STAT6 DEGRADERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to European Patent Application No. EP24167026.4, filed March 27, 2024, which is incorporated herein in its entirety for all purposes.

FIELD

Provided herein are novel compounds and pharmaceutically acceptable salts thereof that modulate STAT6 and pharmaceutical compositions comprising said compounds for use in therapy (e.g., for treating STAT6 associated diseases in a subject in need thereof).

BACKGROUND

The disclosure relates generally to methods and compounds, and pharmaceutically acceptable salts thereof, for modulating a Signal transducer and activator of transcription 6 (STAT6) protein activity and treating STAT6 associated diseases. The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

The present disclosure relates to novel bifunctional compounds and pharmaceutically acceptable salts thereof, which may function to recruit STAT6 proteins to E3 ubiquitin ligase for degradation, compositions containing such compounds, and methods and uses thereof. In some embodiments, the present disclosure provides bifunctional compounds and pharmaceutically acceptable salts thereof, which may find utility as modulators of targeted ubiquitination of STAT6 proteins, which may be then degraded and/or otherwise inhibited by the bifunctional compounds as described herein.

Ubiquitin-Proteasome Pathway (UPP) is a pathway that regulates key regulator proteins and degrades proteins, such as misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it can lead to pathogenesis of a variety of diseases. The attachment of ubiquitin to specific protein substrates can be achieved through the action of E3 ubiquitin ligases.

There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be generally divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (PLOS One, 2008, 3, 1487) titled "Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling."; Bemdsen et al. (Nat. Struct. Mol. Biol., 2014, 21, 301-307) titled "New insights into ubiquitin E3 ligase mechanism"; Deshaies et al. (Ann. Rev. Biochem., 2009, 78, 399- 434) titled "RING domain E3 ubiquitin ligases."; Spratt et al. (Biochem. 2014, 458, 421-437) titled "RBR E3 ubiquitin ligases: new structures, new insights, new questions."; and Wang et al. (Nat. Rev. Cancer., 2014, 14, 233-347) titled "Roles of F-box proteins in cancer."

UPP plays a role in the degradation of short-lived and regulatory proteins important in a variety of basic cellular processes, including regulation of the cell cycle, modulation of cell surface receptors and ion channels, and antigen presentation. The pathway has been implicated in several forms of malignancy,

in the pathogenesis of several genetic diseases (including cystic fibrosis, Angelman's syndrome, and Liddle syndrome), in immune surveillance/viral pathogenesis, and in the pathology of muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

The UPP can be used to induce selective protein degradation, including via use of fusion proteins to ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, can induce proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds can be capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(1): 40-46).

The signal Transducer and Activator of Transcription 6 (STAT6) belongs to a family of transcription factors (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6) which may be structurally and/or functionally related, and which may be involved in mediating signalling from multiple cytokine and/or growth factor receptors.

Without being bound by theory, STAT6 can selectively mediate signaling from IL-4 and IL-13 via the IL-4Ra subunit complexing with either the common gamma chain (γc) to form the type I receptor or with the IL-13Rα1 subunit to form a type II receptor. When IL-4 or IL-13 activates the receptor complex, the Janus Kinases (Jak) associated with the cytoplasmic tail of IL-4Ra can be activated and phosphorylate tyrosine residues on the intracellular part of the receptor. This phosphorylation can generate docking site(s) for STAT6, which can bind to the phosphorylated receptor via its Src homology-2 (SH2) domain. This may allow Jak kinases to phosphorylate tyrosine (Y)-641 on STAT6, potentially leading to activation. Activated STAT6 may form a homodimer and relocate to the nucleus and activate gene transcription. The genes transcribed by activated STAT6 can be cell specific and could in general induce Th2 immune responses (Walford and Taylor 2013: STAT6 and lung inflammation. JAK-STAT 2:4, e25301; October/November/December 2013; © 2013 Landes Bioscience).

STAT6 is expressed in numerous cell types including epithelial cells, fibroblasts and immune cells. Without being bound by theory, inhibition of STAT6 activity can inhibit the IL-4 and IL-13 mediated effects in cells, including the differentiation of T-cells into Th2 cells and B-cell class shift into

IgE and IgG1 producing cells (Walford). In epidermal keratinocytes, a STAT6 inhibitor could inhibit the secretion of pro-inflammatory chemokines and revert the cytokine-induced inhibition of barrier function proteins such as filaggrin (Tollenaire et al 2017: Skin Barrier and Inflammation Genes Associated with Atopic Dermatitis are Regulated by Interleukin-13 and Modulated by Tralokinumab In vitro. Acta Derm Venereol 2021; 101: adv00447.

Antibodies targeting Th2 immune responses, such as the IL-4Ra (dupilumab) or IL-13 (tralokinumab, lebrikizumab), have shown efficacy in a number of Th2-driven diseases. Targeting STAT6 with a small molecule inhibitor allows for targeting the same pathway by an oral or dermal administration route and may have efficacy in diseases where dupilumab has shown effect. A compound antagonizing STAT6 could, therefore, have utility in treating conditions characterized by Th2-mediated inflammation such as atopic dermatitis, prurigo nodularis, Bullous phemphigoid, asthma, chronic rhinosinusitis with nasal polyposis, urticaria (such as chronic spontaneous urticaria), rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD.

STAT6 is also involved in differentiation and activity of M2 macrophages, including the tumor-associated macrophages (TAMs) in solid tumors. TAMs protect the tumor from immune attack by inducing a pro-tumor immunosuppressive environment. TAMs may inhibit T-cell proliferation, block migration of CD8 T-cells into the tumor and recruit Tregs into the tumor microenvironment (Karpathiou et al 2021: STAT6: A review of a signaling pathway implicated in various diseases with a special emphasis in its usefulness in pathology. Pathology - Research and Practice 223 (2021) 153477).

In addition, IL-13 may act as a growth factor for some tumors and for some tumors gain-of-function mutations in STAT6 have been described as oncogenes (Karpathiou et al 2021: STAT6: A review of a signaling pathway implicated in various diseases with a special emphasis in its usefulness in pathology. Pathology - Research and Practice 223 (2021) 153477).

Together these data suggests that a STAT6 degraders may treat different cancers such as lymphomas, non-small cell lung cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors.

Although various antibodies against IL-4R or IL-13 are approved for medical use, there are currently no approved, orally available degraders of STAT6.

Therefore, there remains a continuous need to develop degraders of STAT-6, particularly small molecules suitable for oral administration.

In addition, some patients may be treated by topical application of degraders of STAT-6. This can be particularly suitable, for example, for patients with skin lesions that are readily accessible and limited to areas on the body surface. Topical treatment may also be prescribed for certain patients who could benefit from avoiding systemic modulation of the STAT-6 pathway, for example when undergoing treatment for infections or gastrointestinal problems.

SUMMARY

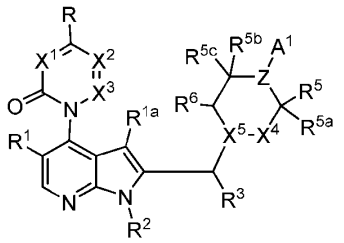
The inventors have surprisingly found that the novel compounds and salts thereof as described in the present disclosure exhibit modulating effects on the STAT-6 signalling pathway.

For example, the compounds and pharmaceutically acceptable salts thereof as described herein may be beneficial in preventing, treating or ameliorating a variety of diseases which involve up-regulation or de-regulation of STAT-6.

Furthermore, the compounds and pharmaceutically acceptable salts thereof as described herein have advantageous properties such as high metabolic stability, membrane permeability and/or solubility that make them particularly suitable for oral administration.

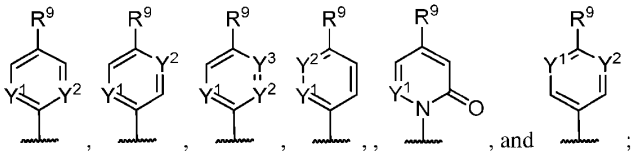
Moreover, some patients may be treated by topical application of degraders of STAT-6. This can be particularly suitable, for example, for patients with skin lesions that are readily accessible and limited to areas on the body surface. Topical treatment may also be prescribed for certain patients who could benefit from avoiding systemic modulation of the STAT-6 pathway, for example when undergoing treatment for infections or gastrointestinal problems. Thus, some aspects of the present disclosure relate to methods for the topical application of the compounds and salts thereof as described herein.

Accordingly, in some embodiments, the present disclosure provides a compound according to formula (I)



(I)

wherein:

A^1 is selected from  ;

R^9 is -A-L-LBM;

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is selected from CR^4R^4 and CO;

X^5 is selected from N and oxidized N;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Y^3 is selected from N and CR^{17};

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl- C_{1-4}alkyl, halo-C_{1-4}alkyl, $-(CH_2)_n$-O-C_{1-4}alkyl, $-(CH_2)_n$-CO-R', and $-(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituents independently selected from

halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R", -CONR'R", and -CO_2R', and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1 or 2;

R^1 and R^{1a} are independently selected from hydrogen, fluoro, and C_{1-4}alkyl;

R^2 is selected from hydrogen, C_{1-5}alkyl, -SO_2-C_{1-4}alkyl and deuterated C_{1-4}alkyl, wherein said C_{1-5}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

each of R^4 and R^6 is independently selected from hydrogen, C_{1-4}alkyl, and C_{1-4} alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen;

or R^5 and R^{5a} are both fluoro or R^5 and R^{5a} together with the atom attached thereto form a CO group;

R^{5b} and R^{5c} are each independently selected from hydrogen and fluoro;

R^7, R^8, and R^{17} are each independently selected from hydrogen, halogen, cyano, C_{1-4}alkyl and C_{1-4}alkoxy,and C_{3-4}cycloalkyl, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

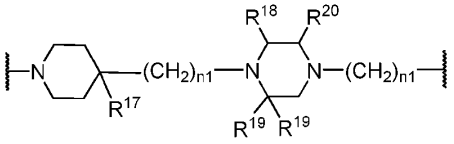
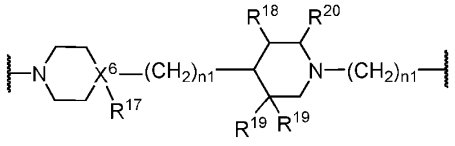
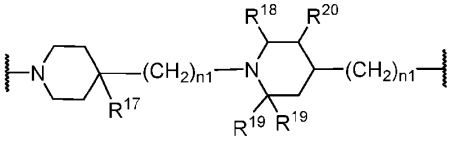
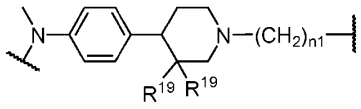
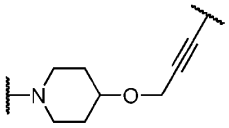
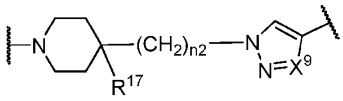
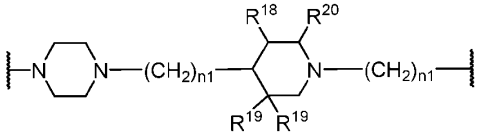
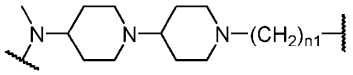
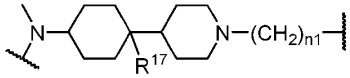
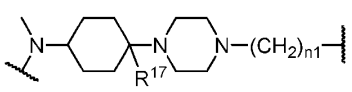
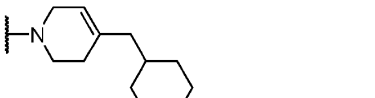
R^{11}, R^{12}, and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", -CO_2R', and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl; or

