min

Method 4

Column: Acquity UPLC BEH C18, 1.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 0.05% FA +3.75 mM AA, B: isopropanol + 0.05% FA

Flow Rate 0.4 mL/min

Gradient from 5 to 60% B in 8.4 min, then from 60 to 98% B in 1 min

Method 5

Column: CORTECS™ C18, 2.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 4.76% IPA +0.05% FA +3.75 mM AA, B: isopropanol + 0.05% FA

Flow Rate 1.0 mL/min

Gradient from 1 to 50% B in 1.4 min, then from 50 to 98%B in 0.3 min

Method 6

Column: XBridge® BEH™ C18 2.5µm, 2.1x50 mm

Column Temperature:80°C

Eluents: A: water + 5 mM NH4OH, B: acetonitrile + 5 mM NH4OH

Flow Rate 1.0 mL/min

Gradient: from 2 to 98 % B in 1.4 min

Method 7

Column: CORTECS™ C18, 2.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 0.05 % FA + 3.75 mM AA, B: isopropanol + 0.05 % FA

Flow Rate 1.0 mL/min

Gradient from 1 to 98 % B in 1.7 min

Method 8

Column: Ascentis™ Express C18, 2.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 4.76 % isopropanol + 0.05 % FA + 3.75 mM AA, B: isopropanol + 0.05 % FA

Flow Rate 1.0 mL/min

Gradient from 1 to 50 % B in 1.7 min, then 50 - 98 % B in 0.3 min

Method 9

Column: Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm

Column Temperature:40°C

Eluents A: Water + 0.1 % TFA, B: acetonitrile

Flow Rate 1.0 mL/min

Gradient from 1 to 98 % B in 1.4 min

Method 10

Column: Ascentis™ Express C18, 2.7 µm, 2.1 x 50 mm

Column Temperature:80°C

Eluents A: water + 4.76 % isopropanol + 0.05 % FA + 3.75 mM AA, B: isopropanol + 0.05 % FA

Flow Rate 1.0 mL/min

Gradient from 1 to 50 % B in 1.4 min, then 50 - 98 % B in 0.3 min

Method 11

Column: CORTECS™ C18+ 2.7µm; 2.1x50 mm

Column Temperature: 80.0 °C

Gradient: from 1 to 50 % B in 1.4 min; 50 to 98 % B in 0.3 min Flow: 1.0 mL/min

Eluent A: water + 4.76 % isopropanol + 0.05 % FA + 3.75 mM AA

Eluent B: isopropanol + 0.05 % FA Description:LIMAFA2-002-EXP025-t=2h

Method 12

Column: Ascentis® Express C18 2.7 µm; 2.1x50 mm

Column Temperature: 80 °C

Gradient: from 1 to 50 % B in 1.4 min; 50 - 98 % B in 0.30 min Flow: 1.0 mL/min

Eluent A: water + 4.76% isopropanol + 0.05 % FA + 3.75 mM AA

Eluent B: isopropanol + 0.05 % FA

Method 13

Column: Waters Xbridge C18 150x4.6mm,5µ

Column Temperature: 40° C

Gradient : 0 min/10% B; 2 min/20% B ; 10 min/70% B ; 15 min/100% B

Eluent A: 0.05 % NH_4OH in water

Eluent B : acetonitrile

Flow: 1 ml/min

Method 14

Column: ZORBAX C18 150x4.6mm 5.0µ

Column Temperature: 40°C

Gradient: 1 min 5% B; 6 min 100% B; 8 min 100 %

Eluent A: 0.01 % TFA in water

Eluent B: acetonitrile

Flow:1.0 ml/min

Method 15

Column: AG/CHIRALPAK-IC (250 x 4.6 mm , 5 micron)

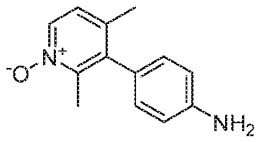
Column Temperature :25°C

Eluent A: n-hexane ,
Eluent B: ethanol
Flow rate:1.0 mL/min
Isocratic :30:70

Method 16
Column: Kinetex, EO, C18 150 x 4.6mm 5.0µm
Column Temperature 40°C
Gradient: Time/%B: 1.0 min 5% B, then in 5 min to 100% B
Eluent A: 0.01% TFA in water;
Eluent B: acetonitrile
Flow rate:1.0 mL/min

SYNTHESIS OF THE INTERMEDIATES

Intermediate 1-1: 3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide



Step 1: 3-bromo-2,4-dimethylpyridine 1-oxide

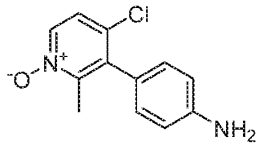
To a solution of 3-bromo-2,4-dimethylpyridine (80 g, 0.430 mol) in DCM (800 mL) was added m-CPBA (90 g, 0.516 mol, 1.2 eq) at 10 ~ 15 °C. After stirring for 3 hours at the same temperature HPLC analysis indicated complete conversion of the starting material. The mixture was poured into 10% Na_2SO_3 aqueous solution, stirred for 5 minutes and the layers were separated. The aqueous phase was extracted with DCM (400 mL). The organic phases were combined and washed with 10% aqueous Na_2CO_3. The aqueous phase was re-extracted with DCM (400 mL). The organic phases were combined, washed twice with brine (400 mL), dried (Na_2SO_4) and concentrated to yield the title compound (68 g, 78% yield) as an off-white solid.
1H NMR (400 MHz, DMSO) δ 8.22 (d, 1H), 7.30 (d, 1H), 2.57 (s, 3H), 2.34 (s, 3H) ppm.

Step 2: 3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide

To a solution of 3-bromo-2,4-dimethylpyridine 1-oxide (70 g, 0.346 mol) in dioxane (700 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (91 g, 0.416 mol), Na_2CO_3 (110 g, 1.038 mol), water (140 mL) and Pd(dppf)Cl_2·DCM complex (12.7 g, 0.017 mol). The reaction mixture was purged with nitrogen, and stirred at 100°C for 16 hours. HPLC analysis indicated complete conversion of the starting material. The reaction mixture was filtered, the filtrate was concentrated, taken-up with DCM (700 mL) and washed with brine (350 mL). The aqueous phase was extracted with DCM (350 mL x 5). The organic phases were combined, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (DCM : MeOH 15 : 1) to yield the title compound (53.4 g, 72% yield) as a light brown solid.

1H NMR (400 MHz, DMSO-d6) δ 8.14 (d, J = 6.6 Hz, 1H), 7.17 (d, J = 6.6 Hz, 1H), 6.84 (d, J = 8.3 Hz, 2H), 6.66 (d, J = 8.3 Hz, 2H), 5.26 (s, 2H), 2.11 (s, 3H), 1.99 (s, 3H) ppm.

Intermediate 1-2: 3-(4-aminophenyl)-4-chloro-2-methylpyridine 1-oxide



Step 1: 3-iodo-2-methylpyridin-4-ol

To a solution of 2-methylpyridin-4-ol (9.9 g, 88 mmol) in water (100mL) was added NIS (14.59 g, 61.6 mmol) and the mixture was stirred at RT for 4 hours. The reaction mixture was filtered and the cake was washed with 0.5N HCl (50 mL). Then the filtrate was concentrated in vacuo to remove most of water, the residue was adjusted to pH =3 with sodium hydroxide and suspension was filtered and dried under reduced pressure to yield title compound (7.1 g, 33% yield) as a pinkish solid.

LC-MS: Rt = 0.38 min; MS m/z = 236.0 $[MH]^+$ (Method 1).

Step 2: 4-chloro-3-iodo-2-methylpyridine

To a solution of 3-iodo-2-methylpyridin-4-ol (6.25 g, 26.1 mmol) in ACN (30 mL) were added slowly $POCl_3$ (18.16 g, 117 mmol) and P_2O_5 (154 mg, 1.04 mmol). The reaction mixture was stirred under reflux for 3 hours, then cooled to RT and concentrated to ca. 8 mL. The residue was treated carefully with water (70 mL) with external cooling to keep the internal temperature below 45 °C. The precipitate formed was removed by filtration. The pH of the mixture was adjusted to pH = 6-7

with sodium hydroxide, the solid was filtered, washed with water and dried on high vacuum to yield title compound (5.6 g, 83 % yield) as a beige solid.
LC-MS: Rt = 0.99 min; MS m/z = 254.0 $[MH]^+$ (Method 1).

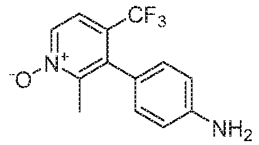
Step 3: 4-chloro-3-iodo-2-methylpyridine 1-oxide

To a solution of 4-chloro-3-iodo-2-methylpyridine (10 g, 38.7 mmol) in THF (100 mL) was added m-CPBA (13.43 g, 60 mmol) in 3 portions at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then at RT overnight. The mixture was cooled to 5 – 10 °C, the solid was filtered and washed with MTBE and dried on high vacuum to yield title compound (8.5 g, 81 % yield) as a colorless solid.
LC-MS: Rt = 0.64 min; MS m/z = 269.9 $[MH]^+$ (Method 1).

Step 4: 3-(4-aminophenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of 4-chloro-3-iodo-2-methylpyridine 1-oxide (8.3 g, 30.5 mmol) in dioxane (150 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (7.10 g, 31.1 mmol), 2M aq. Na_2CO_3 (44.2 mL, 88 mmol) and Pd(dppf)Cl_2·DCM complex (1.509 g, 1.83 mmol). The reaction mixture was purged with argon and stirred at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate and washed with Na_2CO_3 1M aqueous solution and brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (ISCO system, 100% EtOAc), followed by recrystallization from TBME:DCM 10:1 to yield the title compound (4.6 g, 62% yield) as a white solid.
LC-MS: Rt = 0.56 min; MS m/z = 235.1 $[MH]^+$ (Method 1).
1H NMR (400 MHz, DMSO-d6) δ 8.24 (d, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 6.9 – 6.87 (m, 2H), 6.65 (d, 8.3 Hz, 2H), 5.54 (s, 2H), 2.16 (s, 3H) ppm.

Intermediate 1-3: 3-(4-aminophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



Step 1: 2-chloro-3-iodo-4-(trifluoromethyl)pyridine

To a solution of 2-chloro-4-(trifluoromethyl)pyridine (360 g, 1.98 mol) in THF (3.5 L) was added dropwise at -78°C LDA (2M in THF/hexanes, 1.04 L, 2.08 mol). The reaction mixture was stirred at -78°C for 2 hours, then iodine (538 g, 2.12 mol) was added portionwise and the mixture was stirred at -78°C for 2 hours under N_2 atmosphere. The crude mixture was quenched with a saturated NH_4Cl solution (100 mL) at 0°C and concentrated. The residue was taken up in water (2 L) and extracted twice with EtOAc (2.5 L). The combined organic phases were washed with brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was triturated in petroleum ether and filtered to yield the title compound (300 g, 49% yield) as a yellow solid.
1H NMR (400 MHz, CDCl3) δ 8.49 (d, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H) ppm.

Step 2: tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate

To a solution of 2-chloro-3-iodo-4-(trifluoromethyl)pyridine (200 g, 650 mmol) in dioxane (2 L) were added tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (169 g, 715 mmol), Cs_2CO_3 (445 g, 1.37 mol), water (400 mL) and Pd(dppf)Cl_2·DCM complex (26.5 g, 32.5 mmol). The reaction mixture was purged with nitrogen, and stirred at 80°C for 8 hours. The reaction mixture was filtered through a celite pad. The filtrate was concentrated, taken-up with water (1.5 L) and extracted twice with EtOAc (1.5 L). The combined organic phase was washed with brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was triturated with TBME (100 mL) and filtered to yield the title compound (180 g, 74% yield) as a yellow solid.
1H NMR (400 MHz, DMSO-d6) δ 9.56 (s, 1H), 8.69 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 1.49 (s, 9H) ppm.

Step 3: tert-butyl (4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate

To a solution of tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate (170 g, 456 mmol) in dioxane (2 L) were added methylboronic acid (81.9 g, 1.37 mol), Pd(dppf)Cl_2·DCM complex (18.6 g, 22.8 mmol) and K_2CO_3 (126 g, 912 mmol). The reaction mixture was stirred at 110°C for 10 hours under N_2 atmosphere. Volatiles were evaporated, the residue diluted with water (1 L) and extracted twice with EtOAc (1L). The combined organic phase were washed with brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (petroleum ether / EtOAc 10:1 to 1:1) to yield the title compound (122 g, 76% yield) as a yellow solid.

1H NMR (400 MHz, CDCl3) δ 8.65 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.39 (m, 3H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.70 (br.s, 1H), 2.32 (s, 3H), 1.54 (s, 9H) ppm.

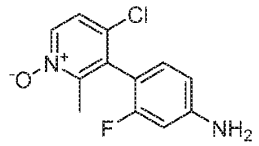
Step 4: 3-(4-((tert-butoxycarbonyl)amino)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of tert-butyl (4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate (120 g, 340 mmol) in DCM (150 mL) was added m-CPBA (91.8 g, 425 mmol) in 3 portions at 0 °C. The reaction mixture was stirred at 25°C for 10 hours. The mixture was quenched with ice water (600 mL) and extracted twice with DCM (1.5 L). The combined organic phase was washed with brine (1.5 L), dried (Na_2SO_4) and concentrated. The crude product was triturated in TBME (300 mL) and filtered to yield title compound (83 g, 65 % yield) as a yellow solid.
LC-MS: Rt = 1.04 min; MS m/z = 369.2[MH]$^+$ (Method 5).

Step 5: 3-(4-aminophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of 3-(4-((tert-butoxycarbonyl)amino)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (80 g, 217 mmol) in EtOAc (500 mL) was added HCl/EtOAc (200 mL) at 0°C. The reaction mixture was stirred at 25°C for 10 hours. The mixture was quenched with $NaHCO_3$ saturated solution (300 mL), diluted with water (200 mL) and extracted twice with EtOAc (400 mL). The combined organic phase was washed with brine (300 mL), dried (Na_2SO_4) and concentrated to yield title compound (55 g, 93 % yield) as a yellow solid.
MS: m/z = 269.1 [MH]$^+$
1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 6.8 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.87 (br s, 2H), 2.25 (s, 3H) ppm.

Intermediate 1-4: 3-(4-amino-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide



Step 1: Tert-butyl (4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)carbamate

To a solution of 3-bromo-4-chloro-2-methylpyridine (6.18 g, 30.0 mmol) in toluene (230 mL) were added tert-butyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (10.1 g, 30.0 mmol), CataCXium A Pd G3 (2.181 g, 3.00 mmol) and K_3PO_4 1.5M (59.9 ml, 90 mmol). The

reaction mixture was purged with nitrogen, and stirred at 100°C for 2 hours. The reaction mixture was diluted with EtOAc, washed with a saturated Na_2CO_3 solution and water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (cyclohexane / EtOAc 9:1 to 4:1) to yield the title compound (9.04 g, 90% yield) as a yellow foam.
LC-MS: Rt = 1.16 min; MS m/z = 337.1 $[MH]^+$ (Method 3).

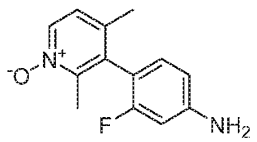
Step 2: 3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of tert-butyl (4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)carbamate (7 g, 20.8 mmol) in DCM (87 mL) was added m-CPBA (6.17 g, 35.75 mmol) in 3 portions at 0 °C. The reaction mixture was stirred at RT for 6 hours. The mixture was diluted with DCM, washed with NaOH 1M and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (EtOAc/MeOH 9 : 1) to yield title compound (5.73 g, 72 % yield) as a pale yellow solid.
LC-MS: Rt = 1.07 min; MS m/z = 353.2 $[MH]^+$ (Method 3).

Step 3: 3-(4-amino-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide (5.73 g, 16.25 mmol) was treated with 4M HCl in dioxane (60.9 ml, 244 mmol) and the mixture was stirred at RT for 20 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1M NaOH (122 mL) followed by water (2 x 200 mL). The combined aqueous phases were re-extracted with EtOAc (200 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to yield title compound (4.176 g, 95 % yield) as a yellow solid.
LC-MS: Rt = 0.66 min; MS m/z = 253.1 $[MH]^+$ (Method 3).
^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 7.0 Hz, 1H), 7.52 (dd, J = 7.1, 0.7 Hz, 1H), 6.94 (t, J = 8.5 Hz, 1H), 6.51 – 6.40 (m, 2H), 5.72 (s, 2H), 2.16 (s, 3H) ppm.

Intermediate 1-5: 3-(4-amino-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide



Step 1: Tert-butyl (4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)carbamate

A microwave tube was charged with 3-bromo-2,4-dimethylpyridine (2 g, 10.75 mmol), tert-butyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (3.62 g, 10.75 mmol) and Pd(dppf)Cl_2·DCM complex (0.878 g, 1.075 mmol) under argon atmosphere. Dioxane (50 mL) was added, followed by 2M Na_2CO_3 (10.75 mL, 21.50 mmol). The flask was closed and heated to 130°C for 30 minutes in a microwave oven. After cooling, the mixture was diluted with EtOAc, washed with a saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (0-40% EtOAc in heptane) to yield the title compound (2.48 g, 70% yield) as a colorless oil.
LC-MS: Rt = 0.93 min; MS m/z = 316.8 $[MH]^+$ m/z = 315.1 $[M-H]^-$ (Method 3).

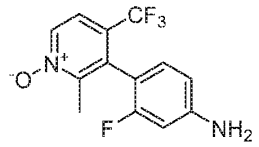
Step 2: 3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide

To a solution of tert-butyl (4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)carbamate (2.48 g, 7.84 mmol) in THF (40 mL) was added m-CPBA (3.51 g, 15.68 mmol), and the resulting mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc and quenched with a saturated $NaHCO_3$ solution. Phases were separated and the organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (0 -10% MeOH in DCM) to yield the title compound (1.65 g, 62% yield) as white solid.
LC-MS: Rt = 0.97 min; MS m/z = 333.2 $[MH]^+$ (Method 3).

Step 3: 3-(4-amino-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide

3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide (1.65 g, 4.96 mmol) was treated with 4M HCl in dioxane (24.82 ml, 99 mmol) and stirred at RT for 3 hours. The reaction mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The solid was triturated with Et_2O and filtered to yield the title compound (1.02 g, 88% yield) an off-white solid.
LC-MS: Rt = 0.62 min; MS m/z = 233.1 $[MH]^+$ (Method 3).
1H NMR (400 MHz, DMSO-d6) δ 8.18 (d, J = 6.6 Hz, 1H), 7.21 (d, J = 6.6 Hz, 1H), 6.87 (t, J = 8.5 Hz, 1H), 6.56 - 6.35 (m, 2H), 5.70 (br. s, 2H), 2.11 (s, 3H), 1.99 (s, 3H) ppm.

Intermediate 1-6: 3-(4-amino-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



Step 1: 2-chloro-3-iodo-4-(trifluoromethyl)pyridine

To a solution of 2-chloro-4-(trifluoromethyl)pyridine (0.71 mL, 5.40 mmol) in THF (10 mL) was added dropwise at -78 °C LDA 1M in THF/hexane (5.94 mL, 5.94 mmol). The reaction mixture was stirred at -20°C for 2 hours, then cooled again down to -78°C, and a solution of iodine (1.64 g, 6.48 mmol) in THF (5 mL) was added. The mixture was stirred overnight at RT. The reaction was quenched with sat. NH_4Cl and extracted twice with EtOAc. The combined organic phase were washed with 10% sodium thiosulfate and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (4 - 12% EtOAc in heptane) to yield the title compound (500 mg, 30% yield) as white solid.
LC-MS: Rt = 1.16 min (Method 3).
1H NMR (400 MHz, DMSO-d6) δ 8.63 (d, *J* = 5.0 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H) ppm.

Step 2: Tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)-3-fluorophenyl)carbamate

To a mixture of tert-butyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (3.62 g, 10.75 mmol), $PdCl_2(PPh_3)_2$ (57 mg, 0.08 mmol) and Cs_2CO_3 (1060 mg, 3.25 mmol) was added a solution of 2-chloro-3-iodo-4-(trifluoromethyl)pyridine (500 mg, 1.63 mmol) in dioxane (8 mL) and water (1.7 mL). The reaction mixture was stirred at 80°C for 3.5 hours, cooled to RT and concentrated. The residue was taken up in EtOAc, washed with water and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (0 - 17% EtOAc in heptane) to yield the title compound (270 mg, 42% yield) as a white foam.
LC-MS: Rt = 1.21 min; MS m/z = 391.4 $[MH]^+$ (Method 3).

Step 3: Tert-butyl (3-fluoro-4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate

To a solution of tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)-3-fluorophenyl)carbamate (255 mg, 0.64 mmol) in dioxane (5 mL) and water (1 mL) was added trimethylboroxine (0.135 mL, 0.96 mmol), Pd(dppf)Cl_2·DCM complex (52.2 mg, 0.06 mmol) and K_2CO_3 (265 mg, 1.92 mmol). The reaction mixture was stirred overnight at 110 °C. After cooling the mixture was concentrated, taken up in EtOAc, washed with water and brine, dried (Na_2SO_4) and concentrated. The crude product

was purified by column chromatography on silica (7 - 40% EtOAc in heptane) to yield the title compound (235 mg, 97% yield) as a white foam.
LC-MS: Rt = 1.18 min; MS m/z = 371.1 $[MH]^+$ (Method 3).

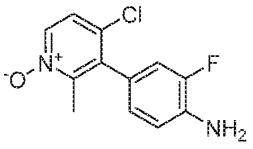
Step 4: 3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of tert-butyl (3-fluoro-4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate (230 mg, 0.62 mmol) in DCM (7 mL) was added m-CPBA (182 mg, 1.06 mmol). The reaction mixture was stirred at RT for 3 hours. The crude mixture was diluted with DCM (7 mL), washed with 1M NaOH and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (35 -100% EtOAc in heptane) to yield the title compound (192 mg, 80% yield) as a white solid.
LC-MS: Rt = 1.08 min; MS m/z = 387.1 $[MH]^+$ (Method 3).

Step 5: 3-(4-amino-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

3-(4-((tert-butoxycarbonyl)amino)-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (187 mg, 0.48 mmol) was treated with 4M HCl in dioxane (5ml, 20.00 mmol) and stirred at RT for 45 minutes. The mixture was concentrated, diluted with EtOAc, washed twice with sat. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (40- 80% EtOAc in heptane) to yield the title compound (114 mg, 82% yield) as a white solid.
LC-MS: Rt = 0.79 min; MS m/z = 287.1 $[M+H]^+$ (Method 3).
1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, 1H), 7.69 (d, 1H), 6.90 (t, 1H), 6.50 - 6.38 (m, 2H), 5.69 (s, 2H), 2.10 (s, 3H) ppm.
19F NMR (376 MHz, DMSO-d6) δ -58.99, -115.29 (t, J = 10.1 Hz) ppm.

Intermediate 1-7: 3-(4-amino-3-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

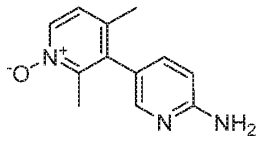


To a solution of 4-chloro-3-iodo-2-methylpyridine 1-oxide (Intermediate 1-2, step 3; 500 mg, 1.8 mmol) in dioxane (8 mL) were added 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (462 mg, 1.87 mmol), 2M aq. Na_2CO_3 (2.97 mL, 5.94 mmol) and Pd(dppf)Cl_2. DCM complex (89 mg, 0.108 mmol). The mixture was purged with argon and stirred at 100°C for 3 hours. After cooling the mixture was diluted with EtOAc and washed with sat. $NaHCO_3$ solution and brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica (25-90% EtOAc in heptane) to yield the title compound (400 mg, 87% yield) as a brown oil.

LC-MS: Rt = 0.69 min; MS m/z = 253.0 $[MH]^+$ (Method 2).

1H NMR (400 MHz, DMSO-d6) δ 8.27 (d, 1H), 7.50 (dd, 1H), 6.98 (dd, 1H), 6.85 (dd, 1H), 6.78 (dd, 1H), 5.41 (s, 2H), 2.15 (s, 3H) ppm.

Intermediate 1-8: 6'-amino-2,4-dimethyl-[3,3'-bipyridine] 1-oxide



Step 1: 3-bromo-2,4-dimethylpyridine 1-oxide

To a solution of 3-bromo-2,4-dimethylpyridine (1.9 g, 9.8 mmol) in THF (25 mL) was added m-CPBA (3.63 g, 16.18 mmol) in 3 portions at 0 °C. The reaction mixture was stirred overnight at RT. Saturated Na_2CO_3 solution was added and the mixture extracted with DCM (4 times). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to yield the title compound (1.68 g, 84% yield) as a yellow solid which was used in the next step without further purification.

LC-MS: Rt = 0.49 min; MS m/z = 202.0-204.0 $[MH]^+$ (Br pattern) (Method 5).

Step 2: 6'-((tert-butoxycarbonyl)amino)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide

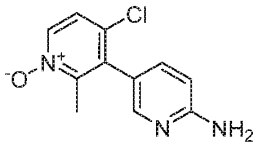
To a solution of 3-bromo-2,4-dimethylpyridine 1-oxide (1.68 g, 8.33 mmol) in dioxane (35 mL) were added tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (2.83 g, 8.58 mmol), 2M aq. Na_2CO_3 (14.58 mL, 29.2 mmol) and Pd(dppf)Cl_2·DCM complex (0.62 g, 0.75 mmol). The reaction mixture was purged with argon and stirred at 100 °C for 6 hours. After cooling 5% aq. Na_2CO_3 was added and the mixture was extracted with DCM (4 times). The combined organic

phases were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica (25-100% EtOAc + 10%MeOH in heptane) to yield the title compound (1.5 g, 57% yield) as a brown oil.
LC-MS: Rt = 0.82 min; MS m/z = 316.2 $[MH]^+$ (Method 5).

Step 3: 6'-amino-2,4-dimethyl-[3,3'-bipyridine] 1-oxide

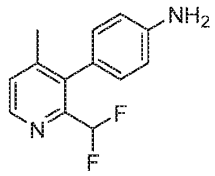
To a solution of 6'-((tert-butoxycarbonyl)amino)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide (1.45 g, 4.14 mmol) in dioxane (5 mL) was added 4M HCl in Dioxane (15.52 mL, 62.1 mmol) and the reaction mixture was stirred at RT for 3 hours. The mixture was concentrated and the residue was triturated with EtOAc (10 mL). The solid was filtered, washed with EtOAc and dried to yield the title compound (1.1 g, quantitative yield) as a beige solid.
LC-MS: Rt = 0.13 min; MS m/z = 216.1 $[MH]^+$ (Method 3).

Intermediate 1-9: 6'-amino-4-chloro-2-methyl-[3,3'-bipyridine] 1-oxide



A solution of 4-chloro-3-iodo-2-methylpyridine 1-oxide (Intermediate 1-2, step 3; 1.5 g, 5.51 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine in dioxane (20 mL) and 2M aq Na_2CO_3 (8.82 mL, 17.6 mmol) was purged with argon. $PdCl_2(dppf)\cdot DCM$ adduct (250 mg, 0.30 mmol) was added and the mixture was heated to 100 °C for 2.5 hours. After cooling, the mixture was partitioned between DCM and 5% aq. $NaHCO_3$. The aq. phase was extracted with DCM (5 times), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica (60 to 100 % EtOAc/10%MeOH/1%NEt_3 in heptane) to yield the title compound (950 mg, 66% yield) as a brown foam.
1H NMR (400 MHz, DMSO-d6) δ 8.28 (dd, 1H), 7.81 (dd, 1H), 7.52 (dd, 1H), 7.31 (dd, 1H), 6.54 (dd, 1H), 6.22 (s, 2H), 2.19 (s, 3H).

Intermediate 1-10
4-(2-(difluoromethyl)-4-methylpyridin-3-yl)aniline



Step 1: tert-butyl (4-(2-chloro-4-methylpyridin-3-yl)phenyl)carbamate

A solution of 3-bromo-2-chloro-4-methylpyridine (1.50 g, 7.26 mmol), (4-((tert-butoxycarbonyl)amino) phenyl)boronic acid (2.07 g, 8.71 mmol) and Na_2CO_3 (2.31 g, 21.79 mmol) in dioxane (100 mL) and H_20 (10 mL) was purged with Ar for 5 min. $PdCl_2$(dppf) (0.53 g, 0.73 mmol) was added, and purging with Ar repeated for 5 min. The mixture was then heated to 100° for 4 h. The resulting mixture was cooled to RT, filtered through a pad of celite, and the pad washed with EtOAc. The filtrates were washed with water, brine, and concentrated under reduced pressure to afford the crude product. Purification by chromatography on silica afforded the title compound (1.15 g, 50%) as a brown solid.
LC-MS: Rt = 1.76 min; MS m/z = 318.9 $[MH]^+$ (Method 16).

Step 2: tert-butyl (4-(4-methyl-2-vinylpyridin-3-yl)phenyl)carbamate

A solution of tert-butyl (4-(2-chloro-4-methylpyridin-3-yl)phenyl)carbamate (1.15 g, 3.61 mmol), potassium vinyltrifluoroborate (1.93 g, 14.43 mmol) and Cs_2CO_3 (3.52 g, 10.82 mmol) in dioxane (100 mL) and H_20 (10 mL) was purged with Ar for 5 min. $PdCl_2$(dppf) (0.26 g, 0.36 mmol) was added, and purging with Ar repeated for 5 min. The mixture was then heated to 100° for 16 h. The resulting mixture was cooled to RT, filtered through a pad of celite, and the pad washed with EtOAc. The filtrates were washed with water, brine, and concentrated under reduced pressure to afford the crude product. Purification by chromatography on silica afforded the title compound (0.80 g, 71%) as a brown solid.
LC-MS: Rt = 0.50 min; MS m/z = 311.3 $[MH]^+$ (Method 16).

Step 3: tert-butyl (4-(2-formyl-4-methylpyridin-3-yl)phenyl)carbamate

To a solution of tert-butyl (4-(4-methyl-2-vinylpyridin-3-yl)phenyl)carbamate (0.80 g, 2.58 mmol) in dioxane (50 mL) and t-BuOH (25 mL), a solution of OsO_4 (0.039 g, 0.154 mmol) in little t-BuOH was added at RT, and the resulting solution stirred for 5 min. A solution of $NaIO_4$ (2.21 g, 10.31 mmol) in H_2O (50 mL) was added, and the mixture strirred at RT for 16 h. The reaction mixture was

poured into water and extracted with EtOAc. The organic extract was washed with water and brine, and concentrated under reduced pressure. The crude product was purified by chromatography on silica to afford the title compound (0.40 g, 50%).

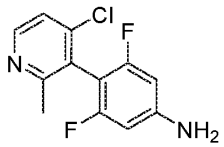
Step 4: tert-butyl (4-(2-(difluoromethyl)-4-methylpyridin-3-yl)phenyl)carbamate

A solution of tert-butyl (4-(2-formyl-4-methylpyridin-3-yl)phenyl)carbamate (0.40 g, 1.28 mmol) in DCM (100 mL) was cooled to 0°. DAST (0.62 g, 3.84 mmol) was added, and the resulting mixture stirred at 0° for 2h. The reaction was quenched with aq. sat. $NaHCO_3$, and then stirred at 0° for 10 min. The resulting mixture was extracted with DCM, and the extract washed with water, brine, and then concentrated under reduced pressure. Purification by chromatography on silica afforded the title compound (0.25 g, 58%).
LC-MS: Rt = 1.72 min; MS m/z = 335.2 $[MH]^+$ (Method 16).

Step 5: 4-(2-(difluoromethyl)-4-methylpyridin-3-yl)aniline

To a cooled (0°C) solution of tert-butyl (4-(2-(difluoromethyl)-4-methylpyridin-3-yl)phenyl)carbamate (0.20 g, 0.59 mmol) in dioxane (2 mL), was added 20% HCl in dioxane (8 mL). The resulting mixture was allowed to reach RT and stirred at this temperature for 4h. The mixture was then poured into ice water and extracted with EtOAc. The extract was washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by repeatedly washing with Et_2O to afford the crude title compound (0.20 g) as a brown solid.
LC-MS: Rt = 0.28 min; MS m/z = 234.9 $[MH]^+$ (Method 16).

Intermediate 1-11: 4-(4-chloro-2-methylpyridin-3-yl)-3,5-difluoroaniline



Step 1: **3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline**

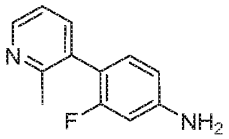
A mixture of 4-bromo-3,5-difluoroaniline (2.6 g, 12.25 mmol), $PdCl_2$(dppf)·DCM adduct (0.91 mg, 1.10 mmol), bis(pinacolato)diborane (4.71 g, 18.37 mmol) and sodium acetate (2.79 g, 2.75 mmol) in dioxane (30 mL) was purged with argon and then stirred at 100 °C overnight. After cooling the reaction mixture was diluted with EtOAc and washed with a saturated Na_2CO_3 solution and brine.

The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (elution with 10% to 50% EtOAc in heptane) to yield the title compound (900 mg, 28%) as a brown oil.
LC-MS: Rt = 0.94 min; MS m/z = 255.1 $[MH]^+$ (Method 1).

Step 2: **4-(4-chloro-2-methylpyridin-3-yl)-3,5-difluoroaniline**

A solution of 3-bromo-4-chloro-2-methylpyridine (870 mg, 3.34 mmol) , 2M aq. Na_2CO_3 (4.5 mL, 9 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (64 mg, 0.134 mmol) in DME (20 mL) was purged with argon. XPhos-Pd-G2 (106 mg, 0.134 mmol) was added and the suspension was again purged with argon. The reaction mixture was heated to 80 °C for 90 min, cooled to RT and diluted with EtOAc. The mixture was washed with saturated Na_2CO_3 solution and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica (25% to 80% EtOAc in heptane), to yield the title compound (230 mg, 21 %) as a brown solid.
LC-MS: Rt = 3.75 min; MS m/z = 255.1 $[MH]^+$ (Method 5).

Intermediate 1-12:
3-fluoro-4-(2-methylpyridin-3-yl)aniline



Step 1: Tert-butyl (3-fluoro-4-(2-methylpyridin-3-yl)phenyl)carbamate, Tert-butyl (3-fluoro-4-(2-methylpyridin-3-yl)phenyl)carbamate

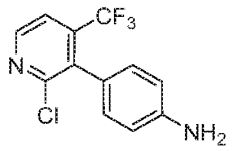
A solution of 3-bromo-2-methylpyridine (900 mg, 5.23 mmol), tert-butyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (1764 mg, 5.23 mmol) and 2M aq. Na_2CO_3 (8.50 mL, 17 mmol) in dioxane (39 mL) was purged with argon. PdCl2(dppf)·DCM (302 mg, 0.366 mmol) was added and the mixture heated to 100 °C for 4.5 hours. After cooling to RT the mixture was diluted with EtOAc, washed twice with saturated $NaHCO_3$ solution and brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (0 % to 63 % EtOAc in heptane) to yield the title compound (2.0 g, quantitative yield) as a yellow foam.

LC-MS: Rt = 0.97 min; MS m/z = 303 $[M+H]^+$ (Method 1).

Step 2: 3-fluoro-4-(2-methylpyridin-3-yl)aniline

tert-Butyl (3-fluoro-4-(2-methylpyridin-3-yl)phenyl)carbamate (2 g, 5.23 mmol) was treated with 4N HCl in dioxane for 5 hours at RT. The mixture was evaporated and dried to yield the title compound (1.33 g, quant.) as an off-white solid which was used in the next steps without further purification.
LC-MS: Rt = 0.38 min; MS m/z = 203 $[MH]^+$ (Method 1).

Intermediate 1-13:
4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)aniline



Step 1: 2-chloro-3-iodo-4-(trifluoromethyl)pyridine

To a cooled (-78 °C) solution of 2-chloro-4-(trifluoromethyl)pyridine (10.0 g, 55.1 mmol) in THF (60 mL) was slowly added 2M LDA in hexane (30.3 mL, 60.6 mmol). The mixture stirred at -78 °C for 2h, then a solution of iodine (16.78 g, 66.1 mmol) in THF (20 mL) was slowly added. The mixture was allowed to warm to 0°C over 1h and was then quenched by addition of sat. aq. NH4Cl. The mixture was extracted with EtOAc, the organic layer washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure: The residue was purified by column chromatography on silica (elution with a gradient of 0 to 15% EtOAc in hexanes) to yield the title compound (9,20 g, 54%).
TLC: Rf = 0.39 (EtOAc/hexane = 1:1).

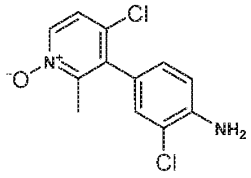
Step 2: tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate

A solution of 2-chloro-3-iodo-4-(trifluoromethyl)pyridine (step 1; 8.00 g, 26 mmol), (4-((tert-butoxycarbonyl)amino) phenyl)boronic acid (6.79 g, 28.6 mmol) and Cs_2CO_3 (16.96 g, 52 mmol) in dioxane/water 10:1 (55 mL) was degassed with Ar. $PdCl_2$(dppf)*DCM (1.06 g, 1.30 mmol) was added and the mixture was stirred a 80°C for 8 h. The mixture was coled to rt, diluted with water

and extracted with EtOAc.The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chroatography on silica (gradient of 5% to 35 % of EtOAc in hexanes to yield the title compound (8.92 g, 93 %).
1H NMR (600 MHz, DMSO-d6) δ 8.56 (d, 1H), 7.59 (d, 1H), 7.48 (d, 2H), 7.24 (d, 2H), 6.62 (br. s, 1H), 1.53 (s, 9H) ppm.

Step 3: 4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)aniline hydrochloride
A solution of tert-butyl (4-(2-chloro-4-(trifluoromethyl)pyridin-3-yl)phenyl)carbamate (400 mg, 1.07 mmol) in 4M HCl in dioxane (4 mL) was stirred under nitrogen atmosphere at 27-30°C for 3 h. The volatiles were evaporated under reduced pressure to yield the title compound (369 mg, quant.) which was used in the next steps without further purification.
^{1}H NMR (600 MHz, $CDCl_3$) δ 11.0-10.8 (br.s, 2H), 8.64 (d, 1H), 7.75 (d, 2H), 7.63 (d, 1H), 7.36 (d, 2H), 3.70 (s, 3H) ppm.

Intermediate 1-14:
3-(4-amino-3-chlorophenyl)-4-chloro-2-methylpyridine 1-oxide



Step 1: 3-bromo-4-chloro-2-methylpyridine 1-oxide

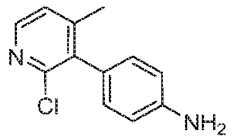
To an ice-cooled solution of 3-bromo-4-chloro-2-methylpyridine (650 mg, 3.02 mmol) in THF (4 mL) was added MCPBA in three portions. After stirring for 10 min at 0-10°C, the reaction mixture was allowed to warm to rt overnight. The mixture was diluted with EtOAc, washed with 10% aqueous Na_2CO_3, dried (Na_2SO_4) and evaporated. The residue was recrystallized from EtOAc to yield the title compound (380 mg, 55 %) as a colorless solid.
LC-MS: Rt = 0.62 min; MS m/z = $[M+H]^+$ 224.0 (Method 1).

Step 2: **3-(4-amino-3-chlorophenyl)-4-chloro-2-methylpyridine 1-oxide**

To an Ar-purged solution of 3-(4-amino-3-chlorophenyl)-4-chloro-2-methylpyridine 1-oxide (370 mg, 1.65 mmol), 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (439 mg, 1.70 mmol)

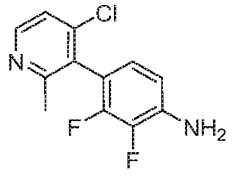
and 2M aqueous Na_2CO_3 (2.7 mL, 5.4 mmol) in dioxane (10 mL) was added $PdCl_2(dppf)$-CH_2Cl_2 (81 mg, 0.1 mmol) and the mixture was heated to reflux for 3 hours. After cooling to rt, the mixture was diluted with EtOAc, washed with sat. aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was purified by by column chromatography on silica (ISCO system, column RediSep 40g, elution wielution with 5% to 100% EtOAc in heptane), to yield the title compound (260 mg, 55 %) as a brown oil.
LC-MS: Rt = 0.71 min; MS m/z = $[MH]^+$ 269.0 (Method 1).

Intermediate 1-15:
4-(2-chloro-4-methylpyridin-3-yl)aniline



A solution of 2-chloro-3-iodo-4-methylpyridine (5.3 g, 20.5 mmol), 4-aminophenylboronic acid pinacolester (4.8 g, 21.1 mmol) and 2M aq. Na_2CO_3 (33.3 mL, 66.6 mmol) in dioxane (80 mL) was purged with argon. $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct was added and the reaction mixture was heated to reflux for 3 hours. After cooling the mixture was diluted with EtOAc and washed with sat. $NaHCO_3$ solution and brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (25% to 80 % EtOAc in heptane) to yield the title compound (4.0 g, 89% yield) as a brown oil.
LC-MS: Rt = 0.81 min; MS m/z = 219.1 $[M+H]^+$ (Method 3).

Intermediate 1-16:
4-(4-chloro-2-methylpyridin-3-yl)-2,3-difluoroaniline



Step 1: Tert-butyl (4-(4-chloro-2-methylpyridin-3-yl)-2,3-difluorophenyl)carbamate

A mixture of 3-bromo-4-chloro-2-methylpyridine (700 mg, 3.32 mmol), (4-((tert-butoxycarbonyl)amino)-2,3-difluorophenyl)boronic acid (972 mg, 3.49 mmol), K_2CO_3 (1.16 g, 8.31 mmol) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (80 mg, 0.166 mmol) in DME (12 mL) and water (3 mL) was purged with argon. XPhos-Pd-G2 (133 mg, 0.166 mmol) was added and the suspension was again purged with argon. The reaction mixture was heated to 65 °C for 70 min, cooled to RT and diluted with EtOAc. The mixture was washed with saturated Na_2CO_3 solution and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica (elution with 20% to 70% EtOAc in heptane), to yield the title compound (440 mg, 32 %) as a brown oil.

LC-MS: Rt = 1.19 min; MS m/z = 354.2 $[MH]^+$ (Method 2).

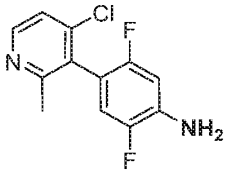
Step 2: 4-(4-chloro-2-methylpyridin-3-yl)-2,3-difluoroaniline

To a solution of tert-butyl (4-(4-chloro-2-methylpyridin-3-yl)-2,3-difluorophenyl)carbamate (Step 1; 460 mg, 1.1 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.2 mL, 15.4 mmol) and the reaction mixture was stirred at RT for 4 hours. The mixture was diluted with EtOAc and washed with 10% aq. Na_2CO_3. The aqueous phase was re-extracted with EtOAc, and the combined organic phases were evaporated and dried in vacuo to yield the title compound (300 mg, quant.) as a yellow resin.

LC-MS: Rt = 0.71 min; MS m/z = 255.1 $[MH]^+$ (Method 2).

Intermediate 1-17:

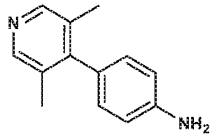
4-(4-chloro-2-methylpyridin-3-yl)-2,5-difluoroaniline



A solution of 4-chloro-3-iodo-2-methylpyridine (680 mg, 2.60 mmol), 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (753 mg, 2.86 mmol), Cs_2CO_3 (2.14 g, 6.5 mmol) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (38 mg, 0.078 mmol) in DME (12 mL) and water (3 mL) was purged with argon. XPhos-Pd-G2 (62 mg, 0.078 mmol) was added and the suspension was again purged with argon. The reaction mixture was heated to 60 °C for 30 min, cooled to RT and diluted with EtOAc. The mixture was washed with sat. Na_2CO_3 and brine, dried (Na_2SO_4) and

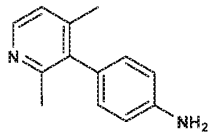
concentrated. The residue was purified by column chromatography on silica (25% to 80% EtOAc in heptane), to yield the title compound (220 mg, 30 %) as a brown oil.
LC-MS: Rt = 0.92 min; MS m/z = 255.1 $[MH]^+$ (Method 2).

Intermediate 1-18:
4-(3,5-dimethylpyridin-4-yl)aniline



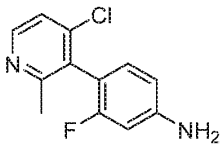
To a solution of 2 g 4-bromo-3,5-dimethylpyridine (2g, 9 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 (734 mg, 0.9 mmol) in dioxane (90 mL) was added 4-aminophenylboronic acid pinacolester (2.56 g, 11.7 mmol) and 2M aq. Na_2CO_3 (18 mL, 36 mmol) under an atmosphere of Ar.The reaction mixture was heated to 100 °C overnight. After cooling to RT, the mixture was diluted with EtOAc and washed with sat. $NaHCO_3$, water and brine. The org. phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (elution with 5% to 100% EtOAc in heptane), to yield the title compound (1.56 g, 88 %) as a yellow oil which crystallized on standing.
LC-MS: Rt = 0.38 min; MS m/z = 199.2 $[MH]^+$ (Method 1).