R^{11} and R^0 together with the atoms attached thereto form a 5-6 membered heteroaromatic or heterocyclic ring containing one or two N atoms, wherein said 5-6 membered heteroaromatic ring or heterocyclic ring containing one or two N atoms is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -$COCF_3$, -NR'R", -CONR'R", and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl;

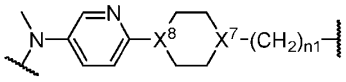
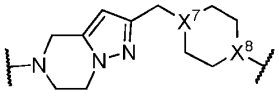
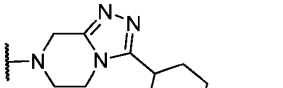
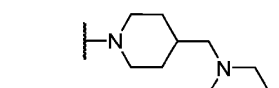
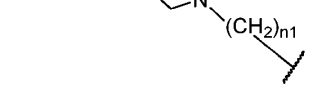
R^{12} and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl;

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L is selected from


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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

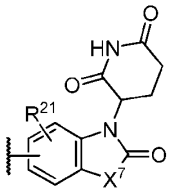
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

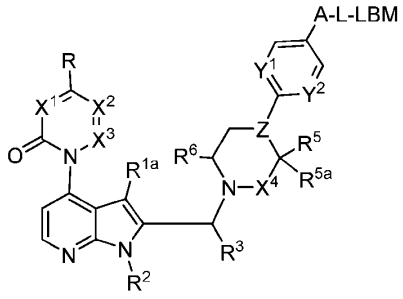
R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, the present disclosure provides a compound according to formula (I')



(I')

Wherein:

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is CR^4R^4 or CO;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl-C_{1-4}alkyl, halo-C_{1-4}alkyl, -$(CH_2)_n$-O-C_{1-4}alkyl, -$(CH_2)_n$-CO-R', and -$(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, - NR'R'', -CONR'R'', and -CO_2R', and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1, or 2;

R^{1a} is hydrogen;

R^2 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl; wherein said C_{1-4}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

R^4 and R^6 are independently selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted with one or more halogens;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen; or R^5 and R^{5a} are both fluoro;

R^7 and R^8 are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may independently optionally be substituted with one or more halogen;

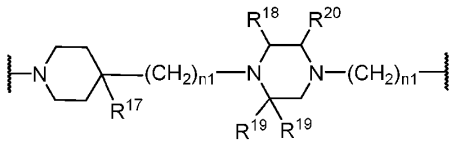
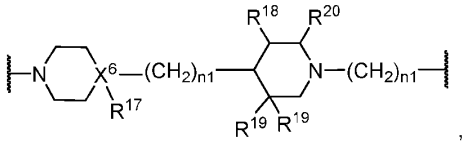
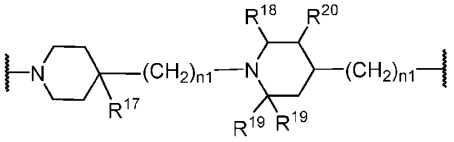
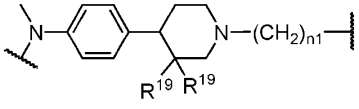
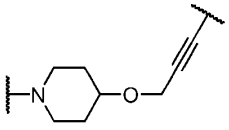
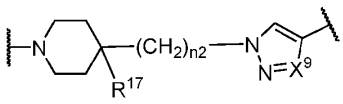
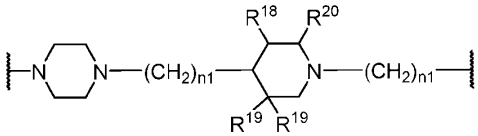
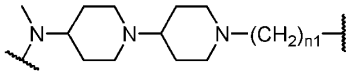
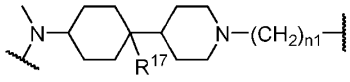
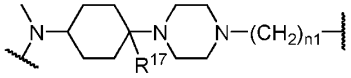
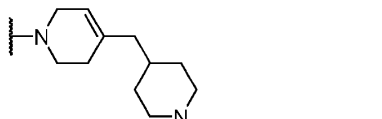
R^{11} is selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', - CO_2R', -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl; or

R^{11} and R^0 together with the atoms attached thereto may form a 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N, wherein said 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R'', -CONR'R'' and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl;

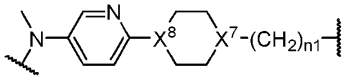
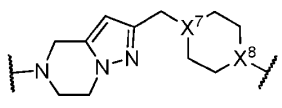
R^{12} and R^{13} are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy, and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R´ and R´´ are each independently selected from hydrogen and C_{1-4}alkyl;

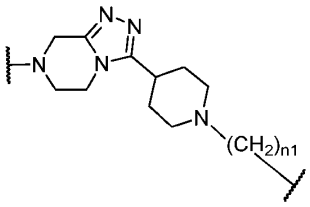
A is CO;

L is selected from

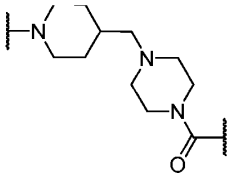

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, and



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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

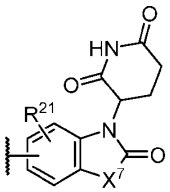
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient.

In another embodiment, the present disclosure provides a method of treating an immune mediated disease or condition in a subject in need thereof, the method comprising administering to the

subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In another embodiment, the present disclosure provides a method of modulating a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In another embodiment, the present disclosure provides a method of treating a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In another embodiment, the present disclosure provides a method of treating a disease or condition mediated by interleukin 4 (IL-4) or interleukin 3 (IL-3) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In one embodiment the disclosure provides a method of preventing, treating or ameliorating a diseases characterized by Th2-mediated inflammation.

In another embodiment, the present disclosure provides a method for manufacturing a medicament for treating a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, characterized in that a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is used.

In another embodiment, the present disclosure provides a method for manufacturing a medicament for the treatment of a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein in a subject.

In some embodiments, the present disclosure provides a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in treating a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein in a subject in need thereof.

In some embodiments, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the results of anHiBit Assay, dose-response curve for Examples **3u208**, **3u246**, **3u118**, **3u119**, **3u120**, and **3u74** (where percent degradation is plotted *vs.* test compound concentration in M on a log-scale).

FIG. 2 shows data from the human whole blood [illegible] assay for Examples **3u200**, **3u240**, **3u118**, **3u119**, **3u120**, and **3u74** (where the effect in % is plotted against the test concentration in M on a log scale).

DETAILED DESCRIPTION

Definitions

Whenever the compound of formula (I) is mentioned herein it should be understood that the compound of formula (I'), (I''), (II), (II'), (III), (IV), (IV'), (VII), (VIII), (VIII'), (IX), (IXa), and (IXb), and other subformulas described herein, are subgroups of the compound of formula (I) and that a statement related to the compound of formula (I) relates equally well to its subgroups.

The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-4} alkyl" indicates that the alkyl group has from 1 to 4 carbon atoms.

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art. The term "C_{1-4}alkyl" is used herein to refer to hydrocarbon radical obtained when one hydrogen atom is removed from a branched or linear hydrocarbon. Said alkyl comprises (1-4) carbon atoms, 1-3 carbon atoms, 2-3 carbon atoms or 1-2 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

The term "C_{1-4}alkyl" is used herein to refer to hydrocarbon radical obtained when one hydrogen atom is removed from a branched or linear hydrocarbon. Said alkyl comprises (1-4) carbon atoms, 1-3 carbon atoms, 2-3 carbon atoms or 1-2 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*.-butyl, and *tert*.-butyl.

The term "(C_1-C_4)alkoxy" is used herein to refer to a radical of the formula –OR', wherein R' is (C_1-C_4)alkyl as indicated herein, wherein the (C_1-C_4)alkyl group is appended to the parent molecular moiety through an oxygen atom, e.g. methoxy (-OCH_3), and ethoxy (-OCH_2CH_3).

The term "cyano" is used herein to refer to a –CN group attached to the parent molecular moiety through the carbon atom.

The term "(C_3-C_4)cycloalkyl" is used herein to refer to a saturated (C_3-C_4)cycloalkane hydrocarbon radical, comprising 3-4 carbon atoms, e.g. cyclopropyl, or cyclobutyl.

The term "halogen" or "halo" is used herein to refer to chloro, bromo, fluoro, or iodo. In some embodiments, halogen is chloro, bromo, or fluoro.

"Aromatic ring" or "aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. An aryl may have 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl regardless of point of attachment. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl regardless of point of attachment. If one or more aryl groups are fused with a cycloalkyl, the resulting ring system is cycloalkyl regardless of point of attachment.

"Heteroaromatic ring" or "heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur unless specified otherwise. A heteroaryl may include 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, thiophenyl (i.e., thienyl), triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

"Heterocyclic ring" or "heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur, unless specified otherwise. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or

N-oxide ($-O^-$) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. A heterocyclyl may have 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocyclyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl.

The term "halo-C_{1-4}alkyl" or "halo-C_{1-4}alkoxy" is used herein to refer to an "C_{1-4}alkyl" or "C_{1-4}alkoxy" group respectively as defined above in which one or more hydrogen atoms have been replaced by halogen (e.g. fluorine). Examples of "halo-C_{1-4}alkyl" or "halo-C_{1-4}alkoxy" include $-CHF_2$, -CF3, $-CH_2CF_3$, $-CF_2CF_3$ or $-OCF_3$.

The term "deuterated C_{1-4}alkyl" is used herein to refer to an "C_{1-4}alkyl" group in which one or more hydrogen atoms have been replaced by deuterium. Examples of "deuterated C_{1-4}alkyl" include $-CH_2D_2$, $-CHD_2$ or -CD3.

The term "C_{1-4}alkoxyl-C_{1-4}alkyl" is used herein the refer to "C_{1-4}alkyl" group in which one hydrogen atom have been replaced by (C_1-C_4)alkoxy. Examples of "C_{1-4}alkoxyl-C_{1-4}alkyl" " include methoxymethyl or methoxyethyl.

The term "(C_3-C_4)cycloalkyl-C_{1-4}alkyl" is used herein the refer to "C_{1-4}alkyl" group in which one hydrogen atom have been replaced by (C_3-C_4)cycloalkyl. Examples of "(C_3-C_4)cycloalkyl-C_{1-4}alkyl" include cyclopropylmethyl.

The term "phenyl-C_{1-4}alkyl" is used herein the refer to "C_{1-4}alkyl" group in which one hydrogen atom has been replaced by phenyl. Examples of "phenyl-C_{1-4}alkyl" include benzyl.

If substituents are described as being independently selected from a group, each substituent is selected independent of the other. Each substituent may therefore be identical or different from the other substituent(s).

The term "optionally substituted" means "unsubstituted or substituted". In some embodiments, formulas described herein encompasses compounds containing the specified optional substituent(s) as well as compounds that do not contain the optional substituent(s).

In certain embodiments, as used herein, the phrase "one or more" refers to one to five. In certain embodiments, as used herein, the phrase "one or more" refers to one to three.

As used herein whenever a molecular drawing of a substituent contains an arrow – the arrow indicates the bond attaching the substituent to the rest of the molecule.

The term "pharmaceutically acceptable salt" is intended to indicate non-toxic salts a free base form of a compound that possesses the desired pharmacological activity of the free base. These salts may be derived from an appropriate basic moiety, with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroacetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic, succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxyethanesulfonic acid, toluenesulfonic, sulfamic or fumaric acid.

In some embodiments, pharmaceutically acceptable salts of compounds of formula (I) comprising an acidic moiety may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, zinc hydroxide, barium hydroxide, ammonia or the like, or suitable non-toxic amines, such as lower alkylamines (such as diethylamine, tetraalkylammonium hydroxide), hydroxy-lower alkylamines (such as diethanolamine, 2-(diethylamino)-ethanol, ethanolamine, triethanolamine, tromethamine, deanol), cycloalkylamines, ethylene diamine, or benzylamines, (such as benethamine and benzathine), betaine, choline hydroxide, N-methyl-glucamine, hydrabamine, 1H-imidazole, 4-(2-hydroxyethyl)-morpholine, piperazine, 1-(2-hydroxyethyl)-pyrrolidine, L-arginine or L-lysine. Further examples of pharmaceutical acceptable salts are listed in Berge, S.M.; J. Pharm. Sci.; (1977), 66(1), 1-19, and Stahl, P.H. and in Wermuth, C.G, Handbook of Pharmaceutical Salts, Properties, Selection and Use, 2nd Edition, Wiley-VCH, 2011 both of which are incorporated herein by reference.

The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a crystalline form. When water is the solvent, said species is referred to as a hydrate.

The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the amelioration, alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The term may also include prevention of the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition or disorder and includes the

administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects.

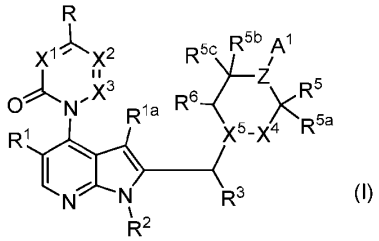
"Administering" refers to oral administration, administration as a suppository, topical contact (e.g., transdermal), parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intranasal, inhaled, intradermal, and/or subcutaneous administration, intrathecal administration, and/or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject. The administration can be carried out according to a schedule specifying frequency of administration, dose for administration, and other factors.

"Co-administration" as used herein refers to administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound of the present disclosure is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the present disclosure within seconds or minutes. In some embodiments, a unit dose of a compound of the present disclosure is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the present disclosure. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the patient.

Compounds

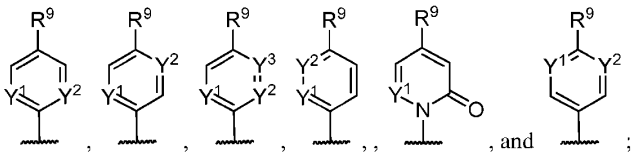
Provided herein are compounds that modulate the activity of STAT6.

In one embodiment the disclosure provides a compound of formula (I)



(I)

wherein:

A^1 is selected from  ;

R^9 is -A-L-LBM;

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is selected from CR^4R^4 and CO;

X^5 is selected from N and oxidized N;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Y^3 is selected from N and CR^{17};

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl- C_{1-4}alkyl, halo-C_{1-4}alkyl, $-(CH_2)_n$-O-C_{1-4}alkyl, $-(CH_2)_n$-CO-R', and $-(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituents independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R", -CONR'R", and $-CO_2$R', and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1 or 2;

R^1 and R^{1a} are independently selected from hydrogen, fluoro, and C_{1-4}alkyl;

R^2 is selected from hydrogen, C_{1-5}alkyl, $-SO_2$-C_{1-4}alkyl and deuterated C_{1-4}alkyl, wherein said C_{1-5}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

each of R^4 and R^6 is independently selected from hydrogen, C_{1-4}alkyl, and C_{1-4} alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen;

or R^5 and R^{5a} are both fluoro or R^5 and R^{5a} together with the atom attached thereto form a CO group;

R^{5b} and R^{5c} are each independently selected from hydrogen and fluoro;

R^7, R^8, and R^{17} are each independently selected from hydrogen, halogen, cyano, C_{1-4}alkyl and C_{1-4}alkoxy, and C_{3-4}cycloalkyl, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

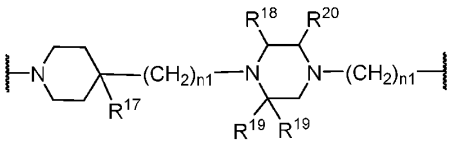
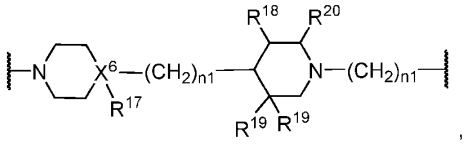
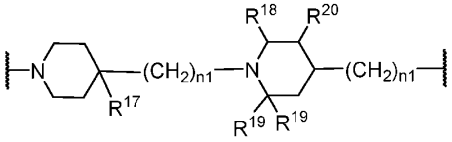
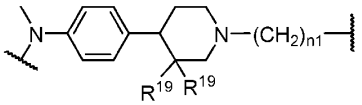
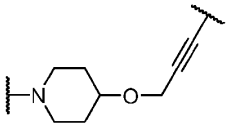
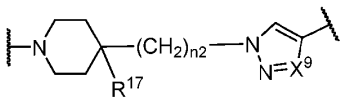
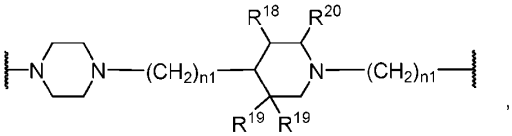
R^{11}, R^{12}, and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", $-CO_2$R', and $-CO-(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl; or

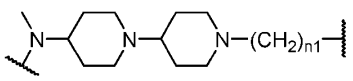
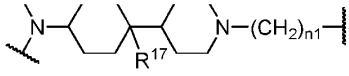
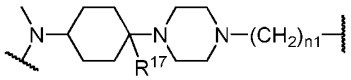
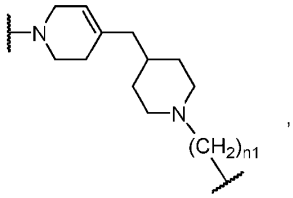
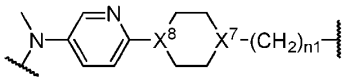
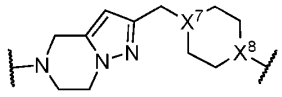
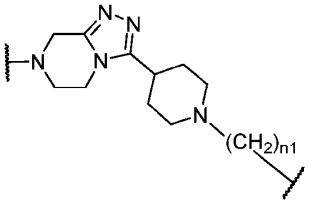
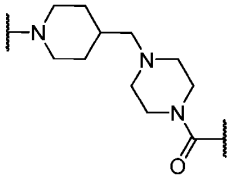
R^{11} and R^0 together with the atoms attached thereto form a 5-6 membered heteroaromatic or heterocyclic ring containing one or two N atoms, wherein said 5-6 membered heteroaromatic ring or heterocyclic ring containing one or two N atoms is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -$COCF_3$, -NR'R", -CONR'R", and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl; and

R^{12} and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl;

A is CO;

L is selected from


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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

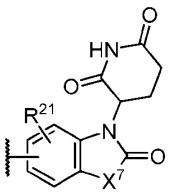
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

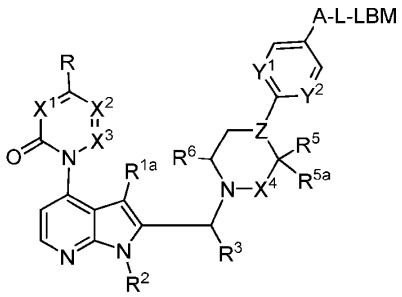
R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In one embodiment the disclosure provides a compound of formula (I')



(I')

wherein:

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is CR^4R^4 or CO;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl-C_{1-4}alkyl, halo-C_{1-4}alkyl, -$(CH_2)_n$-O-C_{1-4}alkyl, -$(CH_2)_n$-CO-R', and -$(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, - NR'R'', -CONR'R'', and -CO_2R', and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1, or 2;

R^{1a} is hydrogen;

R^2 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl; wherein said C_{1-4}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

R^4 and R^6 are independently selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted with one or more halogens;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen; or R^5 and R^{5a} are both fluoro;

R^7 and R^8 are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may independently optionally be substituted with one or more halogen;

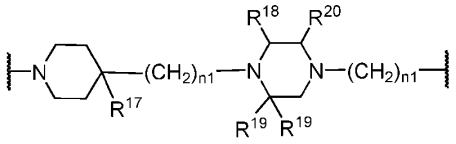
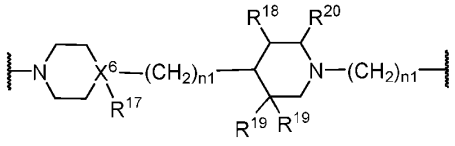
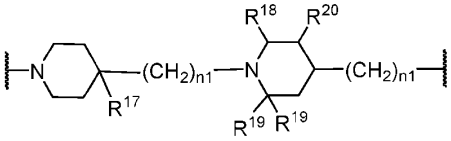
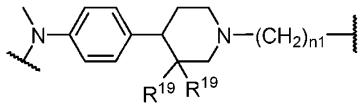
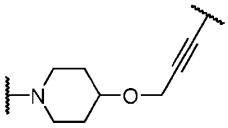
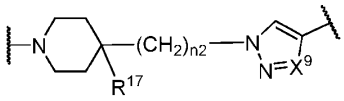
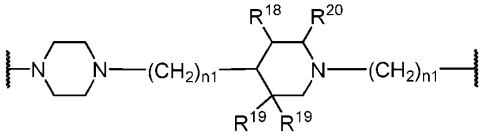
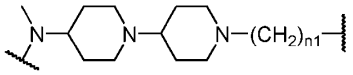
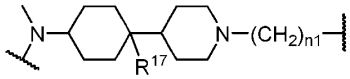
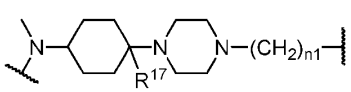
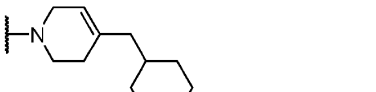
R^{11} is selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', - CO_2R', -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl; or

R^{11} and R^0 together with the atoms attached thereto may form a 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N, wherein said 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R'', -CONR'R'' and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl;

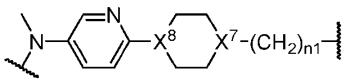
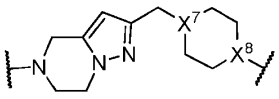
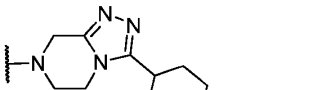
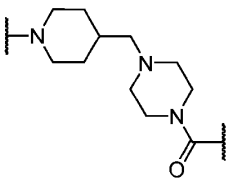
R^{12} and R^{13} are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy, and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl;

A is CO;

L is selected from


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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

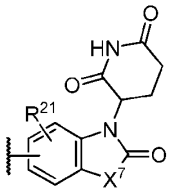
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

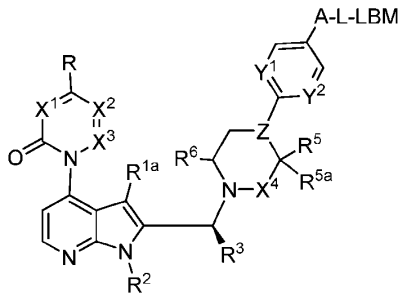
R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

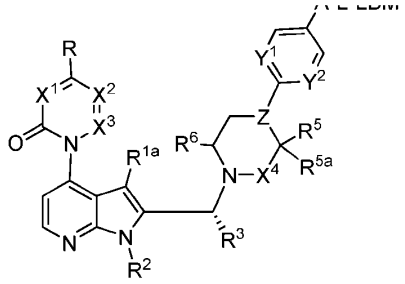
both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In one embodiment the disclosure provides a compound of formula (II) or (II´)



(II)



(II')

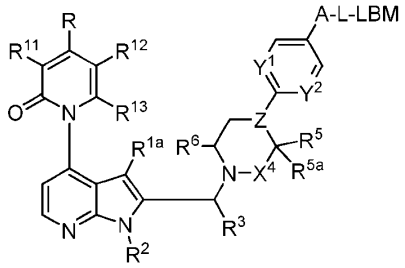
wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Z, R, R^{1a}, R^2, R^5, R^{5a}, R^6, A, L, and LBM are as defined anywhere herein; and R^3 is C_{1-4}alkyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, X^1 is N, X^2 is CR^{12}, X^3 is CR^{13}, and X^4 is CR^{14}.