Intermediate 1-19
4-(2,4-dimethylpyridin-3-yl)aniline



The title compound was prepared by Suzuki-coupling of 3-bromo-2,4-dimethylpyridine with 4-Aminophenylboronic acid pinacolester using a method similar to that used in the synthesis of Intermediate 1-18.
LC-MS: Rt = 0.38 min; MS m/z = 199.3 $[MH]^+$ (Method 1).

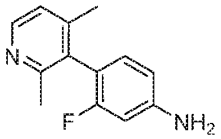
Intermediate 1-20:
4-(4-chloro-2-methylpyridin-3-yl)-3-fluoroaniline



tert-Butyl (4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)carbamate (Intermediate 1-2, step 1; 6.3 g, 18.71 mmol) was treated with 4M HCl in dioxane (30 mL) for 3.5 h at rt, followed by filtration of the resulting solid and drying in vacuo to yield the title compound (5.83 g, 100 %) as a yellow solid.
LC-MS: Rt = 0.85 min; MS m/z = 237 and 239 $[MH]^+$ (Method 3).

Intermediate 1-21:

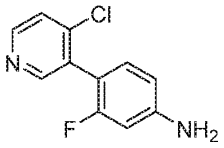
4-(2,4-dimethylpyridin-3-yl)-3-fluoroaniline



tert-butyl (4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)carbamate (Intermediate 1-5, step 1; 957 mg, 3.0 mmol) was treated with excess 4M HCl in dioxane for 3.5 h at rt, followed by evaporation and drying in vacuo to yield the title compound (832 mg, 100 %) as a colorless solid.
LC-MS: Rt = 0.38 min; MS m/z = 217.1 $[MH]^+$ (Method 2).

Intermediate 1-22

4-(4-chloropyridin-3-yl)-3-fluoroaniline

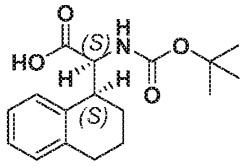


The title compound was prepared by Suzuki-coupling of 3-bromo-4-chloropyridine with 4-(Boc-amino)-2-fluorobenzne boronic acid pinacolester, followed by Boc-cleavage using a method similar to that usewd in the synthesis of Intermediate 1-16.
LC-MS: Rt = 0.85 min; MS m/z = 223.2 $[MH]^+$ (Method 2).

Synthesis of Intermediates 2-1 to 2-12

Intermediate 2-1

(S)-2-((tert-butoxycarbonyl)amino)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid

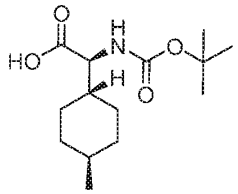


To a cooled (0°C) mixture of 2-(1,2,3,4-tetrahydronaphthalen-1-yl)glycine (2 g, 9.74 mmol) in a mixture of dioxane (30 mL) and 1M aq. NaOH (15 mL) was added di-tert.-butyl-dicarbonate (3.4 g, 14.6 mmol). After stirring for 5 h at RT, the mixture was partitioned between EtOAc and aq. 10 % $KHSO_4$. The organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was triturated with DCM/methanol 1:1, the resulting solid was filtered and dried in vacuo. The mother liqour was purified by column chromatography on silica (column: RediSep 40g; elution with 5 to 70 % EtOAc in heptane). Pure fractions were evaporated and combined with the filtered material to yield a stereoisomeric mixture of the title compound (2.37 g, 76 %) as a colorless solid. The sparation of the individual stereoisomers was achieved by chiral SFC (column: ChiralPak AY, 300×50 mm I.D., 10 µm; 25 % ethanol, flow: 100 mL/min.

Analytical chiral SFC (ChiralPak AY, 150×4.6mm I.D., 3µm, 5 – 40 % ethanol +0.05 % DEA; flow = 2.5 mL/min, T = 35 °C):
Peak 1: Rt = 2.41 min: 873 mg
Peak 2: Rt = 2.99 min: 130 mg
Peak 3: Rt = 3.29 min: 1040 mg
Peak 4: Rt = 4.71 min: 78 mg

LC-MS: Rt = 5.05 min; MS m/z = 304.2 $[M-H]^+$ (Method 2).
The stereochemistry of the eluted compound of peak 3 (designated intermediate 2-1) was determined as (S,S) by X-ray crystallography.

Intermediate 2-2: (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetic acid



Step 1: ((1r,4r)-4-methylcyclohexyl)methanol

To a cooled (0°C) mixture of $LiAlH_4$(18.7g, 492 mmol) in THF (400 mL) was added dropwise a solution of (1r,4r)-4-methylcyclohexane-1-carboxylic acid (70.0g, 492mmol) dissolved in THF (90 mL) was added. The reaction mixture was stirred for 1.5h at -5 – 5°C under nitrogen and then warmed to rt. TLC (PE: EtOAc = 3: 1, Rf = 0.50) indicated complete conversion of the starting material. Water (500 mL) and 10% NaOH (500 mL) were added. After stirring for 3h at rt the mixture was filtered and the organic layer was concentrated to yield the title compound (55.0 g, 87%) as a yellow liquid which was used in the next step without further purification.

Step 2: (1r,4r)-4-methylcyclohexane-1-carbaldehyde

To a solution of ((1r,4r)-4-methylcyclohexyl)methanol (Step 1; 55.0 g, 428 mmol) in DMSO (100 mL) and DCM (300 mL) was added DIPEA (123.2 ml, 1.29 mol). The mixture was cooled to 0 °C before Py·SO3 (136g, 857mmol) was slowly added. After the addition was complete, the reaction mixture was stirred at rt for 16h. TLC (PE: EtOAc = 3: 1, Rf =0.88) indicated complete conversion of the starting material. The reaction mixture was washed with aq. sat. citric acid (3x 1.0 L) and brine (500 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to yield the title compound. (54 g) which was used in the next step without further purification.

Step 3: (S)-N-((E)-((1r,4S)-4-methylcyclohexyl)methylene)benzenesulfinamide

To a solution of (1r,4r)-4-methylcyclohexane-1-carbaldehyde (Step 2; 54.0 g, 427 mmol) in DCM (300 mL) was added (S)-(+)-p-toluenesulfineamide (66.4g, 427 mmol) and $Ti(OEt)_4$ (292g, 1.28 mol). After stirring for 3h at 40 °C TLC (PE: EtOAc = 3: 1, Rf = 0.24) indicated complete conversion of the starting material. The mixture was cooled to 0 °C. Water (500 mL) was added and the resulting thick paste was filtered through a celite pad and washed with DCM (500 mL). The organic

layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was crystallized with petroleum ether to yield the title compound as a colorless solid. (84 g, 75%).

Step 4: ((S)-N-((S)-cyano((1r,4S)-4-methylcyclohexyl)methyl)benzenesulfinamide

To a cooled (- 65°C) solution of Et_2AlCN (1M in THF, 478 mL) in THF (200 mL) was added i-PrOH (50 mL) followed by a precooled (- 65 °C) solution of (S)-N-((E)-((1r,4S)-4-methylcyclohexyl)methylene)benzenesulfinamide (Step 3; 84.0 g, 319 mmol) in THF (400 mL). The reaction mixture was stirred for 3h at -65°C. TLC (PE: EtOAc = 3: 1, R_f = 0.33) indicated complete conversion of the starting material. The mixture was warmed to 0 °C before aq. NH_4Cl (200 mL) was added. After stirring for 30 min the mixture was filtered through a pad of Celite, washed with water and EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica (eluent: petroleum ether/EtOAc 50:1 to 10:1) to yield the title compound as a colorless solid (23 g, 25 %).

Step 5: (S)-cyano((1r,4S)-4-methylcyclohexyl)methanaminium chloride

A solution of ((S)-N-((S)-cyano((1r,4S)-4-methylcyclohexyl)methyl)benzenesulfinamide (Step 4; 23.0 g, 79.1 mmol) in HCl/MeOH (4M, 19.8 mL) was stirred at RT for 30min. TLC (PE: EtOAc = 1:1, Rf = 0.0) indicated complete consumption of the starting material. The mixture was concentrated to yield the title compound (16g, 85%) as a colorless solid.
^{1}H NMR (400 MHz, DMSO) δ 8.34 (s, 3H), 4.52 (s, 1H), 1.98-1.70 (m, 5H), 1.14-1.14 (m, 3H),1.09-1.06 (m, 1H), 0.90-0.85 (m, 5H) ppm.

Step 6: (S)-carboxy((1r,4S)-4-methylcyclohexyl)methanaminium chloride

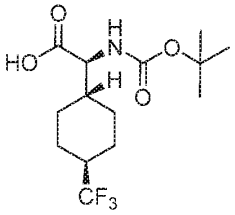
A solution of (S)-cyano((1r,4S)-4-methylcyclohexyl)methanaminium chloride (Step 5; 16.0 g, 85.7 mmol) in 6M HCl (160 mL) and AcOH (16 mL, 279mmol) was stirred for 2h at 125°C. Then 12M HCl (74.6 mL) was added and the reaction mixture was stirred for another 6h. The reaction mixture was cooled to RTand filtered of to yield the title compound (15g) as a colorless solid which was used in the next step without further purification.
^{1}H NMR (400 MHz, DMSO) δ 8.47 (s, 3H), 3.66 (s, 1H), 1.71-1.60 (m, 5H), 1.28-1.12 (m, 3H), 0.88-0.83 (m, 5H).

Step 7: (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetic acid

To a cooled (10°C) soluttion of (S)-carboxy((1r,4S)-4-methylcyclohexyl)methanaminium chloride (Step 6; 15.0 g, 72.2 mmol) in dioxane (150 mL) was added a solution of Na_2CO_3 (22.9 g, 216 mmol) in H2O (300 mL). The mixture was cooled to 0°C before $(Boc)_2O$ (20.4 g, 93.8 mmol) was added. After stirring for 16h at rt the reaction mixture was neutralized to pH=5 with 1M HCl and extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was trituated with n-heptane (100 ml) and filtered of to yield the title compound (10.5 g, 100%) as a colorless solid.

^{1}H NMR (400 MHz, CDCl3) δ 12.42 (s,1H), 6.92-6.59 (m, 1H), 3.79-3.64 (m, 1H), 1.67-1.55 (m, 5H), 1.39 (s, 9H), 1.12-1.08 (m, 1H), 1.08-1.05 (m, 2H), 0.87-0.81 (m, 5H) ppm.

Intermediate 2-3: (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetic acid



Step 1: ((1r,4r)-4-(trifluoromethyl)cyclohexyl)methanol

To a cooled (0 °C) solution of (1r,4r)-4-(trifluoromethyl)cyclohexane-1-carboxylic acid (20.7 g, 106 mmol) in THF (300 mL) was added dropwise a solution of $LiAlH_4$ (1M in THF, 79 mL, 79 mmol) within 20 min. After the addition was complete, the mixture was stirred at RT for 1.5h, followed by addition of another batch of $LiAlH_4$ (2M in Et_2O, 10.55 mL, 21.10 mmol). After stirring at reflux overnight, the mixture was cooled to 0°C, and water (20 mL) was added carefully. Once the evolution of gas has ceased, Na_2SO_4 (160 g) were added and the mixture was vigorously stirred for 20 min. The precipitate was filtered off and washed with ethyl acetate. The combined filtrate was washed with water and evaporated to yield the title compound (12.45 g, 65 %) as a colorless oil.

1H NMR (400 MHz, DMSO-d6) δ 4.44 (t, 1H), 3.21 (dd, 2H), 2.23 – 2.08 (m, 1H), 1.88 – 1.78 (m, 4H), 1.39 – 1.28 (m, 1H), 1.27 – 1.16 (m, 2H), 0.99 – 0.88 (m, 2H) ppm.

Step 2: **(1r,4r)-4-(trifluoromethyl)cyclohexane-1-carbaldehyde**

To a mixture of pyridine-sulfur trioxide complex (21.75 g, 137 mmol) and pyridine (11.05 ml, 137 mmol) was added DMSO (15 mL) at RT and the mixture was stirred for 10 min to afford a white suspension.This suspension was slowly added to a cooled (- 10°C) solution of ((1r,4r)-4-(trifluoromethyl)cyclohexyl)methanol (12.45 g, 68.3 mmol) and DIPEA (59.7 mL, 342 mmol) in DCM (95 mL) and DMSO (15 mL) over 10 min. The reaction mixture was stirred at -10°C to 0°C for 1h, then at 0°C for 2h followed by stirring overnight at RT. The mixture was diluted with DCM (250 mL) and extracted with 2 x 200 mL of 10 % citric acid, followed by 200 mL of brine. The combined aqueous layers were re-extracted with DCM, the organic layers were combined, dried ($MgSO_4$) and evaporated to yield the title compound (13.89 g, quant.) as a purple oil, which was used in the next step without further purification.

1H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 1H), 2.36 – 2.17 (m, 2H), 2.03 – 1.92 (m, 4H), 1.16 – 1.18 (m, 4H) ppm.

Step 3: **(S)-4-methyl-N-((E)-((1r,4S)-4-(trifluoromethyl)cyclohexyl)methylene) benzenesulfinamide**

To a solution of (1r,4r)-4-(trifluoromethyl)cyclohexane-1-carbaldehyde (4g, 22.20 mmol) and (S)-(+)-p-toluenesulfinamide (3.45 g, 22.20 mmol) in DCM (120 mL) was added titanium(IV)ethoxide (13.92 mL, 68.8 mmol). After heating to reflux for 2h followed by stirring at RT for 16h the mixture was partitioned between water and EtOAc. The resulting thick suspension was filtered through a bed of hyflo and rinsed with EtOAc. The layers were separated, the water layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and evapoarted. The residue was purified by column chromatography on silica (Redisep120g, elution with 5 to 40% EtOAc in cyclohexane) to yield the title compound (3.99 g, 57 %) as a pale yellow oil which solidified on standing.

^{1}H NMR (400 MHz, DMSO) δ 8.08 (d, 1H), 7.52 (d, 2H), 7.38 (d, 2H), 2.49 – 2.44 (m, 1H), 2.30 – 2.21 (m, 1H), 1.99 – 1.87 (m, 4H), 1.37 – 1.22 (m, 4H) ppm.

Step 4: **(S)-N-(cyano((1r,4S)-4-(trifluoromethyl)cyclohexyl)methyl)-4-methyl benzenesulfinamide**

To a cooled (-78°C) solution of diethylaluminium cyanide (1M in toulene, 18.83 mL, 18.83 mmol) in THF (70 mL) was added anhydrous 2-propanol (0.97 mL, 12.56 mmol). The mixture was stirred at -78°C for 60 minutes, then slowly added to a cooled (-78 °C) solution of (S)-4-methyl-N-((E)-

((1r,4S)-4-(trifluoromethyl)cyclohexyl)methylene)benzenesulfinamide (3.985 g, 12.56 mmol) in THF (90 mL). Stirring was continued at -78°C for 20 min, then the mixture was allowed to warm to room temperature and was stirred overnight. The mixture was cooled in an ice bath, then sat. aq. NH_4Cl was carefully added. After stirring for 1h the mixture was filtered through Celite, the pad was washed with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80g, 5 – 30 % EtOAc in cyclohexane) to yield the title compound (4.23 g, 98 %) as a colorless solid.
LC-MS: Rt = 1.11 min; MS m/z = 345.3 $[MH]^+$ (Method 2).

Step 5: **(S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetonitrile**

To a solution of (R)-N-((S)-cyano((1r,4S)-4-(trifluoromethyl)cyclohexyl)methyl)-4-methylbenzenesulfinamide (4.22 g, 12.25 mmol) in methanol (70 mL) was added 4M HCl in dioxane (64.6 mL, 259 mmol) at RT within 5 min. After stirring at RT for 2h the solvents were evaporated and the residue was triturated under sonication with diethyl ether. The formed precipitate was filtered and dried in vacuo to yield the title compound (2.96 g, quant.) as a colorless solid which was used in the next step without further purification.
^{1}H NMR (400 MHz, DMSO) δ 9.21 (br. s, 3H), 4,56 (d, 1H), 2.36 – 2.32 (m, 1H), 2.02 – 1.89 (m, 5H), 1.31 – 1.11 (m, 4H) ppm.

Step 6: **(S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetic acid**

A solution of (S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetonitrile (2.963 g, 14.37 mmol) in a mixture of AcOH (10.33 mL, 180 mmol) and HCl conc. (56.4 mL, 687 mmol) was heated to reflux. More HCl conc. (16.75 ml, 204 mmol each) was added after 2 and 4h of heating. After a total of 5h at reflux the mixture was cooled to RT. The precipitate was filtered, washed with diethyl ether and dried in vacuo to yield the title compound (2.55 g) as a colorless solid. A second crop (331 mg) could be isolated by evaporating the filtrate, followed by tituration of the residue with cold water under sonication, filtration, and drying the solid in vacuo to give a combined yield of 2.88 g (89%).
^{1}H NMR (400 MHz, DMSO) δ 13.83 (br. s, 1H), 8.38 (br. s, 3H), 3.78 (s, 1H), 2.27 – 2.12 (m, 1H), 1.98 – 1.69 (m, 5H), 1.40 – 1.10 (m, 4H) ppm.

Step 7: **(S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetic acid**

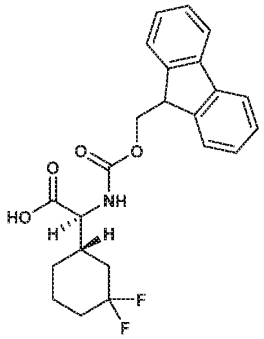
To a suspension of (S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetic acid (2.88 mg, 12.8 mmol) in water (31 mL) was added solid Na_2CO_3 (5.84 g, 55.1 mmol) followed by dropwise addition of a solution of Boc_2O (4.2 g, 19.2 mmol) in dioxane (46.5 mL). After stirring at RT overnight, the main amount of solvents were evaporated. The resulting suspension was cooled in an ice bath and acidified to pH=1 with 1N HCl. The mixture was extracted with EtOAc, the aqueous layer was extracted twice with EtOAc. The combined organic layers were evaporated and the residue was triturated with heptanes, filtered and dried in vacuo to yield the title compound (3.00 g, 72 %) as a colorless solid.

1H NMR (400 MHz, DMSO) δ 12.5 (br. s, 1H), 6.97 (d, 1H), 3.79 (m, 1H), 2.22 – 2.08 (br. m, 1H), 1.91 – 1.83 (m, 2H), 1.74 – 1.63 (m, 3H), 1.38 (s, 9H), 1.24 – 1.12 (m, 4H) ppm.

.

Intermediate 2-4

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetic acid



Step 1: Tert-butyl (S)-2-((diphenylmethylene)amino)-2-((S)-3-oxocyclohexyl)acetate

To a solution of diphenylmethylene-glycine t-butyl ester (5.0 g, 16.93 mmol) in DCM (340 mL) was added O(9)-allyl-N-9-anthracenylmethylcinchonidinium bromide (1.14 g, 1.64 mmol), followed by cesium hydroxide monohydrate (29.6 g, 169 mmol).The mixture was cooled to -75ºC, before a solution of cyclohex-2-en-1-one (5.50 mL, 54.2 mmol) in DCM (10 mL) was added dropwise over 15 min. After stirring at -75ºC for 30 min and for further 6h at -60 ºC, the mixture was filtered through Celite. The filtrate was washed with water and brine, the organic. phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (ISCO system; eluent: 3 – 15% EtOAc in heptane; column: RediSep 220 g) to yield the title compound (6.07 g, 92 %) as a purple solid.

LC-MS: Rt = 1.37 min; MS m/z = 392.3 $[MH]^+$ (Method 5).

Step 2: Tert-butyl (S)-2-((S)-3,3-difluorocyclohexyl)-2-((diphenylmethylene)amino)acetate

To tert-butyl (S)-2-((diphenylmethylene)amino)-2-((S)-3-oxocyclohexyl)acetate (6.0 g, 15.33 mmol) was added DAST (20.49 ml, 155 mmol). After stirring at 60ºC to RT for 2.5h the mixture was cooled in an ice bath and diluted with DCM (250 mL). 1M Na_2CO_3 (190 mL) was added dropwise over a period of 2h, followed by solid Na_2CO_3 (20 g) and stirring was continued for 30 min at 0ºC. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 220 g; eluent: 0 – 10 % EtOAc in heptane) to yield the title compound (4.02 g, 63 %) as a yellow oil.
LC-MS: Rt = 1.63 min; MS m/z = 414.3 $[MH]^+$ (Method 5).

Step 3: Tert-butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetate

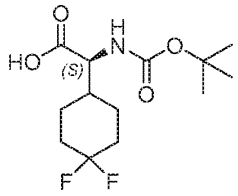
To a solution of tert-butyl (S)-2-((S)-3,3-difluorocyclohexyl)-2-((diphenylmethylene)amino)acetate (4.02 g, 9.72 mmol) in THF (100 mL) was added 15% aq. citric acid solution (62 mL) and the mixture was stirred at 40 ºC for 1.5h. The mixture was cooled to RT, and $NaHCO_3$ (6.53g, 78 mmol) followed by (9H-fluoren-9-yl)methyl carbonochloridate (5.03g, 19.44 mmol) was added. After stirring at RT for 18h the mixture was diluted with EtOAc and was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 220g; eluent: 0 – 20 % EtOAc in heptane) to yield the title compound (3.73 g, 81 %) as a colorless foam.
HPLC: Rt = 1.57 min (Method 5).

Step 5: (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetic acid

To a solution of tert-butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetate (3.73 g, 7.91 mmol) in DCM (80 mL) was added TFA (18.3 mL, 237 mmol). After stirring the mixture at RT for 8h the mixture was evaporated and the residue was purified by column chromatography on silica (column: RediSep 120 g; eluent: 5 -75 % EtOAc in heptane) to yield the title compound (3.06 g, 93 %) as a white foam.
LC-MS: Rt = 1.24 min; MS m/z = 416.3 $[MH]^+$ (Method 5).

Intermediate 2-5

(S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetic acid



Step 1: Methyl (S)-2-amino-2-(4-hydroxyphenyl)acetate

HCl gas was slowly bubbled though a solution of (S)-2-amino-2-(4-hydroxyphenyl)acetic acid (20 g, 120 mmol) in MeOH (250 mL) at 50°C for 2.5h. After cooling, the volatiles were evaporated and the residue was dried in vacuo to yield the title compound as a brown solid (26.5 g, quant.) which was used in the next step without further purification.
LC-MS: Rt = 0.24 min; MS m/z = 182.2 $[MH]^+$ (Method 3).

Step 2: Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4-hydroxyphenyl)acetate

To a suspension of methyl (S)-2-amino-2-(4-hydroxyphenyl)acetate (Step 1; 26.5 g, 122 mmol) and DIPEA (63.8 mL, 365 mmol) in THF (80 mL) was added Boc_2O (26.6 g, 122 mmol). After stirring at RT for 17h the solvent was evaporated, the residue was dissolved in EtOAc and washed with aq. NH_4Cl and water. The organic layer was dried (Na_2SO_4) and evaporated to yield the title compound as a brown solid (33.89 g, 95 %) which was used in the next step without further purification.
LC-MS: Rt = 0.88 min; MS m/z = 282.3 $[MH]^+$ (Method 3).

Step 3: Methyl (2S)-2-((tert-butoxycarbonyl)amino)-2-(4-hydroxycyclohexyl)acetate

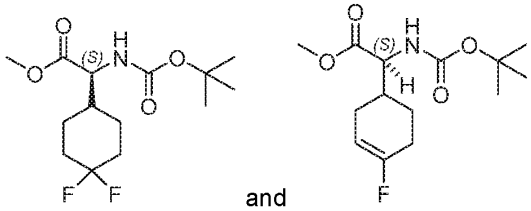
In a hydrogenation shaker, a mixture of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4-hydroxyphenyl)acetate (Step 2; 33 g, 117 mmol) and rhodium-platinum oxide (Nishimura catalyst, 3.3 g, 117 mmol) in MeOH (1320 mL) was shaken under an atmosphere of 1 bar hydrogen overnight. The mixture was filtered through a 5 µm PTFE membrane filter and the filtrate was evaporated to yield the title compound (33 g, 93 %) as a yellow oil.
LC-MS: Rt = 0.89 min; MS m/z = 288.2 $[MH]^+$ (Method 3).

Step 4: Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4-oxocyclohexyl)acetate

To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4-hydroxycyclohexyl)acetate (Step 3; 23.0 g, 80 mmol) in DCM (500 mL) was added portionwise Dess-Martin iodinane (50.9 g, 120 mmol) over a period of 4h. After the addition was complete, the mixture was stirred for 1h at RT, then the solvent was evaporated, the residue was taken up in EtOAc and washed with sat. aq. $NaHCO_3$ solution and water. The aqueous layers were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by column chromatography on silica (column: RediSep 330g; eluent: 5 – 50% EtOAc in cyclohexane) to yield the title compound (20.22 g, 84 %) as a yellow oil.

1H NMR (400 MHz, DMSO-d6) δ 7.31 (d, 1H), 4.06 – 3.97 (m, 1H), 3.64 (s, 3H), 2.45 – 2.26 (m, 2H), 2.23 – 2.10 (m, 3H), 1.88 – 1.82 (br. m, 2H), 1.61 – 1.34 (m, 2H), 1.38 (s, 9H) ppm.

Step 5: Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetate
and
methyl (S)-2-((tert-butoxycarbonyl)amino)-2-((R)-4-fluorocyclohex-3-en-1-yl)acetate


and

To a cooled (0°C) solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4-oxocyclohexyl)acetate (Step4; 20.22 g, 70.9 mmol) in DCM (200 mL) was added dropwise a 50% solution of DAST (56.2 mL, 425 mmol) in THF (56 mL) during 75 min. After stirring for 30 min at 0°C and overnight at RT the reaction mixture was diluted with DCM and extracted with aq. $NaHCO_3$ solution. The aqueous layer was re-extracted twice with DCM, the combined organic layers were washed with water and evaporated in vacuo. The residue was purified by column chromatography on silica (column: RediSep 330g; eluent: 5 to 50 % EtOAc in cyclohexane) to yield two fractions:

P1: 7.5 g (34 %) methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetate as pale yellow oil.
LC-MS: Rt = 1.09 min; MS m/z = 308.8 [MH]+ (Method 2)
1H NMR (400 MHz, DMSO-d6) δ 7.30 (d, 1H), 4.10 – 3.91 (m, 1H), 3.63 (s, 3H), 2.08 – 1.91 (m, 2H), 1.91 – 1.58 (m, 4H), 1.38 (s, 9H), 1.36 – 1.11 (m, 3H) ppm.

P2: 4.6 g (23 %) methyl (S)-2-((tert-butoxycarbonyl)amino)-2-((R)-4-fluorocyclohex-3-en-1-yl)acetate as pale yellow solid

LC-MS: Rt = 1.11 min; MS m/z = 288.2 [MH]+ (Method 2)

1H NMR (400 MHz, DMSO-d6) δ 7.31 (d, 1H), 5.16 (d, 1H), 4.02 – 3.91 (m, 1H), 3.64 (s, 3H), 2.29 – 2.05 (m, 2H), 2.04 – 1.64 (m, 4H), 1.38 (s, 9H)1.36 – 1.31 (m, 2H) ppm.

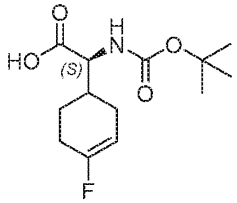
Step 6: (S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetic acid

To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetate (Step 5-P1; 708 mg, 2.304 mmol) in MeOH (5 mL) was added 4M aq. NaOH (1.15 mL, 4.61 mmol). After stirring the mixture at 50°C for 1h, 2M HCl (4.61 mL) was added. The mixture was diluted with water (50 mL) and was extracted twice with EtOAc. The combined organic layers were evaporated to yield the title compound (643 mg, 85%) as a colorless solid.

LC-MS: Rt = 0.90 min; MS m/z = 292.2 $[M-H]^+$ (Method 3).

Intermediate 2-6

(2S)-2-((tert-butoxycarbonyl)amino)-2-(4-fluorocyclohex-3-en-1-yl)acetic acid

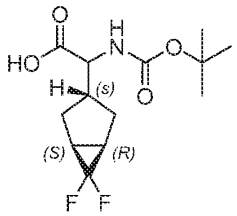


The title compound was prepared from Intermediate 2-5, step 5 P2 by a procedure similar to Intermediate 2-5 step 6 to to yield the title compound as a yellow solid (2.62 g, 102 %).

LC-MS: Rt = 0.94 min; MS m/z $[M-H]^+$ = 272.2 (Method 3).

Intermediate 2-7

2-((tert-butoxycarbonyl)amino)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)acetic acid



Step 1: cyclopent-3-en-1-yl benzoate

To a cooled (0°C) solution of cyclopent-3-en-1-ol (10.0 g, 118.8 mmol) in DCM (200 mL) was added NEt_3 (19.77 mL, 142.6 mmol) and the resulting solution was stirred for 15 min. Benzoyl chloride (16.57 mL, 142.6 mmol) was slowly added, and the resulting mixture was stirred at RT for 15h. Water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford 18.21 g (76%) of the title compound.
1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H), 7.54 (t, 1H), 7.42 (t, 2H), 5.77 (s, 1H), 5.62 (m, 1H), 2.85 (dd, 2H), 2.60 – 2.51 (m, 2H).

Step 2: 6,6-difluorobicyclo[3.1.0]hexan-3-yl benzoate

A solution of cyclopent-3-en-1-yl benzoate (Step 1; 3.0 g, 15.95 mmol), trifluoromethyl)trimethylsilane (4.54 g, 63.80 mmol) and sodium iodide (5.26 g, 35.09 mmol) in THF (24 mL) was heated to 150°C in a microwave reactor for 40 min. Another portion of trifluoromethyl)trimethylsilane (4.54 g, 63.80 mmol) was added and heating continued for another 40 min. Water was added, and the mixture extracted with DCM. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford 1.50 g (79%) of the title compound.
1H NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.55 (t, 1H), 7.43 (t, 2H), 5.55 (m, 1H), 2.63 (m, 2H), 2.11 – 1.92 (m, 4H).

Step 3: (1R,3r,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl 4-methylbenzenesulfonate

A solution of 6,6-difluorobicyclo[3.1.0]hexan-3-yl benzoate (Step 2; 3.0 g, 12.60 mmol) and KOH (0.71 g in 7.1 mL water, 12.6 mmol) in MeOH (15 mL) was stirred at RT for 6 h. Extractive aqueous work-up with EtOAc provided the crude intermediate alcohol, which was dissolved in DCM (25 mL). p-Toluenesulfonyl chloride (4.80 g, 25.2 mmol) and pyridine (3.99 g, 50.4 mmol) were added, and the mixture stirred at RT for 16h. Water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford 1.80 g (38%) of the title compound.
1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H), 7.34 (d, 2H), 5.11 – 4.97 (m, 1H), 2.45 (s, 3H), 2.43 – 2.29 (m, 2H), 1.98 – 1.82 (m, 4H).

Step 4: Ethyl 2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-((diphenylmethylene)amino) acetate

To a solution of (1R,3r,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl 4-methylbenzenesulfonate (Step 3; 1.80 g, 6.25 mmol) in toluene (20 mL) were added N-(diphenylmethylene)glycine ethyl ester (2.17 g, 8.12 mmol) followed by 1M LiHMDS in THF (9.99 mL, 9.99 mmol), and the mixture heated to 100° in a microwave reactor for 5h. After cooling the mixture was diluted with DCM and washed with water. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford 1.65 g (69%) of the title compound.
LC-MS: Rt = 2.04 min; MS m/z = 384.3 $[MH]^+$ (Method 16).

Step 5: Ethyl 2-amino-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)

To a solution of ethyl 2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-((diphenylmethylene)amino)acetate (Step 4; 1.65 g, 4.30 mmol) in THF (8.25 mL), 2.0 N aq. HCl (8.25 mL, 4.12 mmol) was added and the resulting solution stirred at RT for 3h. The mixture was diluted with water and extracted with EtOAc. The organic extract was discarded. The aqeous layer was basified with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude title compound (0.74 g) which was used for the next step without purification.
LC-MS: Rt = 0.11 min; MS m/z = 220.2 $[MH]^+$ (Method 16).

Step 6: Ethyl 2-((tert-butoxycarbonyl)amino)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)acetate

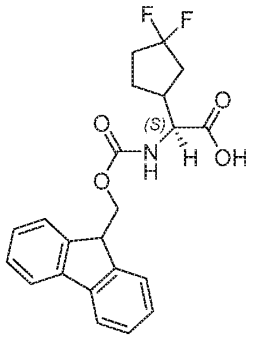
To a solution of ethyl 2-amino-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)acetate (Step 5; 0.74 g, 3.37 mmol) in DCM (10 mL), Boc_2O (1.06 g, 4.86 mmol) and Et_3N (2.36 mL, 16.88 mmol) were added and the resulting mixture stirred at RT for 16h. The solution was diluted with DCM and washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford the crude product (0.95 g, 88%) which was used for the next step without purification.
LC-MS: Rt = 1.76 min; MS m/z = 264.3 $[MH]^+$ (Method 16).

Step 7: 2-((tert-butoxycarbonyl)amino)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)acetic acid

To a solution of ethyl 2-((tert-butoxycarbonyl)amino)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0] hexan-3-yl)acetate (Step6; 0.95 g, 2.98 mmol) in THF (10 mL) and EtOH (10 mL), a solution of LiOH monohydrate (0.62 g, 14.88) in H_2O (10 mL) was added, and the resulting solution stirred at RT for 16h. All volatiles were evaporated under reduced pressure, and the residue treated with 1.0 N aq. HCl at 0°. The resulting mixture was extracted with MeOH/DCM 1:9, the organic extract was washed with water and brine, and dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude title compound (0.75 g) which was used for the next step without further purification.

Intermediate 2-8

(2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3,3-difluorocyclopentyl)acetic acid



Step 1: Tert-butyl (2S)-2-((diphenylmethylene)amino)-2-(3-oxocyclopentyl)acetate

Tetrakis(acetonitrile)copper(I) hexafluorophosphate (25.2 mg, 0.068 mmol) and (S)-1-(diphenylphosphino)-2-[(S)-4-isopropyloxazolin-2-yl]ferrocene (32.6 mg, 0.068 mmol) were added to a dried, argon flushed reaction vessel. THF (8 mL) was then added and the mixture was stirred for 30 minutes at rt. The resulting solution was then cooled to -78 °C and a solution of N-(N,N-diphenylmethyleneglycine-tert.butylester (2000 mg, 6.77 mmol) and 2-cyclopenten-1one (0.624 mL, 7.45 mmol) in THF (10 mL) was added. After 25 min, a solution of DBU (10.21 µl, 0.068 mmol) in THF (2 mL) was added. The yellow solution was stirred for 100h while warming up to RT. The reaction mixture was dissolved in of EtOAc (70 mL) and extracted with water, and brine. The aqueous layers were re-extracted with EtOAc. The combined organic layers were evaporated and the residue was purified by column chromatography on silica (column: RediSep 40 g; eluent:0 – 20 % EtOAc in heptane) to yield the title compound (707mg, 24 %) as a yellow solid.

LC-MS: Rt = 1.30 min; MS m/z = 378.3 $[M-H]^+$ (Method 3).

Step 2: Tert-butyl (2S)-2-(3,3-difluorocyclopentyl)-2-((diphenylmethylene)amino)acetate

The title compound was prepared from tert-butyl (2S)-2-((diphenylmethylene)amino)-2-(3-oxocyclopentyl)acetate (Step 1; 700 mg, 1.854 mmol) by a procedure similar to that used for Intermediate 2-5, step 5, to to yield the title compound as a yellow oil (370 mg, 42 %).
LC-MS: Rt = 1.60 min; MS m/z = 400.2 $[MH]^+$ (Method 3).

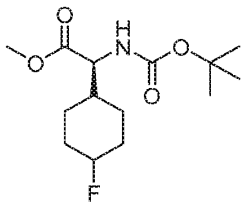
Step 3: Tert-butyl (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3,3-difluorocyclopentyl) acetate

To a solution of tert-butyl (2S)-2-(3,3-difluorocyclopentyl)-2-((diphenylmethylene)amino)acetate (Step 2; 368 mg, 0.921 mmol) in THF (9 mL) was added 15% citric acid in H_2O (5.36 mL, 4.61 mmol). After stirring the reaction mixture at 45°C for 20h, $NaHCO_3$ (619 mg, 7.37 mmol) and Fmoc-Cl (481 mg, 1.842 mmol) were added and the reaction mixture was stirred at RT for 5h. The mixture was diluted with EtOAc and extracted with sat aq.$NaHCO_3$ solution, followed by brine. The aqueous layers were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by column chromatography RP-18 (column: RediSep 86 g silicagel RP-18; eluent: water / acetonitrile 95:5 to 0:100) to yield the title compound 390mg, 86 %) as a yellow solid.
(LC-MS: Rt = 1.47 min; MS m/z = 402.3 $[M-H]^+$ (Method 3).

Step 4: (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3,3-difluorocyclopentyl)acetic acid

To a solution of tert-butyl (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3,3-difluorocyclopentyl)acetate (Step 3; 380 mg, 0.831 mmol) in DCM (1 mL) was added TFA (128 µl, 1.661 mmol). After stirring at RT for 3h the volatiles were evaporated and the residue was treated with again with TFA (2 mL) at RT for 1h. The volatikes were evaporated and the residue was dried in vacuoto to yield the title compound (361mg, 104 %) as a green sticky oil.
LC-MS: Rt = 1.17 min; MS m/z = 402.3 $[M-H]^+$ (Method 3).

Intermediate 2-9
Methyl (2S)-2-((tert-butoxycarbonyl)amino)-2-(4-fluorocyclohexyl)acetate, Methyl (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetate

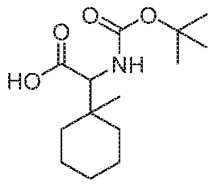


To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-2-((R)-4-fluorocyclohex-3-en-1-yl)acetate (Intermediate 2-5,step 5-P2; 1.0g, 3.48 mmol) in EtOH (40 mL), was added a spatula of activated carbon and 3 spatulas of silica gel. The mixture was stirred for 10min, filtered, washed with EtOH and evaporated. The residue was dissolved in EtOH (60 mL), the solution was purged with Ar and Pd/C (0.370 g, 0.348 mmol) was added followed by purging the mixture with hydrogen. The reaction mixture was stirred under H_2 atmosphere for 50 min followed by filtration and evaporation to yield the title compound (855 mg, 85%) which was used in the next steps without further purification.

LC-MS: Rt = 1.02 min; MS m/z = 290.2 $[M+H]^+$ (Method 3).

Intermediate 2-10

2-((tert-butoxycarbonyl)amino)-2-(1-methylcyclohexyl)acetic acid

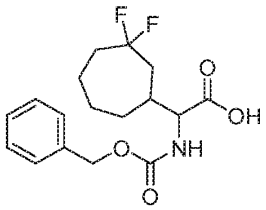


To a suspension of 2-amino-2-(1-methylcyclohexyl)acetic acid hydrochloride (500 mg, 2.407 mmol) in THF (12 mL) was added BOC_2O (0.615 mL, 2.65 mmol) followed by Et3N (0.434 mL, 3.13 mmol) and a spatula tip of DMAP. After stirring at RT overnight the reaction mixture was partitioned between aq. $NaHCO_3$ and EtOAc. The organic layer was discarted, the aqueous layer was acidified with citric acid (5%) and extracted with twice with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to yield the title compound (61 mg, 9%) as an off-white foam.

LC-MS: Rt = 1.06 min; MS m/z = 270.1 $[M-H]^+$ (Method 2).

Intermediate 2-11

2-(((benzyloxy)carbonyl)amino)-2-(3,3-difluorocycloheptyl)acetic acid



Step 1: Tert-butyl 2-((diphenylmethylene)amino)-2-(3-oxocycloheptyl)acetate

To a solution of cyclohept-2-en-1-one (2.081 mL, 14.93 mmol) and diphenylmethylene-glycine tert-butyl ester (3 g, 9.95 mmol) in THF (40 mL) was added DBU (0.450 mL, 2.99 mmol). After stirring at 60°C for 12h, the mixture was cooled to -78°C and 1M KHMDS in THF (9.65 mL, 9.65 mmol) was added. After stirring at -78°C for 4h, the reaction was quenched at -78°C with sat. aq. NH_4Cl and warmed to RT. The mixture was extracted three times with EtOAc, the combined organic layers were dried ($MgSO_4$) and evaporated.The residue was purified by column chromatography (columns: RediSep 120 g and RediSep 80g; eluents: 10 – 100% DCM in cyclohexane, then 10 – 100 % EtOAc in cyclohexane) to yield the title compound as a yellow oil (2.18g, 51 %).
LC-MS: Rt = 1.41 min; MS m/z = 406.4 $[MH]^+$ (Method 1).

Step 2: Tert-butyl 2-(3,3-difluorocycloheptyl)-2-((diphenylmethylene)amino)acetate

tert-Butyl 2-((diphenylmethylene)amino)-2-(3-oxocycloheptyl)acetate (Step 1; 901 mg, 2.111 mmol) was was treated with neat DAST (5 ml, 37.8 mmol) at 60°C for 2h.The mixture was added dropwise to a mixture of ice and solid $NaHCO_3$ and was extracted twice with DCM. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 120 g; eluent: 0 to 100 % EtOAc in cyclohexane to yield the title compound as a pale yellow oil (543 mg, 51 %).
LC-MS: Rt = 1.52 min; MS m/z = 428.4 $[MH]^+$ (Method 1).

Step 3: Tert-butyl 2-(((benzyloxy)carbonyl)amino)-2-(3,3-difluorocycloheptyl)acetate

To a solution of tert-butyl 2-(3,3-difluorocycloheptyl)-2-((diphenylmethylene)amino)acetate (Step 2; 543 mg, 1.143 mmol) in THF (15 mL) was added 15 % aq. citric acid (6.65 mL, 5.72 mmol). After stirring at 40°C for 2h, the mixture was cooled to RT and $NaHCO_3$ (776 mg, 9.14 mmol) followed by benzyl chloroformate (0.326 mL, 2.286 mmol) were added. After stirring at RT for 12h the mixture was diluted with EtOAc and washed with sat.NaHCO3 and brine. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (column: RediSep

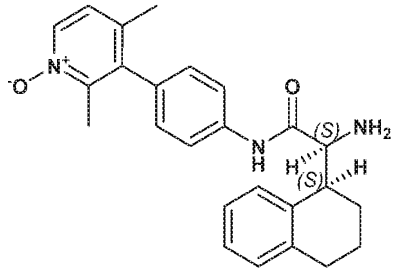
120 g; eluent: 3 to 15% TBME in cyclohexane) to yield the title compound (397mg, 87 %) as a colourless oil.
LC-MS: Rt = 1.34 min; MS m/z = 398 $[MH]^+$ (Method 1).

Step 4: 2-(((benzyloxy)carbonyl)amino)-2-(3,3-difluorocycloheptyl)acetic acid

To a solution of tert-butyl 2-(((benzyloxy)carbonyl)amino)-2-(3,3-difluorocycloheptyl) (Step 3; 490 mg, 1.233 mmol) in DCM (7 mL) was added TFA (6 mL, 26.0 mmol). After stirring at RT for 2h the volatiles were evaporated and the residue was dried in vacuo to yield the title compound (524mg, 100%) which was used in the next steps without further purification.
LC-MS: Rt = 0.97 min; MS m/z = 342.3 $[MH]^+$ (Method 1).

Synthesis of Intermediates 3-1 to 3-60

Intermediate 3-1:
3-(4-((S)-2-amino-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



Step 1: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

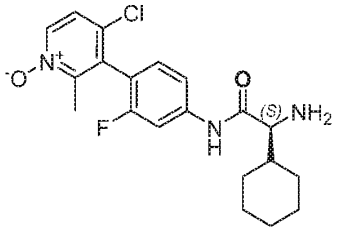
To a solution of 3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 1-1; 1.26 g, 5.89 mmol) in DMF (30 mL) were sequentially added (S)-2-((tert-butoxycarbonyl)amino)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid (Intermediate 2-1, compound of peak 3; 1.50 g, 4.91 mmol), HATU (2.24 g, 5.89 mmol) and Et_3N (2.04 mL, 14.74 mmol). The mixture was stirred at RT for 18h, then diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water, and brine. The organic phase was dried (Na_2SO_4) and all volatiles were evaporated under reduced pressure. The residue was

purified by column chromatography on silica (eluent: 0% to 25% TBME in MeOH) to yield the title compound (1.97 g, 80%) as a slightly yellow solid.
LC-MS: Rt = 1.08 min; MS m/z = 502.3 $[MH]^+$ (Method 12).

Step 2: 3-(4-((S)-2-amino-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

To a solution of 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (1.97 g, 3.93 mmol) in dioxane (40 mL), was added dropwise 4M HCl in dioxane (40 mL) and the solution stirred for 18h at RT. All volatiles were removed under reduced pressure. The residue was diluted with 1M aq. Na_2CO_3 and extracted three times with DCM/isopropanol 4:1. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica (0% to 10% TBME in MeOH) to yield the title compound (1.47 g, 91%) as a white foam.
LC-MS: Rt = 0.62 min; MS m/z = 402.2 $[MH]^+$ (Method 12).