In some embodiments, X^1 is CR^{11}, X^2 is CR^{12}, X^3 is CR^{13}, and X^4 is CR^{14}.

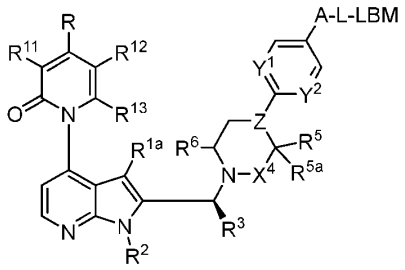
In one embodiment the disclosure provides a compound of formula (III)



(III)

wherein Y^1, Y^2, X^4, Z, R, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^{11}, R^{12}, R^{13}, A, L, and LBM are as defined anywhere herein; or a pharmaceutically acceptable salt or stereoisomer thereof.

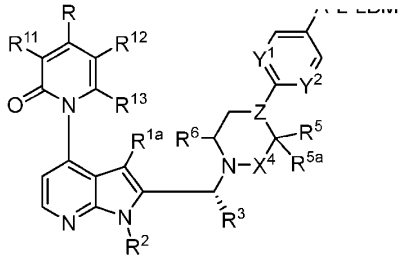
In one embodiment the disclosure provides a compound of formula (IV)



(IV)

wherein Y^1, Y^2, X^4, Z, R, R^{1a}, R^2, R^5, R^{5a}, R^6, R^{11}, R^{12}, R^{13}, A, L, and LBM are as defined anywhere herein; and R^3 is C_{1-4}alkyl; or a pharmaceutically acceptable salt or stereoisomer thereof.

In one embodiment the disclosure provides a compound of formula (IV')



(IV')

wherein Y^1, Y^2, X^4, Z, R, R^{1a}, R^2, R^5, R^{5a}, R^6, R^{11}, R^{12}, R^{13}, A, L, and LBM are as defined anywhere herein; and R^3 is C_{1-4}alkyl; or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, each of R^{11}, R^{12}, R^{13}, and R^{14}, when present, is independently selected from hydrogen, halogen, and C_{1-4}alkoxy.

In some embodiments, R^{12} and R^{13} are both hydrogen.

In some embodiments, R^{11}, R^{12}, and R^{13} are all hydrogen.

In some embodiments, X^1 is CR^{11}; X^2 is CR^{12}; X^3 is CR^{13}; X^4 is CR^{14}; and R^{11} and R^0 together with the atoms attached thereto may form a 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N, wherein said 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R'', -CONR'R'' and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl.In some embodiments, the 5-6 membered heteroaromatic ring containing one or two N atoms is a pyrazole ring.

In some embodiments, the 5-6 membered heterocyclic ring containing one or two N atoms is a pyrrolidine ring.

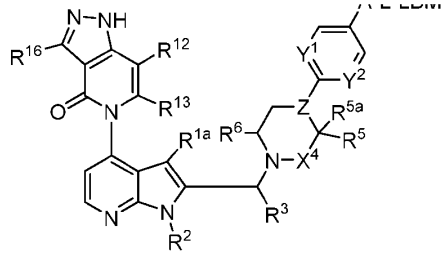
In some embodiments, R is NHR^0 and R^0 is hydrogen.

In some embodiments, R is NHR^0 and R^0 is selected from C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl-C_{1-4}alkyl, halo-C_{1-4}alkyl, -$(CH_2)_n$-O-C_{1-4}alkyl, -$(CH_2)_n$-CO-R', and -$(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, - NR'R'', -CONR'R'', and -CO_2R', and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1, or 2;

In some embodiments, R is NHR^0 and R^0 is selected from hydrogen and C_{1-4}alkyl.

In some embodiments, R is NHR^0 and R^0 is C_{1-4}alkyl (e.g., methyl).

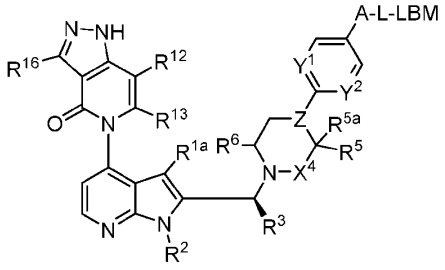
In one embodiment the disclosure provides a compound of formula (VII)



(VII)

wherein Y^1, Y^2, X^4, Z, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^{12}, R^{13}, A, L and LBM are as defined anywhere herein, R^{16} is selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen.

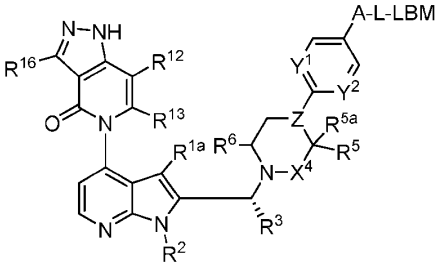
In one embodiment the disclosure provides a compound of the formula (VIII)



(VIII)

wherein Y^1, Y^2, X^4, Z, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^{12}, R^{13}, A, L and LBM are as defined anywhere herein, and R^{16} is selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen.

In one embodiment the disclosure provides a compound of the formula (VIII')

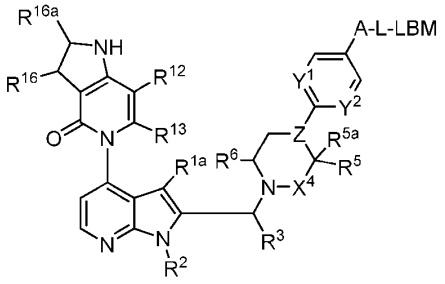


(VIII')

wherein Y^1, Y^2, X^4, Z, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^{12}, R^{13}, A, L and LBM are as defined anywhere herein, and R^{16} is selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen.

In some embodiments, R^{16} is hydrogen.

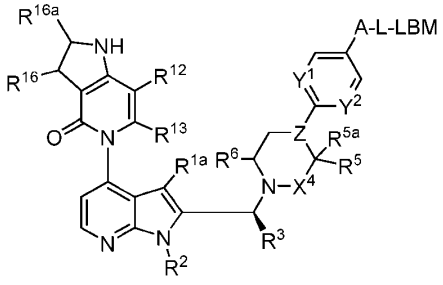
In one embodiment the disclosure provides a compound of the formula (IX):



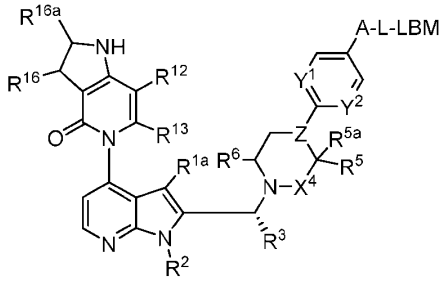
(IX)

wherein R^{16} and R^{16a} are selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen; or a pharmaceutically acceptable salt or stereoisomer thereof.

In one embodiment the disclosure provides a compound of the formula (IXa) or (IXb):



(IXa) or



(IXb)

wherein R^{16} and R^{16a} are selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen; or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, R^{16} and R^{16a} are both hydrogen.

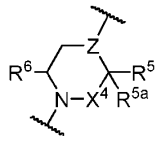
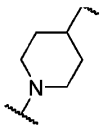
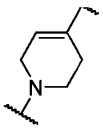
In some embodiments, Z is N.

In some embodiments, Z is CR^{10} and R^5 and R^{10} together form a bond between the two carbons to which they are attached.

In some embodiments, Z is CR^{10} and R^{10} is hydrogen.

In some embodiments, R^{5a} is hydrogen.

In some embodiments, X^4 is CR^4 and R^4 is selected from hydrogen and C_{1-4}alkyl.

In some embodiments, the  moiety is  or .

In some embodiments, Y^1 is N and Y^2 is CR^8.

In some embodiments, Y^1 is N and Y^2 is N.

In some embodiments, Y^1 is CR^7 and Y^2 is CR^8.

In some embodiments, the disclosure provides a compound as described herein, wherein

(a)both of R^7 and R^8 is C_{1-4}alkyl;

(b)both of R^7 and R^8 is halogen;

(c)one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen;

(d)one of R^7 and R^8 is C_{1-4}alkyl and the other is hydrogen; or

(e)one of R^7 and R^8 is halogen and the other is hydrogen.

In some embodiments, the disclosure provides a compound as described herein, wherein

(a)both of R^7 and R^8 is C_{1-4}alkyl;

(b)both of R^7 and R^8 is halogen;

(c)one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen;

(d)one of R^7 and R^8 is C_{1-4}alkyl and the other is hydrogen; (e)one of R^7 and R^8 is halogen and the other is hydrogen; and

(f) both of R^7 and R^8 are hydrogen;

In some embodiments, both of R^7 and R^8 are halogen; or one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen; or both of R^7 and R^8 are hydrogen. In some embodiments, both of R^7 and R^8 are halogen, or one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen.

In some embodiments, R^7 is halogen and R^8 is methyl.

In some embodiments, the halogen in b) c) and e) is fluoro.

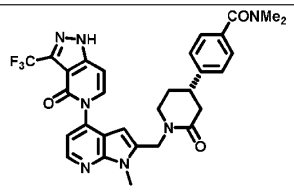
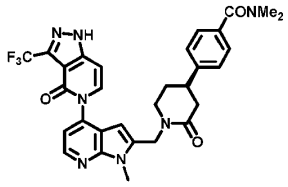
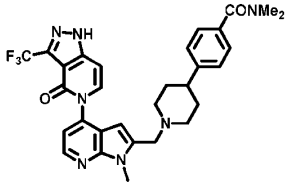
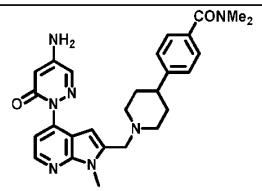
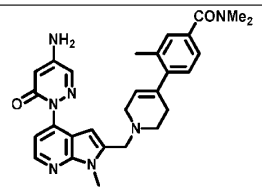
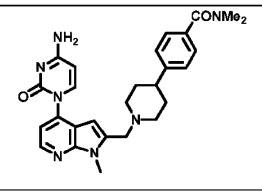
In some embodiments, the disclosure provides a compound as described herein, wherein R^2 is methyl.

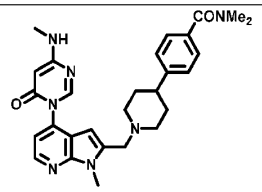
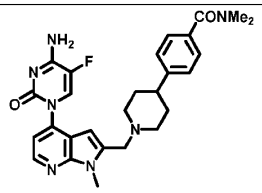
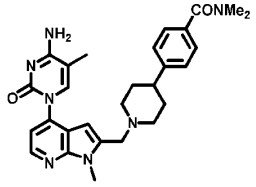
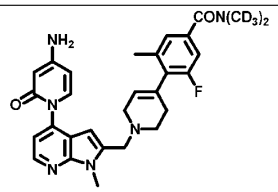
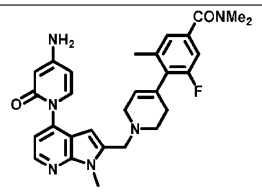
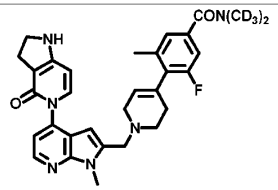
In some embodiments, the disclosure provides a compound as described herein, wherein R^3 is hydrogen or C_{1-4}alkyl.

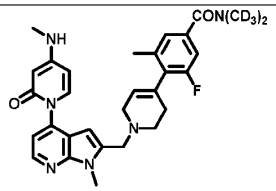
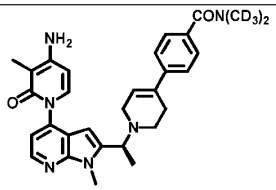
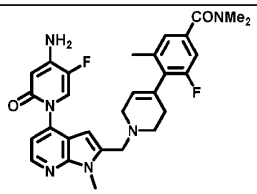
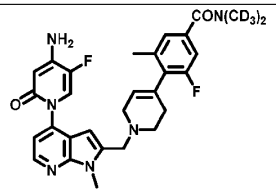
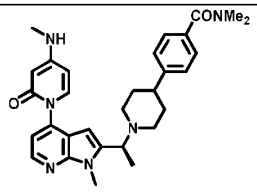
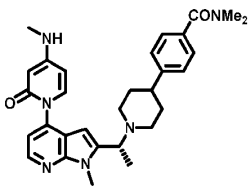
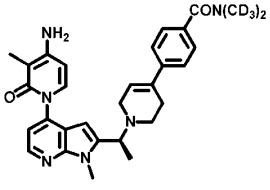
In some embodiments, the disclosure provides a compound as described herein, wherein R^3 is methyl.

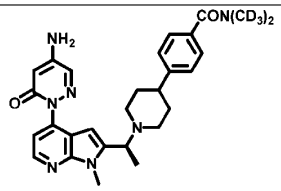
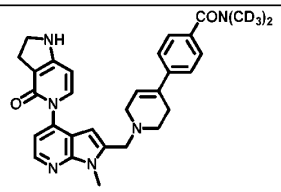
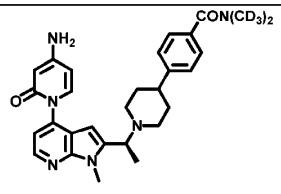
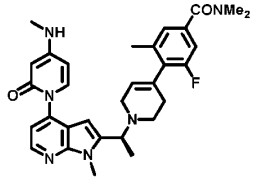
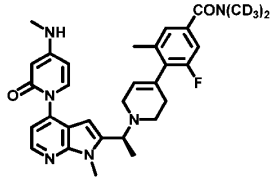
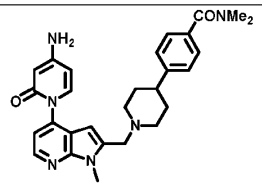
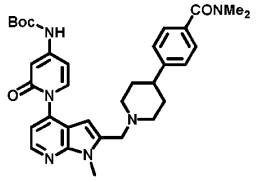
Precursor

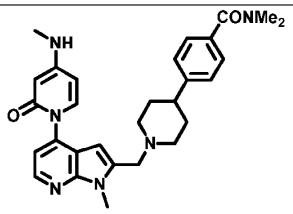
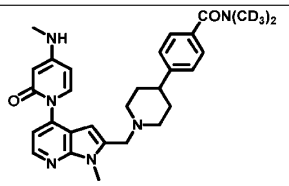
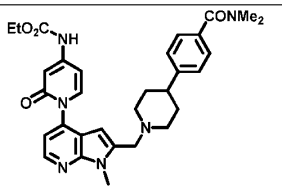
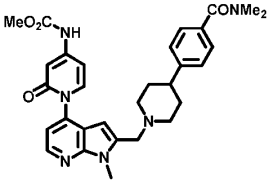
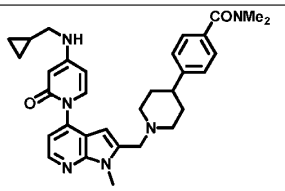
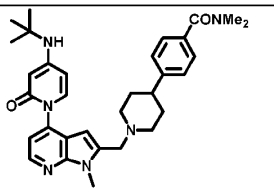
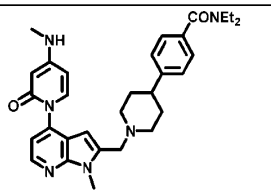
In some embodiments, compounds of formula (I) are prepared from precursors in the following table, and subsequently derivatized at the appropriate position to achieve compounds of formula (I) (i.e. wherein R^9 is -A-L-LBM).