Intermediate 3-2:
3-(4-((S)-2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide



Step 1: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

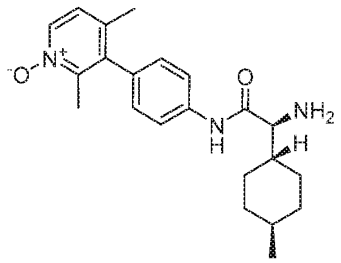
To a solution of (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (3.56 g, 6.79 mmol), 3-(4-amino-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 1-4; 1.75 g, 6.79 mmol) and DIPEA (4.43 g, 33.9 mmol) in DMF (50 mL) was added HATU (5.74 g, 14.93 mmol) and the mixture was stirred for 18h at RT. A second portion of (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (0.5 g, 0.95 mmol) and HATU (0.6 g, 1.56 mmol) was added, and stirring continued for 48h. The reaction mixture was diluted with EtOAc and washed with with aq. citric acid solution, sat. aq. Na_2CO_3 and brine. The organic phase was dried (Na_2SO_4) and evaporated. The

residue was purified by column chromatography on silica (column: RediSep 220g; eluent: 70 to 100 % EtOAc in heptane/EtOAc, then 10% MeOH in EtOAc) to yield the title compound (1.85 g, 49.9%) as a brown foam.
LC-MS: Rt = 1.14 min; MS m/z = 492.3 $[MH]^+$ (Method 2).

Step 2: 3-(4-((S)-2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide (Step 1; 1.80 g, 3.11 mmol) in DCM (10 mL), was added dropwise TFA (2.42 mL, 31.1 mmol). After stirring at RT for 14h, the reaction mixture was diluted with EtOAc and washed with 10% aq. Na_2CO_3. The Na_2CO_3 layer was re-extracted with EtOAc, and the combined layers were concentrated under reduced pressure, resulting in the crude title compound (1.11 g, 80% yield, 88% pure by LC-MS) as a yellow resin that was used for the next step without further purification.
LC-MS: Rt = 0.71 min and 0.72 min, 1.1 mixture of atropisomers; MS m/z = 492.3 $[MH]^+$ (Method 2).

Intermediate 3-3:
3-(4-((S)-2-amino-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



Step 1: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

A solution of (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetic acid (Intermediate 2-2; 160 mg, 0.590 mmol), 2,4,6-collidine (0.314 ml, 2.359 mmol) and HATU (247 mg, 0.649 mmol) in DMF (2 mL) was stirred at RT for 10 min. To the resulting colourless solution,

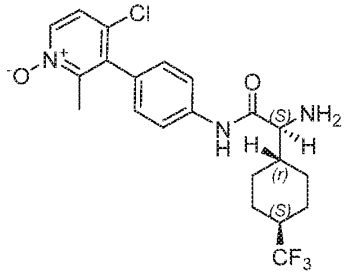
3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 1-1; 126 mg, 0.590 mmol) was added at RT in one portion, and this mixture stirred at RT for 72 h. The resulting solution was diluted with sat. aq. $NaHCO_3$ and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and all volatiles evaporated under reduced pressure. Purification by preparative RP HPLC (H_2O/ACN+0.1%TFA) and lyophilization afforded the title compound (156 mg, 55.4%) as a white solid.
LC-MS: Rt = 1.18 min; MS m/z = 468.3 $[MH]^+$ (Method 1).

Step 2: 3-(4-((S)-2-amino-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetamido)-phenyl)-2,4-dimethylpyridine 1-oxide (Step 1; 140 mg, 0.299 mmol) was treated with 4M HCl in dioxane (2 mL). After stirring at RT for 1h the mixture was concentrated under reduced pressure and dried in HV to yield the title compound (127 mg, 100%) as a white solid, which was used for the next step without further purification.
LC-MS: Rt = 0.79 min; MS m/z = 468.2 $[MH]^+$ (Method 1).

Intermediate 3-4:

3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



Step 1: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido) phenyl)-4-chloro-2-methylpyridine 1-oxide

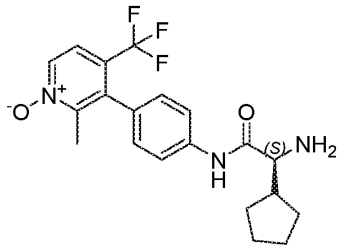
To a solution of 3-(4-aminophenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 1-2; 600 mg, 2.43 mmol) in acetonitrile/DMF 1:1 (5 mL) were sequentially added (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)-cyclohexyl)acetic acid (Intermediate 2-3; 1.04 g, 3.04 mmol), Et_3N (745 mg, 7.29 mmol) and HATU (1.31 g, 3.40 mmol). The resulting mixture

was stirred at RT for 18h, then diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica (column: RediSep 40g; eluent: 70 – 100 % (EtOAc+5%MeOH) in heptane) to yield the title compound (1.30 g, 97%).
LC-MS: Rt = 1.39 min; MS m/z = 542.3 $[MH]^+$ (Method 5).

Step 2: 3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)-acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide (1.25 g, 1.96 mmol)) in dioxane (10 mL) was slowly added 4M HCl in dioxane (7.35 mL, 29.4 mmol). After stirring at RT for 14h the mixture was diluted with 10% aq. Na_2CO_3 and extracted twice with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from TBME to yield the title compound (630 mg, 72%) as yellow crystals.
LC-MS: Rt = 0.67 min; MS m/z = 442.2 $[MH]^+$ (Method 5).

Intermediate 3-5:
(S)-3-(4-(2-amino-2-cyclopentylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



Step 1: (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-cyclopentylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

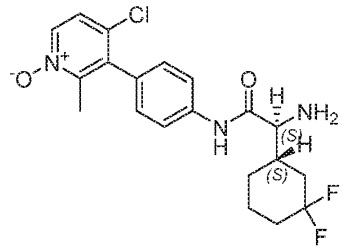
To a solution of 3-(4-aminophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 1-3; 6.2 g, 23.11 mmol) in DMF (70 mL), were sequentially added Boc-L-cyclopentylglycine (8.15 g, 33.5 mmol), 2,4,6-collidine (10.16 mL, 76 mmol) and HATU (17.58 g, 46.2 mmol), and the solution stirred at RT for 18h. The mixture was concentrated in vacuo, and the residue dissolved in EtOAc. Sat. aq. Na_2CO_3 solution was added and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried and concentrated under reduced pressure.

Purification of this crude material by column chromatography on silica afforded 12.13 g (98%) of the title compound as a foam.
LC-MS: Rt = 1.19 min; MS m/z 494.4 $[MH]^+$ = (Method 5).

Step 2: (S)-3-(4-(2-amino-2-cyclopentylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-cyclopentylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Step 1; 12.13 g, 22.61 mmol) in dioxane (40 mL), was slowly added 4M HCl in dioxane (67.8 mL, 271 mmol). After stirring for 1.5 h at RT the mixture was concentrated and dried in vacuo to afford the title compound (11.19 g, 100%) as hydrochloride salt, which was used for the next step without further purification.
LC-MS: Rt = 0.52 min; MS m/z = 394.3 $[MH]^+$ (Method 5).

Intermediate 3-6:
3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



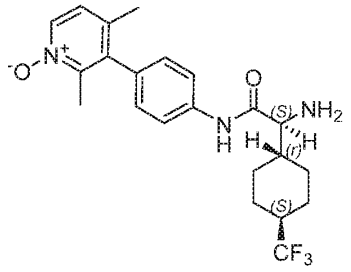
Step 1: 3-(4-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl) acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of 3-(4-aminophenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 1-2; 750 mg, 3.20 mmol) in acetonitrile (40 mL) were added (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)-acetic acid (Intermediate 2-4; 1328 mg, 3.20 mmol) and DIPEA (1.675 mL, 9.59 mmol) followed by dropwise addition of T_3P (50% in EtOAc, 3.80 mL, 6.39 mmol). After stirring at RT for 18h the mixture was diluted with EtOAc, and sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica to yield the title compound (1.44 g, 68.4%) as a colorless solid.
LC-MS: Rt = 1.31 min; MS m/z = 632.3 $[MH]^+$ (Method 5).

Step 2: 3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

To a solution of 3-(4-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide (Step 1; 1.44 g, 2.278 mmol) in DMF (30 mL) was added piperidine (0.564 mL, 5.70 mmol), and the solution stirred at RT for 2h. The mixture was concentrated in vacuo, and the residue purified by column chromatography on silica, affording the title compound (850 mg 86%).
LC-MS: Rt = 0.46 min; MS m/z = 410.4 $[MH]^+$ (Method 5).

Intermediate 3-7:
3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



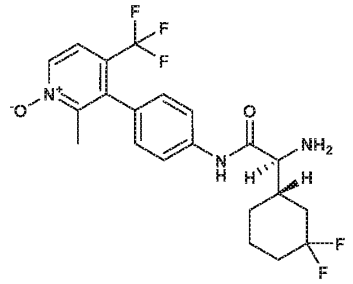
Step 1: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl) cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

To a stirred solution of 3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 1-1; 220 mg, 0.924 mmol) in acetonitrile/DMF 1:1 (3 mL), were added (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)-cyclohexyl)acetic acid (411 mg, 1.20 mmol), Et_3N (0.45 mL, 3.23 mmol) and HATU (497 mg, 1.29 mmol) at RT. After stirring RT for 18h the mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic layer washed with water and brine, dried (Na_2SO_4) and evaporated. Crystallization of the residue from TBME/acetonitrile 1:5 afforded the title compound (190 mg, 33.5%) as colorless crystals.
LC-MS: Rt = 1.23 min; MS m/z = 522.2 $[MH]^+$ (Method 5).

Step 2: 3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

To a solution of 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)-acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Step 1; 950 mg, 1.80 mmol) in DCM (10 mL) was added dropwise TFA (1.68 mL). The resulting solution was stirred at RT for 14 h and was then charged on a cation exchange column (Agilent BondElut SCX). The resin was extensively washed with MeOH, then a 2M solution of NH_3 in MeOH was passed through the column to release the product. Evaporation afforded the title compound (750 mg, 90% pure by LC-MS, 89% yield) as a yellow resin that was used for the next step without further purification.
LC-MS: Rt = 0.58 min; MS m/z = 421.2 $[MH]^+$ (Method 5).

Intermediate 3-8:
3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



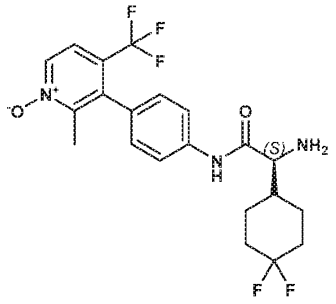
Step 1: 3-(4-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of 3-(4-aminophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 1-3; 835 mg, 3.1 mmol) in acetonitrile (35 mL) were sequentially added (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetic acid (Intermediate 2-4; 1.25 g, 3.01 mmol), DIEA (1.20 g, 9.30 mmol) and T_3P (50 wt. % in EtOAc, 3.69 mL, 6.20 mmol) at RT.The resulting solution was stirred at RT for 18h. A second portion of DIEA (1.7 mL) and T_3P (2 mL) was added and stirring was continued for another 24h. The resulting mixture was diluted with EtOAc and washed with sat. aq. Na_2CO_3, water and brine, dried (Na_2SO_4), and evaporated to yield the title compound (3.12 g) as a yellow foam, which was used for the next step without further purification.
LC-MS: Rt = 6.64 min; MS m/z = 666.3 $[MH]^+$ (Method 4).

Step 2: 3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a cooled (0°) solution of 3-(4-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Step 1; 2.06 g, 3.1 mmol) in DMF (15 mL) was added dropwise piperidine (0.78 mL, 7.75 mmol) and stirring was continued at 0° for 2h. All volatiles were removed under reduced pressure to afford a brown solid which was purified by chromatography on silica (0% to 100% TBME in MeOH) to yield the title compound (1.3 g, 90%) as a yellow foam.
LC-MS: Rt = 2.60 min; MS m/z = 444.3 $[MH]^+$ (Method 4).

Intermediate 3-9:
(S)-3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



Step 1: (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a solution of 3-(4-aminophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 1-3; 275 mg, 1.023 mmol) in DMF (6 mL) were sequentially added (S)-2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)-acetic acid (Intermediate 2-5; 300 mg, 1.023 mmol), HATU (467 mg, 1.227 mmol) and Et_3N (0.71 mL, 5.11 mmol) at RT. After stirring at RT for 18h the mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water, and brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica to yield the title compound (337 mg, 57%) as a yellow foam.
LC-MS: Rt = 5.59 min; MS m/z = 544.2 $[MH]^+$ (Method 4).

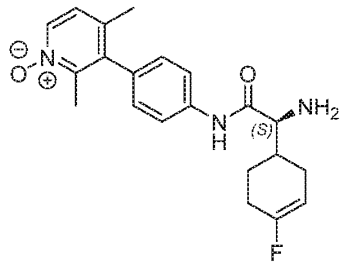
Step 2: (S)-3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide

To a stirred solution of (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)-acetamido)-phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Step 1; 300 mg, 0.552 mmol) in dioxane (5.5 mL) was added dropwise 4M HCl in dioxane (5.5 mL, 22.08 mmol) at RT. Stirring was continued at RT for 18h. The resulting solution was then evaporated to dryness under reduced pressure, the residue diluted with 1M aq. Na_2CO_3 (30 mL), and extracted with DCM/IPA 4:1 (3x30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica (column: RediSep 24g; eluent: 5 to 100% EtOAc in Heptane, then 0 to 2% MeOH in EtOAc) to yield the title compound (209 mg, 81%) as a yellow foam.

LC-MS: Rt = 2.51 min; MS m/z = 444.2 $[MH]^+$ (Method 4).

Intermediate 3-10:

3-(4-((2S)-2-amino-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



Step 1: 3-(4-((2S)-2-((tert-butoxycarbonyl)amino)-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

To a solution of (2S)-2-((tert-butoxycarbonyl)amino)-2-(4-fluorocyclohex-3-en-1-yl)acetic acid (Intermediate 2-6; 200 mg, 0.732 mmol), 3-(4-aminophenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 1-1; 172 mg, 0.805 mmol) and 2,4,6-collidine (0.292 mL, 2.195 mmol) in DMF (4 mL), was added HATU (306 mg, 0.805 mmol). After stirring at RT for 16h the mixture was concentrated under reduced pressure. The residue was dissolved in ACN/MeOH 9:1 (6 mL) and heated to reflux for 2 min. Cooling to RT and storage for 15 min led to an off-white precipitate, which was filtered, washed with acetonitrile (3x2 mL) and dried to afford the title compound (291 mg, 83%) as an off-white solid.

LC-MS: Rt = 1.09 min; MS m/z = $[MH]^+$ 470.3 (Method 5).

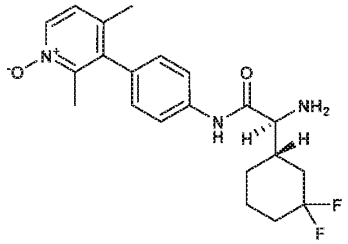
Step 2: 3-(4-((2S)-2-amino-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

To a suspension of 3-(4-((2S)-2-((tert-butoxycarbonyl)amino)-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Step 1; 290.8 mg, 0.619 mmol) in dioxane (3 mL) was added 4M HCl in dioxane (3.10 mL, 12.39 mmol). After stirring at RT for 3h the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (water/ACN +0.1% TFA) to yield the title compound (132 mg, 57.7%) as a colorless solid.
LC-MS: Rt = 0.50 min; MS m/z = 370.3 $[MH]^+$ (Method 5).
The diastereomers were separated by chiral HPLC (column: Chiralpak IG 206x30mm 5µm, eluent: DCM/MeOH/n-Heptane 30:25:30 +0.1%DEA):

Peak 1: Rt = 5.60 min: 72.9 mg white solid, ee = 99.5 %.
Peak 2: Rt = 8.40 min: 57.6 mg white solid, ee = 99.5 %.

Intermediate 3-11

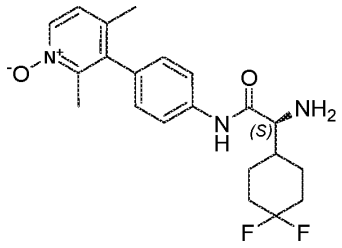
3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-1 and intermediate 2-4, to yield the title compound as an off-white foam (515 mg, 36 %).
LC-MS: Rt = 1.93 min; MS m/z = 390.4 $[MH]^+$ (Method 4).

Intermediate 3-12

3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-

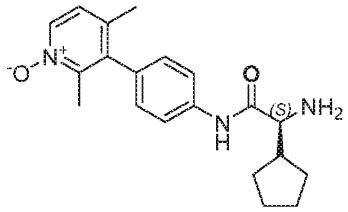


The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and intermediate 2-5, to yield the title compound (175 mg, 39 %).

LC-MS: Rt = 0.54 min; MS m/z = 390.2 $[MH]^+$ (Method 1).

Intermediate 3-13

(S)-3-(4-(2-amino-2-cyclopentylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide

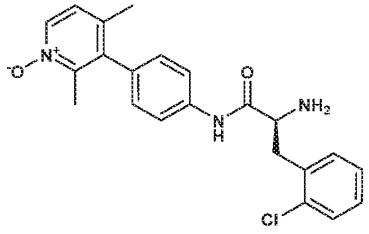


The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopentylacetic acid, to yield the title compound (2.9 g, 61 %) as off-white crystals.

LC-MS: Rt = 0.40 min; MS m/z = 340.2 $[MH]^+$ (Method 11).

Intermediate 3-14

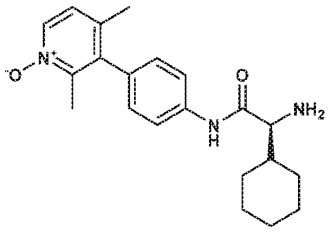
(S)-3-(4-(2-amino-3-(2-chlorophenyl)propanamido)phenyl)-2,4-dimethylpyridine 1-



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and commercial (S)-2-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)propanoic acid, to yield the title compound (661 mg, 69 %) as a white foam.
LC-MS: Rt = 0.41 min; MS m/z = 396.4 $[MH]^+$ (Method 12).

Intermediate 3-15

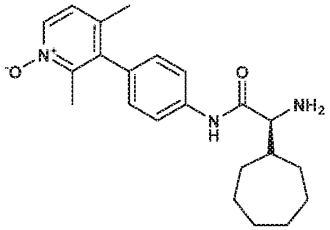
(S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (1008 mg, 57 %) as a white foam.
LC-MS: Rt = 2.05 min; MS m/z = 354.3 $[MH]^+$ (Method 4).

Intermediate 3-16

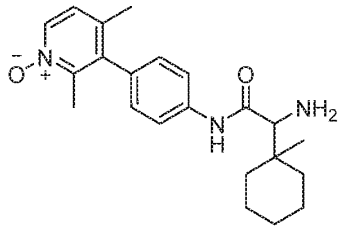
(S)-3-(4-(2-amino-2-cycloheptylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cycloheptylacetic acid, to yield the title compound (5.98 g, 77 %) as an off-white foam.
LC-MS: Rt = 2.40 min; MS m/z = 368.3 $[MH]^+$ (Method 4).

Intermediate 3-17

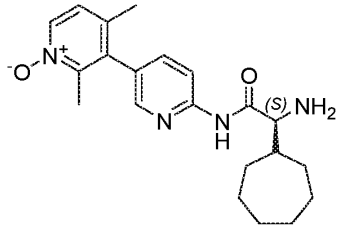
3-(4-(2-amino-2-(1-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and intermediate 2-10, to yield the title compound (74 mg, 75 %) as a white solid.
LC-MS: Rt = 0.61 min; MS m/z = 368.3 $[MH]^+$ (Method 11).

Intermediate 3-18

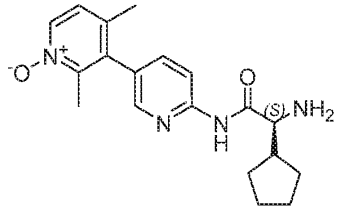
(S)-6'-(2-amino-2-cycloheptylacetamido)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-8 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cycloheptylacetic acid, to yield the title compound (400 mg, 43 %) as a yellow resin.
LC-MS: Rt = 0.45 min; MS m/z = 392.2 $[MH]^+$ (Method 3).

Intermediate 3-19

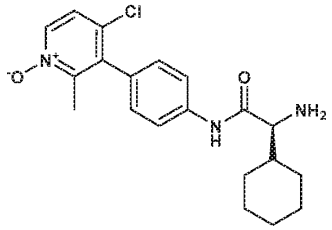
(S)-6'-(2-amino-2-cyclopentylacetamido)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-8 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopentylacetic acid, to yield the title compound (490 mg, 46 %) as off-white crystals.
LC-MS: Rt = 0.33 min; MS m/z = 341.2 $[MH]^+$ (Method 5).

Intermediate 3-20

(S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

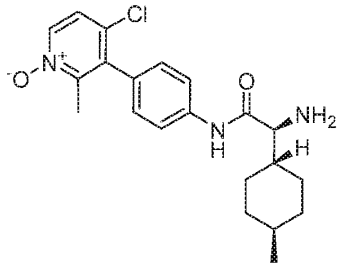


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (1.31 g, 62 %) as a white foam.

LC-MS: Rt = 2.31 min; MS m/z = 374.2 $[MH]^+$ (Method 4).

Intermediate 3-21

3-(4-((S)-2-amino-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

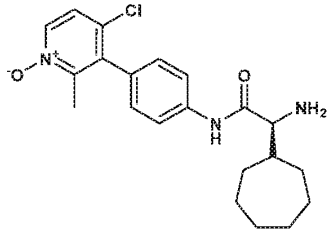


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and intermediate 2-2, to yield the title compound (122 mg, 50 %) as a white solid.

LC-MS: Rt = 0.79 min; MS m/z = 401.2 $[MH]^+$ (Method 1).

Intermediate 3-22

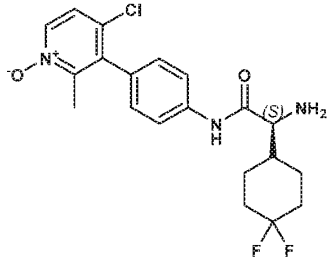
(S)-3-(4-(2-amino-2-cycloheptylacetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cycloheptylacetic acid, to yield the title compound (347 mg, 44 %) as a white solid.
LC-MS: Rt = 2.71 min; MS m/z = 388.4 $[MH]^+$ (Method 11).

Intermediate 3-23

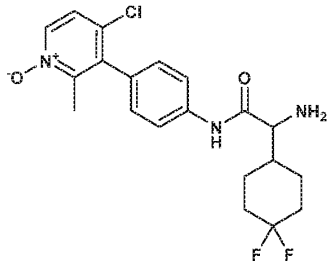
(S)-3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and intermediate 2-5, to yield the title compound (84 mg, 31 %) as a yellow foam.
LC-MS: Rt = 2.17 min; MS m/z = 410.1 $[MH]^+$ (Method 4).

Intermediate 3-24

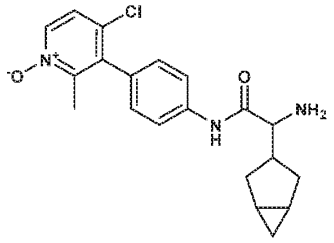
(S)-3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and commercial Boc-(4,4-difluorocyclohexyl)-acetic acid, to yield the title compound (660 mg, 80 %) as a yellow foam.
LC-MS: Rt = 2.17 min; MS m/z = 410.1 $[MH]^+$ (Method 4).

Intermediate 3-25

3-(4-(2-amino-2-(bicyclo[3.1.0]hexan-3-yl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide

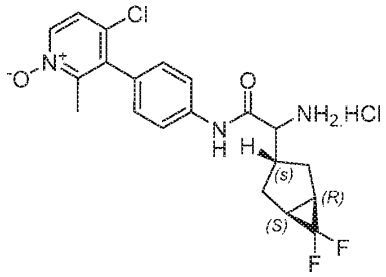


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and commercial 2-(bicyclo[3.1.0]hexan-3-yl)-2-((tert-butoxycarbonyl)amino)acetic acid, to yield the title compound (787 mg, 49 %) as a yellow foam.

LC-MS: Rt = 2.17 min; MS m/z = 372.2 $[MH]^+$ (Method 4).

Intermediate 3-26

3-(4-(2-amino-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide hydrochloride

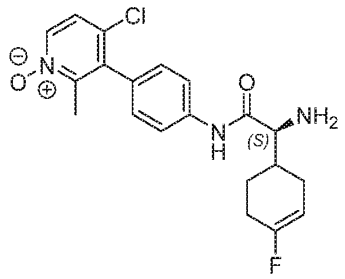


The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-2 and intermediate 2-7, to yield the title compound (0.20 g, 68 %).

LC-MS: MS m/z = 516.3 $[MH]^+$ (Method 16).

Intermediate 3-27

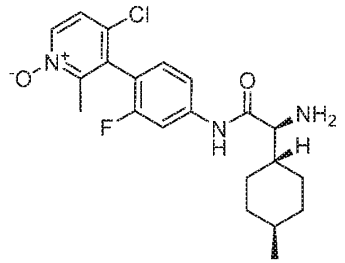
3-(4-((2S)-2-amino-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-2 and intermediate 2-6, to yield the title compound (287 mg, 72 %) as an off-white solid.
LC-MS: Rt = 0.47 min; MS m/z = 390.1 $[MH]^+$ (Method 5).

Intermediate 3-28

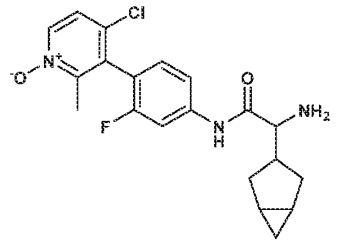
3-(4-((S)-2-amino-2-((1r,4S)-4-methylcyclohexyl)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-2, using intermediate 1-4 and intermediate 2-2, to yield the title compound (57 mg, 14 %) as a white solid.
LC-MS: Rt = 0.80 min; MS m/z = 406.2 $[MH]^+$ (Method 1).

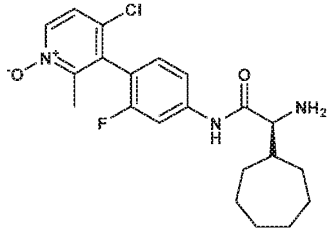
Intermediate 3-29

3-(4-(2-amino-2-(bicyclo[3.1.0]hexan-3-yl)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide



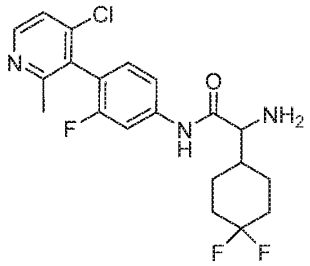
The title compound was prepared by a procedure similar to Intermediate 3-2, using intermediate 1-4 and commercial 2-(bicyclo[3.1.0]hexan-3-yl)-2-((tert-butoxycarbonyl)amino)acetic acid, to yield the title compound (210 mg, 50.4 %) as a white solid.
LC-MS: Rt = 2.33 and 2.44 min, 1:1 mixture of atropisomers; MS m/z = 390.1 $[MH]^+$ (Method 4).

Intermediate 3-30
3-(4-((S)-2-amino-2-cycloheptylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-2, using intermediate 1-4 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cycloheptylacetic acid, to yield the title compound (64 mg, 35 %) as an orange foam.
LC-MS: Rt = 2.88 and 3.01 min, 1:1 mixture of atropisomers; MS m/z = 406.1 $[MH]^+$ (Method 4).

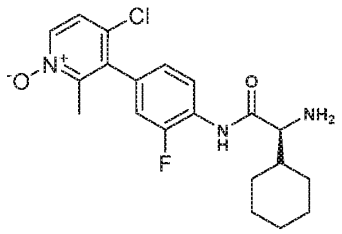
Intermediate 3-31
2-amino-N-(4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)-2-(4,4-difluorocyclohexyl)acetamide



The title compound was prepared by a procedure similar to Intermediate 3-2, using intermediate 1-11 and commercial tert-butoxycarbonylamino-(4,4-difluoro-cyclohexyl)-acetic acid, to yield the title compound as a colorless solid.
LC-MS: Rt = 0.81 min; MS m/z = 412 and 414 $[MH]^+$ (Method 2).

Intermediate 3-32

(S)-3-(4-(2-amino-2-cyclohexylacetamido)-3-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

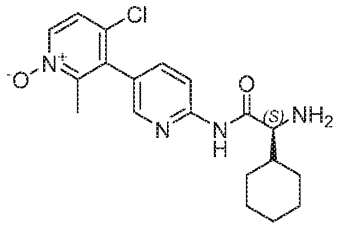


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-7 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (21 mg, 10 %) as a yellow resin.

LC-MS: Rt = 0.60; MS m/z = 392.3 $[MH]^+$ (Method 11).

Intermediate 3-33

(S)-6'-(2-amino-2-cyclohexylacetamido)-4-chloro-2-methyl-[3,3'-bipyridine] 1-oxide

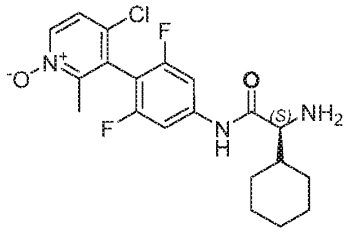


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-9 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (200 mg, 20 %) as a yellow resin.

LC-MS: Rt = 0.68; MS m/z = 375.1 $[MH]^+$ (Method 2).

Intermediate 3-34

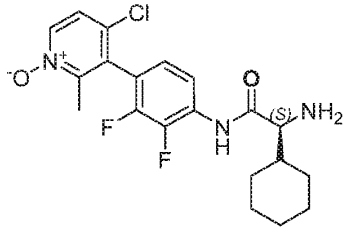
(S)-3-(4-(2-amino-2-cyclohexylacetamido)-2,6-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-11 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (75 mg, 17 %) as a yellow resin.
LC-MS: Rt = 0.74 min; MS m/z = 236.1 $[MH]^+$ (Method 12).

Intermediate 3-35

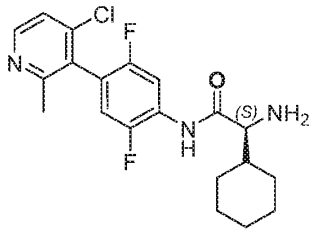
3-(4-((S)-2-amino-2-cyclohexylacetamido)-2,3-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide



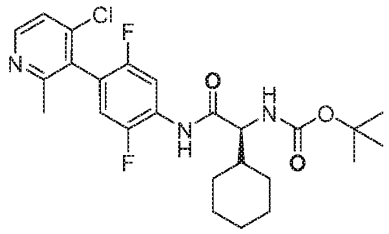
The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-16 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound (190 mg, 39 %) as yellow resin.
LC-MS: Rt = 0.74 and 0.75 min, 1:1 mixture of atropisomers; MS m/z = 410.1 $[MH]^+$ (Method 2).

Intermediate 3-36

3-(4-((S)-2-amino-2-cyclohexylacetamido)-2,5-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide



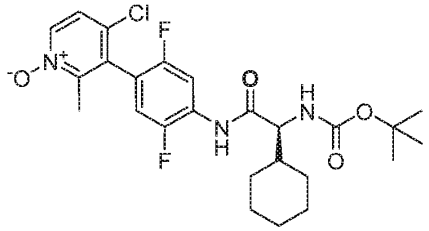
Step 1: tert-butyl ((1S)-2-((4-(4-chloro-2-methylpyridin-3-yl)-2,5-difluorophenyl)amino)-1-cyclohexyl-2-oxoethyl)carbamate



To a cooled (-30°C) solution of 4-(4-chloro-2-methylpyridin-3-yl)-2,5-difluoroaniline (Intermediate 1-17; 170 mg, 0.66 mmol), pyridine (950 mg, 11.9 mmol) and Boc-L-cyclohexylglycine (221 mg, 0.83 mmol) in DCM (0.8 mL) was added $POCl_3$ (169 mg, 1.09 mmol) with the temperature maintained between -20 and -30°C. The mixture was stirred at this temperature for 12 min and was then poured into ice-water. The mixture was extracted with DCM, the organic layer was washed with 0.5N HCl, 10% Na_2CO_3 and with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chroatography on silica (column: RediSep 40g; eluent: 40 to 100 % EtOAc+5%MeOH in heptane) to yield the title compound (160 mg, 46 %) as a brown oil.

LC-MS: Rt = 1.29 min, MS m/z = 494.2 $[MH]^+$ (Method 2).

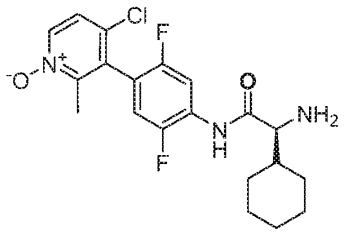
Step 2: 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-2,5-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by treatment of tert-butyl ((1S)-2-((4-(4-chloro-2-methylpyridin-3-yl)-2,5-difluorophenyl)amino)-1-cyclohexyl-2-oxoethyl)carbamate (Step 1; 150 mg, 0.27 mmol) with mCPBA (98 mg, 0.44 mmol) following the proceduere describe for Intermediate 1-1, step 1 to yield the title compound (115 mg, 70%) as a yellow resin.

LC-MS: Rt = 1.18 min, MS m/z = 509.2 $[MH]^+$ (Method 2).

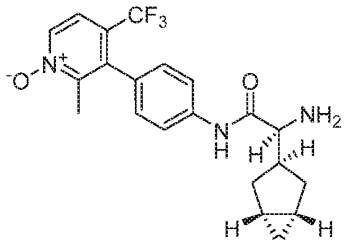
Step 3: 3-(4-((S)-2-amino-2-cyclohexylacetamido)-2,5-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by treatment of 3-(4-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-2,5-difluorophenyl)-4-chloro-2-methylpyridine 1-oxide (Step 2; 110 mg, 0.183 mmol) with TFA (98 mg, 0.44 mmol) following the proceduere describe for Intermediate 3-2, step 2 to yield the title compound (80 mg, 64%) as a yellow solid.
LC-MS: Rt = 0.62 and 0.72 min (1:1 mixture of atropisomers), MS m/z = 410.1 $[MH]^+$ (Method 2).

Intermediate 3-37

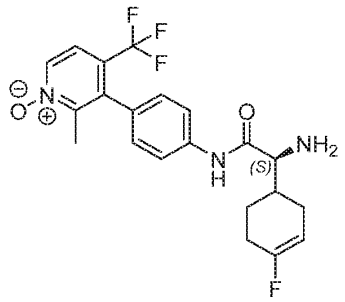
3-(4-((S)-2-amino-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-3 and (S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-((tert-butoxycarbonyl)amino)acetic acid (prepared according to WO2014/65791 A1), to yield the title compound as a brown solid.
TLC (DCM/MeOH = 95:5) Rf = 0.22; MS m/z = 406.3 $[MH]^+$

Intermediate 3-38

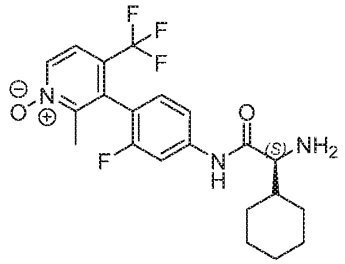
3-(4-((2S)-2-amino-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-5, using intermediate 1-3 and intermediate 2-6, to yield the crude title compound (326 mg, 67 %) as a yellow solid.
LC-MS: Rt = 0.61; MS m/z = 424.3 $[MH]^+$ (Method 4).

Intermediate 3-39

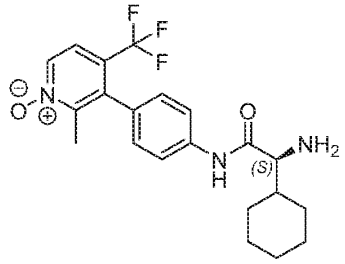
3-(4-((S)-2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-5, using intermediate 1-6 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid.
LC-MS: Rt = 0.79 and 0.81 min, 1:1 mixture of atropisomers; MS m/z = 426.2 $[MH]^+$ (Method 1).

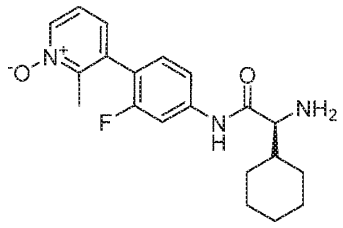
Intermediate 3-40

(S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



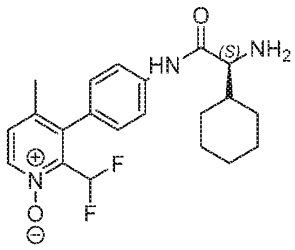
The title compound was prepared by a procedure similar to Intermediate 3-5, using intermediate 1-3 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid as an off-white amorphous solid.
LC-MS: Rt = 0.71; MS m/z 408.4 $[MH]^+$ (Method 4).

Intermediate 3-41
(S)-3-(4-(2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-12 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid as a yellow solid.
LC-MS: Rt = 0.64; MS m/z = 358.3 $[MH]^+$ (Method 2).

Intermediate 3-42
(S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide



Step 1: tert-butyl (S)-(1-cyclohexyl-2-((4-(2-(difluoromethyl)-4-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)carbamate

To a solution of 4-(2-(difluoromethyl)-4-methylpyridin-3-yl)aniline (intermediate 1-10, 0.20 g, 0.85 mmol), (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (0.26 g, 1.02 mmol) and HATU (0.65 g, 1.71 mmol) in DMF (10 mL) was added DIEA (0.44 g, 3.41 mmol) and the mixture stirred at RT for 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The extracts were washed with sat. aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under

reduced pressure afforded the crude product, which was purified by column chromatography on silica to yield the title compound (0.20 g, 44%) as a brown solid.
LC-MS: Rt = 1.86 min; MS m/z = 474.1 $[M+H]^+$ (Method 16).

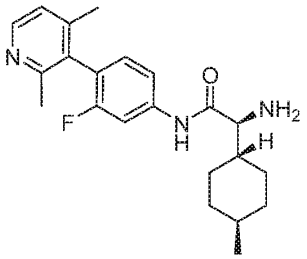
Step 2: (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide

To a solution of tert-butyl (S)-(1-cyclohexyl-2-((4-(2-(difluoromethyl)-4-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)carbamate (Step 1; 0.20 g, 0.42 mmol) in $CHCl_3$ (15 mL), mCPBA (0.22 g, 1.27 mmol) was added and the resulting mixture stirred at RT for 4h. The reaction mixture was poured into aq. sat. $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water and brine, and concentrated under reduced pressure to afford the crude product. Purification by chromatography on silica afforded the title compound (0.17 g, 82%) as a white solid.
LC-MS: Rt = 1.66 min; MS m/z = 490.3 $[MH]^+$ (Method 16).

Step 3: (S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide

To a cooled (0°C) solution of (S)-3-(4-(2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide (Step 2; 0.17 g, 0.35 mmol) in dioxane (2 mL) was added 20% HCl in dioxane (8 mL). The resulting mixture was allowed to reach RT and stirred at this temperature for 4h. The mixture was then poured into ice water and extracted with EtOAc. The extract was washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by repeatedly washing with Et_2O to afford the crude title compound (0.17 g) as a brown solid.
LC-MS: Rt = 0.12 min; MS m/z = 390.5 $[MH]^+$ (Method 16).

Intermediate 3-43
(2S)-2-amino-N-(4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)-2-((1r,4S)-4-methylcyclohexyl)acetamide



Step 1: 4-(2,4-dimethylpyridin-3-yl)-3-fluoroaniline

To a solution of 3-bromo-2,4-dimethylpyridine (500 mg, 2.69 mmol) in dioxane (10 mL) and water (5 mL), 4-amino-2-fluorophenylboronic acid pinacol ester (637 mg, 2.69 mmol), XPhos Pd G2 (106 mg, 0.134 mmol), TBAB (26.0 mg, 0.081 mmol) and K_3PO_4 (1711 mg, 8.06 mmol) was added. The vial was purged with argon for 5 min at RT, then the mixture was stirred at 70° for 2.5h and for 16h at RT. The reaction mixture was poured into EtOAc and washed with sat. aq. Na_2CO_3 and water. The aqueous layers were extracted with EtOAc, the organic phases were combined and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80g; eluent: 10 to 100 % EtOAc in cyclohexane) to yield the title compound (532 mg, 92%) as a yellow oil.
LC-MS: Rt = 0.39 min; MS m/z = 217.1 $[MH]^+$ (Method 2).

Step 2: Tert-butyl ((1S)-2-((4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)amino)-1-((1r,4S)-4-methylcyclohexyl)-2-oxoethyl)carbamate

A solution of (S)-2-((tert-butoxycarbonyl)amino)-2-((1r,4S)-4-methylcyclohexyl)acetic acid (Step 1; 180 mg, 0.663 mmol), 2,4,6-trimethylpyridine (0.353 ml, 2.65 mmol) and HATU (277 mg, 0.730 mmol) in DMF (2 mL) was stirred at RT for 10 min. To the resulting colorless solution, 4-(2,4-dimethylpyridin-3-yl)-3-fluoroaniline (143 mg, 0.663 mmol) was added at RT in one portion, and the mixture stirred at RT for 72h. The mixture was diluted with aq. sat. $NaHCO_3$ and extracted twice with Et_2O. The extracts were washed with brine, dried (Na_2SO_4) and evaporated. Purification by preparative HPLC afforded the title compound (237 mg, 75%) as a white solid.
LC-MS: Rt = 1.19 min; MS m/z = 470.2 $[MH]^+$ (Method 1).

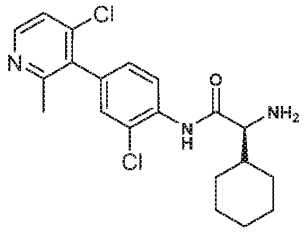
Step 3: (2S)-2-amino-N-(4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)-2-((1r,4S)-4-methylcyclohexyl)acetamide

A solution of tert-butyl ((1S)-2-((4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)amino)-1-((1r,4S)-4-methylcyclohexyl)-2-oxoethyl)carbamate (Step 2; 200 mg, 0.426 mmol) in 4M HCl in dioxane (4 mL) was stirred at RT for 1 h, resulting in a white suspension. Evaporation of all volatiles under reduced pressure afforded the title compound (170 mg, 96%) as a colorless solid that was used for the next steps without further purification.

LC-MS: Rt = 0.79 min; MS m/z = 401.1 $[MH]^+$ (Method 1).

Intermediate 3-44

(S)-2-amino-N-(2-chloro-4-(4-chloro-2-methylpyridin-3-yl)phenyl)-2-cyclohexylacetamide

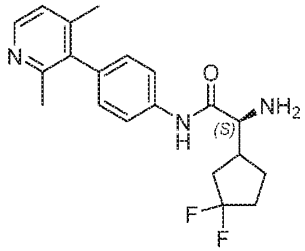


The title compound was prepared by a procedure similar to Intermediate 3-43, using intermediate 1-14 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as a yellow resin.

LC-MS: Rt = 0.79 min; MS m/z = 392.2 $[MH]^+$ (Method 11).

Intermediate 3-45

(2S)-2-amino-2-(3,3-difluorocyclopentyl)-N-(4-(2,4-dimethylpyridin-3-yl)phenyl)acetamide

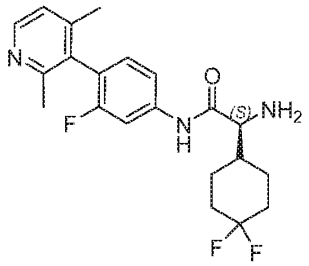


The title compound was prepared by a procedure similar to Intermediate 3-6, using intermediate 1-19 and intermediate 2-8 to yield the title compound as an off-white amorphous solid.

LC-MS: Rt = 0.21 min; MS m/z = 360.3 $[MH]^+$ (Method 11).

Intermediate 3-46

(2S)-2-amino-2-(4,4-difluorocyclohexyl)-N-(4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)acetamide

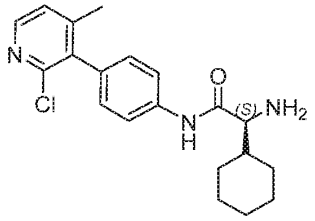


The title compound was prepared by a procedure similar to Intermediate 3-43, using intermediate 1-21, and Intermediate 2-5 to yield the title compound as a yellow foam.

LC-MS: Rt = 0.61 and 0.63 min, 1:1 mixture of atropisomers; MS m/z = 392.3 $[MH]^+$ (Method 2).

Intermediate 3-47

(S)-2-amino-N-(4-(2-chloro-4-methylpyridin-3-yl)phenyl)-2-cyclohexylacetamide

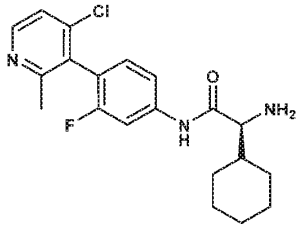


The title compound was prepared by a procedure similar to intermediate 3-43, using intermediate 1-15 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as a yellow resin.