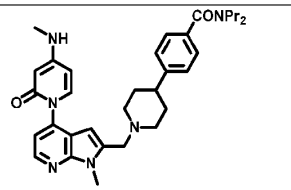
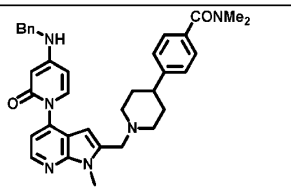
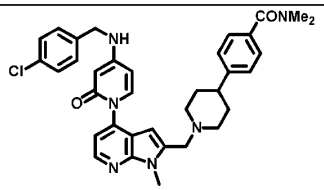
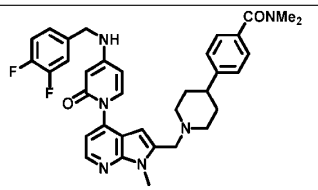
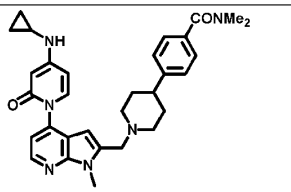
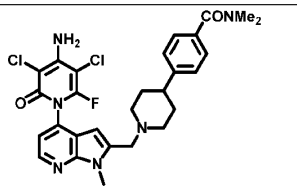
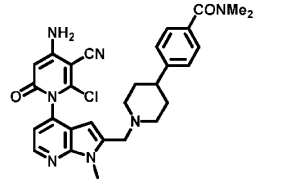
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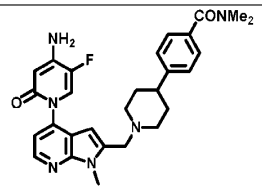
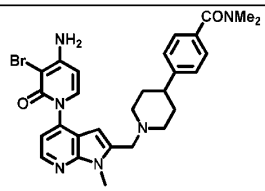
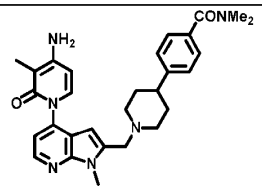
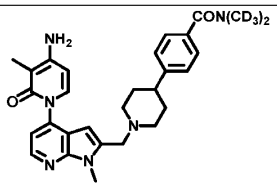
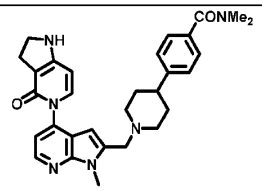
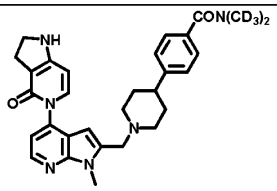
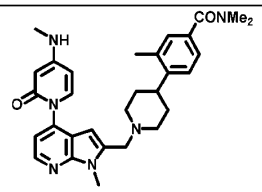
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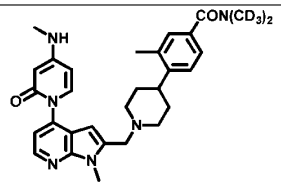
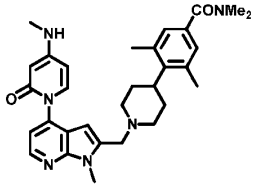
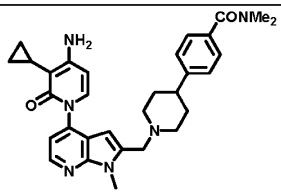
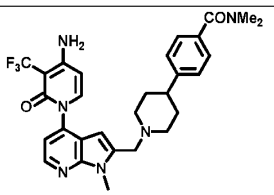
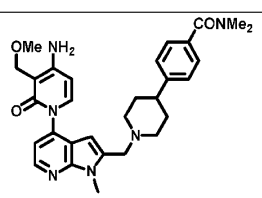
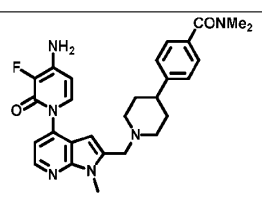
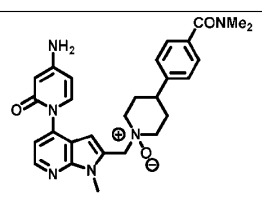
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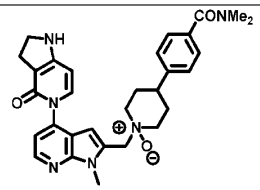
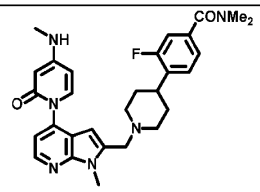
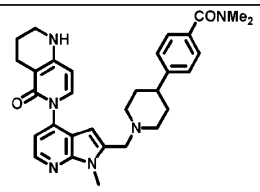
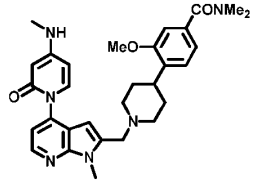
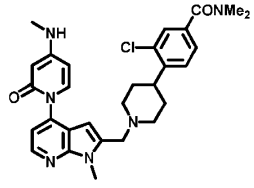
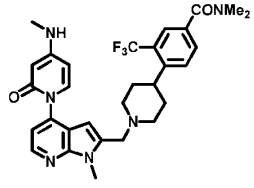
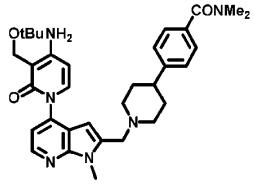
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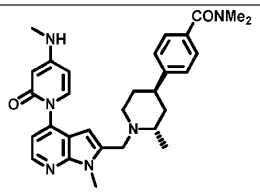
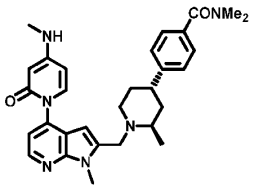
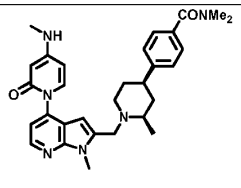
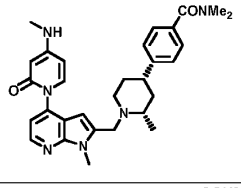
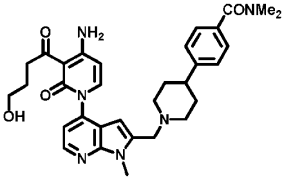
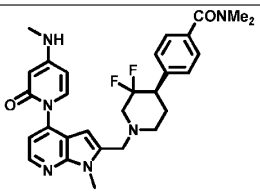
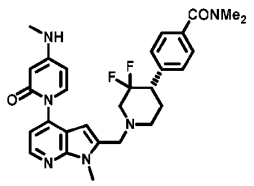
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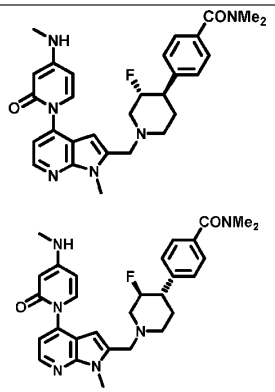
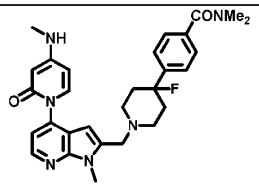
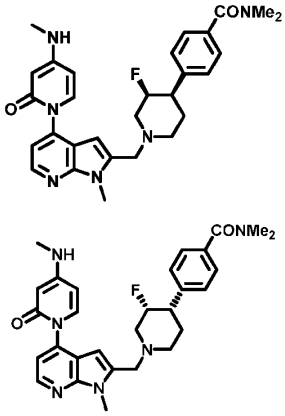
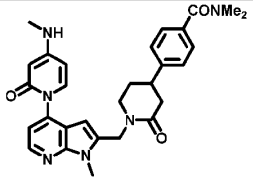
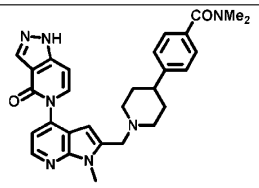
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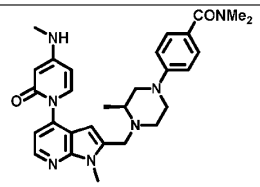
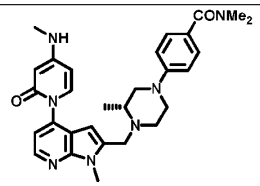
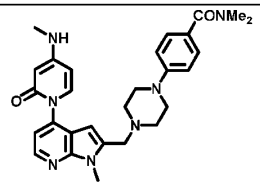
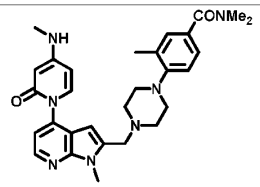
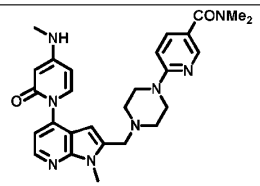
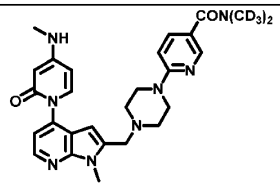
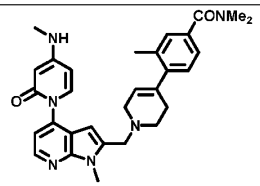
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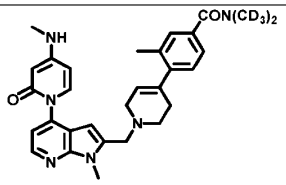
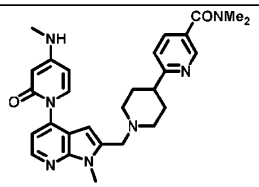
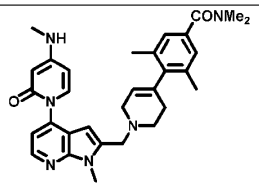
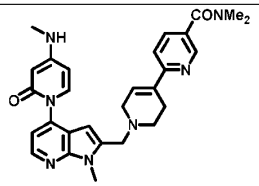
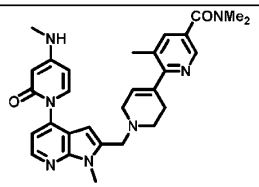
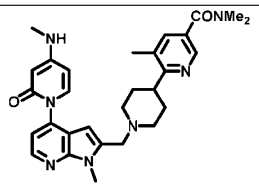
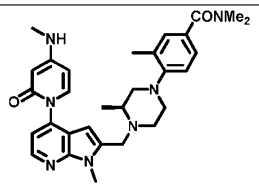
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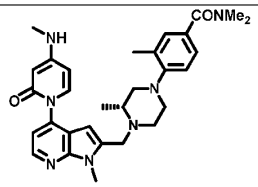
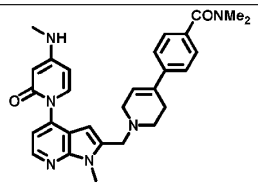
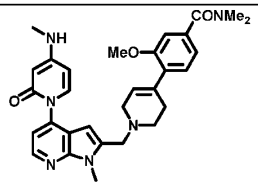
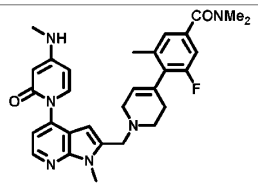
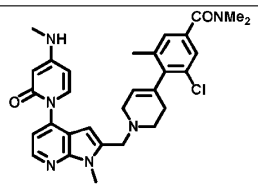
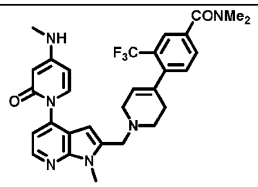
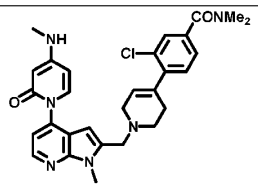
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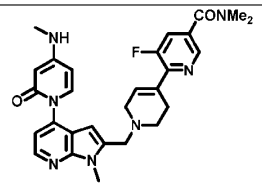
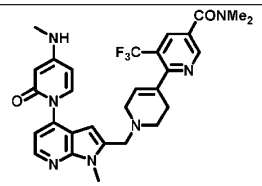
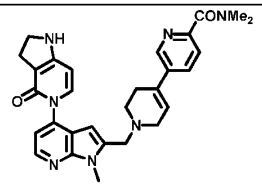
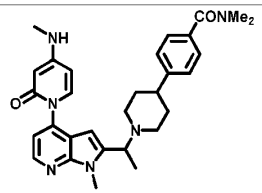
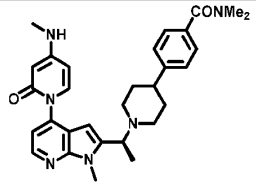
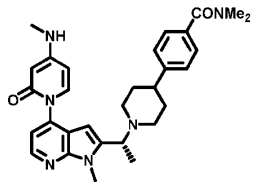
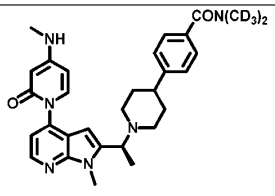
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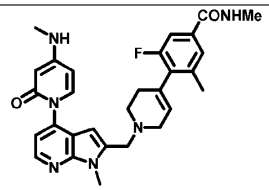
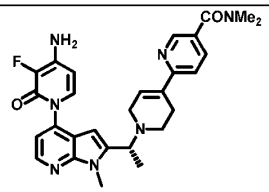
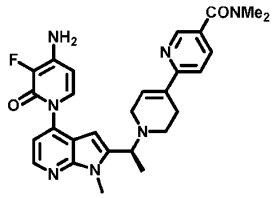
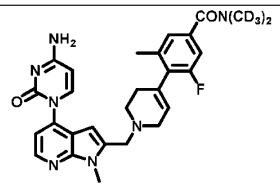
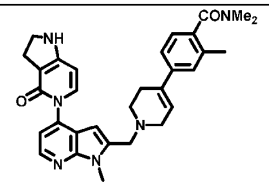
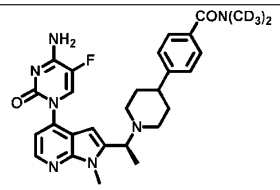
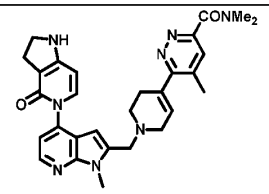
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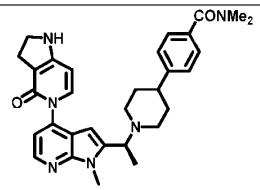
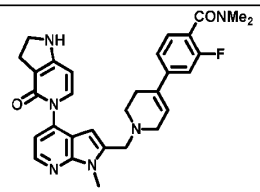
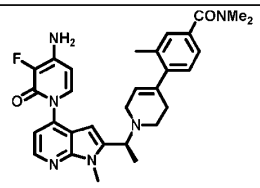
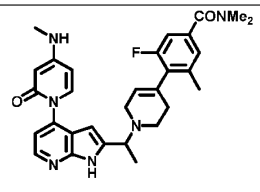
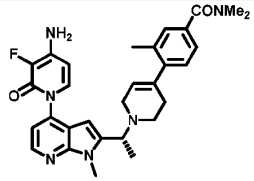
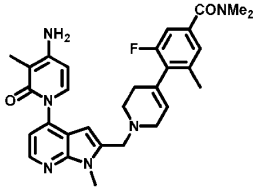
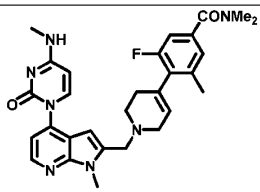
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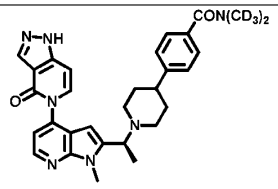
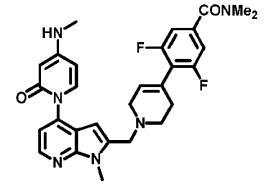
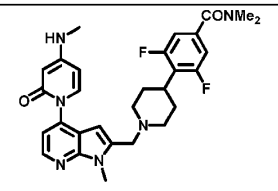
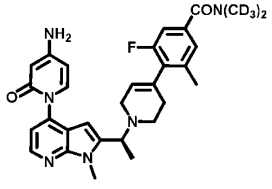
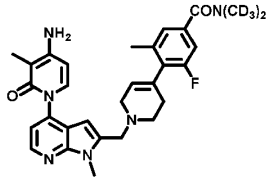
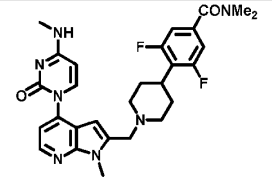
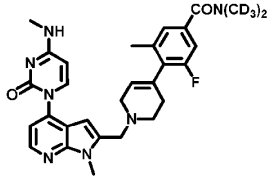
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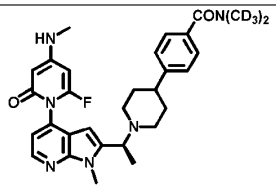
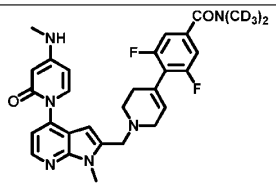
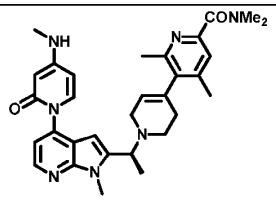
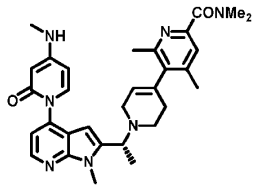
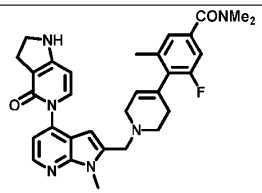
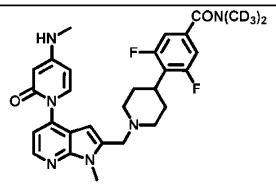
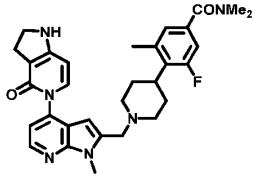
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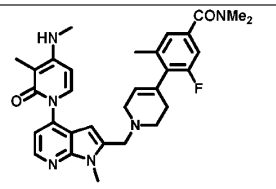
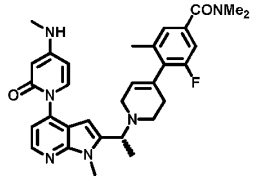
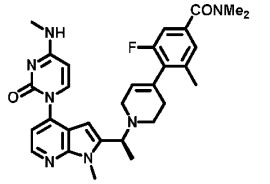
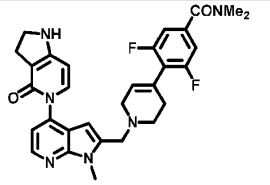
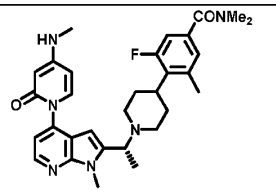
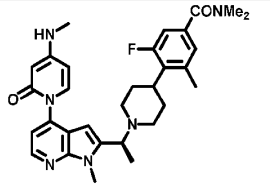
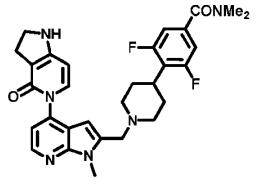
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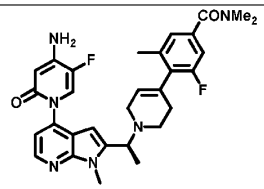
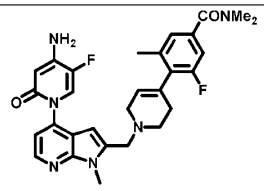
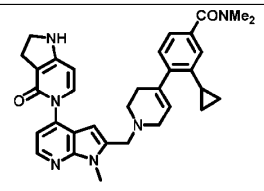
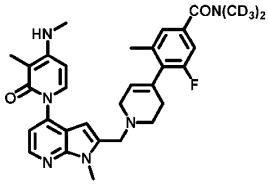
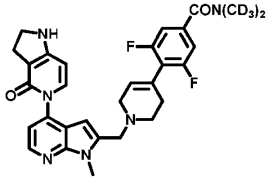
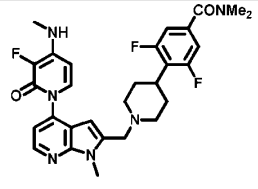
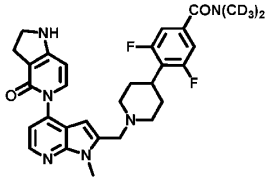
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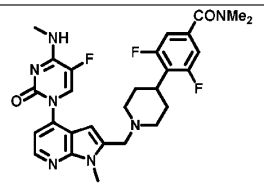
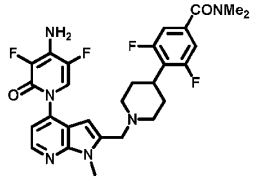
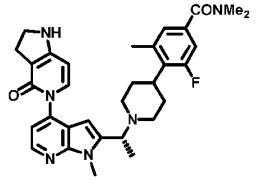
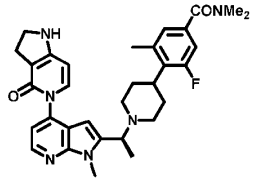
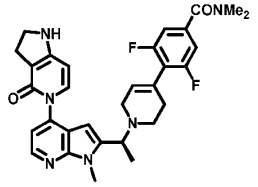
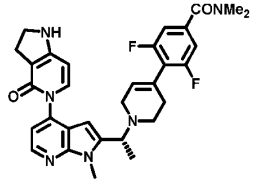
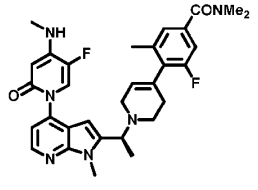
No.	Structure
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1m84	
1m85	
1m86	
1m87	
1m88	