LC-MS: Rt = 0.84 min; MS m/z = 358.3 $[MH]^+$ (Method 2).

Intermediate 3-48

(2S)-2-amino-N-(4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)-2-cyclohexylacetamide

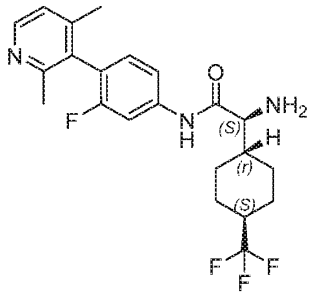


The title compound was prepared by a procedure similar to intermediate 3-43, using intermediate 1-20 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as an off-white foam.

LC-MS: Rt = 3.52 and 3.61 min, 1:1 mixture of atropisomers; MS m/z = 376.3 $[MH]^+$ (Method 4).

Intermediate 3-49

(2S)-2-amino-N-(4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamide

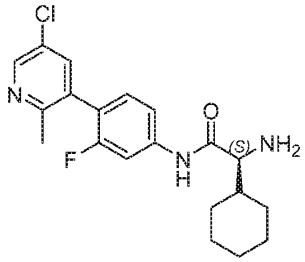


The title compound was prepared by a procedure similar to Intermediate 3-43, using Intermediate 1-21 and intermediate 2-3, to yield the title compound as a colorless solid.

LC-MS: Rt = 0.76 and 0.77 min, 1:1 mixture of atropisomers; MS m/z = 424.2 $[MH]^+$ (Method 2).

Intermediate 3-50

(S)-2-amino-N-(4-(5-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)-2-cyclohexylacetamide

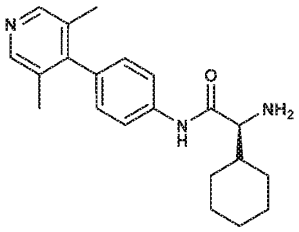


The title compound was prepared by a procedure similar to intermediate 3-43, using 3-bromo-5-chloro-2-methylpyridine and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as an off-white solid.

LC-MS: Rt = 0.89 min; MS m/z = 376.3 $[MH]^+$ (Method 1).

Intermediate 3-51

(S)-2-amino-2-cyclohexyl-N-(4-(3,5-dimethylpyridin-4-yl)phenyl)acetamide

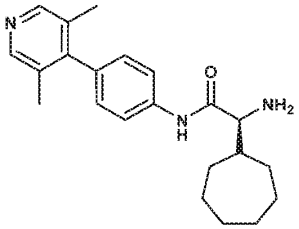


The title compound was prepared by a procedure similar to Intermediate 3-43, using intermediate 1-18 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as a colorless solid.

LC-MS: Rt = 1.97 min; MS m/z = 338.2 $[M+H]^+$ (Method 4).

Intermediate 3-52

(S)-2-amino-2-cycloheptyl-N-(4-(3,5-dimethylpyridin-4-yl)phenyl)acetamide

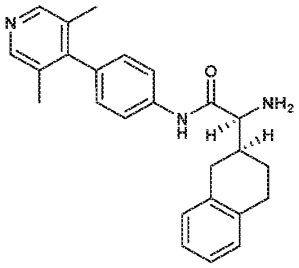


The title compound was prepared by a procedure similar to Intermediate 3-43, using intermediate 1-18and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cycloheptylacetic acid, to yield the title compound as a colorless solid.

LC-MS: Rt = 2.33 min; MS m/z = 352.3 $[MH]^+$ (Method 4).

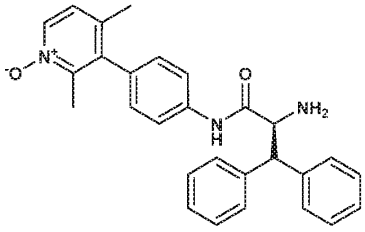
Intermediate 3-53

(S)-2-amino-N-(4-(3,5-dimethylpyridin-4-yl)phenyl)-2-((S)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide



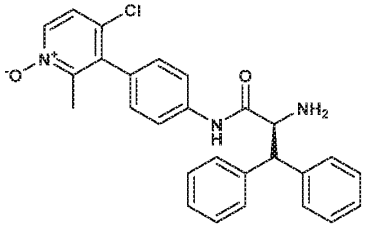
The title compound was prepared by a procedure similar to Intermediate 3-43, using Intermediate 1-18 and Intermediate 2-12, to yield the title compound as a yellow solid.
LC-MS: Rt = 0.51 min; MS m/z = 386.2 $[MH]^+$ (Method 1).

Intermediate 3-54
(S)-3-(4-(2-amino-3,3-diphenylpropanamido)phenyl)-2,4-dimethylpyridine 1-oxide



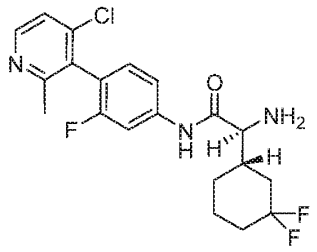
The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-1 and commercial (S)-2-((tert-butoxycarbonyl)amino)-3,3-diphenylpropanoic acid, to yield the title compound as an off-white solid.
LC-MS: Rt = 2.80 min; MS m/z = 438.2 $[MH]^+$ (Method 4).

Intermediate 3-55
(S)-3-(4-(2-amino-3,3-diphenylpropanamido)phenyl)-4-chloro-2-methylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-2 and commercial (S)-2-((tert-butoxycarbonyl)amino)-3,3-diphenylpropanoic acid, to yield the title compound as an off-white solid.
LC-MS: Rt = 3.06 min; MS m/z = 458.4 $[MH]^+$ (Method 4).

Intermediate 3-56
2-amino-N-(4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)-2-(3,3-difluorocyclohexyl)acetamide

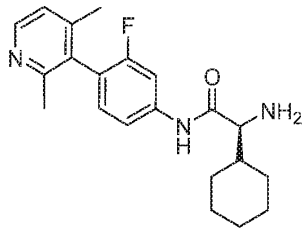


The title compound was prepared by a procedure similar to Intermediate 3-6, using Intermediate 1-4 and Intermediate 2-4, to yield the title compound as an off-white foam

LC-MS: Rt = 0.86 min; MS: m/z = 412.1 $[MH]^+$ (Method 2).

Intermediate 3-57:

(2S)-2-amino-2-cyclohexyl-N-(4-(2,4-dimethylpyridin-3-yl)-3-fluorophenyl)acetamide

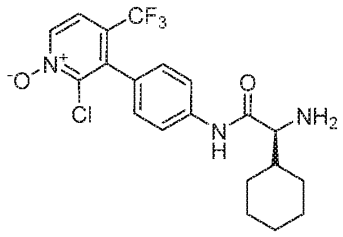


The title compound was prepared by a procedure similar to Intermediate 3-43, using Intermediate 1-21 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as a colorless solid.

LC-MS: Rt = 0.57 and 0.58 min (1:1 mixture of atropisomers); MS: m/z = 356.2 $[MH]^+$ (Method 1).

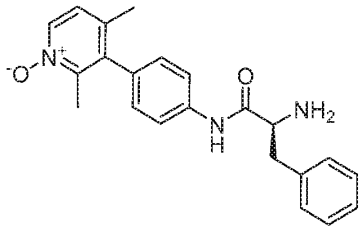
Intermediate 3-58:

(S)-3-(4-(2-amino-2-cyclohexylacetamido)phenyl)-2-chloro-4-(trifluoromethyl)pyridine 1-oxide



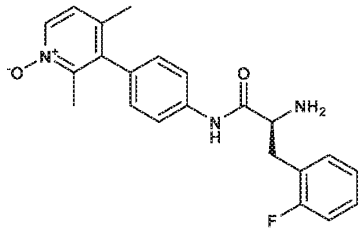
The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-13 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as an off-white solid.
TLC (EtOAc/hexane = 1:1) Rf = 0.04; MS: m/z = 428.3 $[MH]^+$.

Intermediate 3-59:
(S)-3-(4-(2-amino-3-phenylpropanamido)phenyl)-2,4-dimethylpyridine 1-oxide



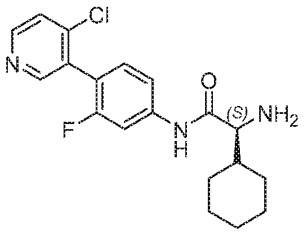
The title compound was prepared by a procedure similar to Intermediate 3-1, using intermediate 1-2 and commercial Boc-(L)-phenylalanine, to yield the title compound as an off-white solid.
LC-MS: Rt = 1.02 min; MS m/z = 462.3 $[MH]^+$ (Method 2).

Intermediate 3-60:
(S)-3-(4-(2-amino-3-(2-fluorophenyl)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared by a procedure similar to Intermediate 3-6, using Intermediate 1-2 and commercial Fmoc-2-fluoro-L-phenylalanine, to yield the title compound as an off-white foam.
LC-MS: Rt = 1.71min; MS m/z $[MH]^+$ = 380.2 (Method 4).

Intermediate 3-61:
(S)-2-amino-N-(4-(4-chloropyridin-3-yl)-3-fluorophenyl)-2-cyclohexylacetamide

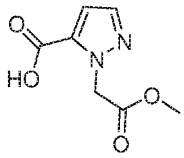


The title compound was prepared by a procedure similar to Intermediate 3-43, using Intermediate 1-22 and commercial (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid, to yield the title compound as a colorless solid.

LC-MS: Rt = 0.88 min; MS: m/z = 362.3 $[MH]^+$ (Method 3).

Intermediate 4-1:

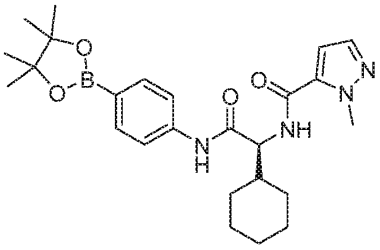
1-(2-methoxy-2-oxoethyl)-1H-pyrazole-5-carboxylic acid



A solution of t-butyl 1-(2-methoxy-2-oxoethyl)-1H-pyrazole-5-carboxylate (200 mg, 0.832 mmol) in DCM (500 µl) was treated with TFA (96 µl, 1.249 mmol). The mixture was stirred at RT for 1 h, then additional 200 µl of TFA were added, followed by stirring at RT overnight. The mixture was evaporated. The crude products of two similar experiments were combined and purified by column chromatography on RP-18 (ISCO system; eluent: water/acetonitrile 95:5 to 0:100; column: RediSep 43 g silicagel RP-18) to yield the title compound (287 mg, 94 %) as a colorless oil.
1H NMR (400 MHz, DMSO-d6) δ 13.46 (s, 1H), 7.59 (d, 1H), 6.88 (d, 1H), 5.32 (s, 2H), 3.67 (s, 3H).

Intermediate 4-2:

(S)-N-(1-cyclohexyl-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethyl)-1-methyl-1H-pyrazole-5-carboxamide



Step 1: Tert-butyl (S)-(1-cyclohexyl-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethyl)carbamate

To a solution of Boc-(L)-cyclohexylglycine (6.0 g, 23.32 mmol) in DMF (120 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5.62 g, 25.6 mmol) followed by NEt_3 (9.70 mL, 69.9 mmol) and HATU (10.64 g, 28.0 mmol). After stirring the mixture at RT for 16h at RT the solvent was evaporated and the residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine, the combined aqeous layers were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by column chromatography on silica (600 g silica, elution with 20 % EtOAc in cyclohexane) to yield the title compound (10.81 g, 96 %) as an off-white solid.
LC-MS: Rt = 1.35 min; MS: m/z = 459.4 $[MH]^+$ (Method 3).

Step 2: (S)-2-amino-2-cyclohexyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide

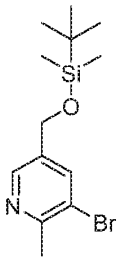
To a cooled (0°C) solution of tert-butyl (S)-(1-cyclohexyl-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethyl)carbamate (Step1; 10.8 g, 23.56 mmol) in 1,4-dioxane (10 mL) was added 4M HCl in dioxane (88 mL, 353 mmol). After stirring the mixture at RT for 2h PLC-MS indicated the complete consumption of the starting material. The volatiles were evaporated and the residue was dried in HV to yield the title compound (8.64 g, 93%) as an off-white solid which was used in the next step without further purification.
LC-MS: Rt = 0.99 min; MS: m/z = 359.4 $[MH]^+$ (Method 3).

Step 3: (S)-N-(1-cyclohexyl-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethyl)-1-methyl-1H-pyrazole-5-carboxamide

To a solution of (S)-2-amino-2-cyclohexyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (Step 2; 8.64 g, 21.89 mmol) and 2,4,6-collidine (11.66 mL, 88 mmol) in DMF (30 mL) was added 1-methyl-1H-pyrazole-5-carboxylic acid (4.14 g, 32.8 mmol), followed by HATU (16.64 g, 43.8 mmol) was added. After stirring the reaction mixture for 2h at RT HPLC-MS indicated the complete consumption of the starting material. The mixture was diluted with EtOAc and washed with 0.5M Na_2CO_3 solution and with brine. The combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was suspended in DCM (100 mL) and stirred for 20 min. Pentane (50 mL) was added dropwise and stirring was continued for 20 min at RT. The mixture was filtered through a 5 µm PTFE membrane filter, the filter cake was washed with DCM/pentane 1:1 (3 x 20 mL) and dried in vacuo to yield the title compound (7.81 g, 77 %) as a colorless solid.
LC-MS: Rt = 1.29 min; MS: m/z = 467.4 $[MH]^+$ (Method 3).

Intermediate 4-3:

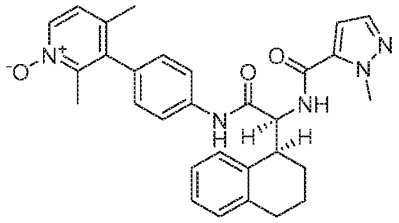
3-bromo-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylpyridine



To a solution of (5-bromo-6-methylpyridin-3-yl)methanol (US 2016/0222028 A1, 850 mg, 4.21 mmol) and imidazole (573 mg, 8.41 mmol) in DCM (30 mL) was added TBDMSCl (951 mg, 6.31 mmol). After stirring the mixture at RT overnight the volatiles were evaporated and the residue was partitioned between EtOAc and sat. Na_2CO_3. The organic layer was washed with brine, the combined aqueous layers were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by column chromatography on silica (column: Redisep 80g; elution with 0 – 40 % EtOAc in cyclohexane) to yield the title compound (792 mg; 60 %) as a yellow oil.
LC-MS: Rt = 1.44 min; MS m/z = 318.1 $[MH]^+$ (Method 3).

Example 1:

2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide



To a solution of 3-(4-((S)-2-amino-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 3-1; 1.10 g, 2.46 mmol) in DMF (15 mL) were added 1-methyl-1H-pyrazole-5-carboxylic acid (530 mg, 4.2 mmol) followed by HATU (1.9 g, 4.93 mmol), and finally triethylamine (1.7 mL, 12.3 mmol). After stirring at RT overnight, the reaction mixture was diluted with EtOAc (200 mL) and extracted with sat. aq. $NaHCO_3$, water (twice) and with brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80g; eluent:TBME/MeOH 100:0 to 0:100) to yield a pale yellow solid which was triturated with DCM/MeOH 4:1 at 0 °C, followed by filtering and washing the solid with cold isopentane to yield the title compound (771 mg, 62 %) as a colorless solid.

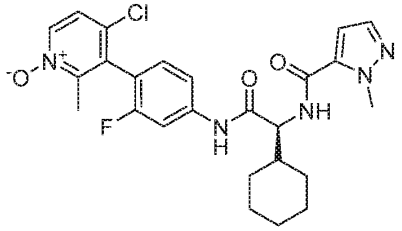
LC-MS: Rt = 4.48 min; MS: m/z = 510 $[MH]^+$ (Method 4)

1H NMR (400 MHz, DMSO-d6) δ 10.57 (s, 1H), 8.95 (d, 1H), 8.20 (d, 1H), 7.83 (d, 2H), 7.46 (d, 1H), 7.40 (d, 1H), 7.28 - 7.16 (m, 3H), 7.11 - 7.05 (m, 3H), 7.05 - 6.94 (m, 1H), 4.82 (dd, 1H), 3.90 (s, 3H), 3.38 - 3.34 (m, 1H), 2.93 - 2.71 (m, 2H), 2.23 – 2-12 (br. m, 1H), 2.09 (s, 3H), 1.97 (s, 3H), 1.85 - 1.65 (m, 3H) ppm.

The absolute stereochemical configuration was confirmed as (S,S) by X-ray crystallography.

Example 2:

4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



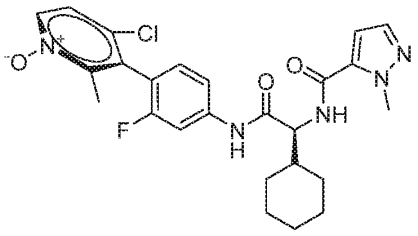
To a solution of 3-(4-((S)-2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 3-2; 2.10 g, 5.36 mmol) in DMF (30 mL) were added 1-

methyl-1H-pyrazole-5-carboxylic acid (1.01 g, 8.04 mmol) followed by HATU (3.46 g, 9.11 mmol), and finally triethylamine (3.71 mL, 26.8 mmol). After stirring at RT for 2h, the reaction mixture was diluted with EtOAc (150 mL) and extracted with sat. aq. $NaHCO_3$, water (twice) and with brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 120g; eluent:TBME/MeOH 100:0 to 0:100) to yield an off-white foam, which was triturated with acetonitrile, filtered, washed with MTBE and dried on HV to yield the title compound (1.95 g, 72 %) as a colorless solid (mixture of atropisomers).

LC-MS: Rt = 4.68 and 4.75 min (double peak, ratio 1:1, due to atropisomers); MS: m/z = 500 and 502 $[MH]^+$ (Method 4).
1H NMR (400 MHz, DMSO-d6) δ 10.63 (s, 1H), 8.57 (d, 1H), 8.36 (d, 1H), 7.81 (m, 1H), 7.59 (d, 1H), 7.55 - 7.42 (m, 2H), 7.34 (dd, 1H), 7.07 (d, 1H), 4.40 (t, 1H), 4.03 (s, 3H), 2.15 (s, 3H), 1.98-1.81 (br. m, 2H), 1.78 – 1.69 (br. m, 2H), 1.67 – 1.57 (br. m, 2H), 1.32 - 0.89 (m, 5H) ppm.

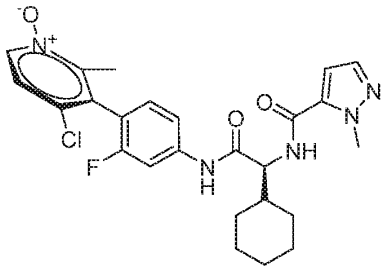
The absolute stereochemical configuration at the chiral carbon atom was confirmed as (S) by X-ray crystallography.

Example 2a and Example 2b:



(Ra,S atropisomer)

or

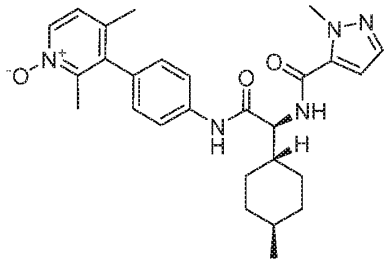


(Sa,S atropisomer)

250 mg of the mixture of atropisomers obtained from Example 2 was separated by chiral prep. HPLC (Gilson Trilution system, eluent: n-heptane : DCM : MeOH = 60:30:10 (v:v:v); Column: Chiralpak IG, 250x30mm 5um) to afford the individual atropisomers.
Analytical chiral HPLC (Column: Chiralpak IG, 250x4.6mm, 5um; solvent: n-heptane : DCM : MeOH = 60:30:10 (v:v:v) + 0.1% DEA; flow = 2.5 mL/min, T = 35 °C):
Example 2a (single atropisomer absolute stereoconfiguration at bond of rotation not determined, Ra,S or Sa,S) = Peak 1: Rt = 8.66 min.

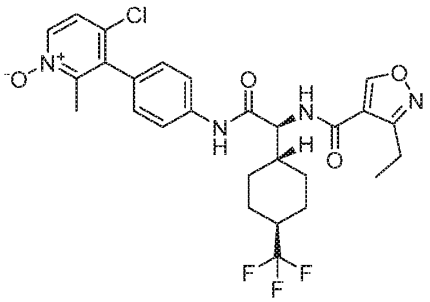
Example 2b (single atropisomer absolute stereoconfiguration at bond of rotation not determined, Ra,S or Sa,S) = Peak 2: Rt = 12.43 min.
The individual atropisomers were found to interconvert on standing.

Example 3:
2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide



To a solution of 1-methyl-1H-pyrazole-5-carboxylic acid (29.7 mg, 0.235 mmol), 2,4,6-collidine (0.125 ml, 0.941 mmol) in DMF (2 mL) was added HATU (98 mg, 0.259 mmol) and the resulting solution was stirred for 10min. 3-(4-((S)-2-amino-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 3-3, 100 mg, 0.235 mmol) was added at RT in one portion, and stirring was continued at RT for 2h. The reaction mixture was partitioned between aq. 10 % $NaHCO_3$ and EtOAc, the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by prep HPLC (column: Sunfire 30x100 mm; gradient of acetonitrile/water+0.1% TFA) to yield the title compound (72 mg, 63 %) as a colorless solid.
LC-MS: Rt = 1.02 min; MS: m/z = 476 $[MH]^+$ (Method 3).
1H NMR (400 MHz, DMSO-d6) δ 10.36 (s, 1H), 8.54 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.46 (d, 1H), 7.26 – 7.14 (m, 3H), 7.07 (d, 1H), 4.40 (t, 1H), 4.03 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.94 – 1.80 (m, 2H), 1.76 – 1.59 (m, 3H), 1.36 – 1.14 (m, 2H), 1.14 – 1.00 (m, 1H), 0.96 – 0.81 (m, 5H) ppm.

Example 4:
4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide



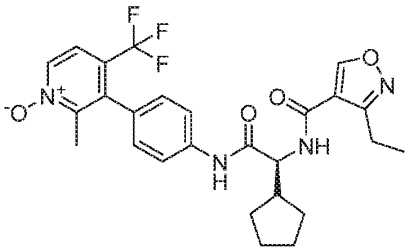
To a solution of 3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 3-4; 473 mg, 1.070 mmol), 3-ethyl-4-isoxazolecarboxylic acid (166 mg, 1.177 mmol) and 2,4,6-collidine (0.214 ml, 1.606 mmol) in DMF (10 mL) was added HATU (611 mg, 1.61 mmol). After stirring the reaction mixture for 1h at RT, the solvent was evaporated and residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine and the combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on RP-18 (column: RediSep 43 g; eluent: water / acetonitrile 95:5 to 0:100) to yield the title compound (428 mg, 69 %) as an off-white solid.

LC-MS: Rt = 1.13 min; MS: m/z = 565 and 567 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.42 (s, 1H), 8.56 (d, 1H), 8.31 (d, 1H), 7.77 (m, 2H), 7.54 (d, 1H), 7.24 (d, 2H), 4.48 (dd, 1H), 2.85 (q, 2H), 2.13 (s, 3H), 2.01 – 1.71 (m, 5H), 1.36 – 1.15 (m, 5H), 1.16 (t, 3H) ppm.

Example 5:

(S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



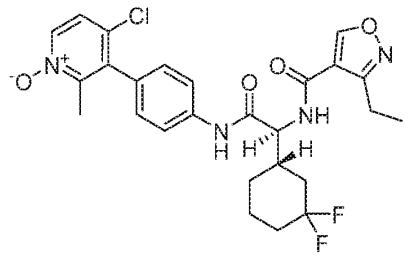
To a solution of (S)-3-(4-(2-amino-2-cyclopentylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 3-5, 5 g, 10.1 mmol) in DMF (40 mL) were added 3-ethylisoxazole-4-carboxylic acid (2.13 g, 15.1 mmol) and triethylamine (7.33 mL, 52.9 mmol), followed by HATU (6.51 g, 17.1 mmol) and the reaction mixture was stirred overnight at RT. Most

of the DMF was removed in vacuo, the residue was taken up in EtOAc and washed with half-saturated brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica (column: RediSep 330g; eluent:cyclohexane/EtOAc+5% MeOH 50:50 to 10:90) to yield an off-white foam (5.19 g) which was crystallized from TBME/EtOAc/MeOH (80/15/5, 6 mL) to yield the title compound (3.54 g, 66 %) as colorless crystals, mp 149-151 °C.
LC-MS: Rt = 1.06 min; MS: m/z = 517.3 $[MH]^+$ (Method 5).
1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.41 (s, 1H), 8.67 (d, 1H), 8.48 (d, 1H), 7.75 (d, 2H), 7.70 (d, 1H), 7.24 (d, 2H), 4.43 (t, 1H), 2.85 (q, 2H), 2.32 (q, 1H), 2.05 (s, 3H), 1.90 – 1.21 (m, 8H), 1.17 (t, 3H) ppm.

The absolute stereochemical configuration was confirmed as (S) by X-ray crystallography.

Example 6:

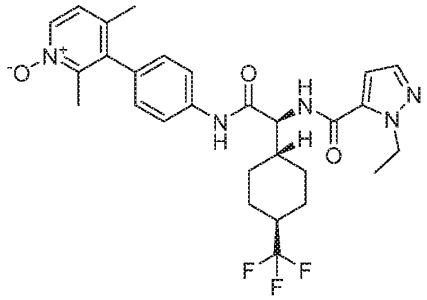
4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide



To a solution of 3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 3-6, 840 mg, 2.05 mmol) in DMF (11 mL) were added 3-ethylisoxazole-4-carboxylic acid (434 mg, 3.1 mmol), HATU (1325 mg, 3.5 mmol) and triethylamine (1.420 mL, 10.25 mmol). After stirring at RT overnight the reaction mixture was partitioned between EtOAc and aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried via phaseseparator and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80g; eluent: EtOAc/MeOH 100:0 to 70:30) to yield a colorless solid. This material was stirred in water, filtered and dried to yield the title compound (1.02 g, 91 %) as colorless crystals, mp 247-250°C.
LC-MS: Rt = 0.96 min; MS: m/z = 533 and 535 $[MH]^+$ (Method 5).
1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1 H) 9.44 (s, 1 H) 8.62 (d, 1 H) 8.31 (d, 1 H) 7.71 - 7.87 (m, 2 H) 7.54 (d, 1 H) 7.26 (d, 2 H) 4.63 (t, 1 H) 2.85 (q, 2 H) 1.57 - 2.25 (m, 10 H) 1.11 - 1.53 (m, 5 H) ppm.

Example 7:

3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



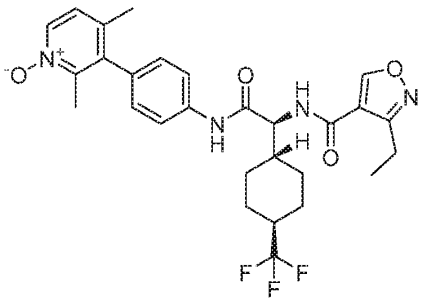
To a solution of 3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 3-7; 350 mg, 0.83 mmol), 1-ethylpyrazole-5-carboxylic acid (128 mg, 0.91 mmol) and 2,4,6-collidine (0.332 ml, 2.5 mmol) in DMF (10 mL) was added HATU (474 mg, 1.246 mmol). After stirring the reaction mixture for 1h at RT, the solvent was evaporated and residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine and the combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on RP-18 (column: RediSep 43g; eluent: water / acetonitrile 95:5 to 0:100) to yield the title compound (330 mg, 73 %) as an off-white solid.

LC-MS: Rt = 1.03 min; MS: m/z = 544.4 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.56 (d, 1H), 8.19 (d, 1H), 7.81 – 7.72 (m, 2H), 7.49 (d, 1H), 7.28 – 7.14 (m, 3H), 7.03 (d, 1H), 4.52 – 4.39 (m, 3H), 3.52 (dd, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 2.01 – 1.83 (m, 5H), 1.75 (d, 1H), 1.36 – 1.19 (m, 5H), 1.22 – 1.08 (m, 1H) ppm

Example 8:

3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



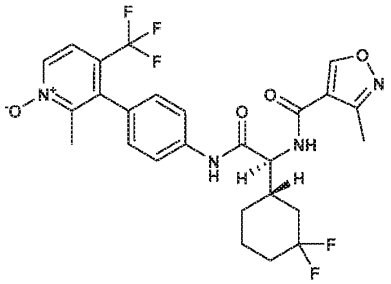
To a solution of 3-(4-((S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 3-7; 350 mg, 0.83 mmol), 3-ethyl-4-isoxazolecarboxylic acid (117 mg, 0.83 mmol) and 2,4,6-collidine (0.332 ml, 2.5 mmol) in DMF (10 mL) was added HATU (474 mg, 1.246 mmol). After stirring the reaction mixture for 1h at RT, the solvent was evaporated and residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine and the combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on RP-18 (column: RediSep 43g; eluent: water / acetonitrile 95:5 to 0:100) to yield the title compound (355 mg, 78%) as a colorless solid.

LC-MS: Rt = 1.06 min; MS: m/z = 545.4 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.42 (s, 1H), 8.57 (d, 1H), 8.20 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.18 (d, 2H), 4.47 (dd, 1H), 2.84 (q, 2H), 2.33 – 2.20 (br. m, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.95 – 1.72 (br. m, 5H), 1.35 1.22 (m, 4H), 1.18 (t, 3H) ppm.

Example 9:

3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



To a solution of 3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 3-8; 400 mg, 0.90 mmol) and 3-methylisoxazole-4-carboxylic acid (172 mg, 1.35 mmol) in DMF (9 mL) were added HATU (583 mg, 1.53 mmol),

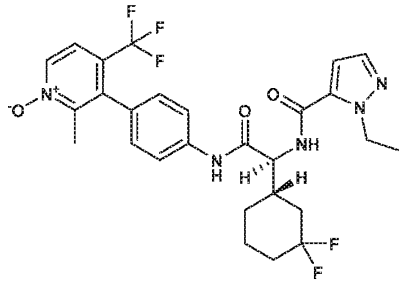
followed by triethylamine (0.625 mL, 4.5 mmol). After stirring at RT overnight, the reaction mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic layer was washed with water and brine, the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80g; eluent: TBME/MeOH 100:0 to 75:25) to yield the title compound (429 mg, 86 %) as an off-white solid.

LC-MS: Rt = 4.62 min; MS: m/z = 553.2 $[MH]^+$ (Method 4).

1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.47 (s, 1H), 8.60 (d, 1H), 8.48 (d, 1H), 7.83 - 7.64 (m, 3H), 7.25 (d, 2H), 4.63 (dd, 1H), 2.38 (s, 3H), 2.24 - 2.11 (br. m, 2H), 2.05 (s, 3H), 2.03 – 1.92 (br. m, 1H), 1.89 - 1.60 (br. m, 4H), 1.53 - 1.35 (br. m, 1H), 1.30 - 1.19 (br. m, 1H) ppm.

Example 10:

3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



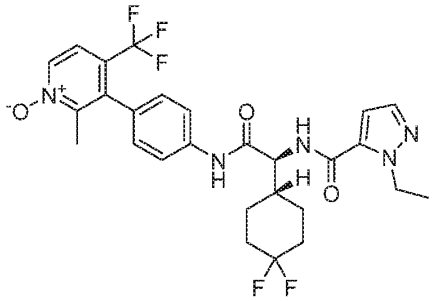
To a solution of 3-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 3-8; 400 mg, 0.90 mmol) and 1-ethyl-1H-pyrazole-5-carboxylic acid (190 mg, 1.35 mmol) in DMF (9 mL) were added HATU (583 mg, 1.53 mmol), followed by triethylamine (0.625 mL, 4.5 mmol). After stirring at RT overnight, the reaction mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic layer was washed with water and brine, the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80 g; eluent: TBME/MeOH 100:0 to 78:22) to yield the title compound (424 mg, 81 %) as an off-white solid.

LC-MS: Rt = 4.86 min; MS: m/z = 566.3 $[MH]^+$ (Method 4).

1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.65 (d, 1H), 8.48 (d, 1H) 7.75 (m, 2H), 7.70 (d, 1H), 7.49 (d, 1H), 7.25 (d, 2H), 7.06 (d, 1H), 4.61 (dd, 1H), 4.48 (q, 2H), 2.30 – 2.19 (br. m, 1H), 2.18 – 2.09 (br. m, 1H), 2.04 (s, 3H), 2.04 – 1.95 (br. m, 1H), 1.89 - 1.62 (br. m, 4H), 1.48 - 1.36 (br. m, 1H), 1.29 (t, 3H), 1.26 – 1.20 (br. m, 1H) ppm.

Example 11:

(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide



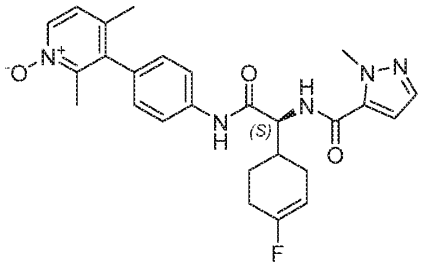
To a solution of (S)-3-(4-(2-amino-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide (Intermediate 3-9; 546 mg, 1.14 mmol), 1-ethyl-1H-pyrazole-4-carboxylic acid (159 mg, 1.14 mmol) and 2,4,6-trimethylpyridine (0.455 ml, 3.41 mmol) in DMF (10 mL) was added HATU (649 mg, 1.71 mmol). After stirring the reaction mixture for 16h at RT, the solvent was evaporated and residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine and the combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by prep. HPLC on RP-18 (column: Xbridge 50x100 mm, flow 100 mL/min; eluent: water+0.1 %TFA / acetonitrile 80:20 to 50:50,) to yield the title compound (309 mg, 48 %) as an off-white solid.

LC-MS: Rt = 1.01 min; MS: m/z = 566.3 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ ppm 10.50 (s, 1H), 8.73 (br. m, 1H), 8.48 (d, 1H), 7.81 - 7.64 (m, 3H), 7.49 (d, 1H), 7.25 (d, 2H), 7.03 (d, 1H), 4.60 - 4.39 (m, 3H), 2.18 – 2.00 (br. m, 3H), 2.05 (s, 3H), 1.99 – 1.69 (br. m, 4H) 1.52 – 1.32 (br. m, 2H), 1.28 (t, 3H) ppm.

Example 12:

3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



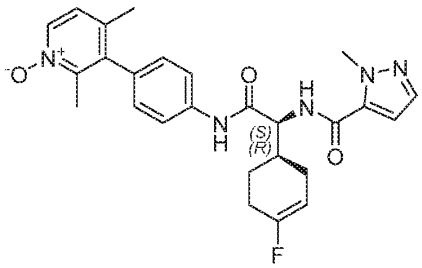
To a solution of 3-(4-((2S)-2-amino-2-(4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Intermediate 3-10; 707 mg, 1.742 mmol), 1-methyl-1H-pyrazole-5-carboxylic acid (242 mg, 1.916 mmol) and 2,4,6-collidine (0.928 ml, 6.97 mmol) in DMF (10 mL) was added HATU (993 mg, 2.61 mmol). After stirring the reaction mixture for 16h at RT, the solvent was evaporated and residue was partitioned between EtOAc and sat. aq. Na_2CO_3. The organic layer was washed with brine and the combined aqueous layers were re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by prep. HPLC on RP-18 (column: Waters SunFire 30x100 mm, flow 40 mL/min; eluent: water+0.1 %TFA / acetonitrile+0.1%TFA 95:5 to 0:100) to yield the title compound (542 mg, 65 %) as an off-white solid.

LC-MS: Rt = 0.84 min; MS: m/z = 478.3 $[MH]^+$ (Method 5).

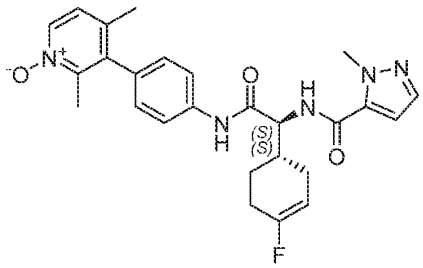
1H NMR (400 MHz, DMSO-d6) δ 10.49 (d, 1H), 8.71 (dd, 1H), 8.21 (d, 1H), 7.83 – 7.74 (m, 2H), 7.47 (t, 1H), 7.24 (d, 1H), 7.18 (d, 2H), 7.09 (d, 1H), 5.23 (d, 1H), 4.54 (m, 1H), 4.04 (s, 3H), 2.30 – 2.15 (m, 4H), 2.09 (s, 3H), 2.06 – 2.00 (br. m, 1H), 1.97 (s, 3H), 1.94 – 1.74 (br. m, 1H), 1.64 – 1.41 (m, 1H) ppm.

Examples 12a and 12b:

3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide or 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide

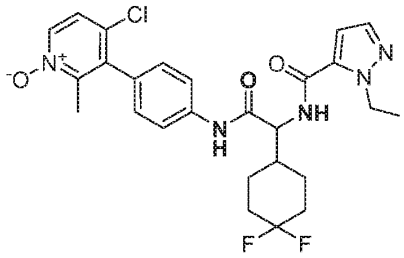


or



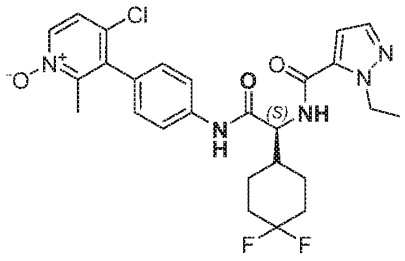
The product from Example 12 was separated into two pure diastereomers by chiral prep. HPLC (Gilson Trilution system, eluent: n-heptane : DCM : MeOH = 30:30:10 (v:v:v) +0.05% DEA; Column: 250x30mm 5um Chiralpak ID; flow = 20 mL/min).
Analytical chiral HPLC (Column: Chiralpak ID, 250x4.6mm, 5um; solvent: n-heptane : DCM : MeOH = 60:30:10 (v:v:v) + 0.1% DEA; flow = 2.5 mL/min, T = 35 °C):
Example 12a (S,R or S,S) = Peak 1: Rt = 11.1 min.
Example 12b (S,R or S,S) = Peak 2: Rt = 13.66 min.

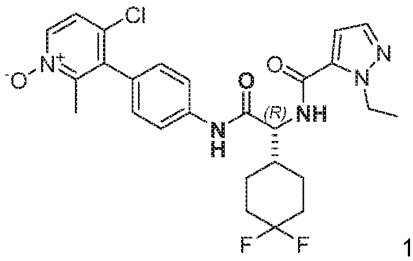
Example 13:
4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide



The title compound was prepared from Intermediate 3-24 and 1-ethyl-1H-pyrazole-5-carboxylic acid by a procedure similar to that of Example 1.
LC-MS: Rt = 0.96 min; MS: m/z = 532 and 534 $[MH]^+$ (Method 2).
1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H), 8.68 (d, 1H), 8.31 (d, 1H), 7.77 (m, 2H), 7.54 (d, 1H), 7.49 (d, 1H), 7.26 (d, 2H), 7.03 (d, 1H), 4.61 - 4.38 (m, 3H), 2.13 (s, 3H), 2.10 - 1.60 (br. m, 7H), 1.57 - 1.30 (m, 2H), 1.28 (t, 3H) ppm.

Example 13a:
(*S*)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide and
Example 13b:
(*R*)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide

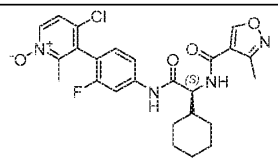

13a

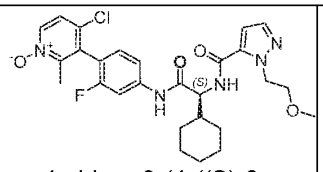
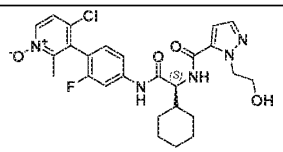
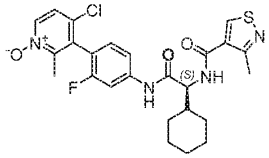
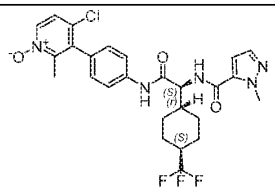

13b

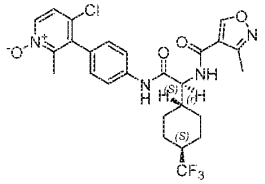
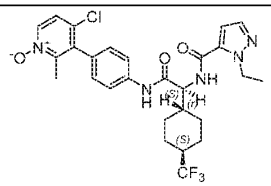
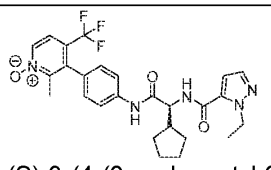
280 mg of the racemic mixture obtained from Example 13 were separated by chiral SFC (column: Chiralpak IC 250x30mm ID; 5µm, 10 µm; 45 % IPA+0.1%NH_3, flow: 80 mL/min).

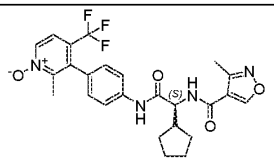
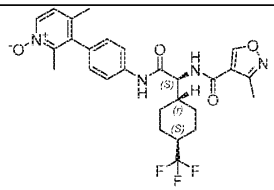
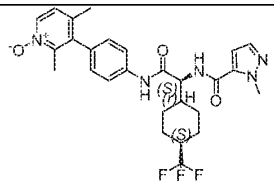
Analytical chiral SFC (ChiralPak IC, 100×4.6mm I.D., 5µm, 45 % IPA+0.1%NH_3),
Example 13a = Peak 1: Rt = 2.14 min: 128 mg; 99% ee
Example 13b = Peak 2: Rt = 3.26 min: 125 mg; 99% ee
The faster eluting compound was assigned as the (S)-enantiomer based on the higher potency observed with the TR-FRET assay.

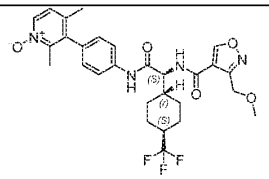
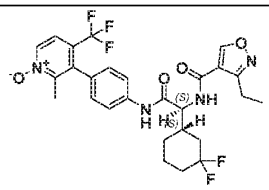
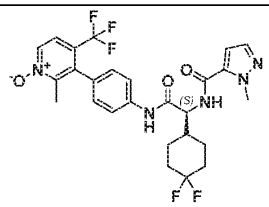
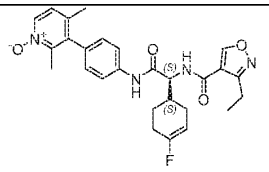
The following Examples were prepared by amide bond formation of Intermediate 3-x and the corresponding carboxylic acids (prepared as Intermediates 4-x or commercially available) by procedures similar to that of Examples 1 - 13.

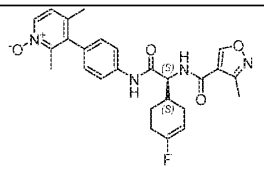
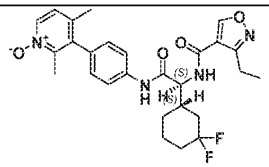
Example	Structure/Name	Inter-mediate 3-x	Inter-mediate 4-x	LC-MS (Method)	1H NMR
14	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-2	3-methylisoxazole-4-carboxylic acid	Rt = 1.02 min; MS: m/z = 501.2 $[MH]^+$ (Method 3)	1H NMR (500 MHz, DMSO-d6, 120 °C) δ 10.12 (s, 1H), 9.33 (s, 1H), 8.29 (d, 1H), 7.95 (d, 1H), 7.79 – 7.71 (m, 1H), 7.57 – 7.52 (m, 1H), 7.49 (d, 1H), 7.29 (t, 1H), 4.54 (t, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.01 – 1.63 (m, 6H), 1.36 – 1.10 (m, 5H) ppm.

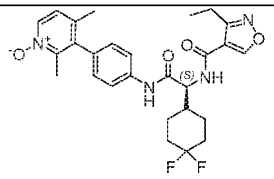
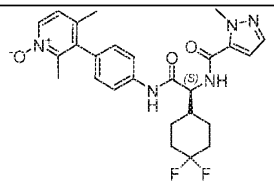
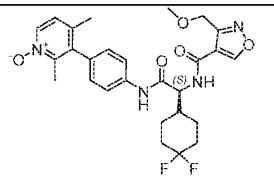
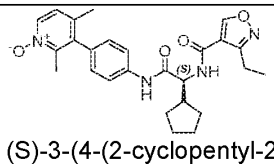
15	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-methoxyethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-2	1-(2-methoxyethyl)-1H-pyrazole-5-carboxylic acid	Rt = 0.99 and 1.01 min (atropisomers); MS: m/z = 544 and 546 $[MH]^+$ (Method 8)	1H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.59 (d, 1H), 8.36 (d, 1H), 7.81 (m, 1H), 7.59 (d, 1H), 7.54 – 7.45 (m, 2H), 7.34 (t, 1H), 6.99 (d, 1H), 4.63 (t, 2H), 4.40 (t, 1H), 3.63 (t, 2H), 3.16 (s, 3H), 2.15 (s, 3H), 2.01 – 1.79 (m, 2H), 1.72 (s, 2H), 1.62 (s, 2H), 1.31 – 0.96 (m, 5H) ppm
16	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-hydroxyethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-2	1-(2-hydroxyethyl)-1H-pyrazole-5-carboxylic acid	Rt = 0.92 and 0.93 min (atropisomers); MS: m/z = 530.5 and 532.5 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.62 (d, 1H), 8.36 (d, 1H), 7.81 (m, 1H), 7.59 (d, 1H), 7.47 - 7.53 (m, 2H), 7.34 (m, 1H), 6.99 (d, 1H), 4.88 (m, 1H), 4.51 (m, 2H) 4.41 (t, 1H) 3.69 (m, 2H), 2.15 (s, 3H), 1.52 - 1.99 (m, 6H), 0.94 - 1.33 (m, 5H) ppm.
17	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-methylisothiazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-2	3-methylisothiazole-4-carboxylic acid	Rt = 1.04 min; MS: m/z = 517 and 519 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.51 (s, 1H), 8.59 (d, 1H), 8.36 (d, 1H), 7.82 (m, 1H), 7.59 (d, 1H), 7.51 (m, 1H), 7.34 (m, 1H), 4.41 (dd, 1H), 2.54 (s, 3H), 2.15 (2s, 3H), 1.90 - 1.62 (m, 5H), 1.26 - 1.01 (m, 6H) ppm.
18		3-4	1-methyl-H-pyrazole-5-carboxylic acid	Rt = 1.03 min; MS: m/z = 550 and 552 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.58 (br. s, 1H), 8.31 (d, 1H), 7.78 (m, 2H), 7.54 (d, 1H), 7.47 (d, 1H), 7.25 (d, 2H), 7.07 (d, 1H),

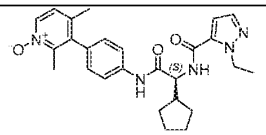
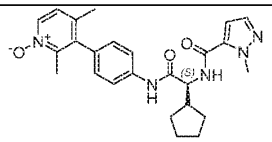
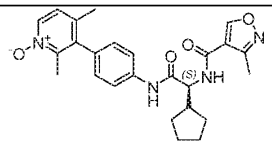
	4-chloro-2-methyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide				4.44 (br. m, 1H), 4.04 (s, 3H), 2.29 - 2.22 (m, 1H), 2.13 (s, 3H), 1.97 - 1.74 (m, 5H), 1.21 (m, 4H) ppm.
19	 4-chloro-2-methyl-3-(4-((S)-2-(3-methylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-4	3-methylisoxazole-4-carboxylic acid	Rt = 1.06 min; MS: m/z = 551 and 553 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.44 (d, 1H), 8.56 (d, 1H), 8.31 (d, 1H), 7.77 (m, 2H), 7.54 (m, 1H), 7.25 (d, 2H), 4.47 (dd, 1H), 2.38 (s, 3H), 2.30 – 2.20 (br. m, 1H), 2.13 (s, 3H), 2.00 – 1.88 (br. m, 3H), 1.86 – 1.73 (br. m, 2H), 1.75 (d, 1H), 1.30 – 1.12 (m, 3H).
20	 4-chloro-3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxi	3-4	3-ethylisoxazole-4-carboxylic acid	Rt = 1.14 min; MS: m/z = 564 and 566 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.51 (s, 1H), 8.67 (d, 1H), 8.31 (d, 1H), 7.79 (m, 2H), 7.54 (d, 1H), 7.48 (d, 1H), 7.25 (d, 2H), 7.04 (d, 1H), 4.46 (q, 2H), 4.42 (dd, 1H), 2.33 – 2.19 (br. m, 1H), 2.13 (s, 3H), 2.01 – 1.87 (br. m, 4H), 1.78 – 1.71 (br. m, 1H), , 1.28 (t, 3H), 1.24 – 1.09 (m, 4H).
21	 (S)-3-(4-(2-cyclopentyl-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-5	3-ethylisoxazole-4-carboxylic acid	Rt = 1.51 min; MS: m/z = 516.3 $[MH]^+$ (Method 16)	1H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.29 (m, 2H), 7.70 – 7.61 (m, 2H), 7.50 – 7.44 (m, 2H), 7.15 (d, 2H), 6.64 (d, 1H), 6.59 (d, 1H), 4.59 (m, 2H), 4.49 (dd, 1H), 2.53 (m, 1H), 2.21 (s, 3H), 2.02 – 1.82 (br. m,

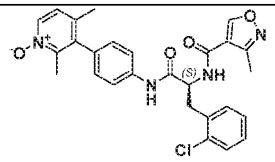
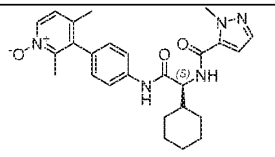
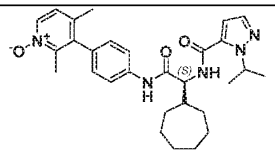
					2H), 1.77 – 1.62 (br. m, 4H), 1.43 (q, 3H), 1.42 – 1.37 (br, m, 1H), 1.33 – 1.21 (br. m, 1H).
22	 (S)-3-(4-(2-cyclopentyl-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-5	3-methylisoxazole-4-carboxylic acid	Rt = 1.48 min; MS: m/z = 503.3 $[MH]^+$ (Method 16)	^{1}H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.43 (s, 1H), 8.64 (d, 1H), 8.48 (d, 1H), 7.80 – 7.65 (m, 3H), 7.24 (d, 2H), 4.43 (dd, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 2.05 (s, 3H), 1.90 – 1.80 (br. m, 1H), 1.70 – 1.29 (br. m, 7H).
23	 2,4-dimethyl-3-(4-((S)-2-(3-methylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-7	3-methyl-4-isoxazole carboxylic acid	Rt = 1.00 min; MS: m/z = 531.3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.45 (s, 1H), 8.58 (d, 1H), 8.19 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 4.47 (dd, 1H), 2.38 (s, 3H), 2.34 – 2.15 (m, 1H), 2.08 (s, 3H), 1.92 (s, 3H), 1.94 – 1.70 (m, 5H), 1.34 – 1.11 (m, 4H) ppm.
24	 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-7	1-methyl-H-pyrazole-5-carboxylic acid	Rt = 1.01 min; MS: m/z = 530.2 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.57 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.47 (d, 1H), 7.26 – 7.14 (m, 3H), 7.07 (d, 1H), 4.44 (dd, 1H), 4.04 (s, 3H), 2.26 (br. m, 1H), 2.08 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.92-1.81 (m, 1H), 1.75 (m, 1H), 1.36 – 1.07 (m, 4H) ppm.

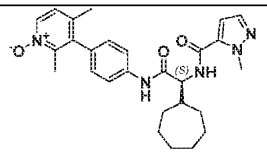
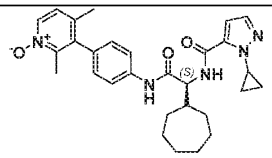
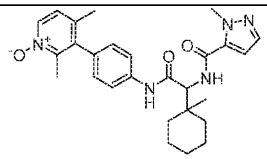
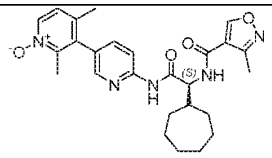
25	 3-(4-((S)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-7	3-(methoxymethyl)-4-isoxazole carboxylic acid	Rt = 1.03 min; MS: m/z = 561.3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.50 (s, 1H), 8.61 (d, 1H), 8.24 (d, 1H), 7.74 (d, 2H), 7.26 (d, 1H), 7.19 (d, 2H), 4.72 (s, 2H), 4.56 (dd, 1H), 3.36 (s, 3H), 2.26 (s, 1H), 2.35 - 2.20 (m, 1H), 2.09 (s, 3H), 1.97 (s, 3H), 2.00 – 1.72 (m, 5H), 1.33 – 1.11 (m, 4H) ppm.
26	 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-8	3-ethylisoxazole-4-carboxylic acid	Rt = 4.98 min; MS: m/z = 567.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H) 9.44 (s, 1H) 8.61 (d, 1H) 8.48 (d, 1H) 7.75 (m, 2H), 7.70 (d, 1H) 7.25 (d, 2H), 4.63 (dd, 1H), 2.85 (q, 2H), 2.24 – 2.10 (br. m, 2H), 2.05, (s, 3H), 2.05 – 1.95 (br. m, 1H), 1.90 – 1.58 (br. m, 4H), 1.41 (m, 1H), 1.30 – 1.21 (m, 1H), 1.18 (t, 3H) ppm.
27	 (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-9	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 4.55 min; MS: m/z = 552.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.67 (d, 1H), 8.48 (d, 1H), 7.75 (m, 2H), 7.69 (d, 1H), 7.47 (d, 1H), 7.25 (d, 2H), 7.07 (d, 1H), 4.52 (dd, 1H), 4.04 (s, 3H), 2.15 – 2.00 (br. m, 3H), 2.05 (s, 3H), 1.98 - 1.69 (br. m, 4H), 1.53 – 1.30 (br. m, 2H).
28		3-10	3-ethyl-4-isoxazole carboxylic acid	Rt = 0.95 min; MS: m/z = 493.3 $[MH]^+$	1H NMR (400 MHz, DMSO-d6) δ 10.47 (d, 1H), 9.43 (d, 1H), 8.68 (d, 1H), 8.20 (d, 1H), 7.77 (d, 2H), 7.22

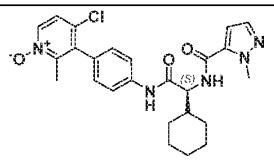
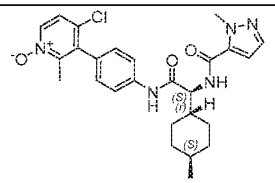
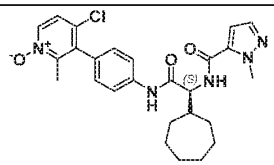
	3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((S)-4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide			(Method 5)	(d, 1H), 7.18 (d, 1H), 5.22 (br. m, 1H), 4.56 (dd, 1H), 2.85 (q, 2H), 2.24 (br. m, 3H), 2.15 – 2.05 (br. m, 1H), 2.08 (s, 3H), 2.01 – 1.90 (br. m, 1H), 1.97 (s, 3H), 1.87 – 1.76 (br. m, 1H), 1.65 - 1.53 (m, 1H), 1.29 – 1.16 (br. m, 1H), 1.18 (t, 3H) ppm.
29	 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-10	3-methyl-4-isoxazole carboxylic acid	Rt = 0.85 min; MS: m/z = 479.3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.48 (d, 1H), 9.46 (s, 1H), 8.67 (dd, 1H), 8.20 (d, 1H), 7.77 (dd, 2H), 7.22 (d, 1H), 7.19 (d, 2H), 5.22 (br. d, 1H), 4.56 (m, 1H), 2.38 (s, 3H), 2.23 (br. m, 3H), 2.14 – 1.94 (br. m, 2H), 2.08 (s, 3H), 1.96 (s, 3H), 1.86 – 1.76 (br. m, 1H), 1.63 – 1.43 (br. m, 1H) ppm.
30	 3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-11	3-ethylisoxazole-4-carboxylic acid	Rt = 4.29 min; MS: m/z = 513.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.44 (s, 1H), 8.61 (d, 1H), 8.19 (d, 1H), 7.76 (d, 2H), 7.23 (d, 1H), 7.19 (d, 2H), 4.63 (dd, 1H), 2.85 (q, 2H), 2.15 (br. m, 2H), 2.08 (s, 3H), 2.05 – 1.95 (m, 1H), 1.97 (s, 3H), 1.88 – 1.60 (m, 4H), 1.48 – 1.35 (m, 1H), 1.30 – 1.19 (m, 1H), 1.18 (t, 3H) ppm.

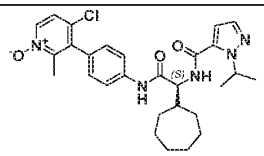
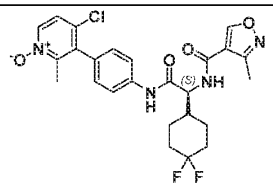
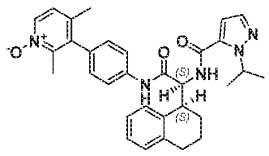
31	 (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-12	3-ethyl-4-isoxazole carboxylic acid	Rt = 0.97 min; MS: m/z = 513.5 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.42 (s, 1H), 8.67 (d, 1H), 8.20 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.19 (d, 2H), 4.54 (dd, 1H), 2.89 - 2.82 (m, 2H), 2.15 – 1.70 (br. m, 7H), 2.08 (s, 3H), 1.96 (s, 3H), 1.51 – 1.32 (br. m, 2H), 1.18 (t, 3H) ppm.
32	 (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-12	1-methyl-[1H]pyrazole-5-carboxylic acid	Rt = 0.87 min; MS: m/z = 498.3 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.68 (d, 1H), 8.20 (d, 1H), 7.77 (d, 2H), 7.47 (d, 1H), 7.22 (d, 1H), 7.16 (d, 2H), 7.07 (d, 1H), 4.51 (dd, 1H), 4.04 (s, 3H), 2.15 – 2.00 (br. m, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.96 – 1.65 (m, 4H), 1.52 – 1.30 (br. m, 2H) ppm.
33	 (S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-12	3-methoxymethyl)isooxazole-4-caboxylic acid	Rt = 0.88 min; MS: m/z = 529.3 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.50 (s, 1H), 8.67 (d, 1H), 8.26 (d, 1H), 7.76 (d, 2H), 7.28 (d, 1H), 7.23 (d, 2H), 4.71 (s, 2H), 4.62 (dd, 1H), 3.36 (s, 3H), 2.10 (s, 3H), 2.09 – 2.06 (br. m, 2H), 1.99 (s, 3H), 2.09 - 1.70 (m, 5H), 1.50 – 1.31 (br.m, 2H) ppm.
34	 (S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)p	3-13	3-ethylisoxazole-4-carboxylic acid	Rt = 0.95 min; MS: m/z = 463,3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.45 (s, 1H), 8.71 (d, 1H), 8.19 (d, 1H), 7.78 (d, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 4.43 (dd, 1H),

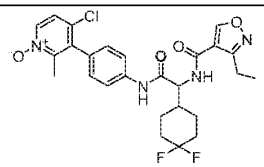
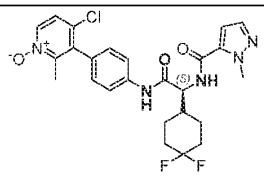
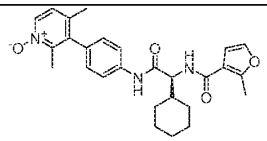
	henyl)-2,4-dimethylpyridine 1-oxide				2.84 (q, 2H), 2.08 (s, 3H), 1.96 (s, 3H), 1.87 – 1.79 (br. m, 1H), 1.69 – 1.29 (br. m, 8H), 1.17 (t, 3H) ppm.
35	 (S)-3-(4-(2-cyclopentyl-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-13	1-ethyl-1H-pyrazole-5-carboxylic acid	Rt = 0.92 min; MS: m/z = 462,3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.52 (s, 1H), 8.78 (d, 1H), 8.19 (d, 1H), 7.79 (d, 2H), 7.48 (d, 1H), 7.22 (d, 1H), 7.17 (d, 2H),7.08 (d, 1H), 4.47 (q, 2H), 4.40 (dd, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.88 – 1.77 (br. m, 1H), 1.69 – 1.25 (br. m, 8H), 1.28 (t, 3H) ppm.
36	 (S)-3-(4-(2-cyclopentyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-13	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.81 min; MS: m/z = 448.5 $[MH]^+$ (Method 10)	1H NMR (400 MHz, DMSO-d6) δ 10.36 (s, 1H), 8.64 (d, 1H), 8.19 (d, 1H), 7.76 (d, 2H), 7.46 (d, 1H), 7.22 (d, 1H), 7.17 (d, 2H), 7.05 (d, 1H), 4.42 (dd, 1H), 4.04 (s, 3H), 2.39 (br. m, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 1.90 – 1.82 (br. m, 1H), 1.71 -1.27(m, 7H) ppm.
37	 (S)-3-(4-(2-cyclopentyl-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-13	3-methylisoxazole-4-carboxylic acid	Rt = 0.87 min; MS: m/z = 449.3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.42 (s, 1H), 8.61 (d, 1H), 8.19 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.18 (d, 2H), 4.43 (dd, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 1.87 - 1.78 (br. m,

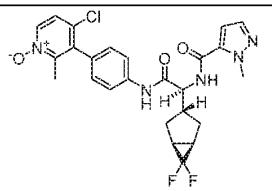
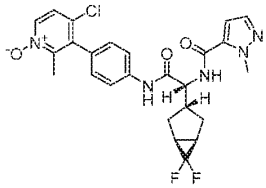
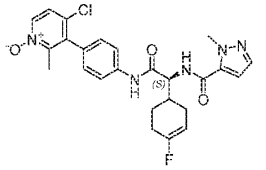
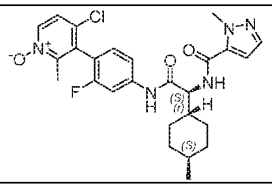
					1H), 1.69 – 1.29 (br. m, 7H) ppm.
38	 (S)-3-(4-(3-(2-chlorophenyl)-2-(3-methylisoxazole-4-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-14	3-methylisoxazole-4-carboxylic acid	Rt = 4.13 min; MS: m/z = 505 and 507 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.35 (s, 1H), 8.79 (d, 1H), 8.19 (d, 1H) 7.74 (d, 2H), 7.43 (m, 2H), 7.27 – 7.21 (m, 3H), 7.17 (d, 2H), 4.97 (m, 1H), 3.34 – 3.28 (m, 1H, partially covered by water peak), 3.15 (m, 1H), 2.31 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H) ppm.
39	 (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-15	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.90 min; MS: m/z = 462.5 $[MH]^+$ (Method 12)	1H NMR (400 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.55 (d, 1H), 8.19 (d, 1H), 7.78 (m, 2H), 7.46 (d, 1H), 7.22 (d, 1H), 7.17 (d, 2H), 7.07 (d, 1H), 4.42 (dd, 1H), 4.04 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.92 – 1.84 (br. m, 2H), 1.73 (br. m, 2H), 1.63 (br. m, 2H), 1.30 - 0.98 (m, 5H) ppm.
40	 (S)-3-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-16	1-isopropyl-1H-pyrazole-5-carboxylic acid	Rt = 5.60 min; MS: m/z = 504.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.51 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.49 (d, 1H), 7.22 (d, 1H), 7.18 (d, 2H), 6.95 (d, 1H), 5.39 (quin, 1H), 4.49 (dd, 1H), 2.16 – 2.09 (br. m, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 1.83 - 1.23 (br. m, 12H), 1.36 (dd, 6H) ppm.

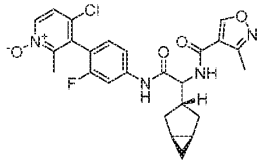
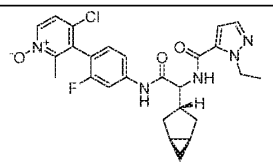
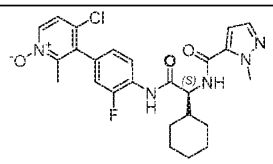
41	 (S)-3-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-16	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 4.75 min; MS: m/z = 476.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.37 (s, 1H), 8.53 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.46 (d, 1H), 7.22 (d, 1H), 7.18 (d, 2H), 7.07 (d, 1H), 4.50 (dt, 1H), 4.04 (s, 3H), 2.17 – 2.09 (br. m, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.27 - 1.86 (br. m, 12H) ppm.
42	 (S)-3-(4-(2-cycloheptyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-16	1-cyclopropyl-1H-pyrazole-5-carboxylic acid	Rt = 4.98 min; MS: m/z = 502.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.54 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.41 (d, 1H), 7.22 (d, 1H), 7.18 (d, 2H), 6.96 (d, 1H), 4.52 (dd, 1H), 4.42 (m, 1H), 2.16 – 2.10 (br. m, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 1.82 – 1.61 (br. m, 4H), 1.58 – 1.34 (br. m, 8H), 1.11 – 1.02 (m, 2H), 0.96 – 0.88 (m, 2H) ppm.
43	 2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-2-(1-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-17	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.93 min; MS: m/z = 476.4 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.27 (d, 1H), 8.15 (d, 1H), 7.78 (m, 2H), 7.46 (d, 1H), 7.26 (d, 1H), 7.19 (d, 2H), 7.11 (d, 1H), 4.72 (d, 1H), 4.03 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H), 1.62 – 1.14 (br. m, 10 H), 1.10 (s, 3H) ppm.
44		3-18	3-methylisoxazole-4-carboxylic acid	Rt = 0.93 min; MS: m/z = 478.3 $[MH]^+$	1H NMR (400 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.44 (s, 1H), 8.43 (d, 1H), 8.27 - 8.16 (m, 3H), 7.72 (dd, 1H),

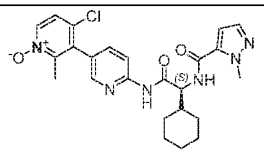
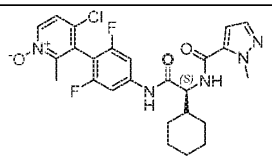
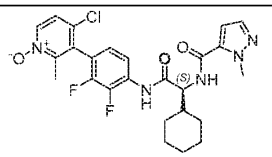
	(S)-6'-(2-cycloheptyl-2-(3-methylisoxazole-4-carboxamido)acetamido)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide			(Method 10)	7.26 (d, 1H), 4.67 (m, 1H), 2.37 (s, 3H), 2.11 (d, 3H), 2.09- 2.02 (br. m, 1H), 2.00 (d, 3H), 1.77 – 1.33 (m, 11H), 1.16 – 1.07 (br. m, 1H) ppm.
45	 (S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamid)phenyl)-2-methylpyridine 1-oxide	3-20	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 4.28 min; MS: m/z = 482 and 484 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H), 8.59 (d, 1H), 8.31 (d, 1H), 7.82 - 7.75 (m, 2H), 7.54 (d, 1H), 7.46 (d, 1H), 7.25 (d, 2H), 7.08 (d, 1H), 4.41 (dd, 1H), 4.03 (s, 3H), 2.13 (s, 3H), 1.93 - 1.81 (br.m, 2H), 1.79 - 1.57 (br.m, 4H), 1.27 – 0.99 (br.m, 5H) ppm.
46	 4-chloro-2-methyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-21	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.07 min; MS: m/z = 496 and 498 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.55 (d, 1H), 8.31 (d, 1H), 7.77 (m, 2H), 7.54 (d, 1H), 7.46 (d, 1H), 7.25 (d, 2H), 7.07 (d, 1H), 4.39 (dd, 1H), 4.03 (s, 3H), 2.13 (s, 3H), 1.92 - 1.78 (m, 2H), 1.75 – 1.66 (br. m, 2H), 1.65 – 1.57 (br. m, 1H), 1.37 - 1.19 (m, 2H), 1.11 – 0.99 (br. m, 1H), 0.94 – 0.80 (m, 5H) ppm.
47	 (S)-4-chloro-3-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-	3-22	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 4.41 min; MS: m/z = 496 and 498 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.55 (d, 1H), 8.31 (d, 1H), 7.78 (m, 2H), 7.54 (d, 1H), 7.46 (s, 1H), 7.25 (d, 2H), 7.07 (s, 1H), 4.50 (dd, 1H), 4.04

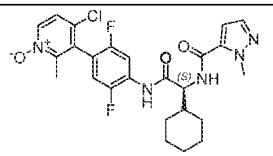
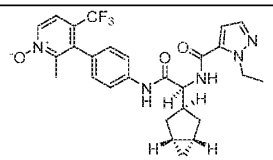
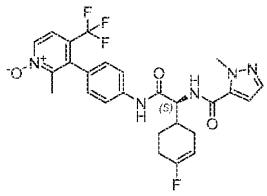
	carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide				(s, 3H), 2.19 – 2.07 (m, 1H), 2.13 (s, 3H), 1.26 (m, 12H) ppm.
48	 (S)-4-chloro-3-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-22	1-isopropyl-1H-pyrazole-5-carboxylic acid	Rt = 5.33min; MS: m/z = 524 and 526 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.53 (d, 1H), 8.31 (d, 1H), 7.77 (m, 2H), 7,54 (d, 1H), 7.49 (s, 1H), 7.25 (d, 2H), 6.95 (s, 1H), 5.39 (sep, 1H), 4.48 (dd, 1H), 2.18 – 2.08 (m, 1H), 2.13 (s, 3H), 1.84 - 1.31 (m, 12H), 1.36 (m, 6H) ppm.
49	 (S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-23	3-methylisoxazole-4-carboxylic acid	Rt = 4.00 min; MS: m/z = 519 and 521 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.44 (s, 1H), 8.62 (d, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 7.54 (d, 1H), 7.26 (d, 2H), 4.55 (dd, 1H), 2.38 (s, 3H), 2.13 (s, 3H), 2.12 – 1.68 (m, 7H), 1.24 - 1.57 (m, 2H) ppm.
50	 3-(4-((S)-2-(1-isopropyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-1	1-isopropyl-1H-pyrazole-5-carboxylic	Rt = 5.07 min; MS: m/z = 538.5 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.54 (s, 1H), 8.92 (d, 1H), 8.20 (d, 1H), 7.82 (d, 2H), 7.49 (d, 1H), 7.38 (d, 1H), 7.29 - 7.15 (m, 3H), 7.08 (d, 2H), 7.02 6.89 (m, 2H), 5.17 (sep, 1H), 4.81 (t, 1H), 3.40 – 3.25 (m, ca 1H, partly covered by water sign -al), 2.97 - 2.64 (m, 2H), 2.27 - 2.09 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.65 - 1.86 (m, 3H), 1.28 (t, 6H) ppm.

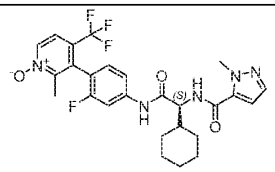
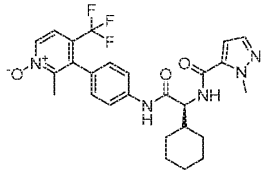
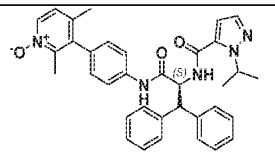
51	 4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-24	3-ethylisoxazole-4-carboxylic acid	Rt = 0.98 min; MS: m/z = 533 and 535 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.42 (d, 1H), 8.66 (d, 1H), 8.32 (dd, 1H), 7.77 (m, 2H), 7.54 (d, 1H), 7.27 (d, 2H), 4.54 (dd, 1H), 2.85 (q, 2H), 2.14 (s, 3H), 2.10 – 1.69 (m, 7H), 1.51 – 1.30 (m, 2H), 1.17 (t, 3H) ppm.
52	 (S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-23	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.84 min; MS: m/z = 518 and 520 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.67 (d, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 7.54 (d, 1H), 7.47 (d, 1H), 7.26 (d, 2H), 7.07 (d, 1H), 4.51 (dd, 1H), 4.04 (s, 3H), 2.13 (s, 3H), 2.11 – 1.67 (br. m, 6H), 1.54 – 1.27 (m, 3H).
53	 (S)-3-(4-(2-cyclohexyl-2-(2-methylfuran-3-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-15	2-methylfuran-3-carboxylic acid	Rt = 1.05 min; MS: m/z = 462.5 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.34 (s, 1H), 8.19 (d, 1H), 8.00 (d, 1H), 7.77 (d, 2H), 7.52 (d, 1H), 7.21 (d, 1H), 7.16 (d, 2H), 7.06 (d, 1H), 4.41 (dd, 1H), 2.50 (Furan-CH_3, covered by water signal), 2.08 (s, 3H), 1.96 (s, 3H), 1.92 – 1.82 (br. m, 2H), 1.76 – 1.68 (br. m, 2H), 1.65 – 1.59 (br.m, 2H), 1.24 – 0.98 (br. m, 5H) ppm.

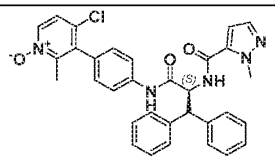
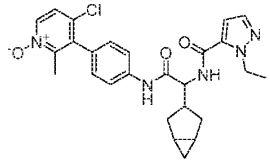
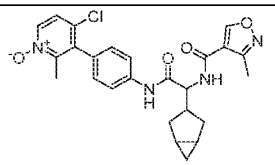
54a	 4-chloro-3-(4-((S)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-26	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 10.15 min; MS: m/z = 516.2 and 518 $[MH]^+$ (Method 13)	^{1}H NMR (300 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.76 (d, 1H), 8.32 (d, 1H), 7.83 – 7.69 (br. m, 2H), 7.55 (d, 1H), 7.47 (d, 1H), 7.26 (d, 2H), 7.07 (d, 1H), 4.45 (dd, 1H), 4.04 (s, 3H), 2.27 – 2.05 (br. m, 4H), 2.13 (s, 3H), 2.05 – 1.76 (m, 3H).
54b	 4-chloro-3-(4-((R)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-26	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 10.15 min; MS: m/z = 516.2 and 518 $[MH]^+$ (Method 13)	^{1}H NMR (300 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.76 (d, 1H), 8.32 (d, 1H), 7.83 – 7.69 (m, 2H), 7.55 (d, 1H), 7.47 (d, 1H), 7.26 (d, 2H), 7.07 (d, 1H), 4.45 (dd, 1H), 4.04 (s, 3H), 2.27 – 2.09 (br. m, 4H), 2.13 (s, 3H), 2.05 – 1.76 (m, 3H).
55	 4-chloro-3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-27	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.89 min; MS: m/z = 498 and 500 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.53 (s, 1H), 8.70 (d, 1H), 8.31 (d, 1H), 7.79 (m, 2H), 7.54 (d, 1H), 7.47 (d, 1H), 7.26 (d, 2H), 7.09 (d, 1H), 5.22 (br. m, 1H), 4.56 (dd, 1H), 4.04 (s, 3H), 2.31 – 2.16 (br. m, 4H), 2.13 (s, 3H), 2.00 – 1.88 (br. m, 1H), 1.86 – 1.77 (br. m, 1H), 1.63 – 1.53 (br. m, 1H) ppm.
56		3-28	1-methyl-1H-pyrazole-5-carboxylic acid	LC-MS: Rt = 1.08 min; MS: m/z = 514 and 516	1H NMR (400 MHz, DMSO-d6) δ 10.63 (s, 1H), 8.59 (d, 1H), 8.36 (d, 1H), 7.81 (m, 1H), 7.59 (d, 1H), 7.54 -

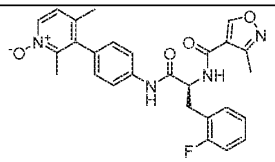
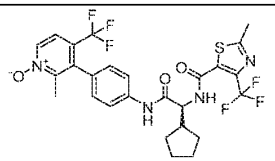
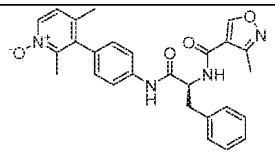
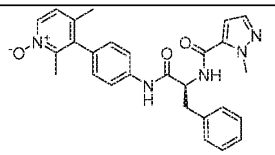
	4-chloro-3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide			[MH]+ (Method 1)	7.44 (m, 2H), 7.34 (m, 1H), 7.07 (d, 1H), 4.37 (dd, 1H), 4.03 (s, 3H), 2.15 (s, 3H), 1.94 - 1.78 (br. m, 2H), 1.77 - 1.66 (br. m, 2H), 1.65 – 1.57 (br. m, 1H), 1.38 - 1.16 (br. m, 2H), 1.12 - 0.98 (m, 1H), 0.96 - 0.79 (m, 5H) ppm.
57	 3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	3-29	3-methylisoxazole-4-carboxylic acid	LC-MS: Rt = 6.34 min; MS: m/z = 499.2 [MH]+ (Method 16)	1H NMR (300 MHz, Methanol-d4) δ 10.40 (s, 1H), 9.12 (s, 1H), 8.46 (d, 1H), 8.39 (d, 1H), 7.78 (d, 1H), 7.61 (d, 1H), 7.47 (d, 1H), 7.27 (dd, 1H), 4.41 (m, 1H), 2.43 (s, 3H), 2.33 (s, 3H), 2.20 – 1.98 (m, 2H), 1.88 – 1.57 (m, 3H), 1.33 (br. m, 2H), 0.41 – 0.22 (m, 2H).
58	 3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	3-29	1-ethyl-1H-pyrazole-5-carboxylic acid	LC-MS: Rt = 6.44 min; MS: m/z = 512.2 [MH]+ (Method 16)	1H NMR (300 MHz, Methanol-d4) δ 10.40 (s, 1H, exchangeable), 8.39 (d, 1H), 7.79 (m, 1H), 7.61 (d, 1H), 7.47 (m, 2H), 7.28 (dd, 1H), 6.86 (d, 1H), 4.56 – 4.39 (m, 3H),2.33 (s, 3H), 2.19 – 2.01 (br. m, 2H), 1.89 – 1.54 (m, 3H), 1.44 – 1.25 (m, 5H), 0.40 – 0.25 (m, 2H).
59		3-32	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.93 min; MS: m/z = 500 and 502 [MH]+	1H NMR (400 MHz, DMSO-d6) δ 10.12 (s, 1H), 8.50 (d, 1H), 8.34 (d, 1H), 8.02 (td, 1H), 7.56 (dd, 1H), 7.46 (d, 1H), 7.33 (dd,

	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-3-fluorophenyl)-2-methylpyridine 1-oxide			(Method 1)	1H), 7.11 (dd, 1H), 7.05 (d, 1H), 4.59 (m, 1H), 4.04 (s, 3H), 2.14 (s, 3H), 1.93 – 1.81 (br. m, 2H), 1.77 – 1.60 (br. m, 4H), 1.27 – 1.02 (br. m, 5H) ppm
60	 (S)-4-chloro-6'-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-methyl-[3,3'-bipyridine] 1-oxide	3-33	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.84 min; MS: m/z = 483 and 485 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.85 (d, 1H), 8.49 (d,1H), 8.36 (d, 1H), 8.31 (d, 1H), 8.22 (d, 1H), 7.79 (dd, 1H), 7.58 (d, 1H), 7.47 (d, 1H), 7.05 (d, 1H), 4.56 (dd, 1H), 4.02 (s, 3H), 2.16 (s, 3H), 1.95 – 1.79 (br. m, 2H), 1.73 (br. m, 2H), 1.62 (br. m, 2H), 1.28 – 1.02 (m, 5H) ppm.
61	 (S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,6-difluorophenyl)-2-methylpyridine 1-oxide	3-34	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.05 min; MS: m/z = 518 and 520 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.61 (d, 1H), 8.42 (d, 1H), 7.65 (dd, 1H), 7.57 (m, 2H), 7.47 (d, 1H), 7.07 (d, 1H), 4.36 (dd, 1H), 4.03 (s, 3H), 2.19 (s, 3H), 1.96 - 1.62 (m, 6H), 1.21 - 0.97 (m, 5H) ppm.
62	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,3-difluorophenyl)-2-methylpyridine 1-oxide	3-35	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.01 and 1.02 min (1:1 mixture of atropisomers); MS: m/z = 518 and 520 $[MH]^+$	1H NMR (500 MHz, DMSO-d6, faster eluting atropisomer) δ 10.37(s, 1H), 8.54 (d, 1H), 8.40 (d, 1H), 7.84 (t, 1H), 7.62 (d, 1H), 7.47 (d, 1H), 7.24 - 7.17 (m, 1H), 7.05 (d, 1H), 4.59 (dd, 1H), 4.04 (s, 3H), 2.18 (s, 3H), 1.95 – 1.81

				(Method 2)	(br. m, 2H), 1.74 (br. m, 2H), 1.65 (br. m, 2H), 1.26 – 1.05 (br. m, 5H) ppm.
63	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,5-difluorophenyl)-2-methylpyridine 1-oxide	3-36	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.00 and 1.02 min (1:1 mixture of atropisomers); MS: m/z = 518 and 520 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6, faster eluting atropisomer) δ 10.34 (s, 1H), 8.53 (d, 1H), 8.39 (d, 1H), 8.08 (dd, 1H), 7.61 (d, 1H), 7.53 - 7.48 (m, 1H), 7.47 (d, 1H), 7.05 (d, 1H), 4.63 (dd, 1H), 4.03 (s, 3H), 2.17 (s, 3H), 1.97 - 1.80 (m, 2H), 1.80 - 1.70 (m, 2H), 1.63 (m, 2H), 1.34 - 0.93 (m, 5H) ppm.
64	 3-(4-((S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-37	1-ethyl-1H-pyrazole-5-carboxylic acid	LC-MS: Rt = 1.38 min; MS: m/z = 528 $[MH]^+$ (Method 15)	1H NMR (300 MHz, Chloroform-d) δ 8.35 (d, 1H), 8.26 (s, 1H), 7.65 (d, 2H), 7.47 (d, 2H), 7.16 (d, 2H), 6.68 – 6.54 (m, 2H), 4.59 (q, 2H), 4.49 (dd, 1H), 2.21 (s, 4H), 2.01 (ddd, 2H), 1.44 (t, 3H), 1.32 (dd, 4H), 0.86 (d, 2H).
65	 3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-	3-38	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.97 min; MS: m/z = 532 $[MH]^+$ (Method 9)	1H NMR (400 MHz, DMSO-d6) δ 10.51 (d, 1H), 8.69 (dd, 1H), 8.48 (d, 1H), 7.83 – 7.75 (m, 2H), 7.70 (d, 1H), 7.47 (m, 1H), 7.25 (d, 2H), 7.09 (d, 1H), 5.23 (br. d, 1H), 4.54 (dt, 1H), 4.04 (s, 3H), 2.61 (br. s, 1H), 2.30 – 2.09 (m, 3H), 2.05 (s, 3H), 2.00 – 1.80 (br. m, 2H), 1.64 –

	(trifluoromethyl)pyridine 1-oxide				1.46 (br. m, 1H) ppm.
66	 3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-39	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.10 min; MS: m/z = 534 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.60 (d, 1H), 8.54 (d, 1H), 7.79 (dd, 1H), 7.76 (d, 1H), 7.50 (dd, 1H), 7.46 (d, 1H), 7.32 (t, 1H), 7.07 (d, 1H), 4.40 (dd, 1H), 4.03 (s, 3H), 2.08 (s, 3H), 1.99 – 1.56 (m, 6H), 1.24 – 1.01 (br. m, 5H).
67	 (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-47	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.52 min; MS: m/z = 516 $[MH]^+$ (Method 7)	1H NMR(400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.55 (d, 1H), 8.48 (d, 1H), 7.75 (m, 2H), 7.70 (d, 1H), 7.46 (d, 1H), 7.24 (d, 2H), 7.07 (d, 1H), 4.42 (dd, 1H), 4.04 (s, 3H), 2.05 (s, 3H), 1.88 (br. m, 2H), 1.79 – 1.69 (br. m, 2H), 1.67 – 1.58 (br. m, 2H), 1.52 – 0.99 (br. m, 5H) ppm.
68	 (S)-3-(4-(2-(1-isopropyl-1H-pyrazole-5-carboxamido)-3,3-diphenylpropanamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-54	1-isopropyl-1H-pyrazole-5-carboxylic acid	Rt = 4.96 min; MS: m/z = 574 $[MH]^+$ (method 8).	1H NMR (400 MHz, DMSO-d6) δ ppm 10.39 (s, 1H), 8.91 (d, 1H), 8.18 (d, 1H), 7.55 (d, 2H), 7.48 - 7.42 (m, 4H), 7.39 (d, 1H), 7.29 - 7.19 (m, 5H), 7.16 – 7.08 (m, 4H), 6.60 (d, 1H), 5.65 (dd, 1H), 5.12 (sep, 1H), 4.63 (d, 1H), 2.03 (s, 3H), 1.92 (s, 3H), 1.29 (d, 3H), 1.21 (d, 3H) ppm.

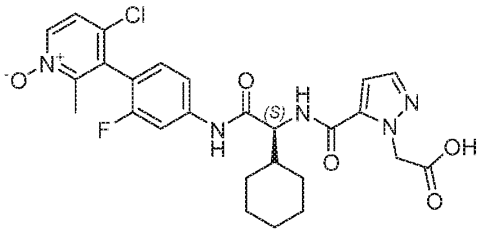
69	 (S)-4-chloro-2-methyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-3,3-diphenylpropanamido)phenyl)pyridine 1-oxide	3-55	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 4.55 min; MS: m/z = 566, 568 $[MH]^+$ (method 8)	1H NMR (400 MHz, DMSO-d6) δ ppm 10.45 (s, 1H), 8.91 (d, 1H), 8.29 (d, 1H), 7.55 (d, 2H), 7.52 – 7.47 (m, 3H), 7.43 (d, 2H), 7.37 (d, 1H), 7.29 – 7.22 (m, 4H), 7.18 – 7.09 (m, 4H), 6.77 (d, 1H), 5.65 (dd, 1H), 4.65 (d, 1H), 2.50 (s, 3H), 2.08 (s, 3H) ppm.
70	 3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	3-25	1-ethyl-1H-pyrazole-5-carboxylic acid	Rt = 1.05 min; MS: m/z = 494, 496 $[MH]^+$ (method 3)	1H NMR (400 MHz, DMSO-d6) δ ppm 10.35 (s, 1H), 8.58 (d, 1H), 8.31 (d, 1H), 7.78 (m, 2H), 7.54 (d, 1H), 7.48 (d, 1H), 7.25 (d, 2H), 7.00 (d, 1H), 4.46 (q, 2H), 4.39 (dd, 1H), 2.19 – 1.97 (m, 2H), 2.13 (s, 3H), 1.78 – 1.64 (m, 2H), 1.56 – 1.48 (m, 1H), 1.20 - 1.38 (m, 5H), 0.34 - 0.28 (m, 1H), 0.21 – 0.17 (m, 1H).
71	 3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	3-25	3-methylisoxazole-4-carboxylic acid	Rt = 4.27 min; MS: m/z = 481, 483 $[MH]^+$ (method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.41 (s, 1H), 8.53 (d, 1H), 8.32 (d, 1H), 7.86 - 7.66 (m, 2H), 7.54 (d, 1H), 7.25 (d, 2H) 4.43 (dd, 1H), 2.37 (s, 3H), 2.13 (s, 3H), 2.10 - 1.91 (m, 2H), 1.77 – 1.65 (m, 2H), 1.58 – 1.52 (m, 1H), 1.27 (br m, 2H), 0.35 – 0.28 (m, 1H), 0.21 - 0.16 (m, 1H) ppm

72	 (S)-3-(4-(3-(2-fluorophenyl)-2-(3-methylisoxazole-4-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-60	3-methylisoxazole-4-carboxylic acid	Rt = 0.85 min; MS: m/z = 489.3 $[MH]^+$ (method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.34 (s, 1H), 8.76 (d, 1H), 8.20 (d, 1H), 7.72 (m, 2H), 7.39 (m, 1H), 7.29 – 7.09 (m, 6H), 4.94 (dt, 1H), 3.23 (m, 1H), 3.06 (m, 1H), 2.31 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H) ppm.
73	 (S)-3-(4-(2-cyclopentyl-2-(2-methyl-4-(trifluoromethyl)thiazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	3-5	2-methyl-4-(trifluoromethyl)thiazole-5-carboxylic acid	Rt = 1.09 min; MS: m/z = 587.2 $[MH]^+$ (method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.29 (d, 1H), 8.48 (d, 1H), 7.78 – 7.67 (m, 3H), 7.25 (d, 2H), 4.45 (dd, 1H), 2.73 (s, 3H), 2.29 (m, 1H), 2.06 (s, 3H), 1.83 – 1.74 (br. m, 1H), 1.69 – 1.57 (br. m, 3H), 1.57 – 1.28 (br. m, 4H) ppm.
74	 (S)-2,4-dimethyl-3-(4-(2-(3-methylisoxazole-4-carboxamido)-3-phenylpropanamido)phenyl)pyridine 1-oxide	3-59	3-methylisoxazole-4-carboxylic acid	Rt = 0.83 min; MS: m/z = 471.4 $[MH]^+$ (method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.34 (s, 1H), 8.75 (d, 1H), 8.20 (d, 1H), 7.74 (m, 2H), 7.38 (d, 2H), 7.29 (t, 2H), 7.20 (m, 4H), 4.86 (m, 1H), 3.17 (dd, 1H), 3.00 (dd, 1H), 2.29 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H) ppm.
75	 (S)-2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-3-phenylpropanamido)phenyl)pyridine 1-oxide	3-59	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.82 min; MS: m/z = 470.3 $[MH]^+$ (method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.79 (d, 1H), 8.20 (d, 1H), 7.76 (d, 2H), 7.45 (d, 1H), 7.41 (d, 2H), 7.29 (t, 2H), 7.21 (m, 4H), 6.96 (d, 1H), 4.86 (m, 1H), 3.18 (dd, 1H), 3.08 (dd, 1H), 2.50 (s, 3H), 2.09

					(s, 3H), 1.97 (s, 3H) ppm.