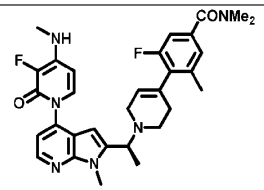
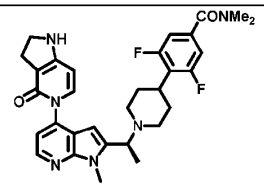
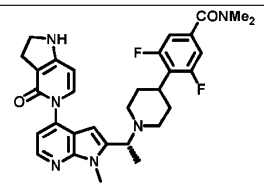
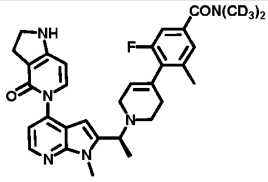
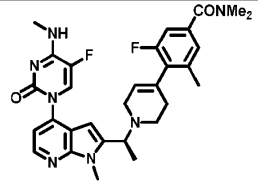
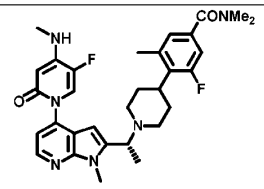
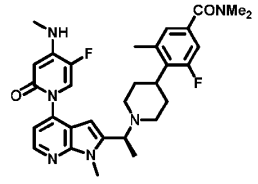
No.	Structure
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1m91	
1m93	
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1m95	
1m96	

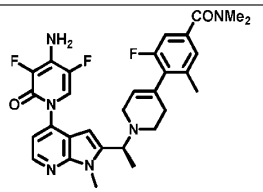
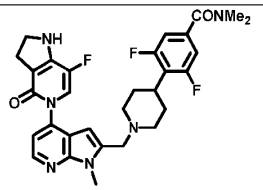
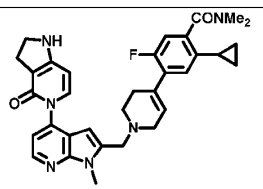
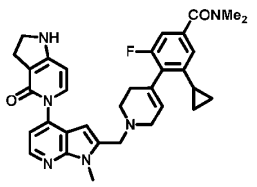
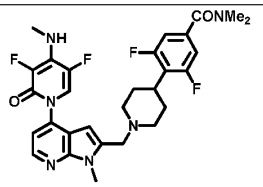
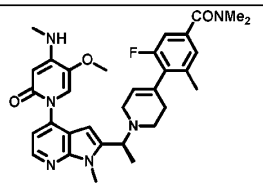
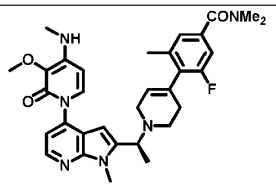
No.	Structure
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1m98	
1m99 1m100	 
1m101	
1m102	
1m103	

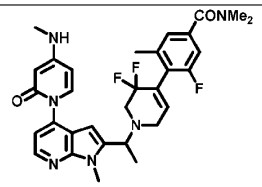
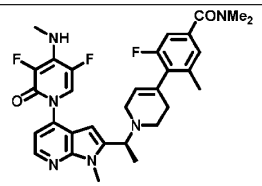
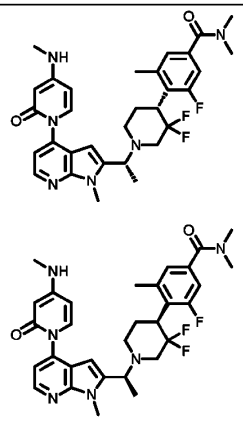
No.	Structure
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1m105	
1m106	
1m107	
1m108	
1m109	
1m110	

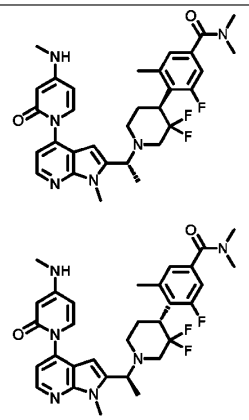
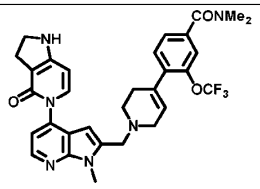
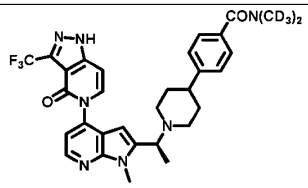
No.	Structure
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1m112	
1m113	
1m114	
1m115	
1m116	
1m117	

No.	Structure
1m118	
1m119	
1m120 1m121	 
1m122	
1m123	
1m124	

No.	Structure
1m125	
1m126	
1m127	
1m128	
1m129	
1m130	
1m131	

No.	Structure
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1m133	
1m134 1m135	 
1m136	
1m137	
1m138	

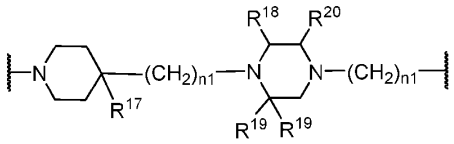
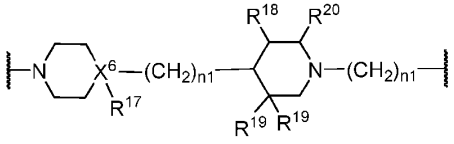
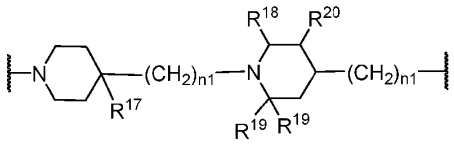
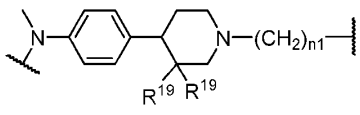
No.	Structure
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1m140	
1m141 1m142 1m143 1m144	

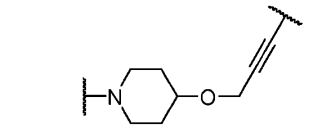
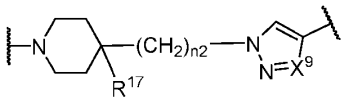
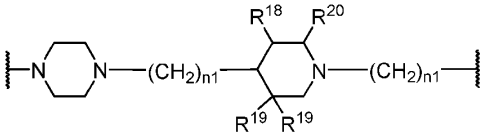
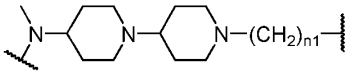
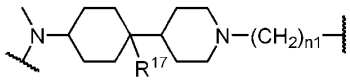
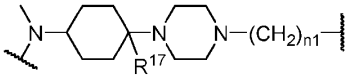
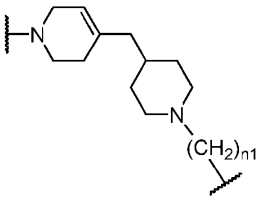
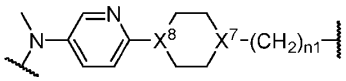
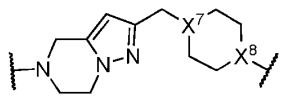
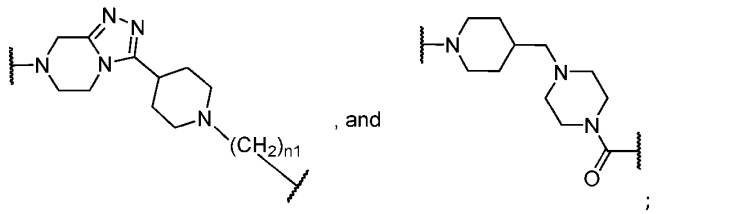
No.	Structure
	
1m146	
1m147	

Moiety A and Moiety L

In some embodiments, A is CO.