Example 76:

4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-methoxy-2-oxoethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



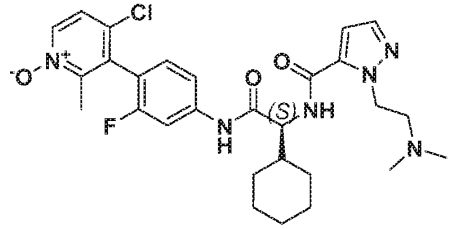
To a solution of 3-(4-((S)-2-amino-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide (Intermediate 3-2, 61 mg, 0.142 mmol), 1-(2-methoxy-2-oxoethyl)-1H-pyrazole-5-carboxylic acid (Intermediate 4-1, 28.8 mg, 0.157 mmol) and 2,4,6-collidine (0.057 ml, 0.427 mmol) in DMF (5 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (50.0 mg, 0.171 mmol) and the reaction mixture was stirred for 80h at RT. The solvent was evaporated, the residue was taken up in EtOAc (50 mL) and extracted with sat Na_2CO_3 followed by water. The combined aqueous layers were re-extracted with EtOAc. LC-MS analysis of the aqueous layer indicated that the initially formed methyl ester was saponified under the extraction conditions to the desired acid. The aqueous layer was evaporated to a volume of ca 5 mL and then acidified to pH 4 by addition of 1M HCl and evaporated again. The residue was taken up in acetonitrile/MeOH 1:1 (4 mL), filtered, and the filtrate was purified by column chromatography on RP-18 (column: RediSep RP-18, 26 g; eluent: water/acetonitrile 95:5 to 0:100,) to yield the title compound (44 mg, 55 %) as a colorless solid.

LC-MS: Rt = 0.87 and 0.88 min (1:1 mixture of atropisomers); MS: m/z = 544 and 546 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.82 (br. s, 1H), 8.36 (d, 1H), 7.87 (m, 1H), 7.58 (m, 2H), 7.40 (br. s, 1H), 7.31 (m, 1H), 6.80 (br. s, 1H), 4.97 – 4.74 (br. m, 2H), 4.38 (m, 1H), 2.15 (s, 3H), 1.95 – 1.84 (br. m, 1H), 1.80 – 1.66 (br. m, 3H), 1.64 – 1.55 (br. m, 2H), 1.25 – 1.07 (br. m, 5H) ppm.

Example 77:

4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



Step 1: 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-oxoethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide

To a cooled (0°C) solution of 100 mg 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-hydroxyethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (Example 17; 100 mg, 0.19 mmol) in DCM (1.9 mL) was added portionwise Dess-Martin periodinane (160 mg, 0.38 mmol). After stirring at 0ºC for 30 min and 2.5h at RT the reaction mixture was diluted with EtOAc and washed with 1M NaOH solution, water and brine washed. The organic phase was dried (Na_2SO_4) and evaporated to yield the title compound (98 mg, 98 %) as a yellow oil which was used in the next step without further purification.

LC-MS: Rt = 0.93 and 0.94 min (atropisomers); MS: m/z = 528 and 530 $[MH]^+$ (Method 3).

Step 2: 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide

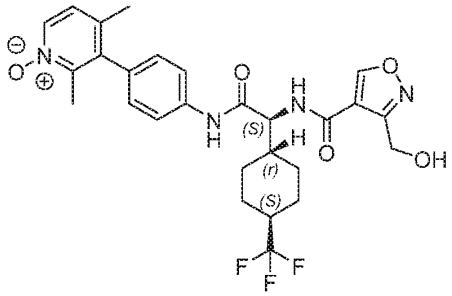
To a solution of 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-oxoethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (Step 1; 90 mg, 0.17 mmol) in methanol (1.7 mL) was added a 2M solution of dimethylamine in methanol (0.51 mL, 1.02 mmol). After stirring the mixture for 10 min at RT, $NaBH_3CN$ (54 mg, 0.85 mmol) and acetic acid (0.02 mL, 0.34 mmol) were added and the reaction mixture was stirred at RT overnight. The mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and evaporated. Purification of the residue by SFC (column: 250x30 Waters Torrus 2-PIC 130A 5um; gradient: 15-24% MeOH in 7min) provided the title compound (33 mg, 33%) as a yellow oil.

LC-MS: Rt = 0.70 and 0.72 min (atropisomers); MS: m/z = 557 and 559 $[MH]^+$ (Method 10)

1H NMR (400 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.75 (d, 1H), 8.37 (d, 1H), 7.82 (m, 1H), 7.44 - 7.64 (m, 3H), 7.34 (m, 1H), 7.11 (d, 1H), 4.69 (br. m, 2H), 4.42 (dd, 1H), 3.03 (br. s, 2H), 2.39 - 2.47 (br. s, 6H), 2.15 (s, 3H), 1.52 - 2.01 (m, 6H), 0.95 - 1.32 (m, 5H) ppm.

Example 78:

3-(4-((S)-2-(3-(hydroxymethyl)isoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



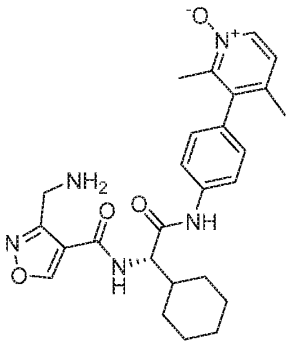
To a cooled (-78°C) solution of 3-(4-((S)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Example 31, 110 mg, 0.196 mmol) in DCM (10 mL) was added dropwise a 1M solution of BBr_3 in DCM (0.59 mL, 0.59 mmol). The mixture was stirred at – 78 °C for 1h, then at 0°C for 1h, then at RT for 4h. The reaction mixture was then diluted with EtOAc, extracted with sat. aq. $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated. The residue was purified by prep. HPLC on RP-18 (column: Waters SunFire 30x100 mm; eluent: water+0.1 %TFA / acetonitrile+0.1%TFA 95:5 to 0:100; flow 15 mL/min) to yield the title compound (63 mg, 57 %) as a colorless solid.

LC-MS: Rt = 0.91 min; MS: m/z = 547.3 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.46 (s, 1H), 8.94 (d, 1H), 8.20 (d, 1H), 7.75 (d, 2H), 7.22 (d, 1H), 7.18 (d, 2H), 6.11 (dd, 1H), 4.74 (d, 2H), 4.55 (t, 1H), 2.34 – 2.20 (br. m, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 2.00 – 1.73 (m, 5H), 1.36 – 1.12 (m, 4H) ppm.

Example 79:

(S)-3-(4-(2-(3-(aminomethyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide



Step 1: (S)-3-(4-(2-(3-(((tert-butoxycarbonyl)amino)methyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide

The title compound was prepared from Intermediate 3-15 and 3-(((tert-butoxycarbonyl)amino)methyl)isoxazole-4-carboxylic acid by a procedure similar to that of Example 1.

LC-MS: Rt = 1.04 min; MS: m/z = 578.5 $[MH]^+$ (Method 2).

Step 2: (S)-3-(4-(2-(3-(aminomethyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide

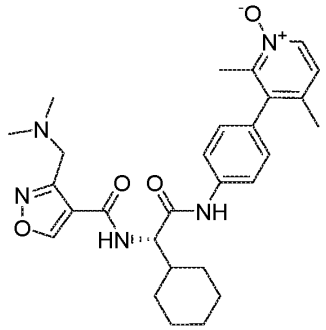
(S)-3-(4-(2-(3-(((tert-butoxycarbonyl)amino)methyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Step 1, 250 mg, 0.433 mmol) was treated with 4N HCl in dioxane (4 mL). A small amount of methanol was added to obtain a clear solution. After stirring at RT for 1h the mixture was evaporated and the residue was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to yield the title compound (273 mg, 100 %) as an off-white solid. For biological testing, a part of this material was further purified by SFC (column: 250x30 Princeton PPU 100A 5um; elution with 15-24% MeOH in 7min).

LC-MS: Rt = 0.71 min; MS: m/z = 578.5 $[MH]^+$ (Method 12).

1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.72 (s, 1H), 8.92 (d, 1H), 8.30 (br. m, 2H), 8.20 (d, 1H), 7.83 - 7.70 (m, 2H), 7.23 (d, 1H), 7.18 (d, 2H), 4.47 (dd, 1H), 4.35 (s, 2H), 2.08 (s, 3H), 1.96 (s, 3H), 1.90 – 1.80 (br. m, 2H), 1.78 – 1.69 (br. m, 2H), 1.67 – 1.60 (br. m, 2H), 1.25 – 1.04 (br. m, 5H) ppm.

Example 80:

(S)-3-(4-(2-cyclohexyl-2-(3-((dimethylamino)methyl)isoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



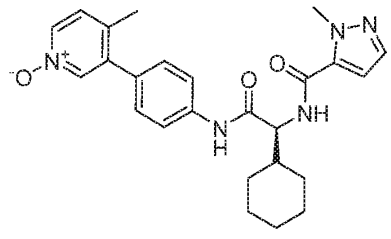
To a stirred solution of (S)-3-(4-(2-(3-(aminomethyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide (Example 62; 200 mg, 0.419 mmol) in MeOH (4 mL) was added 37% aqueous formaldehyde (0.187 ml, 2.51 mmol). After 10min $NaBH_3CN$ (132 mg, 2.1 mmol) and acetic acid (0.048 ml, 0.84 mmol) were added and stirring was continued at RT for 80 min. The mixture was partitioned between EtOAc and sat. $NaHCO_3$, the aqueous layer was extracted twice with EtOAc, the combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by prep. HPLC (column: Sunfire 30x100mm, gradient: 5 – 90 % ACN in water + 0.1 % TFA) to yield the title compound 69 mg, 32 %) as a colorless solid.

LC-MS: Rt = 0.78 min; MS: m/z = 506.5 $[MH]^+$ (Method 2).

1H NMR (400 MHz, DMSO-d6) δ 10.72 (d, 1H), 10.38 (s, 1H), 9.40 (s, 1H), 8.19 (d, 1H), 7.74 (d, 2H), 7.23 (d, 1H), 7.16 (d, 2H), 4.58 (dd, 1H), 3.73 (s, 2H), 2.29 (s, 6H), 2.08 (s, 3H), 1.96 (s, 3H), 1.80 – 1.54 (m, 6H), 1.36 – 0.96 (m, 5H) ppm.

Example 81:

(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-methylpyridine 1-oxide



Step 1: Tert-butyl (S)-(1-cyclohexyl-2-((4-iodophenyl)amino)-2-oxoethyl)carbamate

To a solution of Boc-(L)-cyclohexyl glycine (3.0 g, 11.66 mmol) and 2,4,6-collidine (6.21 ml, 46.6 mmol) in DMF (20 mL) was added HATU (4.88 g, 12.82 mmol). After stirring this mixture for 10 min at RT p-iodoaniline (2.55 g, 11.66 mmol) was added and stirring was continued at RT overnight. The reaction mixture was partitioned between aq. $NaHCO_3$ and EtOAc, the aqueous layer was extracted with EtOAc. The combined porganic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80 g; solvent: 10 – 20 % EtOAc in cyclohexane) to yield the title compound (4.42 g, 78 %) as a colorless solid.
LC-MS: Rt 1.35 min; MS: m/z = 459 $[MH]^+$ (Method 1).

Step 2: (S)-2-amino-2-cyclohexyl-N-(4-iodophenyl)acetamide

Tert-butyl (S)-(1-cyclohexyl-2-((4-iodophenyl)amino)-2-oxoethyl)carbamate (Step 1; 4.42 g, 9.64 mmol) was treated with 4N HCl in dioxane (1 mL). After stirring at RT for 30min HPLC analysis indicated the complete consumption of the starting material. The mixture was evaporated and dried in HV to yield the tiltle compound (3.94 g, 100 %) as an off-white solid which was used in the next step without further purification.
LC-MS: Rt 0.79 min; MS: m/z = 358 $[MH]^+$ (Method 1).

Step 3: (S)-N-(1-cyclohexyl-2-((4-iodophenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide

To a solution of 1-methyl-1H-pyrazole-5-carboxylic acid (0.620 g, 4.92 mmol) and 2,4,6-collidine (2.62 ml, 19.66 mmol) in DMF (20 ml) was added HATU (2.056 g, 5.41 mmol). After stirring this mixture for 10 min at RT, (S)-2-amino-2-cyclohexyl-N-(4-iodophenyl)acetamide (Step 2; 2 g, 4.92 mmol) was added at rt in one portion, and stirring was continued at RT for 1h. The reaction mixture was partitioned between aq. $NaHCO_3$ and EtOAc, the aqueous layer was extracted with EtOAc. The combined porganic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica (column: RediSep 80 g; solvent: 0 – 65 % EtOAc in cyclohexane) to yield the title compound (2.06 g, 86 %) as an off-white solid.
LC-MS: Rt 1.19 min; MS: m/z = 467 $[MH]^+$ (Method 1).

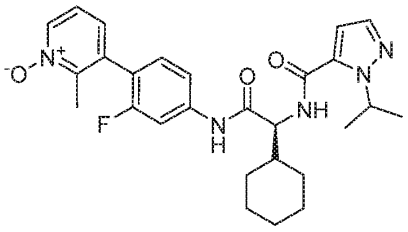
Step 4: (S)-N-(1-cyclohexyl-2-((4-(4-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide

A MW-Vial was charged 3-bromo-4-methylpyridine (100 mg, 0.581 mmol), XPhos Pd G2 (45.7 mg, 0.058 mmol), diboronic acid (78 mg, 0.872 mmol), potassium acetate (171 mg, 1.744 mmol) and XPhos (55.4 mg, 0.116 mmol) in ethanol (7 mL). Ethylene glycol (0.097 mL, 1.744 mmol) was added, and mixture was purged with nitrogen for 5 min, followed by stirring for 90 min at 90°C. After cooling to RT, 1M aq. K_3PO_4 (1.75 mL) and a solution of (S)-N-(1-cyclohexyl-2-((4-iodophenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide (Step 3; 271 mg, 0.581 mmol) in EtOH (2 mL) were added and the mixture was stirred at 90°C for 2h. After cooling, the mixture was diluted with EtOAc (50 mL) and filtered through Celite. The filtrate was washed with 1M Na_2CO_3 solution and water. The aqueous phases were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by prep HPLC (column: Waters SunFire 30x100 mm; C18; 5µm; Flow 40 ml/min solvents: water+0.1% TFA / acetonitrile +0.1% TFA), to yield the title compound (196 mg, 78 %) as a colorless solid.
LC-MS: Rt 0.97 min; MS: m/z = 432.3 $[MH]^+$ (Method 2).

Step 5: (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-methylpyridine 1-oxide

To a solution of (S)-N-(1-cyclohexyl-2-((4-(4-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide (Step 4; 153 mg, 0.355 mmol) in DCM (5 mL) was added mCPBA (73.4 mg, 0.425 mmol) 4 portions over 1h. After stirring the mixture at RT for 1h HPLC indicated complete conversion of the starting material. The mixture was diluted with EtOAc and extracted with sat. aq. Na_2CO_3 solution, followed by water. The aqueous layers were re-extracted with EtOAc and the combined organic layers were evaporated to yield the title compound (93 mg, 59 %) as a colorless solid.
LC-MS: Rt 0.93 min; MS: m/z = 448.4 $[MH]^+$ (Method 2).
1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.55 (d, 1H), 8.10 (d, 1H), 8.04 (d, 1H), 7.75 (d, 2H), 7.46 (d, 1H), 7.37 (d, 2H), 7.33 (d, 1H), 7.07 (d, 1H), 4.41 (dd, 1H), 4.03 (s, 3H), 2.20 (s, 3H), 1.93 – 1.81 (br. m, 2H), 1.76 – 1.68 (br. m, 2H), 1.65 – 1.57 (br. m, 2H), 1.24 – 0.98 (m, 5H) ppm.

Example 82:
(S)-3-(4-(2-cyclohexyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



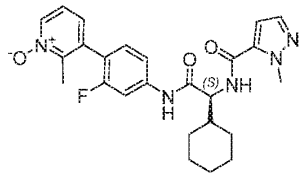
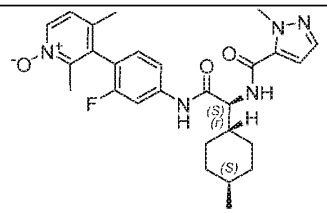
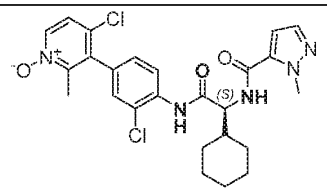
Step 1: (S)-N-(1-cyclohexyl-2-((3-fluoro-4-(2-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1H-pyrazole-5-carboxamide

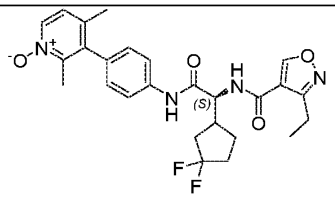
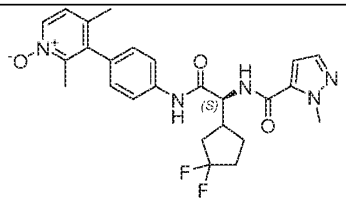
The title compound (100 mg, 46%) was prepared from Intermediate 3-41 (250 mg, 0.44 mmol) and 1-isopropyl-1H-pyrazole-5-carboxylic acid (68 mg, 0.44 mmol) by a procedure similar to that of Example 1.
LC-MS: Rt 1.11 min; MS: m/z = 478.2 $[MH]^+$ (Method 2).

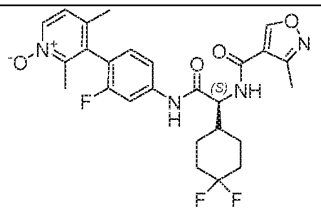
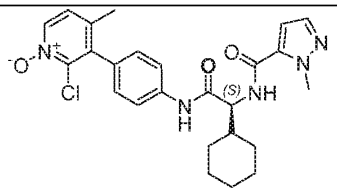
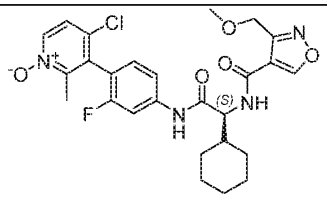
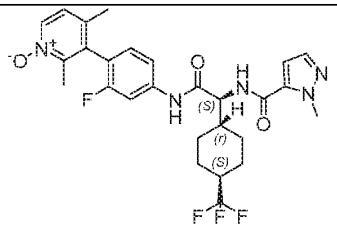
Step 2: (S)-3-(4-(2-cyclohexyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide

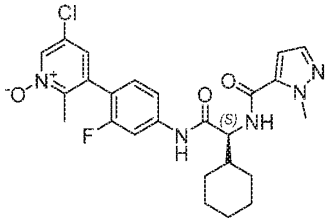
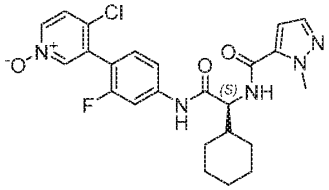
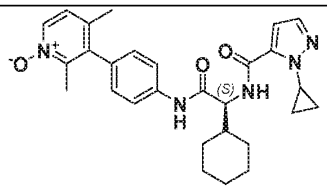
To a solution of (S)-N-(1-cyclohexyl-2-((3-fluoro-4-(2-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1H-pyrazole-5-carboxamide (Step 1, 80 mg, 0.168 mmol) in THF (1.1 mL). was added mCPBA (75 mg, 0.33 mmol). After stirring for 4h at RT, the reaction mixture was partitioned between EtOAc and sat aq. $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by prep. HPLC on RP-18 (column: Waters SunFire 30x100 mm; flow 15 mL/min; eluent: water+0.1 %TFA / acetonitrile + 0.1%TFA 95:5 to 0:100) to yield the title compound (63 mg, 75 %) as a colorless solid.
LC-MS: Rt = 1.04 min; MS: m/z = 494.2 $[MH]^+$ (Method 2).
1H NMR (400 MHz, DMSO-d6) δ 10.60 (d, 1H), 8.56 (d, 1H), 8.34 (d, 1H), 7.78 (dd, 1H), 7.56 – 7.46 (m, 2H), 7.38 (m, 2H), 7.21 (d, 1H), 6.96 (d, 1H), 5.39 (hep, 1H), 4.38 (dd, 1H), 2.21 (s, 3H), 1.95 – 1.54 (br. m, 6H), 1.37 (d, 3H), 1.35 (d, 3H), 1.25 – 1.04 (br. m, 5H) ppm.

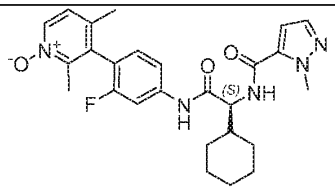
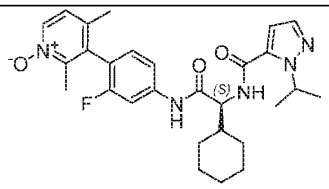
The following Examples were prepared by amide bond formation of Intermediate 3-x and the corresponding carboxylic acids (prepared as Intermediates 4-x or commercially available) followed by oxidation of the pyridine by procedures similar to that of **Example 82.**

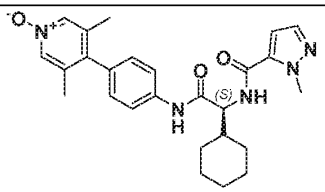
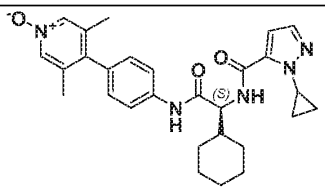
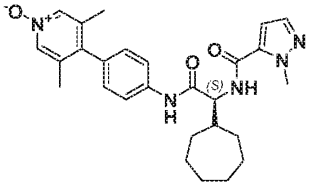
Example	Structure/Name	Inter-mediate 3-x	Inter-mediate 4-x	LC-MS (Method)	1H NMR
83	 (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-41	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 5.07 min; MS: m/z = 538.5 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.58 (d, 1H), 8.34 (dd, 1H), 7.78 (dd, 1H), 7.54 - 7.45 (m, 2H), 7.37 (m, 2H), 7.21 (dd, 1H), 7.07 (d, 1H), 4.40 (dd, 1H), 4.03 (s, 3H), 2.20 (s, 3H), 1.87 (br. m, 2H), 1.72 (br. m, 2H), 1.61 (br. m, 2H), 1.25 - 1.04 (br. m , 5H) ppm.
84	 3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-43	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.04 min; MS: m/z = 494 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.66 (d, 1H), 8.24 (d, 1H), 7.81 (d, 1H), 7.51 (d, 1H), 7.46 (d, 1H), 7.35 – 7.21 (m, 2H), 7.08 (d, 1H), 4.37 (dd, 1H), 4.03 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.93 – 1.77 (br. m, 2H), 1.75 – 1.66 (br. m, 2H), 1.65 – 1.56 (br. m, 1H), 1.37 – 1.14 (br. m, 2H), 1.11 – 0.98 (m, 1H), 0.87 (m, 5H) ppm.
85		3-44	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.98 min; MS: m/z = 516.2 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 9.80 (br. s, 1H), 8.53 (d, 1H), 8.34 (d, 1H), 7.90 (d, 1H), 7.54 (m, 2H), 7.47 (s, 1H), 7.28 (d, 1H), 7.04 (s,

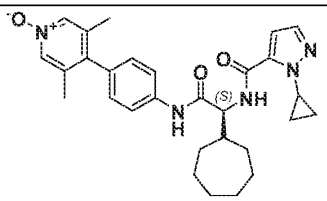
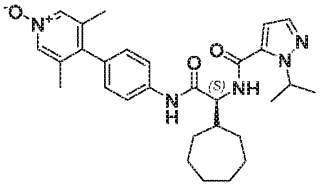
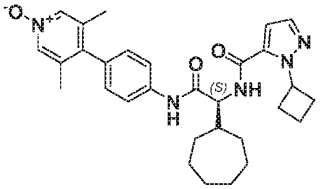
	(S)-4-chloro-3-(3-chloro-4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide				1H), 4.59 (dd, 1H), 4.05 (s, 3H), 2.13 (s, 3H), 2.01 – 1.61 (br. m, 9H), 1.28 – 1.11 (br. m, 2H) ppm.
86	 3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-45	3-ethylisoxazole-4-carboxylic acid	Rt = 0.87 min; MS: m/z = 499.3 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6, 2:1 mixture of diastereomers)) δ 10.44 and 10.40 (2s, ratio ca 2:1, 1H), 9.41 and 9.40 (2s, ratio 1:2, 1H), 8.71 and 8.70 (2d, ratio 2:1, 1H), 8.20 (d, 1H), 7.76 and 7.75 (2d, ratio 2:1, 2H), 7.22 (d, 1H), 7.19 (d, 2H), 4.60 and 4.58 (2dd, ratio 1:2, 1H), 2.85 (q, 2H), 2.72 – 2.55 (br. m, 1H), 2.44 – 1.49 (br. m, 6H), 2.08 (s, 3H), 1.97 (s, 3H), 1.18 (t, 3H) ppm.
87	 3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-45	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.77 min; MS: m/z = 484.2 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.4 and 10.39 (2s, ratio 2:1, 1H), 8.73 (t, 1H), 8.19 (d, 1H), 7.76 and 7.75 (2d, ratio 2:1 2H), 7.48 (d, 1H), 7.23 (d, 1H), 7.18 (dd, 2H), 7.05 (t, 1H), 4.66 – 4.49 (m, 1H), 4.04 (s, 3H), 3.31 (s, 3H), 2.78 – 2.65 (m, 1H), 2.47 – 2.21 (m, 1H), 2.29 – 2.11 (m, 2H), 2.08 (s, 3H), 1.97 (s, 3H) ppm.

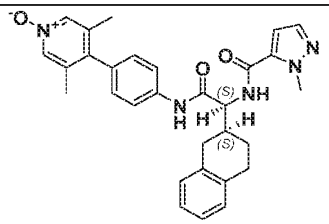
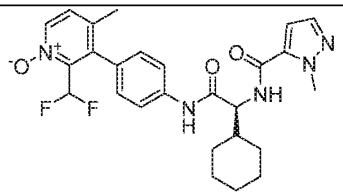
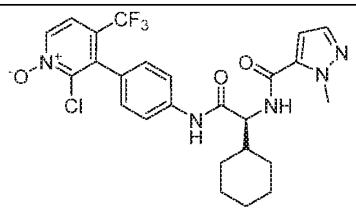
88	 3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-46	3-methylisoxazole-4-carboxylic acid	Rt = 0.92 min; MS: m/z = 517.3 [MH]+ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.44 (s, 1H), 8.67 (d, 1H), 8.24 (d, 1H), 7.80 (d, 1H), 7.49 (d, 1H), 7.31 – 7.25 (m, 2H), 4.50 (dd, 1H), 2.38 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.96 – 1.61 (m, 6H), 1.58 – 1.18 (m, 3H) ppm
89	 (S)-2-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-methylpyridine 1-oxide	3-47	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.94 min; MS: m/z = 482.3 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.52 (d, 1H), 8.38 (d, 1H), 7.83 - 7.72 (m, 2H), 7.46 (d, 1H), 7.37 (dd, 1H), 7.23 (d, 2H), 7.07 (d, 1H), 4.42 (dd, 1H), 4.03 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H) 1.94 - 1.57 (m, 6H), 1.04 (m, 2H) ppm
90	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-48	3-(methoxymethyl)1,2oxazole-4-cabonylic acid	Rt = 1.02; 1.03 min (mixture of atropisomers); MS: m/z = 531 and 533 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.49 (s, 1H), 8.58 (d, 1H), 8.37 (d, 1H), 7.80 (m, 1H), 7.59 (d, 1H), 7.49 (m, 1H), 7.35 (t, 1H), 4.71 (s, 2H), 4.49 (dd, 1H), 3.36 (s, 3H), 2.15 (s, 3H), 1.83 - 1.62 (br. m, 6H), 1.26 - 1.10 (m, 5H) ppm.
91		3-49	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.04 min; MS: m/z = 548 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.62 (d, 1H), 8.24 (d, 1H), 7.81 (dt, 1H), 7.55 – 7.44 (m, 2H), 7.31 – 7.23 (m, 2H),

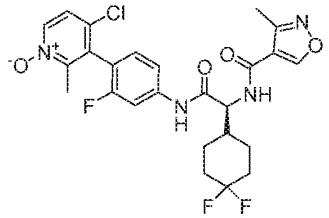
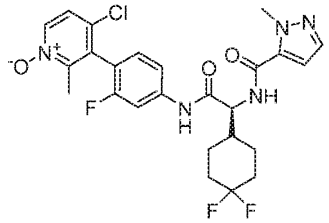
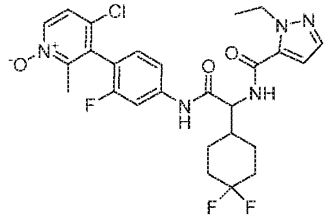
	3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide				7.07 (d, 1H), 4.42 (dd, 1H), 4.04 (s, 3H), 2.34 – 2.19 (br. m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.97 – 1.83 (br. m, 4H), 1.78 – 1.71 (br. m, 1H), 1.33 – 1.09 (m, 4H) ppm.
92	 (S)-5-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-50	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.07 min; MS: m/z = 498, and 500 $[MH]^+$ (Method 9)	1H NMR (400 MHz, DMSO-d6) δ 10.63 (s, 1H), 8.64 (d, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.53 – 7.36 (m, 4H), 7.07 (d, 1H), 4.39 (dd, 1H), 4.03 (s, 3H), 2.17 (s, 3H), 1.92 – 1.55 (br. m, 6H), 1.26 – 0.98 (br. m, 5H) ppm.
93	 (S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)pyridine 1-oxide	3-61	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.00 min; MS: m/z = 486.3 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.58 (d, 1H), 8.35 (d, 1H), 8.27 (dd, 1H), 7.78 (dd, 1H), 7.68 (d, 1H), 7.48 (dd, 2H), 7.42 (m, 1H), 7.07 (d, 1H), 4.39 (dd, 1H), 4.03 (s, 3H), 1.94 – 1.83 (br. m, 2H), 1.76 – 1.69 (br. m, 2H), 1.65 – 1.56 (br. m, 2H), 1.25 – 0.99 (br. m, 5H) ppm
94	 (S)-3-(4-(2-cyclohexyl-2-(1-cyclopropyl-1H-pyrazole-5-	3-48	1-cyclopropyl-1H-pyrazole-5-carboxylic acid	Rt = 4.40 min; MS: m/z = 488.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.54 (d, 1H), 8.19 (d, 1H), 7.77 (d, 2H), 7.42 (d, 1H), 7.22 (d, 1H), 7.17 (d, 2H), 6.97 (d, 1H), 4.48 – 4.37

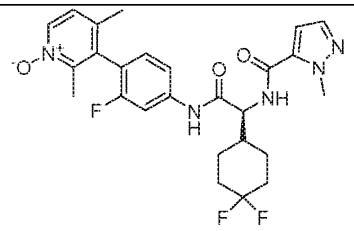
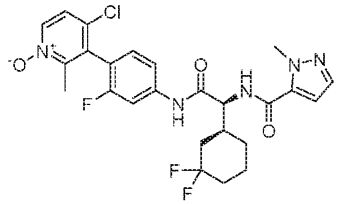
	carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide				(m, 2H), 2.08 (s, 3H), 1.97 (s, 3H), 1.93 – 1.84 (br. m, 2H), 1.77 – 1.69 (br. m, 2H), 1.67 – 1.61 (br. m, 2H), 1.23 – 1.13 (br. m, 4H), 1.16 – 0.79 (m, 5H).
95	 3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	3-57	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.91 min; MS: m/z = 480.2 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.58 (d, 1H), 8.24 (d, 1H), 7.80 (d, 1H), 7.50 (d, 1H), 7.47 (d, 1H), 7.31 - 7.22 (m , 2H), 7.07 (d, 1H), 4.40 (dd, 1H), 4.03 (s, 3H), 2.09 (d, 3H), 1.98 (s, 3H), 1.91 – 1.82 (br. m, 2H), 1.77 – 1.70 (br. m, 2H), 1.67 – 1.56 (br. m, 2H), 1.24 – 1.00 (br. m, 5H) ppm.
96	 3-(4-((S)-2-cyclohexyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	3-56	1-isopropyl-1H-pyrazole-5-carboxylic acid	Rt = 1.00 & 1.01min (Atropisomers); MS: m/z = 508 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 10.59 (s, 1H), 8.56 (d, 1H), 8.24 (d, 1H), 7.80 (d, 1H), 7.55 – 7.47 (m, 2H), 7.34 – 7.22 (m, 2H), 6.96 (d, 1H), 5.39 (hept, 1H), 4.38 (dd, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 1.93 – 1.81 (br. m, 2H), 1.77 – 1.69 (br. m, 2H), 1.66 – 1.57 (br. m, 2H), 1.37 (d, 3H), 1.35 (d, 3H), 1.19 - 1.03 (br. m, 5H) ppm.

97	 (S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-51	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.85 min; MS: m/z = 446.7 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.52 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.46 (d, 1H), 7.16 (d, 2H), 7.07 (d, 1H), 4.41 (dt, 1H), 4.03 (s, 3H), 1.94 (s, 6H), 1.89 – 1.82 (m, 2H), 1.79 – 1.58 (m, 4H), 1.28 – 1.12 (m, 4H), 1.12 – 0.97 (m, 1H) ppm.
98	 (S)-4-(4-(2-cyclohexyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-51	1-cyclopropyl-1H-pyrazole-5-carboxylic acid	Rt = 0.93 min; MS: m/z = 488.4 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.53 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.41 (d, 1H), 7.16 (d, 2H), 6.97 (d, 1H), 4.43 (m, 2H), 1.94 (s, 6H), 1.91 – 1.83 (m, 2H), 1.81 – 1.55 (m, 4H), 1.31 – 1.14 (m, 4H), 1.14 – 0.99 (m, 3H), 0.99 – 0.86 (m, 2H)ppm.
99	 (S)-4-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-52	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.93 min; MS: m/z = 476.4 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.53 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.46 (d, 1H), 7.16 (d, 2H), 7.06 (d, 1H), 4.49 (dd, 1H), 4.04 (s, 3H), 2.22 – 2.05 (m, 1H), 1.94 (s, 6H), 1.83 – 1.74 (m, 1H), 1.73 – 1.62 (m, 3H), 1.61 – 1.27 (m, 8H) ppm.

100	 (S)-4-(4-(2-cycloheptyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-52	1-cyclopropyl-1H-pyrazole-5-carboxylic acid	Rt = 0.99 min; MS: m/z = 502.2 $[MH]^+$ (Method 2)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.54 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.41 (d, 1H), 7.16 (d, 2H), 6.96 (d, 1H), 4.51 (dt, 1H), 4.46 – 4.36 (m, 1H), 2.20 – 2.07 (m, 1H), 1.94 (s, 6H), 1.83 – 1.74 (m, 1H), 1.73 – 1.63 (m, 3H), 1.62 – 1.30 (m, 8H), 1.16 – 1.00 (m, 2H), 0.99 – 0.85 (m, 2H) ppm.
101	 (S)-4-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-52	1-isopropyl-1H-pyrazole-5-carboxylic acid	Rt = 1.03 min; MS: m/z = 504.4 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.51 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.49 (d, 1H), 7.16 (d, 2H), 6.94 (d, 1H), 5.39 (hept, 1H), 4.48 (dd, 1H), 2.19 – 2.06 (m, 1H), 1.94 (s, 6H), 1.83 – 1.74 (m, 1H), 1.72 – 1.62 (m, 3H), 1.60 – 1.38 (m, 8H), 1.37 (d, 3H), 1.34 (d, 3H) ppm
102	 (S)-4-(4-(2-(1-cyclobutyl-1H-pyrazole-5-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide	3-52	1-cyclobutyl-1H-pyrazole-5-carboxylic acid	Rt = 1.07 min; MS: m/z = 516.3 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.52 (d, 1H), 8.09 (s, 2H), 7.75 (d, 2H), 7.54 (d, 1H), 7.16 (d, 2H), 6.98 (d, 1H), 5.66 – 5.47 (m, 1H), 4.47 (dd, 1H), 2.58 – 2.44 (m, 2H), 2.39 – 2.24 (m, 2H), 2.19 – 2.05 (m, 1H),

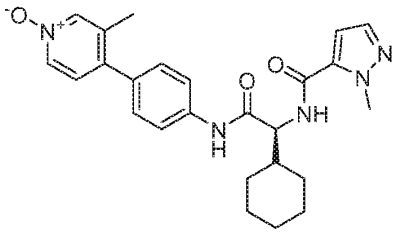
					1.94 (s, 6H), 1.84 – 1.60 (m, 6H), 1.58 – 1.30 (m, 8H) ppm
103	 3,5-dimethyl-4-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamido)phenyl)pyridine 1-oxide	3-53	2-12	Rt = 0.92 min; MS: m/z = 510.1 $[MH]^+$ (Method 1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.71 (d, 1H), 8.18 (s, 2H), 7.79 (d, 2H), 7.48 (d, 1H), 7.18 (d, 2H), 7.12 (d, 1H), 7.10 – 7.04 (m, 4H), 4.60 (dd, 1H), 4.06 (s, 3H), 3.01 – 2.83 (m, 2H), 2.84 – 2.57 (m, 2H), 2.45 – 2.28 (br. m, 1H), 1.97 (s, 6H), 1.93 – 1.85 (br. m, 1H), 1.69 – 1.49 (m, 1H) ppm
104	 (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide	3-42	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.39 min; MS: m/z = 498.4 $[MH]^+$ (Method 14)	1H NMR (300 MHz, DMSO-d6) δ 8.31 (d, 1H), 7.77 - 7.70 (m, 2H), 7.54 (d, 1H), 7.47 (m, 1H), 7.27 - 7.09 (m, 3H), 6.90 (d, 1H), 4.47 (d, 1H), 4.08 (s, 3H), 2.08 (s, 3H), 1.95 - 1.92 (m, 2H), 1.82-1.72 (m, 4H),1.31-1.15 (m, 6H).
105	 (S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3-methylpyridine 1-oxide	3-58	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 1.05 min; MS: m/z = 504 and 506 $[MH]^+$ (Method 5)	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.65 (d, 1H), 8.52 (d, 1H), 7.82 (d, 1H), 7.79 – 7.71 (m, 2H), 7.45 (d, 1H), 7.29 (d, 2H), 7.06 (d, 1H), 4.42 (dd, 1H), 4.03 (s, 3H), 1.94 – 1.81 (br. m, 2H), 1.73 (br. m, 2H), 1.62 (br. m, 2H), 1.62

					– 0.99 (br. m, 5H) ppm.
106	 4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-31	3-methylisoxazole-4-carboxylic acid	Rt = 0.92 min; MS: m/z = 537 and 539 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.44 (s, 1H), 8.67 (d, 1H), 8.37 (d, 1H), 7.81 (m, 1H), 7.59 (d, 1H), 7.49 (m, 1H), 7.35 (m, 1H), 4.51 (dd, 1H), 2.37 (s, 3H), 2.14 (s, 3H), 2.10 – 1.69 (br. m, 7H), 1.50 – 1.31 (m, 2H) ppm.
107	 4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-31	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.94 min; MS: m/z = 536 and 538 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.71 (s, 1H), 8.73 (br. d, 1H), 8.36 (d, 1H), 7.83 (d, 1H), 7.59 (d, 1H), 7.48 (m, 1H), 7.07 (d, 1H), 4.48 (dd, 1H), 4.03 (s, 3H), 2.15 (s, 3H), 2.12 – 1.67 (br. m, 7H), 1.50 – 1.28 (m, 2H) ppm.
108	 4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)-2-	3-31	1-ethyl-1H-pyrazole-5-carboxylic acid	Rt = 1.00 min; MS: m/z = 548 and 550 $[MH]^+$ (Method 3)	1H NMR (400 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.73 (d, 1H), 8.36 (d, 1H), 7.82 (dd, 1H), 7.58 (d, 1H), 7.48 (m, 2H), 7.35 (m, 1H), 7.02 (d, 1H), 4.51 – 4.43 (m, 3H), 2.12 (s, 3H), 2.12 – 1.67 (br. m, 7H), 1.51 –

	fluorophenyl)-2-methylpyridine 1-oxide				1.32 (m, 2H), 1.28 (t, 3H) ppm.
109	 3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	3-46	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.91min; MS: m/z = 516.2 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.72 (br. d, 1H), 8.24 (d, 1H), 7.80 (d, 1H), 7.49 (m, 2H), 7.29 (d, 1H), 7.26 (d, 1H), 7.07 (d, 1H), 4.48 (dd, 1H), 4.04 (s, 3H), 2.09 (s, 3H), 2.08 – 2.01 (br. m, 2H), 1.98 (s, 3H), 1.97 - 1.67 (br. m, 5H), 1.51 – 1.28 (m, 2H) ppm
110	 4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-56	1-methyl-1H-pyrazole-5-carboxylic acid	Rt = 0.91min; MS: m/z = 516.2 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.70 (d, 1H), 8.37 (d, 1H), 7.82 (dd, 1H), 7.59 (d, 1H), 7.53 – 7.46 (m, 2H), 7.36 (m, 1H), 7.10 (d, 1H), 4.59 (dd, 1H), 4.04 (s, 3H), 2.31 – 2.09 (br. m, 2H), 2.15 (s, 3H), 2.00 (br. m, 1H), 1.90 – 1.59 (m, 4H), 1.50 – 1.20 (m, 2H).

Example 111:

(S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3-methylpyridine 1-oxide



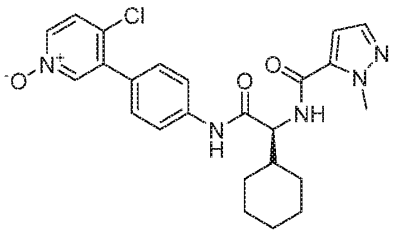
To a solution of (S)-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)boronic acid (Intermediate 4-2; 80 mg, 0.146 mmol) and PdCl2(dppf).DCM (12 mg, 0.015 mmol) in dioxane (1.5 mL) was added 4-bromo-3-methylpyridine 1-oxide (41 mg, 0.22 mmol) and 2M aq. Na_2CO_3 (0.3 mL). The mixture was purged with Ar and then heated to 100°C for 2h. After cooling, the mixture was diluted with EtOAc and washed successively with sat. $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by SFC (column: 250x30 Reprospher PEI 100A 5um, elution with 10-20% MeOH) to yield the title compound (21 mg, 32 %) as an off-white solid.

LC-MS: Rt = 0.84 min; MS: m/z = 448.2 $[MH]^+$ (Method 1).

1H NMR (400 MHz, DMSO-d6) δ 10.37 (s, 1H), 8.52 (d, 1H), 8.22 (d, 1H), 8.09 (dd, 1H), 7.74 (d, 2H), 7.46 (d, 1H), 7.38 (d, 2H), 7.25 (d, 1H), 7.07 (d, 1H), 4.41 (dd, 1H), 4.03 (s, 3H), 2.21 (s, 3H), 1.94 - 1.81 (br. m, 2H), 1.75 – 1.69 (br. m, 2H), .66 – 1.57 (br. m, 2H), 1.31 – 0.95 (br. m, 5H) ppm.

Example 112:

(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)pyridine 1-oxide

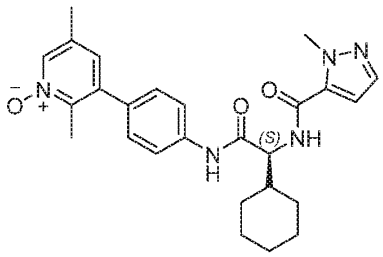


The title compound was prepared by a two-step sequence involving 1.) Suzuki-coupling of Intermediate 4-2 and 3-bromo-4-chloropyridine following a procedure similar to that of Example 111, and 2.) oxidation to the pyridine N-oxide with mCPBA following a procedure similar to that of Example 82, Step 2.

LC-MS: Rt = 4.30 min; MS: m/z = 468 and 470 $[MH]^+$ (Method 4).

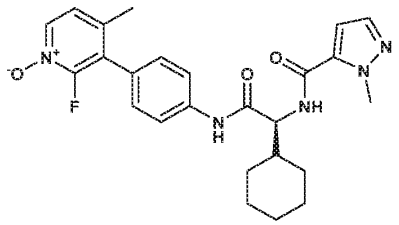
1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.54 (d, 1H), 8.27 (d, 1H), 8.21 (dd, 1H), 7.77 (d, 2H), 7.65 (d, 1H), 7.46 (dd, 3H), 7.07 (d, 1H), 4.42 (dt, 1H), 4.03 (s, 3H), 1.87 (t, 2H), 1.71 (m, 2H), 1.62 (m, 2H), 1.16 (m, 4H), 1.03 (m, 1H) ppm.

Example 113:
(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,5-dimethylpyridine 1-oxide



The title compound was prepared by a two-step sequence involving 1.) Suzuki-coupling of Intermediate 4-2 and 3-bromo-2,5-dimethylpyridine following a procedure similar to that of Example 111, and 2.) oxidation to the pyridine N-oxide with mCPBA following a procedure similar to that of Example 82, Step 2.
LC-MS: Rt = 0.96 min; MS: m/z = 462.5 $[MH]^+$ (Method 3).
1H NMR (400 MHz, DMSO-d6) δ 10.37 (s, 1H), 8.52 (d, 1H), 8.20 (d, 1H), 7.75 (d, 2H), 7.46 (d, 1H), 7.34 (d, 2H), 7.07 (d, 1 H), 7.05 (s, 1H), 4.42 (dd, 1H), 4.03 (s, 3H), 2.25 (s, 6H), 1.93 – 1.81 (m, 2H), 1.74 - 1.55 (m, 4H), 1.25 - 1.03 (m, 1H) ppm.

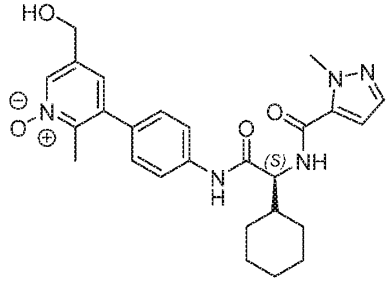
Example 114:
(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-fluoro-4-methylpyridine 1-oxide



The title compound was prepared by a two-step sequence involving 1.) Suzuki-coupling of Intermediate 4-2 and 3-bromo-2-fluoropyridine following a procedure similar to that of Example 111, and 2.) oxidation to the pyridine N-oxide with mCPBA following a procedure similar to that of Example 82, Step 2.

LC-MS: Rt = 4.30 min; MS: m/z = 466.3 $[MH]^+$ (Method 4).
1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.52 (d, 1H), 8.28 (t, 1H), 7.77 (d, 2H), 7.46 (d, 1H), 7.35 (d, 2H), 7.27 (d, 1H), 7.07 (d, 1H), 4.42 (dd, 1H), 4.04 (s, 3H), 2.12 (s, 3H), 1.88 (br. m, 2H), 1.75 – 1.58 (br. m, 4 H) 1.28 - 1.02 (br. m, 5H) ppm.

Example 115:
(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-5-(hydroxymethyl)-2-methylpyridine 1-oxide



Step 1: (S)-N-(2-((4-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylpyridin-3-yl)phenyl)amino)-1-cyclohexyl-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide

The title compound was prepared by Suzuki-coupling of Intermediate 4-2 and Intermediate 4-3 following a procedure similar to that of Example 111.
LC-MS: Rt = 1.34 min; MS: m/z = 576.5 $[MH]^+$ (Method 3).

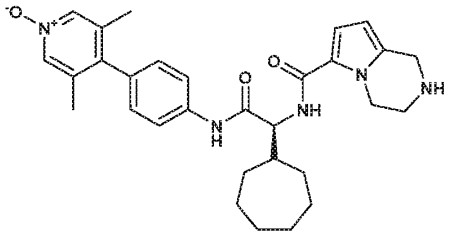
Step 2: (S)-N-(1-cyclohexyl-2-((4-(5-(hydroxymethyl)-2-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide

(S)-N-(2-((4-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylpyridin-3-yl)phenyl)amino)-1-cyclohexyl-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide (Step 1; 545 mg, 0.946 mmol) was treated with 1M TBAF in THF (9465 µl, 9.46 mmol). After stirring at RT for 20h HPLC-MS indicated complete conversion of the starting material The reaction mixture was diluted with EtOAc and extracted with sat. aq. Na_2CO_3 solution, and with brine. The aqueous layers were re-extracted with EtOAc and the combined organic layers were evaporated. The residue was purified by column chromatography on silica (column: Redisep 40g; elution with 0 to 100 % EtOAc in DCM, then with 10% MeOH in EtOAc) to yield the title compound (430 mg, 99 %) as a colorless solid.
LC-MS: Rt = 0.76 min; MS: m/z = 462.5 $[MH]^+$ (Method 5)

Step 3: (S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-5-(hydroxymethyl)-2-methylpyridine 1-oxide

The title compound was prepared from (S)-N-(1-cyclohexyl-2-((4-(5-(hydroxymethyl)-2-methylpyridin-3-yl)phenyl)amino)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide (Step 2) and mCPBA following a procedure similar to that of Example 82, Step 2.
LC-MS: Rt = 0.82 min; MS: m/z = 478.3 $[MH]^+$ (Method 5).
1H NMR (400 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.53 (d, 1H), 8.22 (s, 1H), 7.76 (d, 2H), 7.46 (d, 1H), 7.36 (d, 2H), 7.13 (s, 1H), 7.07 (d, 1H), 4.49 (s, 2H), 4.43 (dd, 1H), 4.03 (s, 3H), 2.28 (s, 3H), 1.93 – 1.80 (br. m, 2H), 1.77 – 1.68 (br. m, 2H), 1.66 – 1.56 (br. m, 2H), 1.25 – 0.98 (br. m, 5H) ppm.

Example 116: (S)-4-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide



Step 1: (S)-tert-butyl 6-((1-cycloheptyl-2-((4-(3,5-dimethylpyridin-4-yl)phenyl)amino)-2-oxoethyl)carbamoyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

The title compound was prepared from Intermediate 3-52 and 2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid by a procedure similar to that of Example 1.
LC-MS: Rt = 1.29 min; MS: m/z = 600.4 $[MH]^+$ (Method 1).
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.32 (s, 2H), 7.90 (d, 1H), 7.75 (d, 2H), 7.13 (d, 2H), 7.03 (d, 1H), 5.95 (d, 1H), 4.53 (s, 2H), 4.44 (dd, 1H), 4.39 – 4.23 (m, 2H), 3.73 – 3.55 (m, 2H), 2.19 – 2.06 (m, 1H), 1.99 (s, 6H), 1.83 – 1.72 (m, 1H), 1.71 – 1.61 (m, 3H), 1.60 – 1.29 (m, 9H), 1.42 (s, 9H) ppm.

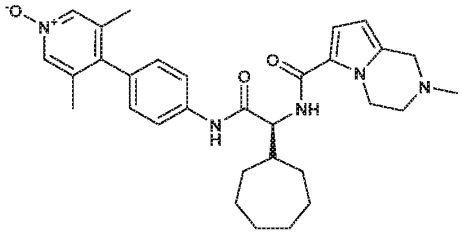
Step 2: (S)-4-(4-(2-(2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide

To a solution of (S)-tert-butyl 6-((1-cycloheptyl-2-((4-(3,5-dimethylpyridin-4-yl)phenyl)amino)-2-oxoethyl)carbamoyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (Step 1, 81 mg, 0.135 mmol) in THF (2.7 mL) was added dropwise at RT a solution of mCPBA (60 mg, 0.270 mmol) in THF (1.8 mL). After stirring at RT for 2h the mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$ (80 mL), water and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica (RediSep 12g; 5% to 100% EtOAc in heptane) to yield the title compound (68 mg, 70 %) as a white foam.
LC-MS: Rt = 1.20 min; MS: m/z = 616.4 $[MH]^+$ (Method 1).
^1H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.09 (s, 2H), 7.91 (d, 1H), 7.74 (d, 2H), 7.15 (d, 2H), 7.03 (d, 1H), 5.95 (d, 1H), 4.53 (s, 1H), 4.43 (dd, 1H), 4.39 – 4.24 (m, 1H), 3.69 – 3.57 (m, 1H), 2.16 – 2.02 (m, 1H), 1.94 (s, 7H), 1.82 – 1.73 (m, 1H), 1.72 – 1.60 (m, 3H), 1.60 – 1.27 (m, 10H) 1.42 (s, 9H) ppm.

Step 3: (S)-4-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide

To a solution of (S)-4-(4-(2-(2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide (Step 2; 60 mg, 0.097 mmol) in DCM (1 mL) was added TFA (75 uL, 0.974 mmol) and the mixture was stirred at RT overnight. The reaction was quenched by addtion of sat. aq. $NaHCO_3$ and extracted with DCM/2-propanol. The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was purified by SFC (column: 250x30 Reprospher PEI 100A 5um; gradient: 26-36% MeOH in 10 min) to yield the title compound (14 mg, 26 %) as an off-white solid.
LC-MS: Rt = 0.72 min; MS: m/z = 516.3 $[MH]^+$ (Method 1)
^1H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.09 (s, 2H), 7.80 – 7.70 (m, 3H), 7.15 (d, 2H), 6.96 (d, 1H), 5.78 (d, 1H), 4.42 (t, 1H), 4.24 – 4.04 (m, 2H), 3.86 (s, 2H), 3.05 – 2.93 (m, 2H), 2.16 – 2.03 (m, 1H), 1.94 (s, 6H), 1.82 – 1.72 (m, 1H), 1.71 – 1.60 (m, 3H), 1.60 – 1.28 (m, 9H) ppm.

Example 117 : (S)-4-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide



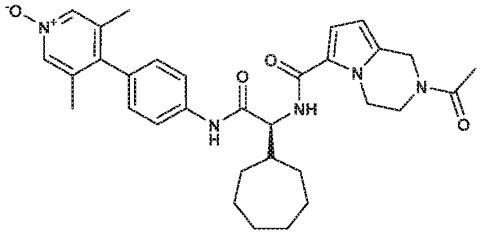
To a solution of (S)-4-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide (Example 116, 60 mg, 0.116 mmol in methanol (1.2 mL) was added 37 % aqueous formaldehyde (55 uL, 0.698 mmol, 6 eq). After stirring the mixture for 10min at RT, sodium cyanoborohydride (37 mg, 0.582 mmol, 5 eq) and acetic acid (13 uL, 0.233 mmol, 2 eq) were added. After stirring at RT for 3h, the reaction was quenched by addition of aq. sat. $NaHCO_3$ and extracted with DCM/isopropanol 4:1.The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was purified by SFC (column: 250x30 Reprosphere PEI 100A 5um; gradient: 12-20% MeOH in10min) to yield the title compound (13 mg, 21 %) as a colorless solid.

LC-MS: Rt = 0.74 min; MS: m/z = 530.6 $[MH]^+$ (Method 2).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.09 (s, 2H), 7.81 (d, 1H), 7.74 (d, 2H), 7.15 (d, 2H), 6.98 (d, 1H), 5.81 (d, 1H), 4.42 (dd, 1H), 4.35 – 4.24 (m, 1H), 4.24 – 4.13 (m, 1H), 3.50 (s, 2H), 2.67 (t, 2H), 2.31 (s, 3H), 2.16 – 2.02 (m, 1H), 1.94 (s, 6H), 1.84 – 1.72 (m, 1H), 1.72 – 1.61 (m, 3H), 1.58 – 1.27 (m, 8H) ppm.

Example 118

(S)-4-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide

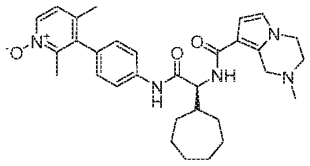


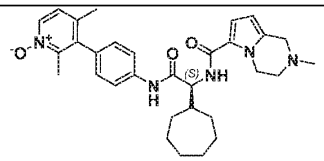
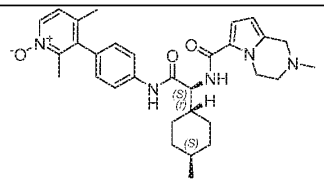
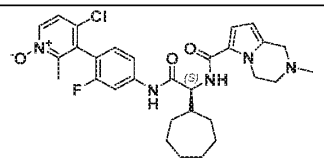
To a cooled (0°C) solution of (S)-4-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide (Example 116; 60 mg, 0.116 mmol) and N-ethyldiisopropylamine (61 uL, 0.349 mmol) in THF (1 mL) was added dropwise a solution of acetyl chloride (11 uL, 0.151 mmol) in THF (160 uL). After stirring at 0ºC for 2h, the mixture was was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by SFC (column: 250x30 Reprospher PEI 100A 5um; gradient: 14-22 % MeOH in 10min) to yield the title compound (10 mg, 15 %) as a colorless solid.

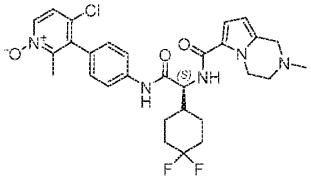
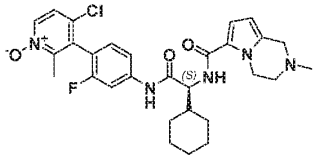
LC-MS: Rt = 0.92 min; MS: m/z = 558.4 $[MH]^+$ (Method 2).

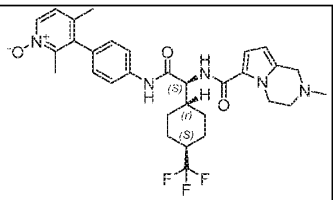
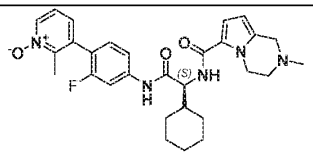
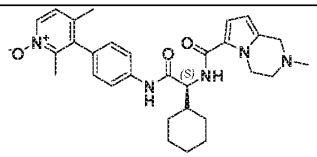
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.09 (s, 2H), 7.95 (dd, 1H), 7.75 (d, 2H), 7.15 (d, 2H), 7.04 (m, 1H), 6.01 – 5.86 (m, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 4.49 – 4.23 (m, 3H), 3.84 – 3.67 (m, 2H), 2.18 – 2.04 (m, 1H), 2.08 (s, 3H), 1.94 (s, 6H), 1.84 – 1.73 (m, 1H), 1.70 – 1.61 (m, 3H), 1.60 – 1.24 (m, 8H) ppm.

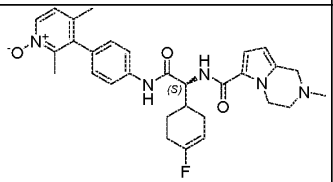
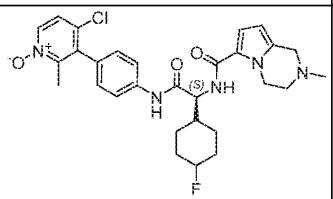
The following Examples were prepared by a three step sequence of 1.) amide bond formation of Intermediate 3-X and the corresponding carboxylic acids, 2.) N-Boc deprotection and 3.) reductive amination by procedures similar to that of **Example 117.**

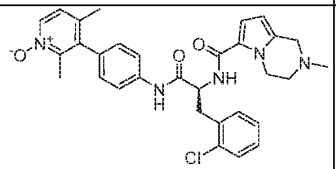
Example	Structure/Name	Inter-mediate 3-x	Carboxylic acid	LC-MS (Method)	1H NMR
119	 (S)-3-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-15	2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxylic acid	Rt = 3.52 min; MS: m/z = 530.2 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.19 (d, 1H), 7.76 (d, 2H), 7.52 (d, 1H), 7.22 (d, 1H), 7.16 (d, 2H), 6.71 (d, 1H), 6.64 (d, 1H), 4.43 (dd, 1H), 3.93 (t, 2H), 3.74 (d, 2H), 2.69 (t, 2H) 2.35 (s, 3H), 2.08 (s, 4H), 1.96 (s, 3H), 1.24 - 1.85 (m, 12H) ppm

120	 (S)-3-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-15	2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid	Rt = 3.87 min; MS: m/z = 530.3 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ ppm 10.26 (s, 1H), 8.19 (d, 1H), 7.80 (d, 1H), 7.76 (d, 2H), 7.21 (d, 1H), 7.16 (d, 2H), 6.99 (d, 1H), 5.81 (d, 1H), 4.43 (dd, 1H) 4.34 - 4.15 (m, 2H) 3.50 (s, 2H) 3.17 (d, 1H), 2.67 (m, 2H), 2.31 (s, 3H), 2.13 - 2.05 (m, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.84 – 1.73 (m, 1H), 1.70 – 1.62 (m, 3H), 1.56 – 1.29 (m, 7H) ppm
121	 2,4-dimethyl-3-(4-((S)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-3	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 0.89 min; MS: m/z = 530.3 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.19 (d, 1H), 7.84 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 7.00 (d, 1H), 5.81 (d, 1H), 4.37 – 4.13 (m, 3H), 3.50 (s, 2H), 2.67 (t, 2H), 2.31 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.92 – 1.84 (m, 1H), 1.83 – 1.77 (m, 1H), 1.73 – 1.59 (br. m, 3H), 1.30 - 1.15 (m, 2H), 1.06 - 0.86 (m, 6H) ppm.
122	 4-chloro-3-(4-((S)-2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-	3-31	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 3.99 and 4.10 min, 1:1 mixture of atropisomers; MS: m/z = 568.3	1H NMR (500 MHz, DMSO-d6) δ 10.02 (s, 1H), 8.29 (d, 1H), 7.81 – 7.64 (m, 1H), 7.50 (dd, 2H), 7.28 (t, 2H), 6.86 (d, 1H), 5.84 (d, 1H), 4.52 (dd, 1H), 4.28 (m, 2H),

	a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide			$[MH]^+$ (Method 4)	3.57 (s, 2H), 2.74 (td, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 2.15 (m, 1H), 1.90 – 1.67 (m, 4H), 1.67 – 1.35 (m, 8H) ppm.
123	 (S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-23	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	LC-MS: Rt = 0.76 min; MS: m/z = 572.4 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.31 (d, 1H), 7.97 (d, 1H), 7.78 (m, 2H), 7.53 (d, 1H), 7.25 (d, 2H), 7.00 (d, 1H), 5.82 (d, 1H), 4.45 (dd, 1H), 4.21 – 4.17 (m, 2H), 3.50 (s, 2H), 2.71 – 2.64 (m, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 2.11 – 1.89 (m, 4H), 1.87 – 1.68 (m, 3H), 1.50 – 1.27 (m, 2H) ppm.
124	 4-chloro-3-(4-((S)-2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-2	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 3.59 and 3.71 min, 1:1 mixture of atropisomers; MS: m/z = 554.2 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.53 (s, 1H), 8.36 (d, 1H), 7.92 - 7.78 (m, 2H), 7.58 (d, 1H), 7.54 - 7.45 (m, 1H), 7.33 (t, 1H) 7.00 (d, 1H), 5.82 (d, 1H), 4.39 - 4.03 (m, 3H), 3.50 (s, 2H) 2.67 (t, 2H), 2.36- 2.26 (m, 1H), 2.31 (s, 3H), 2.15 (s, 3H), 1.92 – 1.82 (br. m, 2H), 1.76 – 1.67 (br. m, 2H), 1.64 – 1.57 (br. m, 2H), 1.24 – 0.96 (br. m, 4H) ppm.

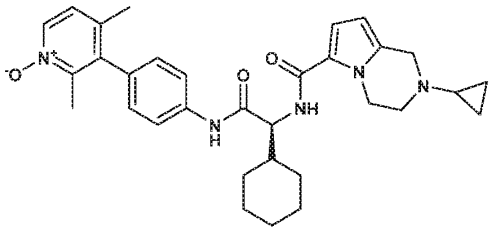
125	 2,4-dimethyl-3-(4-((S)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	3-7	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 0.80 min; MS: m/z = 584.4 $[MH]^+$ (Method 1)	1H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 8.19 (d, 1H), 7.85 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 7.00 (d, 1H), 5.83 (d, 1H), 4.37 (dd, 1H), 4.33 – 4.13 (m, 2H), 3.51 (s, 2H), 2.67 (br. m, 2H), 2.32 (s, 3H), 2.30 – 2.21 (br. m, 1H), 2.08 (s, 3H), 2.00 – 1.72 (m, 5H), 1.97 (s, 3H), 1.31 – 1.06 (m, 4H) ppm.
126	 (S)-3-(4-(2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	3-41	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 0.81 min; MS: m/z = 520.4 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.33 (d, 1H), 7.86 (d, 1H), 7.78 (d, 1H), 7.48 (dd, 1H), 7.39 – 7.34 (m, 2H), 7.21 (dd, 1H), 7.01 (d, 1H), 5.82 (d, 1H), 4.37 – 4.14 (m , 3H), 3.50 (s, 2H), 2.70 – 2.63 (m , 2H), 2.31 (s, 3H), 2.20 (d, 3H), 1.86 (br. m, 2H), 1.75 – 1.69 (m , 2H), 1.63 – 1.56 (br. m, 2H), 1.26 – 1.00 (m , 5H) ppm
127	 (S)-3-(4-(2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-15	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 3.13 min; MS: m/z = 516.3 $[MH]^+$	1H NMR (400 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.19 (d, 1H), 7.81 (d, 1H), 7.76 (d, 2H), 7.22 (d, 1H), 7.16 (d, 2H), 7.00 (d, 1H), 5.81 (d, 1H), 4.37 - 4.12 (m, 3H), 3.50 (s, 2H), 2.70 - 2.63 (m, 2H), 2.31 (s,

					3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.91 – 1.81 (br. m, 2H), 1.76 – 1.67 (br. m, 2H), 1.66 - 1.54 (br. m, 2H), 1.30 – 0.91 (m, 5H) ppm.
128	 3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	3-10	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 0.67 min; MS: m/z = 532.4 $[MH]^+$ (Method 5)	1H NMR (400 MHz, DMSO-d6) δ 10.37 and 10.35 (2s, ratio ca 3:2, 1H), 8.20 (d, 1H), 7.98 (d, 1H), 7.77 (m, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 7.01 (dd, 1H), 5.82 (m, 1H), 5.21 (m, 1H) 4.46 and 4.23 (2dt, ratio 1:2, 3H), 3.51 (s, 2H), 2.72 – 2.56 (br. m, 2H), 2.32 (s, 3H), 2.28 – 1.79 (br. m, 5H), 2.08 (s, 3H), 2.01 (m, 1H), 1.97 (s, 3H), 1.62 – 1.42 (m, 1H) ppm.
129	 4-chloro-3-(4-((2S)-2-(4-fluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	3-28	2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 0.72 and 0.73 min, 1:1 mixture of isomers; MS: m/z = 554.3 $[MH]^+$ (Method 2)	1H NMR (400 MHz, DMSO-d6) δ 10.38 and 10.36 (2s, ratio 1:1, 1H), 8.32 and 8.31 (2s, ratio 1:1, 1H), 7.97 (br. m, 1H), 7.80 – 7.74 (m, 2H), 7.54 (d, 1H), 7.24 (d, 2H), 7.04 (d, 1H), 5.88 (m, 1H), 4.93 – 4.46 (m, 1H), 4.42 – 4.22 (m, 3H), 3.71 (br. m, 1H), 2.84 (br. m, 2H), 2.46 (br. m, 1H), 2.13 (s, 3H), 2.07 (br. m, 1H), 2.00 – 1.84 (br. m, 3H), 1.77 – 1.66 (br. m,

					1H), 1.61 – 1.09 (m, 5H) ppm
130	 (S)-3-(4-(3-(2-chlorophenyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)propanamido) phenyl)-2,4-dimethylpyridine 1-oxide		2-Boc-3,4-dihydro-1H-pyrrolo(1,2a)pyrazine-6-carboxylic acid	Rt = 2.96 min, MS: m/z = 558 and 560 $[MH]^+$ (Method 4)	1H NMR (400 MHz, DMSO-d6) δ 10.90 (br. s, 1H), 10.38 (s, 1H), 8.51 (d, 1H), 8.42 (d, 1H), 7.78 (d, 2H), 7.50 - 7.40 (m, 3H), 7.27 - 7.18 (m, 4H), 7.09 (br. s, 1H), 6.07 (d, 1H), 4.90 (br. m, 2H), 4.34 – 4.19 (br. m, 2H), 3.74 (br. m, 1H), 3.49 (br s, 1H), 3.44 - 3.22 (m, 2H), 2.91 (s, 3H), 2.17 (s, 3H), 2.04 (s, 3H) ppm.

Example 131:

(S)-3-(4-(2-cyclohexyl-2-(2-cyclopropyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



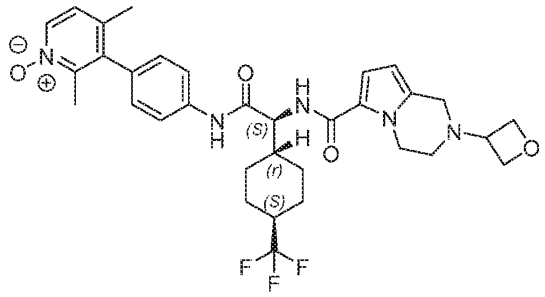
To a solution of (S)-3-(4-(2-cyclohexyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (precursor to example 138, 50 mg, 0.10 mmol) in DMF (0.5 mL), Cs_2CO_3 (97 mg, 0.30 mmol) and cyclopropyl bromide (18.1 mg, 0.15 mmol) were added at RT, and stirred at 60° for 24 h. Another portion of cyclopropyl bromide (300 mg, 2.5 mmol) was added and stirring at 60° continued for 4 days. The mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, water, and brine . The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a yellow oil. Purification by prep. HPLC (column: XBridge-C18 5um, 30x100mm, gradient: 15 – 45% acetonitrile in water +0.1 % TFA) yielded the title compound (1.6 mg, 3%) as a white solid.

LC-MS: Rt = 1.34 min; MS: m/z = 542.5 $[MH]^+$ (Method 5).

1H NMR (400 MHz, $CHCl_3$-d) δ 8.80 (s, 1 H) 8.41 (d,1 H) 7.74 (d, 2 H) 7.19 - 7.25 (m, 1 H) 7.11 (d, 2 H), 6.74 (d, 1 H) 6.56 (d, 1 H) 5.97 - 6.08 (m, 2 H) 5.44 - 5.55 (m, 2 H) 4.63 - 4.81 (m, 2 H) 4.51 (t, 1 H) 4.24 (br s, 2 H), 3.71 (m, 1 H) 2.36 (s, 4 H) 2.11 (s, 3 H) 1.64 - 2.06 (m, 7 H) 0.99 - 1.46 (m, 6 H) ppm.

Example 132:

2,4-dimethyl-3-(4-((S)-2-(2-(oxetan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide



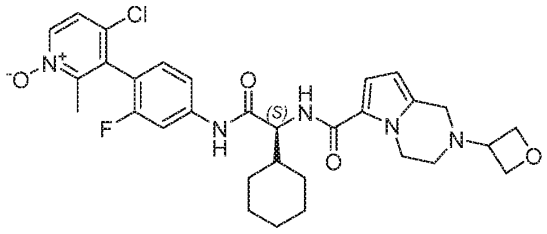
To a solution of 2,4-dimethyl-3-(4-((S)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide (precursor to example 137, 92 mg, 0.162 mmol) in MeOH (5 mL), acetic acid (0.028 mL, 0.485 mmol) and 3-oxetanone (116 mg, 1.615 mmol) was added, and the yellow solution stirred at RT for 45 min. $NaBH(OAc)_3$ (68.5 mg, 0.323 mmol) was added and the reaction mixture stirred at RT for 80 h. All volatiles were removed under reduced pressure, the yellow residue dissolved in EtOAc and washed with sat. aq. $NaHCO_3$ and brine. The aq. phases were re-extracted with EtOAc and the combined organic phases dried (Na_2SO_4) and evaporated to afford a yellow solid. Purification by preparative HPLC (column: Sunfire 30x100mm; gradient: 5 – 80 % acetonitriile in water + 0.1 % TFA) yielded the title compound (57 mg, 55%) as a colorless solid.

LC-MS: Rt = 1.01 min; MS: m/z = 626.4 $[MH]^+$ (Method 5).

1H NMR (400 MHz, DMSO-d6) δ 10.32 (s, 1H), 8.19 (d, 1H), 7.88 (d, 1H), 7.77 (d, 2H), 7.22 (d, 1H), 7.17 (d, 2H), 7.02 (d, 1H), 5.85 (d, 1H), 4.59 (t, 2H), 4.49 (t, 2H), 4.38 (dd, 1H), 4.33 – 4.18 (m, 2H), 3.60 (m, 1H), 3.51 (s, 2H), 2.69 – 2.61 (m, 2H), 2.30 – 2.19 (br. m, 1H), 2.08 (s, 3H), 2.03 – 1.84 (br. m, 4H), 1.96 (s, 3H), 1.78 – 1.71 (br. m, 1H), 1.31 – 1.07 (m, 4H) ppm.

Example 133:

4-chloro-3-(4-((S)-2-cyclohexyl-2-(2-(oxetan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide



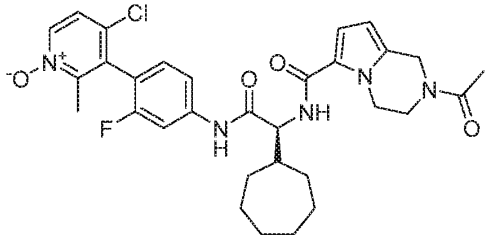
The title compound was prepared as a mixture of atropisomers from 4-chloro-3-(4-((S)-2-cyclohexyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (precursor to example 136) and oxetan-3-one by a procedure similar to that of Example 143. Separation of the two atropisomers by chromatography on chiral stationary phase afforded the title compound as one pure atropisomer.

LC-MS: Rt = 1.01 min; MS: m/z = 596.4 $[MH]^+$ (Method 2).

1H NMR (400 MHz, DMSO-d6) δ 10.59 (s, 1H), 8.36 (d, 1H), 7.92 (d, 1H), 7.83 (dd, 1H), 7.59 (d, 1H), 7.50 (dd, 1H), 7.33 (t, 1H), 7.03 (d, 1H), 5.84 (d, 1H), 4.59 (t, 2H), 4.49 (td, 2H), 4.41 - 4.13 (m, 3H), 3.59 (m, 1H), 3.50 (s, 2H), 2.65 (m, 2H), 2.15 (s, 3H), 1.96 - 1.51 (m, 7H), 1.24 (m, 4H) ppm.

Example 134:

3-(4-((S)-2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide

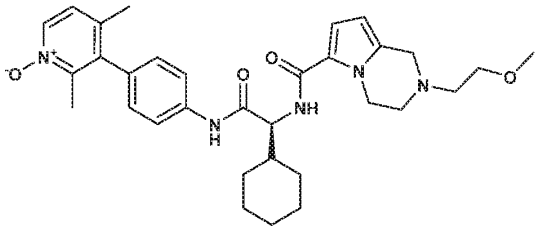


The title compound was prepared from Intermediate 3-30 and Intermediate 4-10 by a procedure similar to that of Example 1.

LC-MS: Rt = 1.34 min; MS: m/z = 594 $[MH]^+$ (Method 14).

1H NMR (300 MHz, Methanol-d4) δ 8.37 (d, 1H), 7.79 (dd, 1H), 7.59 (d, 1H), 7.47 (d, 1H), 7.26 (t, 1H), 6.91 (d, 1H), 6.01 (dd, 1H), 4.79 (s, 1H), 4.71 (d, 1H), 4.53 – 4.42 (m, 2H), 4.39 (br. m, 1H), 3.85 (m, 2H), 2.31 (s, 3H), 2.16 (m, 4H), 1.90 – 1.27 (m, 12H) ppm.

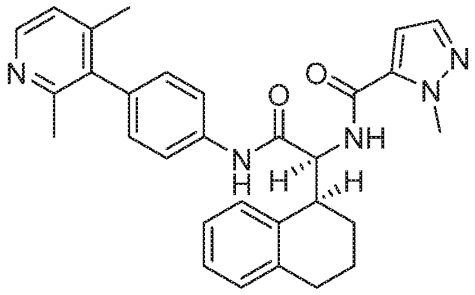
Example 135:
(S)-3-(4-(2-cyclohexyl-2-(2-(2-methoxyethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide



The title compound was prepared from (S)-3-(4-(2-cyclohexyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide (precursor to example 138) and 1-bromo-2-methoxyethane by a procedure similar to that of Example 131.
LC-MS: Rt = 3.47 min; MS: m/z = 560.5 $[MH]^+$ (Method 5).
1H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 8.20 (d, 1H), 8.06 (d, 1H) 7.73 - 7.79 (dd, 2H), 7.23 (d, 1H), 7.18 (d, 2H), 7.15 (d, 1H), 6.07 (br s, 1H), 4.72 (br m, 2H), 4.50 - 4.89 (m, 2H), 4.38 (br. t, 2H), 3.70 (br s, 2H), 3.33 (s, 3H), 3.30 (br. s, 2H), 2.08 (s, 3H), 1.97 (s, 3H), 1.86 (m, 2H), 1.78 (m, 2H), 1.64 (m, 2H) ,0.81 - 1.30 (m, 8H), ppm.

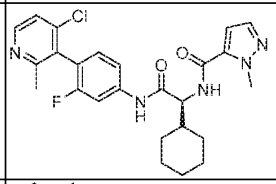
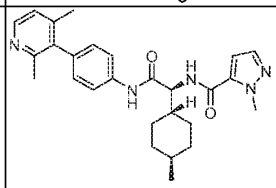
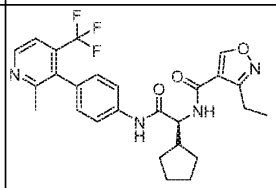
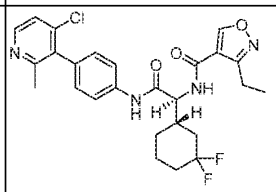
<u>General procedure for the preparation of the corresponding pyridines of Examples 1 – 135:</u>

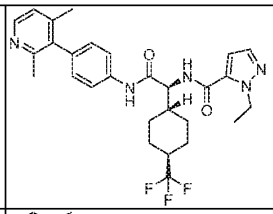
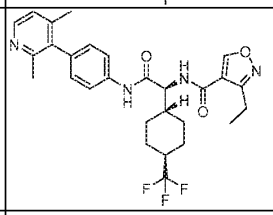
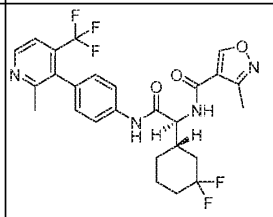
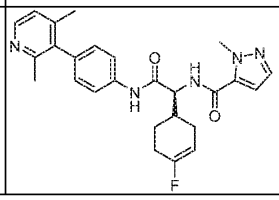
Reference example 136 (corresponding to the N-oxide compound of example 1):
N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl)-1-methyl-1H-pyrazole-5-carboxamide



To a solution of 50 mg (2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide (Example 1; 50 mg, 0.078 mmol) in THF (1.2 mL) was added sat. aq. NH_4Cl (1.2 mL) followed by zinc powder (100 mg; 1.4 mmol). After stirring the reaction mixture overnight at RT, HPLC analysis indicated the complete consumption of the starting material. The mixture was diluted with EtOAc, washed with sat $NaHCO_3$, water, and brine, dried (Na_2SO_4)and the volatiles were evaporated. The residue was purified by SFC to yield the tiltle compound (26 mg, 67 %) as a colorless solid. LC-MS: Rt = 0.85 min; MS: m/z = 494.4 [MH]+ (Method 8).

The following reference examples were prepared by following the procedure described for reference Example 136:

Reference Example number	Example number of corresponding N-oxide	Structure	Name	LC-MS
137	2		N-((1S)-2-((4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)amino)-1-cyclohexyl-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	Rt = 0.84 min; MS: m/z = 492.4 $[MH]^+$ (Method 8)
138	3		N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-1-((1r,4S)-4-methylcyclohexyl)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	Rt = 0.89 min; MS: m/z = 460.5 $[MH]^+$ (Method 8)
139	5		(S)-N-(1-cyclopentyl-2-((4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)amino)-2-oxoethyl)-3-ethylisoxazole-4-carboxamide	Rt = 1.24 min; MS: m/z = 501.3 $[MH]^+$ (Method 5)
140	6		N-((S)-2-((4-(4-chloro-2-methylpyridin-3-yl)phenyl)amino)-1-((S)-3,3-difluorocyclohexyl)-2-oxoethyl)-3-ethylisoxazole-4-carboxamide	Rt = 1.21 min; MS: m/z = 517.3 $[MH]^+$ (Method 5)

141	7		N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((1r,4S)-4-(trifluoromethyl)cyclohexyl)ethyl)-1-ethyl-1H-pyrazole-5-carboxamide	Rt = 0.95 min; MS: m/z = 528.4 $[MH]^+$ (Method 8)
142	8		N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((1r,4S)-4-(trifluoromethyl)cyclohexyl)ethyl)-3-ethylisoxazole-4-carboxamide	Rt = 0.97 min; MS: m/z = 529.4 $[MH]^+$ (Method 8)
143	9		N-((S)-1-((S)-3,3-difluorocyclohexyl)-2-((4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)amino)-2-oxoethyl)-3-methylisoxazole-4-carboxamide	Rt = 1.16 min; MS: m/z = 537.4 $[MH]^+$ (Method 8)
144	12		N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-1-((S)-4-fluorocyclohex-3-en-1-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	Rt = 0.68 min; MS: m/z = 462.3 $[MH]^+$ (Method 8)

BIOLOGICAL ASSAYS AND DATA

The activity of a compound according to the present invention can be assessed by the following *in vitro* methods. A compound of formula (I), or a pharmaceutically acceptable salt thereof, exhibits valuable pharmacological properties, *e.g.* as indicated in tests as provided in the next sections, and are therefore indicated for therapy related to IL-17.

Expression, purification, and labeling of proteins

Biotinylated human IL-17A

For the generation of an IL-17A expression construct, the natural leader-hsIL17A (aa24-155)-APP6 insert was amplified by PCR from an existing construct (C#3713, NPL012065, natLeader-hsIL-17 aa24-151-APP/pRS5a; SEQ ID NO: 1) using specific primers. Forward primer RS198: 5' CATACGATTTAGGTGA (SEQ ID NO: 2) and reverse primer RS4930; 5'CCTCTAGAGCGGCCGCTTAGGAGTCGTGACGGAATTCGGCCACATGGTGGACAATCGGGG TGACACAGGTGCAC (SEQ ID NO: 3). The PCR product was cloned into the pRS5a expression

vector (treated with the appropriate restriction enzymes HindIII and NotI) via the In-Fusion technology to obtain expression plasmid NPL016964 (SEQ ID NO: 4).

The expression of human IL-17A was carried out in HEK293 6E cells using V3 medium (proprietary Novartis cell culture medium, patent: WO2011/134920 A1). Cells were diluted one day before the expression (final density of 1-2×10^6 cells/mL in order to be in the exponential growing phase the next morning. The day of expression, the culture was centrifuged at 300 x rpm during 20 minutes and re-suspended in fresh V3 medium. The expression was started with a cell density of about 3×10^6 cells/mL. One milligram (mg) of plasmid DNA (plasmid NPL016964) per liter (L) (final volume after incubation) was first added to the culture, followed, after mixing, by 4 mg/L of PEI (polyethyleneimine) as transfection reagent. After 4 hours incubation at 120 rpm, 37 °C, with 5% CO_2, the culture was diluted with fresh V3 medium to a final density of 1.5×10^6 cells/mL, in 3L shake flasks (1L/flask). Incubation was performed on an orbital shaking platform at 37 °C, 5% CO_2 and 100 rpm for 5 days. The cultures were then centrifuged at 2000 rpm during 15 minutes and the supernatant concentrated using the Pellicon system (10MWCO membrane). The concentrated sample was loaded onto a CJM112 sepharose 4B column and eluted with 0.1M glycine-HCl pH 2.7. Said column comprised an anti-IL-17A monoclonal antibody (CJM112, described as XAB4 in WO 2014/122613 A1) coupled to CNBr-activated Sepharose 4B (Pharmacia) at a density of 10 mg/ml resin. The fractions were collected in tubes pre-filled with 10% of 1M Tris pH 8 buffer. Pooled fractions were concentrated by ultrafiltration (AMICON 10MWCO membrane) and further purified by size exclusion chromatography (Superdex 75 HiLoad 26/60 column, GE Healthcare) in PBS pH 7.4. Fractions were pooled based on SDS-PAGE analysis.

Chemical biotinylation of human IL-17A was performed with a 5-fold excess of EZ-Link-Sulfo-NHS-LC-LC-Biotin (cat.no. 21338; Thermo Scientific) in PBS pH 7.4. After one hour incubation at room temperature, the reaction was stopped with 1M Tris pH 8 and the excess biotin removed by running the sample on a Zeba Spin Desalting column (Thermo Scientific) in PBS pH 7.4.

<u>AF647-labeled human IL-17RA (PN110235)</u>

The FL (full-length) cDNA clone of hsIL17RA was ordered at imaGenes (C#3784, NPL012318; SEQ ID NO: 5). The CD33-hIL17RA (aa33-320)-APP6-Avi insert was amplified via 2-step PCR using primer sets RS3766/3768 for the first step and RS3767/3769 for the second step. Cloning was carried out using the Gateway technology: Initially the insert was cloned via BP reaction in pDON201 (entry clone) and afterwards via LR reaction in pDESTRS5a to obtain expression plasmid NPL012271 (SEQ ID NO: 6).

Sequences of the primers are as follows: Forward primer 1 RS3766: 5'

CCATGCCCCTGCTCCTGCTGCTGCCCCTGCTGTGGGCCGGAGCCCTGGCCCTGCGACTCCT

GGACCACCGGGCGCTGG (SEQ ID NO: 7), reverse primer 1 RS3768: 5' GCTTCAAAGATATCGTTCAGGCCGCCGCCGGAGTCGTGACGGAATTCCCACAGGGGCATGTA GTCCGGAATTGG (SEQ ID NO: 8), forward primer 2 RS3767: 5' GGGGACAAGTTTGTACAAAAAAGCAGGCTTGGCCGCCACCATGCCCCTGCTCCTGCTGCTGC CCCTGCTGG (SEQ ID NO: 9) and reverse primer 2 RS3769: 5' GGGGACCACTTTGTACAAGAAAGCTGGGTTCATTATTCATGCCACTCAATTTTCTGCGCTTCAA AGATATCGTTCAGGC (SEQ ID NO: 10).

Human IL-17RA was expressed in HEK293 6E cells using V3 medium as described above for IL-17A. The recombinant protein was captured on an anti-APP affinity chromatography column and eluted with a one-step gradient of 0.1 M glycine (pH 2.7). Said column comprised an anti-APP monoclonal antibody coupled to CNBr-activated Sepharose 4B (Pharmacia) at a density of 10 mg/ml resin. The aminoacid sequence of the light chain and heavy chain of the used anti-APP antibody comprised SEQ ID NO 11 and 12, respectively. The pH was immediately raised by addition of 1.0 M of Tris (pH 8.5) to the eluted fractions. The isolated protein was then concentrated by ultrafiltration and further purified by size-exclusion chromatography with a High-Load Superdex-200 26/80 equilibrated with PBS pH 7.4.

Before labelling, the IL-17RA concentration was determined by HPLC. A 5-fold excess of Alexa Fluor647 carboxylic acid succinimidyl ester (cat. no. A200066; Invitrogen) was added, and after one hour incubation at room temperature, the sample was purified over a Zeba Spin Desalting column (Thermo Scientific) equilibrated in PBS pH 7.4 The efficiency of the labeling was then deduced from absorbance measurements at 280 nm and 650 nm.

Human IL-17A x IL-17RA TR-FRET assay

Dilutions of test compounds in DMSO are plated onto white low-volume 384-well plates (Greiner, #784075). Specifically, solutions of graded concentrations (5 mM to 150 nM; sixteen 2-fold dilution steps) are dispensed at 0.2 µL/well to yield final assay concentrations in the range of 100 µM to 3 nM. Each compound concentration is tested in duplicate.

All components of the assay are diluted in PBS containing 0.05% Tween20 (Sigma, #P1379, 5% stock in water), 1 mM EDTA (Invitrogen, #15575-038; 0.5M stock, pH8) and 0.05% bovine serum albumin (Roche; 5% stock in water). The final total assay volume is 10 µL. Reagents are added using a Multidrop Combi device (ThermoFisher, #5840320); between reagents, the instrument is rinsed with buffer:

(i) Biotinylated human IL-17A (PN106276; stock solution: 55.87 µM) is added at 5 µL/well from a 10 nM intermediate dilution to yield a final assay concentration of 5 nM. Each assay plate contains "low controls" where buffer is added in place of IL-17A.

(ii) After 30 minutes of incubation at RT, 2.5 µL/well of AF647-labeled human IL-17RA (PN110235; stock: 2.91 µM) is added from a 120 nM intermediate solution, to yield a final assay concentration of 30 nM.

(iii) Following 30 minutes of incubation at RT, 2.5 µL/well of Eu-Streptavidin (PerkinElmer, #AD0062; stock: 500 µg/mL=8.3 µM) is added from an intermediate dilution of 4 nM to yield a final concentration of 1 nM.

After 30 to 60 minutes of incubation, FRET is measured in an EnVision 2101 Multilabel-Reader (Perkin Elmer) with excitation at 320 nm, and emission at 615 and 665 nm (program "TR-FRET Screening", instrument: NIBR-00013163).

Each plate contains test compounds in columns 1-22 and controls in columns 23 and 24. The neutral control (NC) contains all the assay components, but DMSO instead of test compound. The active control (AC) mimics complete inhibition of the IL-17 ligand interaction, which is achieved by replacing the biotinylated cytokine with buffer. The fluorescence values for emission at 615 nm and 665 nm are loaded to the evaluation software Helios. In a normalization step, reader values are converted to % activity using the formula:

% activity = -100*(x-NC)/(AC-NC)

where NC and AC are the median values of the neutral and active control wells on the same plate.

From the activity data at each compound concentration, the IC50 values are obtained using the 4-parameter logistic function ("Hill-slope model") of Helios.

<u>IL-6 release from NHDF cells (Normal human dermal fibroblasts)</u>

NHDF cells isolated from normal adult mesoderm, connective tissues were cultured in fibroblast growth medium containing 2% supplement. The cells were detached from plastic using an accutase solution, washed and were seeded in 96-well plates at a density of 5x103/well in fibroblast growth medium lacking the supplements. The cells were allowed to adhere overnight before they were incubated with the compound/cytokine cocktail.

Compound stock solutions (10mM in DMSO) were serially diluted in 96-well plates in fibroblast growth medium containing 0.2% supplement to give a maximal assay concentration of 10 µM. Diluted compounds were pre-incubated with recombinant human IL-17AA or IL-17AF plus human TNF-α for 30 minutes at room temperature on a shaker. NHDF cells were re-suspended in fibroblast growth medium/0.2% supplement (100µl/well) followed by addition of the cytokine/compound mix to the cells (100µl/well) to give a final compound starting concentration of

10µ M. The cells were incubated with the compound/cytokines cocktail for 24 hours at 37 °C (5% CO_2). During the culture period, the final concentrations of IL-17AA were 30 pM, IL-17AF were 250 pM, and TNF-α were 6 pM. The final DMSO or plasma concentrations were 0.1% or 20%, respectively. All compound incubations were done in duplicate. The supernatants were collected to quantify IL-6 by ELISA according to the manufacturer`s instructions. The optical density was measured at 450 nm by an EnVision Multilabel Plate Reader (Perkin Elmer). The IL-6 levels produced after TNF-α stimulation were subtracted from the IL-6 produced after IL-17/TNF-α co-stimulation. These IL-17- specific IL-6 concentrations were used for IC50 value calculation. IC50 values for inhibitors were then determined using sigmoidal dose–response curve fitting model (Excel Xlfit, model 205).

The following table provides the potency of Examples 1 – 135 in the cell and TR-FRET assays:

Example	Name	IL17AA+TNF IC50 IL-6 [umol l-1]	IL17AA FRET / IL17Rawt IC50 [umol l-1]
1	2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide	0.004	0.008
2	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (mixture of atropisomers)	0.015	0.024
2a	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (single atropisomer)	0.037	0.049
2b	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide (single atropisomer)	0.014	0.017
3	2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.007	0.024
4	4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide	0.012	0.026

5	(S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.009	0.028
6	4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.005	0.048
7	3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.026	0.046
8	3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.004	0.041
9	3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.004	0.060
10	3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.011	0.093
11	(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.02	0.082
12a	3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide or 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.017	0.112
12b	3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide or 3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.008	0.151
13a	(S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.011	0.016

13b	(R)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	30.4
14	4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.009	0.024
15	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-methoxyethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.010	0.052
16	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-hydroxyethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.013	0.084
17	4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-methylisothiazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.018	0.118
18	4-chloro-2-methyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.028	0.025
19	4-chloro-2-methyl-3-(4-((S)-2-(3-methylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.020	0.026
20	4-chloro-3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxi	n.t.	0.68
21	(S)-3-(4-(2-cyclopentyl-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.031	0.039
22	(S)-3-(4-(2-cyclopentyl-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.066	0.059
23	2,4-dimethyl-3-(4-((S)-2-(3-methylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.006	0.060
24	2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-	0.048	0.114

	(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide		
25	3-(4-((S)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.069	0.178
26	3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.014	0.044
27	(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.115	0.121
28	3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((S)-4-fluorocyclohex-3-en-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.022	0.02
29	3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.047	0.085
30	3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.012	0.046
31	(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.015	0.114
32	(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.05	0.286
33	(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.088	1.15
34	(S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.1	0.081
35	(S)-3-(4-(2-cyclopentyl-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.212.	0.306

36	(S)-3-(4-(2-cyclopentyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.038	1.41
37	(S)-3-(4-(2-cyclopentyl-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.06	0.396
38	(S)-3-(4-(3-(2-chlorophenyl)-2-(3-methylisoxazole-4-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.131	0.017
39	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.02	0.191
40	(S)-3-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.002	0.025
41	(S)-3-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.009	0.024
42	(S)-3-(4-(2-cycloheptyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.012	0.026
43	2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-2-(1-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	n.t.	78.9
44	(S)-6'-(2-cycloheptyl-2-(3-methylisoxazole-4-carboxamido)acetamido)-2,4-dimethyl-[3,3'-bipyridine] 1-oxide	0.018	0.034
45	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamid)phenyl)-2-methylpyridine 1-oxide	0.026	0.026
46	4-chloro-2-methyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.004	0.018
47	(S)-4-chloro-3-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.007	0.017
48	(S)-4-chloro-3-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.001	0.012

49	(S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.031	0.058
50	3-(4-((S)-2-(1-isopropyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.001	0.023
51	4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.062	0.066
52	(S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.08	0.043
53	(S)-3-(4-(2-cyclohexyl-2-(2-methylfuran-3-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.086	0.016
54a	4-chloro-3-(4-((S)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.034	0.028
54b	4-chloro-3-(4-((R)-2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	10.9
55	4-chloro-3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.027	0.038
56	4-chloro-3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide	0.004	0.021
57	3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.012	0.037
58	3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.012	0.044
59	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-3-fluorophenyl)-2-methylpyridine 1-oxide	0.056	0.049

60	(S)-4-chloro-6'-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-methyl-[3,3'-bipyridine] 1-oxide	0.236	0.123
61	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,6-difluorophenyl)-2-methylpyridine 1-oxide	0.016	0.018
62	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,3-difluorophenyl)-2-methylpyridine 1-oxide	0.007	0.015
63	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2,5-difluorophenyl)-2-methylpyridine 1-oxide	0.057	0.247
64	3-(4-((S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.025	0.074
65	3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.024	0.057
66	3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.004	0.018
67	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.015	0.124
68	(S)-3-(4-(2-(1-isopropyl-1H-pyrazole-5-carboxamido)-3,3-diphenylpropanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.016	0.076
69	(S)-4-chloro-2-methyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-3,3-diphenylpropanamido)phenyl)pyridine 1-oxide	0.020	0.090
70	3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.026	0.084
71	3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.035	0.086
72	(S)-3-(4-(3-(2-fluorophenyl)-2-(3-methylisoxazole-4-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	3.4	0.454

73	(S)-3-(4-(2-cyclopentyl-2-(2-methyl-4-(trifluoromethyl)thiazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	n.t.	1.41
74	(S)-2,4-dimethyl-3-(4-(2-(3-methylisoxazole-4-carboxamido)-3-phenylpropanamido)phenyl)pyridine 1-oxide	> 10	1.53
75	(S)-2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-3-phenylpropanamido)phenyl)pyridine 1-oxide	> 10	2.64
76	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-methoxy-2-oxoethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	n.t.	0.603
77	4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.151	0.436
78	3-(4-((S)-2-(3-(hydroxymethyl)isoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	1.69
79	(S)-3-(4-(2-(3-(aminomethyl)isoxazole-4-carboxamido)-2-cyclohexylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.918
80	(S)-3-(4-(2-cyclohexyl-2-(3-((dimethylamino)methyl)isoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	4.45
81	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-methylpyridine 1-oxide	n.t.	3.74
82	(S)-3-(4-(2-cyclohexyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.035	0.085
83	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.115	1.98
84	3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.008	0.014

85	(S)-4-chloro-3-(3-chloro-4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	20.9
86	3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.232	0.119
87	3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.504	0.489
88	3-(4-((2S)-2-(3,3-difluorocyclopentyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.298	0.45
89	(S)-2-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-methylpyridine 1-oxide	0.083	0.286
90	4-chloro-3-(4-((S)-2-cyclohexyl-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.005	0.065
91	3-(2-fluoro-4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.039	0.134
92	(S)-5-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.028	0.372
93	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)pyridine 1-oxide	0.058	0.601
94	(S)-3-(4-(2-cyclohexyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.047	0.128
95	3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	0.019	0.125
96	3-(4-((S)-2-cyclohexyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	0.007	0.070

97	(S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	n.t.	1.73
98	(S)-4-(4-(2-cyclohexyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	n.t.	1.4
99	(S)-4-(4-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.081	0.208
100	(S)-4-(4-(2-cycloheptyl-2-(1-cyclopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.046	0.243
101	(S)-4-(4-(2-cycloheptyl-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.022	0.085
102	(S)-4-(4-(2-(1-cyclobutyl-1H-pyrazole-5-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.017	0.123
103	3,5-dimethyl-4-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamido)phenyl)pyridine 1-oxide	0.045	0.072
104	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-(difluoromethyl)-4-methylpyridine 1-oxide	0.139	1.6
105	(S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3-methylpyridine 1-oxide	0.022	0.041
106	4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.018	0.05
107	4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.015	0.019
108	4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.007	0.03
109	3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2,4-dimethylpyridine 1-oxide	0.084	0.164

110	4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.008	0.023
111	(S)-4-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-3-methylpyridine 1-oxide	n.t.	4.78
112	(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)pyridine 1-oxide	0.162	1.04
113	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,5-dimethylpyridine 1-oxide	0.038	0.339
114	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-fluoro-4-methylpyridine 1-oxide	n.t.	2.79
115	(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-5-(hydroxymethyl)-2-methylpyridine 1-oxide	0.201	1.38
116	(S)-4-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.118	0.304
117	(S)-4-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.121	0.161
118	(S)-4-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)phenyl)-3,5-dimethylpyridine 1-oxide	0.02	0.183
119	(S)-3-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.015	0.13
120	(S)-3-(4-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.004	0.094
121	2,4-dimethyl-3-(4-((S)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-	0.017	0.111

	((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide		
122	4-chloro-3-(4-((S)-2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.009	0.128
123	(S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.059	0.15
124	4-chloro-3-(4-((S)-2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.008	0.172
125	2,4-dimethyl-3-(4-((S)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.018	0.174
126	(S)-3-(4-(2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.062	0.228
127	(S)-3-(4-(2-cyclohexyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.012	0.2355
128	3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.054	0.299
129	4-chloro-3-(4-((2S)-2-(4-fluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	0.382
130	(S)-3-(4-(3-(2-chlorophenyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.956	0.124
131	(S)-3-(4-(2-cyclohexyl-2-(2-cyclopropyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-	n.t.	0.102

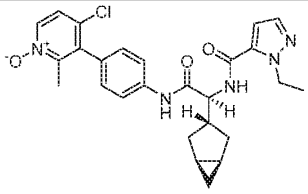
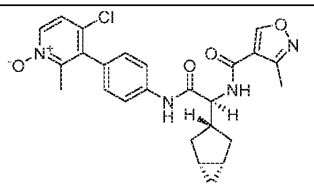
	carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide		
132	2,4-dimethyl-3-(4-((S)-2-(2-(oxetan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	n.t.	0.866
133	4-chloro-3-(4-((S)-2-cyclohexyl-2-(2-(oxetan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.017	0.099
134	3-(4-((S)-2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.007	0.0728
135	(S)-3-(4-(2-cyclohexyl-2-(2-(2-methoxyethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.451

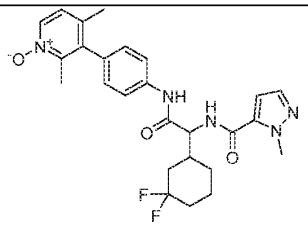
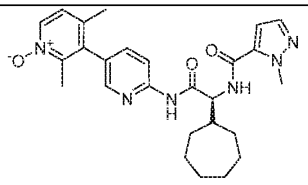
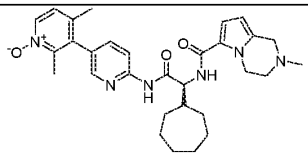
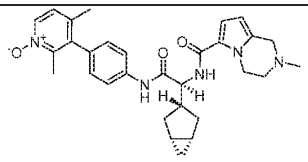
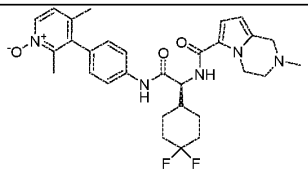
The following table provides the potency of reference examples 136 – 144 in the cell and TR-FRET assays:

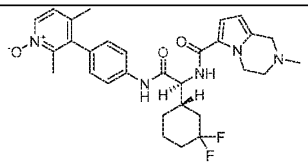
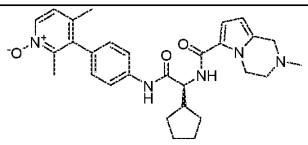
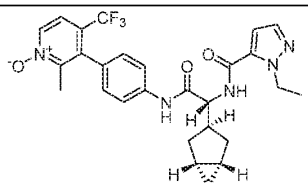
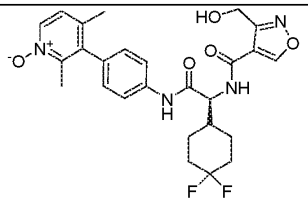
Reference Example	Name	IL17AA+TNF IC_{50} IL-6 [umol l-1]	IL17AA FRET / IL17RAwt IC_{50} [umol l-1]
136	N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl)-1-methyl-1H-pyrazole-5-carboxamide	0.05	0.117
137	N-((1S)-2-((4-(4-chloro-2-methylpyridin-3-yl)-3-fluorophenyl)amino)-1-cyclohexyl-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	0.578	3.79
138	N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-1-((1r,4S)-4-methylcyclohexyl)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	0.055	0.552
139	(S)-N-(1-cyclopentyl-2-((4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)amino)-2-oxoethyl)-3-ethylisoxazole-4-carboxamide	0.152	0.899

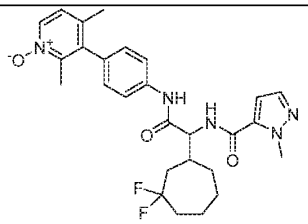
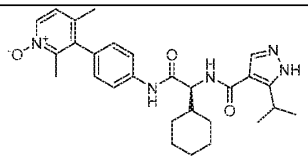
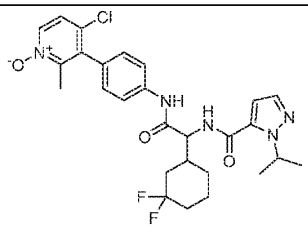
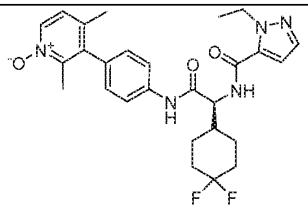
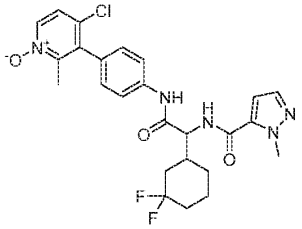
140	N-((S)-2-((4-(4-chloro-2-methylpyridin-3-yl)phenyl)amino)-1-((S)-3,3-difluorocyclohexyl)-2-oxoethyl)-3-ethylisoxazole-4-carboxamide	n.t.	1.22
141	N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((1r,4S)-4-(trifluoromethyl)cyclohexyl)ethyl)-1-ethyl-1H-pyrazole-5-carboxamide	n.t.	2.63
142	N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-2-oxo-1-((1r,4S)-4-(trifluoromethyl)cyclohexyl)ethyl)-3-ethylisoxazole-4-carboxamide	n.t.	4.38
143	N-((S)-1-((S)-3,3-difluorocyclohexyl)-2-((4-(2-methyl-4-(trifluoromethyl)pyridin-3-yl)phenyl)amino)-2-oxoethyl)-3-methylisoxazole-4-carboxamide	n.t.	0.851
144	N-((S)-2-((4-(2,4-dimethylpyridin-3-yl)phenyl)amino)-1-((S)-4-fluorocyclohex-3-en-1-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-5-carboxamide	0.715	4.18

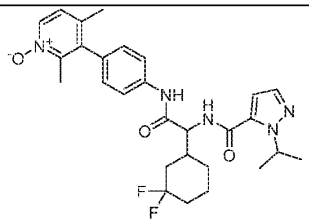
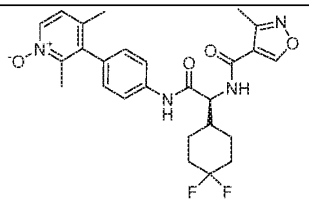
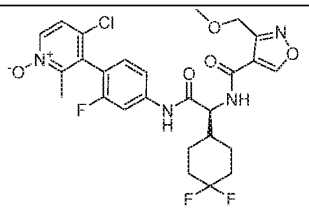
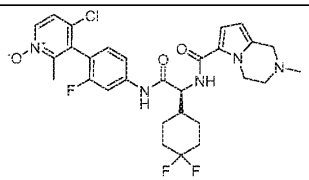
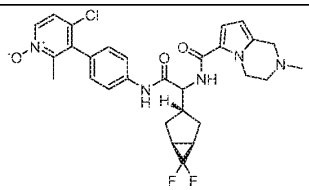
The following table provides the potency of additional Examples 145 – 225 which have been prepared by following the procedures described for Examples 1 to 135 in the cell- and TR-FRET assays:

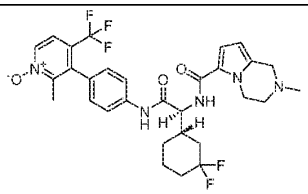
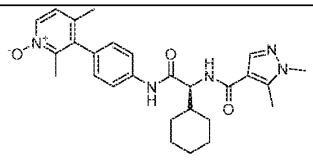
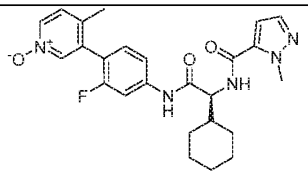
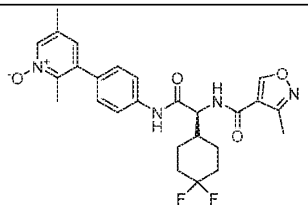
Ex.	Structure	Name	IL17AA+TNF IC50 IL-6 [umol l-1]	IL17AA FRET / IL17Rawt IC50 [umol l-1]
145		3-(4-((S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-4-chloro-2-methylpyridine 1-oxide	0.0235	0.024
146		3-(4-((S)-2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido) phenyl)-4-chloro-2-methylpyridine 1-oxide	0.057	0.0863

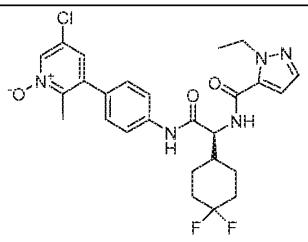
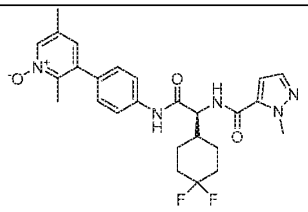
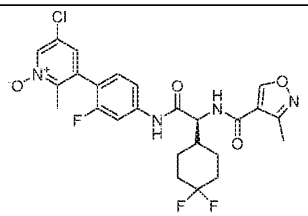
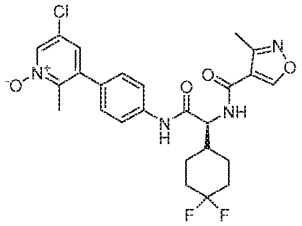
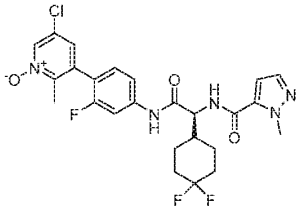
147		3-(4-(2-(3,3-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.193	0.513
148		(S)-6'-(2-cycloheptyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) -2,4-dimethyl-[3,3'-bipyridine] 1-oxide	0.131	0.125
149		(S)-6'-(2-cycloheptyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) -2,4-dimethyl-[3,3'-bipyridine] 1-oxide	0.059	0.118
150		3-(4-((S)-2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.464
151		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.057	0.26

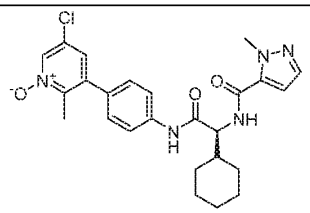
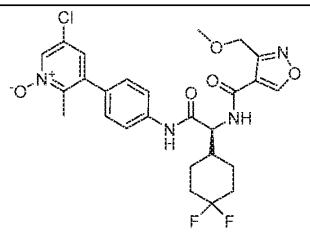
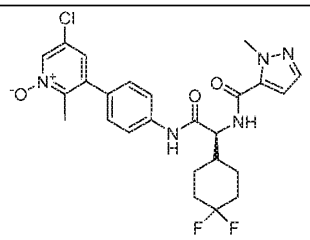
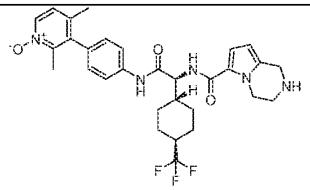
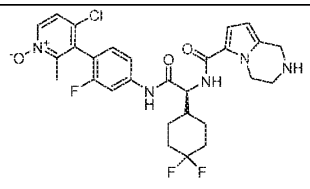
152		3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.391
153		(S)-3-(4-(2-cyclopentyl-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.798
154		3-(4-((R)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	n.t.	6.3
155		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-(hydroxymethyl)isoxazole-4-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	1.15

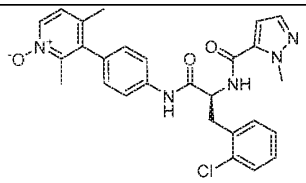
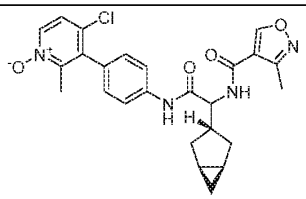
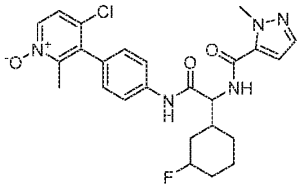
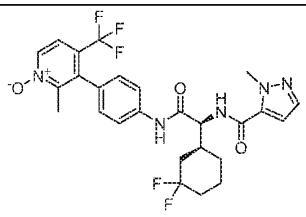
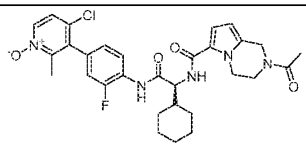
156		3-(4-(2-(3,3-difluorocycloheptyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.0515	0.11
157		(S)-3-(4-(2-cyclohexyl-2-(5-isopropyl-1H-pyrazole-4-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.105	0.17
158		4-chloro-3-(4-(2-(3,3-difluorocyclohexyl)-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide	0.0155	< 0.0061
159		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.031	0.1
160		4-chloro-3-(4-(2-(3,3-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide	0.0523333	0.0895

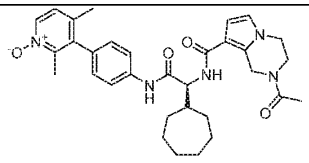
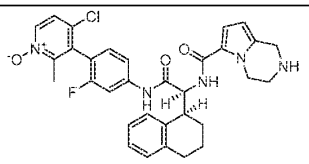
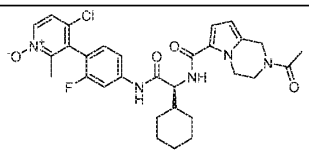
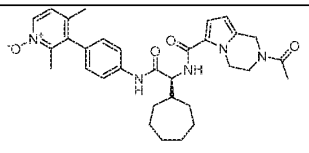
161		3-(4-(2-(3,3-difluorocyclohexyl)-2-(1-isopropyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.0205	0.13
162		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.044	0.186
163		4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.068	0.191
164		4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide	0.045	0.199
165		4-chloro-3-(4-(2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(2-methyl-1,2,3,4-	n.t.	0.301

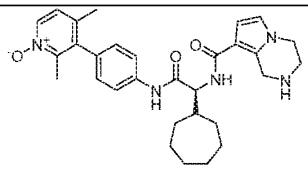
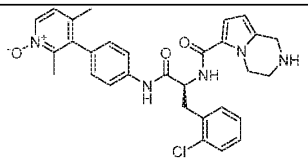
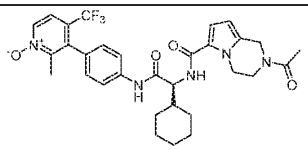
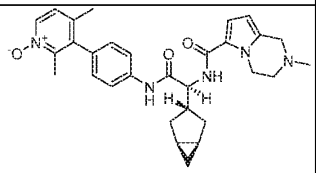
		tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide		
166		3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	n.t.	0.358
167		(S)-3-(4-(2-cyclohexyl-2-(1,5-dimethyl-1H-pyrazole-4-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.21	0.155
168		(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) -2-fluorophenyl)-4-methylpyridine 1-oxide	n.t.	1.47
169		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido) phenyl)-2,5-dimethylpyridine 1-oxide	0.339	0.391

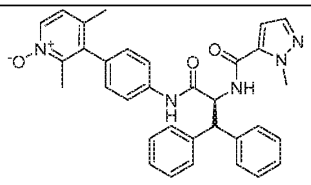
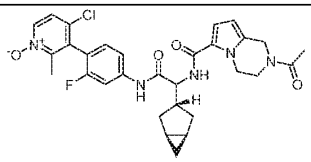
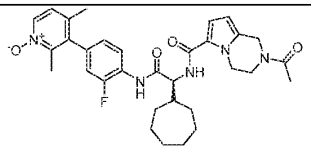
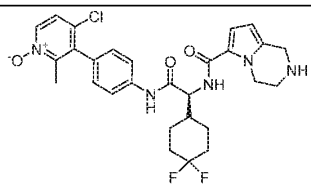
170		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide	0.231	0.402
171		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,5-dimethylpyridine 1-oxide	0.398	0.465
172		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido) -2-fluorophenyl)-2-methylpyridine 1-oxide	0.531	0.596
173		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide	1.681	0.659
174		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) -2-fluorophenyl)-2-methylpyridine 1-oxide	0.286	0.683

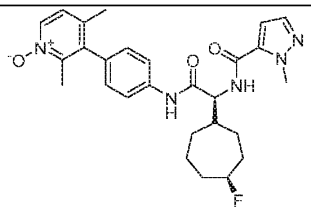
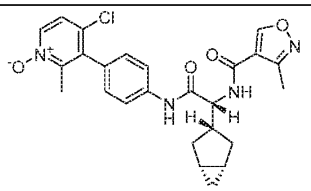
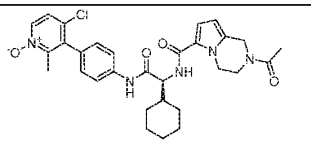
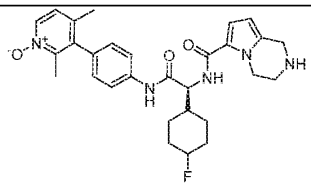
175		(S)-5-chloro-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.13	0.846
176		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(3-(methoxymethyl)isoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	1.61
177		(S)-5-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	2.11
178		2,4-dimethyl-3-(4-((S)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)pyridine 1-oxide	0.03	0.00896
179		4-chloro-3-(4-((S)-2-(4,4-difluorocyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-	0.06	0.0139

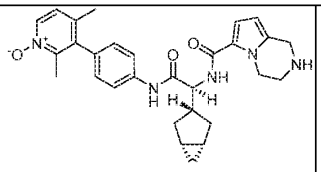
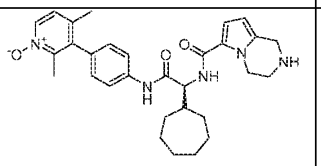
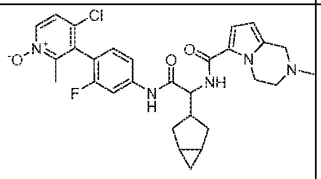
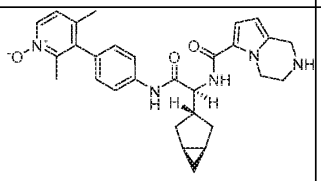
		carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide		
180		(S)-3-(4-(3-(2-chlorophenyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.372	0.052
181		3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.064	0.0548
182		4-chloro-3-(4-(2-(3-fluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.0445	0.0612
183		3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.042	0.0541
184		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-	0.011	0.0599

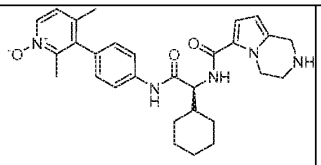
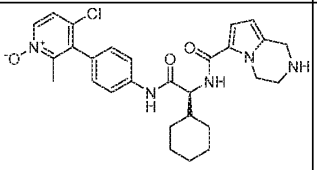
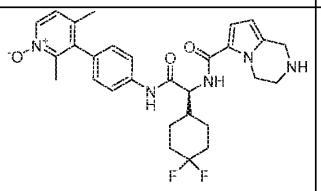
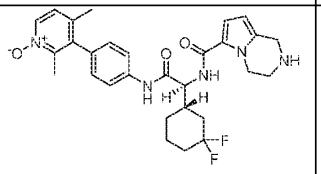
		a]pyrazine-6-carboxamido)-2-cyclohexylacetamido)-3-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide		
185		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxamido)-2-cycloheptylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.00975	0.0771
186		4-chloro-3-(2-fluoro-4-((S)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.034	0.0815
187		3-(4-((S)-2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cyclohexylacetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.017	0.0854
188		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-	0.00605	0.104

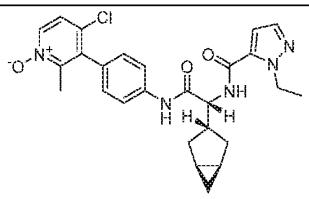
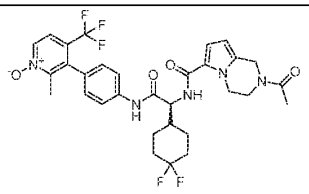
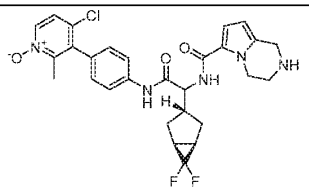
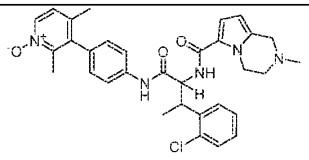
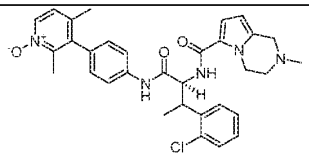
		carboxamido)-2-cycloheptylacetamido)phenyl)-2,4-dimethylpyridine 1-oxide		
189		(S)-3-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-8-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.0155	0.118
190		(S)-3-(4-(3-(2-chlorophenyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.278	0.123
191		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cyclohexylacetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	0.0185	0.128
192		3-(4-((S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)	0.142	0.151

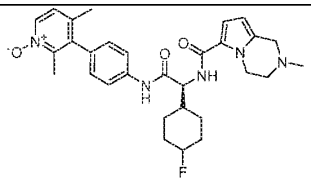
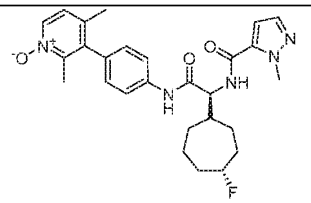
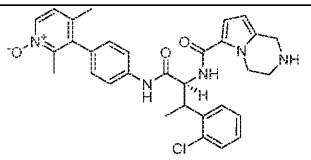
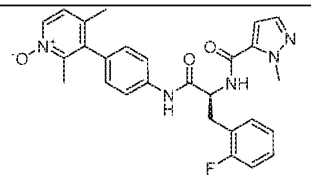
		phenyl)-2,4-dimethylpyridine 1-oxide		
193		(S)-2,4-dimethyl-3-(4-(2-(1-methyl-1H-pyrazole-5-carboxamido)-3,3-diphenylpropanamido)phenyl)pyridine 1-oxide	0.047	0.0973
194		3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)acetamido)-2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.047	0.165
195		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cycloheptylacetamido)-3-fluorophenyl)-2,4-dimethylpyridine 1-oxide	0.0285	0.178
196		(S)-4-chloro-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-	0.0126	0.181

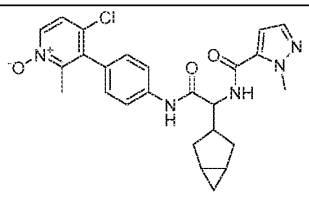
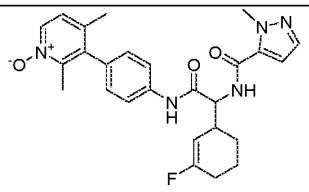
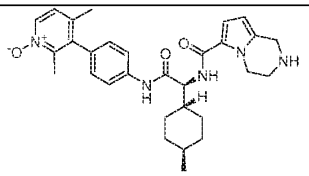
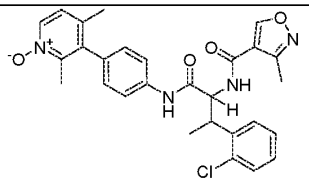
		a]pyrazine-6-carboxamido)acetamido) phenyl)-2-methylpyridine 1-oxide		
197		3-(4-((S)-2-((1S,4S)-4-fluorocycloheptyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.1215	0.213
198		3-(4-((R)-2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(3-methylisoxazole-4-carboxamido)acetamido) phenyl)-4-chloro-2-methylpyridine 1-oxide	0.094	0.222
199		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-cyclohexylacetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.0115	0.237
200		3-(4-((2S)-2-(4-fluorocyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.416	0.246

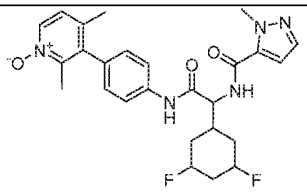
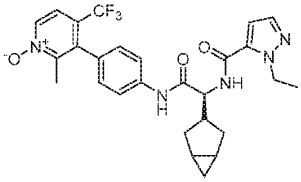
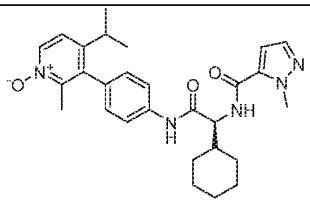
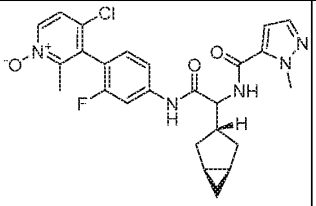
201		3-(4-((S)-2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.061	0.252
202		(S)-3-(4-(2-cycloheptyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.073	0.257
203		3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) -2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.039	0.257
204		3-(4-((S)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	0.095	0.278

205		(S)-3-(4-(2-cyclohexyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.058	0.287
206		(S)-4-chloro-3-(4-(2-cyclohexyl-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	0.063	0.296
207		(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.069	0.303
208		3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.316

209		3-(4-((R)-2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.175	0.381
210		(S)-3-(4-(2-(2-acetyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)-2-(4,4-difluorocyclohexyl)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	n.t.	0.478
211		4-chloro-3-(4-(2-((1R,3s,5S)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide	n.t.	0.499
212		3-(4-(3-(2-chlorophenyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)butanamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.502
213		3-(4-((2S)-3-(2-chlorophenyl)-2-(2-methyl-1,2,3,4-	2.584	0.533

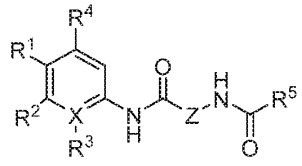
		tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)butanamido)phenyl)-2,4-dimethylpyridine 1-oxide		
214		3-(4-((2S)-2-(4-fluorocyclohexyl)-2-(2-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.69
215		3-(4-((S)-2-((1S,4R)-4-fluorocycloheptyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.138	0.755
216		3-(4-((2S)-3-(2-chlorophenyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)butanamido)phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	0.796
217		(S)-3-(4-(3-(2-fluorophenyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)propanamido)phenyl)-2,4-dimethylpyridine 1-oxide	2.959	1.1

218		3-(4-(2-(bicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-4-chloro-2-methylpyridine 1-oxide	0.0195	0.0675
219		3-(4-(2-(3-fluorocyclohex-2-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.142	2.29
220		2,4-dimethyl-3-(4-((S)-2-((1r,4S)-4-methylcyclohexyl)-2-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamido)acetamido)phenyl)pyridine 1-oxide	n.t.	2.31
221		3-(4-(3-(2-chlorophenyl)-2-(3-methylisoxazole-4-carboxamido)butanamido)phenyl)-2,4-dimethylpyridine 1-oxide	0.264	0.0719

222		3-(4-(2-(3,5-difluorocyclohexyl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2,4-dimethylpyridine 1-oxide	n.t.	7.29
223		3-(4-((2S)-2-(bicyclo[3.1.0]hexan-3-yl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide	n.t.	9.08
224		(S)-3-(4-(2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) phenyl)-4-isopropyl-2-methylpyridine 1-oxide	0.108	2.19
225		3-(4-(2-((1R,3s,5S)-bicyclo[3.1.0]hexan-3-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido) -2-fluorophenyl)-4-chloro-2-methylpyridine 1-oxide	0.012	0.029

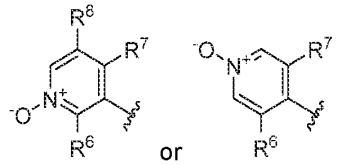
CLAIMS

1. A compound of formula (I):


(I),

wherein,

R^1 is


or wherein,

R^6 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^7 at each occurrence is selected from H, F, Cl, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

R^8 is selected from H, halo, C_1-C_3alkyl and hydroxymethyl;

X is C or N and when X is N, R^3 is absent;

R^2 is selected from H and F;

R^3 is selected from H, F and Cl;

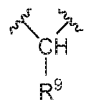
R^4 is selected from H and F;

R^5 is a 5-membered heteroaryl comprising 1 or 2 heteroatoms independently selected from N, S, and O, and wherein said heteroaryl is unsubstituted or substituted with one or two groups independently selected from C_1-C_3alkyl and C_3-C_4cycloalkyl, wherein said C_1-C_3alkyl is unsubstituted or substituted with one or more groups independently selected from F, OH, C_1-C_3alkoxy, -C(O)OH and $NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are independently selected from H and C_1-C_3alkyl;

or

R^5 is a 5-membered heteroaryl comprising one N atom wherein said 5-membered heteroaryl is fused to a 6-membered heterocycle comprising one N atom wherein said heterocycle is unsubstituted or substituted with a group selected from C_1-C_3alkyl, C_1-C_3alkoxyC_1-C_3alkyl, -C(O)C_1-C_3alkyl, C_3-C_4cycloalkyl and oxetanyl;

Z is


, wherein R^9 is selected from

(1) monocyclic C_5-C_8cycloalkyl and C_6-bicycloalkyl,

each of which is independently unsubstituted or substituted with one or more groups independently selected at each occurrence from fluoro, C_1-C_3alkyl and C_1-C_3fluoroalkyl,

and wherein said monocyclic C_5-C_8cycloalkyl is optionally fused to phenyl; wherein said phenyl is unsubstituted or substituted with one or more groups selected from halo, C_1-C_3alkyl, C_3-C_5cycloalkyl or C_1-C_3fluoroalkyl;

(2) monocyclic C_5-C_8cycloalkenyl, which is unsubstituted or substituted with one or more fluoro;

(3) C_1-C_3alkyl, which is unsubstituted or substituted with one or two phenyl groups, wherein said phenyl at each occurrence is independently unsubstituted or substituted with one or more halo;

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R^6 at each occurrence is selected from H, F, Cl, methyl and difluoromethyl.

3. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1 or 2, wherein R^7 at each occurrence is selected from H, F, Cl, methyl and trifluoromethyl.

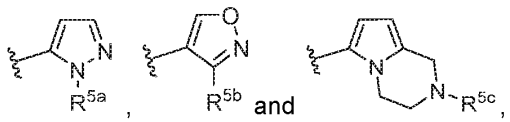
4. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, wherein R^8 is selected from H, chloro, methyl and hydroxymethyl.

5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4, wherein X is C.

6. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5, wherein R^3 is H.

7. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6, wherein R^4 is H.

8. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7, wherein R^5 is selected from



wherein

R^{5a} is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, -$(CH_2)_2OH$, -$(CH_2)_2OCH_3$, -$CH_2C(O)OH$ and -$(CH_2)_2N(CH_3)_2$;

R^{5b} is selected from methyl, ethyl, -CH_2OCH_3, -CH_2OH, -CH_2NH_2 and -$CH_2N(CH_3)_2$; and

R^{5c} is selected from H, methyl, -$C(O)CH_3$, cyclopropyl, oxetanyl and -$(CH_2)_2OCH_3$.

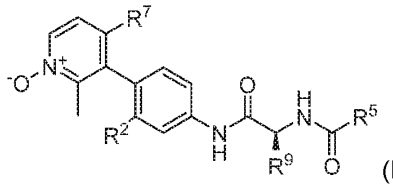
9. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8, wherein R^9 is selected from,

(1) monocyclic C_5-C_7cycloalkyl and C_6-bicycloalkyl,
each of which is independently unsubstituted or substituted with one or two groups independently selected at each occurrence from fluoro, C_1-C_3alkyl and C_1-C_3fluoroalkyl,
and wherein said monocyclic C_5-C_7cycloalkyl is optionally fused to unsubstituted phenyl;

(2) monocyclic C_5-C_8cycloalkenyl, which is unsubstituted or substituted with one fluoro;

(3) methyl, which is unsubstituted or substituted with one or two phenyl groups, wherein said phenyl at each occurrence is independently unsubstituted or substituted with one chloro.

10. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9, wherein the compound is of formula (IB):

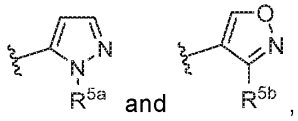

(IB),

wherein,

R^7 is selected from Cl, methyl and trifluoromethyl;

R^2 is selected from H and F;

R^5 is selected from


and

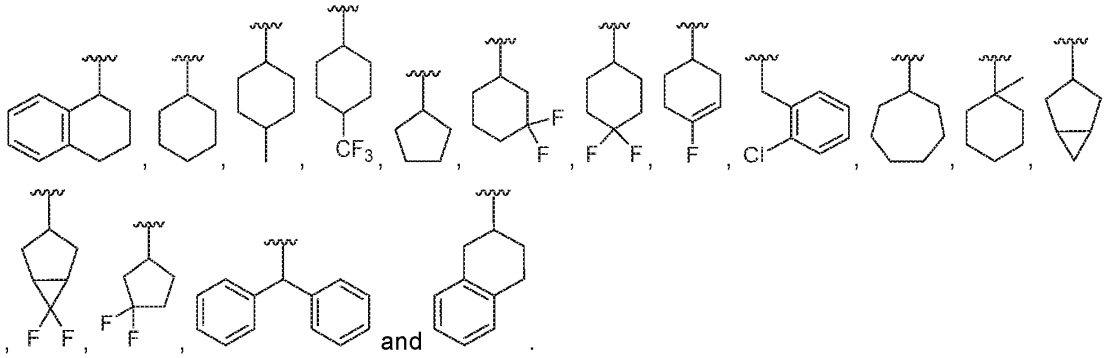
,

wherein,

R^{5a} is selected from methyl and ethyl; and

R^{5b} is selected from methyl and ethyl;

R^9 is selected from



11. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 10, wherein the compound is selected from:

2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide;

4-chloro-3-(4-((S)-2-cyclohexyl-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)-2-fluorophenyl)-2-methylpyridine 1-oxide;

2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-methylcyclohexyl)acetamido)phenyl)pyridine 1-oxide;

4-chloro-3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2-methylpyridine 1-oxide;

(S)-3-(4-(2-cyclopentyl-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;

4-chloro-3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-ethylisoxazole-4-carboxamido)acetamido)phenyl)-2-methylpyridine 1-oxide;

3-(4-((S)-2-(1-ethyl-1H-pyrazole-5-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;

3-(4-((S)-2-(3-ethylisoxazole-4-carboxamido)-2-((1r,4S)-4-(trifluoromethyl)cyclohexyl)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;

3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(3-methylisoxazole-4-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;

3-(4-((S)-2-((S)-3,3-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;

(S)-3-(4-(2-(4,4-difluorocyclohexyl)-2-(1-ethyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide;

3-(4-((2S)-2-(4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide;
3-(4-((S)-2-((R)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide; or
3-(4-((S)-2-((S)-4-fluorocyclohex-3-en-1-yl)-2-(1-methyl-1H-pyrazole-5-carboxamido)acetamido)phenyl)-2,4-dimethylpyridine 1-oxide.

12. The compound 2,4-dimethyl-3-(4-((S)-2-(1-methyl-1H-pyrazole-5-carboxamido)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamido)phenyl)pyridine 1-oxide, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

14. A combination comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 12, and one or more therapeutically active agents.

15. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 12, for use as a medicament.

16. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 12, for use in the treatment, or prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis and non-radiographic axial spondyloarthritis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathis arthritis, osteoarthritis, tendinopathy, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies, including eczema and dermatitis, as well as asthma; in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy,

Grave's disease, sarcoidosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, Behcet disease, lichen planopilaris, lichen planus, hidradenitis suppurativa, acne, recurrent aphthous stomatitis, and periodontitis, pyoderma gangraenosum, and other neutrophil dermatoses, pityriasis rubra pilaris, bullous pemphigoid and ichthyosis, endometriosis, non-alcoholic steatohepatitis, interstitial lung fibrosis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), tumors, multiple sclerosis, autism, depressiona DNA, Alzheimer's disease, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

17. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 12, for use in the treatment, or prevention of psorisasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.