In some embodiments, L is selected from


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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

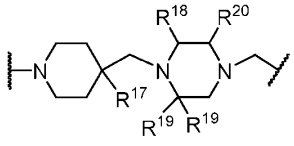
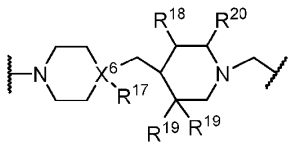
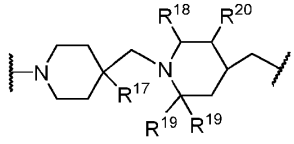
X^6 is C;

X^7 is CR^{24} or N;

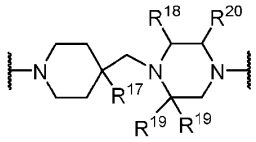
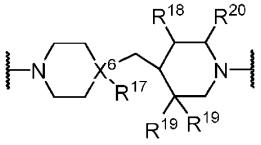
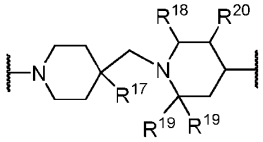
R^{24} is selected from hydrogen and hydroxy; and

X^8 and X^9 are independently CH or N.

In some embodiments, L is selected from:

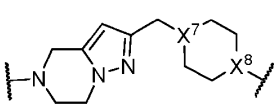
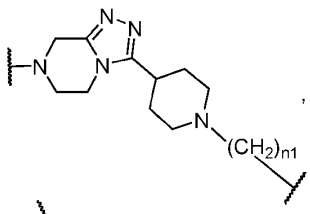
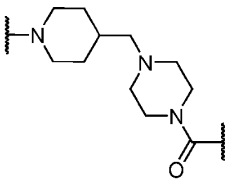
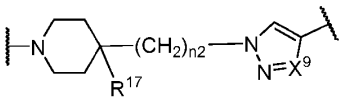

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In some embodiments, L is selected from:

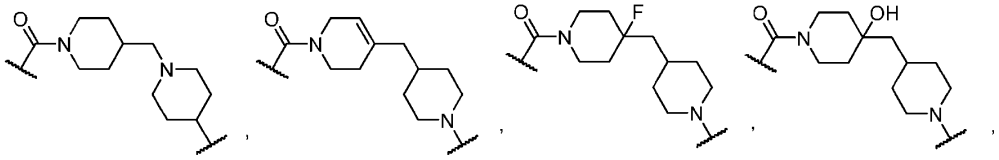

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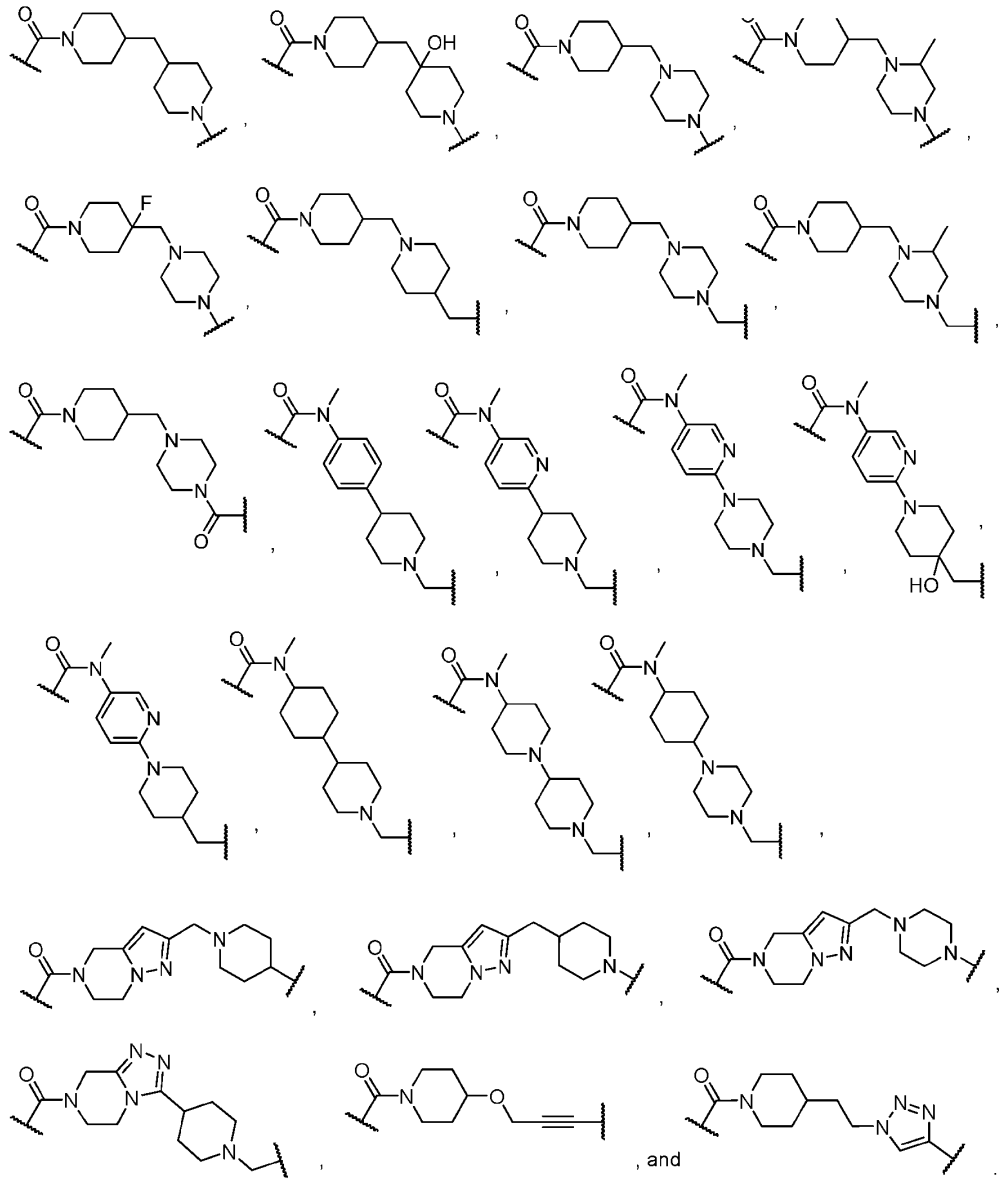
In some embodiments, at least one of the R^{17}, R^{18}, R^{19}, and R^{20} of L moiety is not hydrogen. In some embodiments, R^{17} is hydrogen and at least one of the R^{18}, R^{19}, and R^{20} of L moiety is not hydrogen.

In some embodiments, L is selected from:

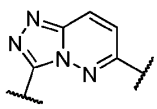

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In some embodiments, A is CO and A-L is selected from:

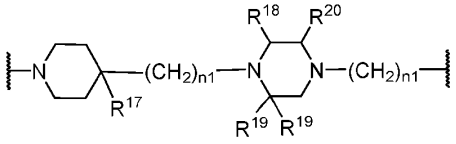
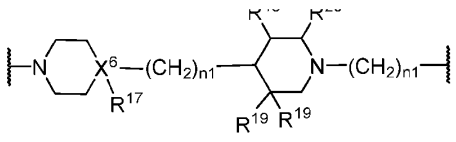
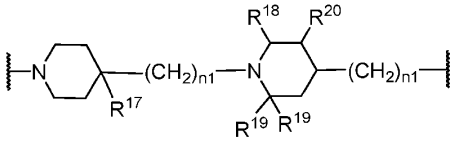
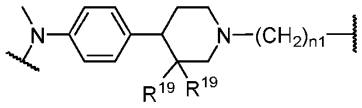
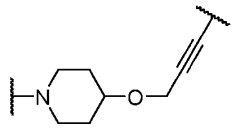
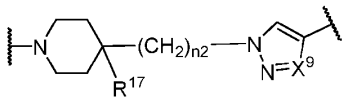
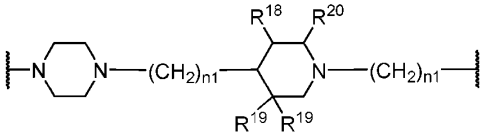

.



In some embodiments, A is CO.

In some embodiments, A is .

In some embodiments, L is selected from:







, and


wherein each n1 is independently selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

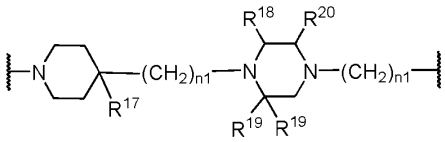
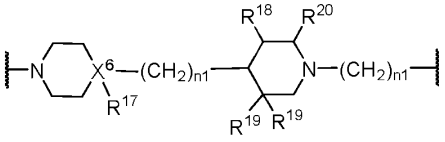
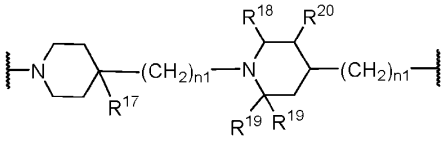
each R^{19} is independently selected from hydrogen, C_{1-4}alkyl, and fluoro;

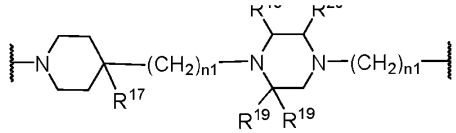
R^{20} is selected from hydrogen and C_{1-4}alkyl;

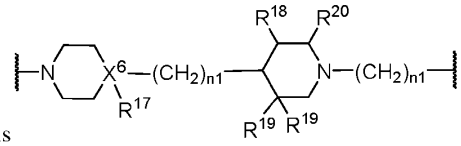
X^6 is C; and

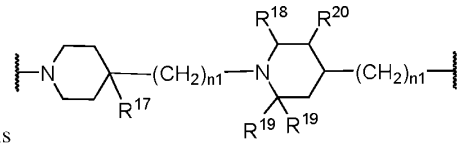
X^9 is CH or N.

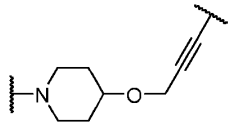
In some embodiments, L is selected from:

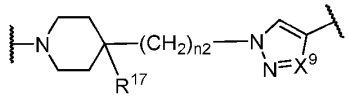


, and


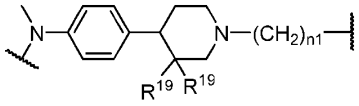
In some embodiments, L is .

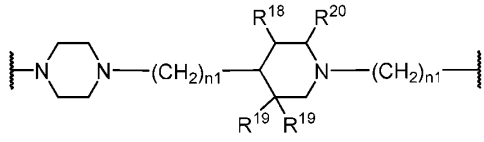
In some embodiments, L is .

In some embodiments, L is .

In some embodiments, L is .

In some embodiments, L is .

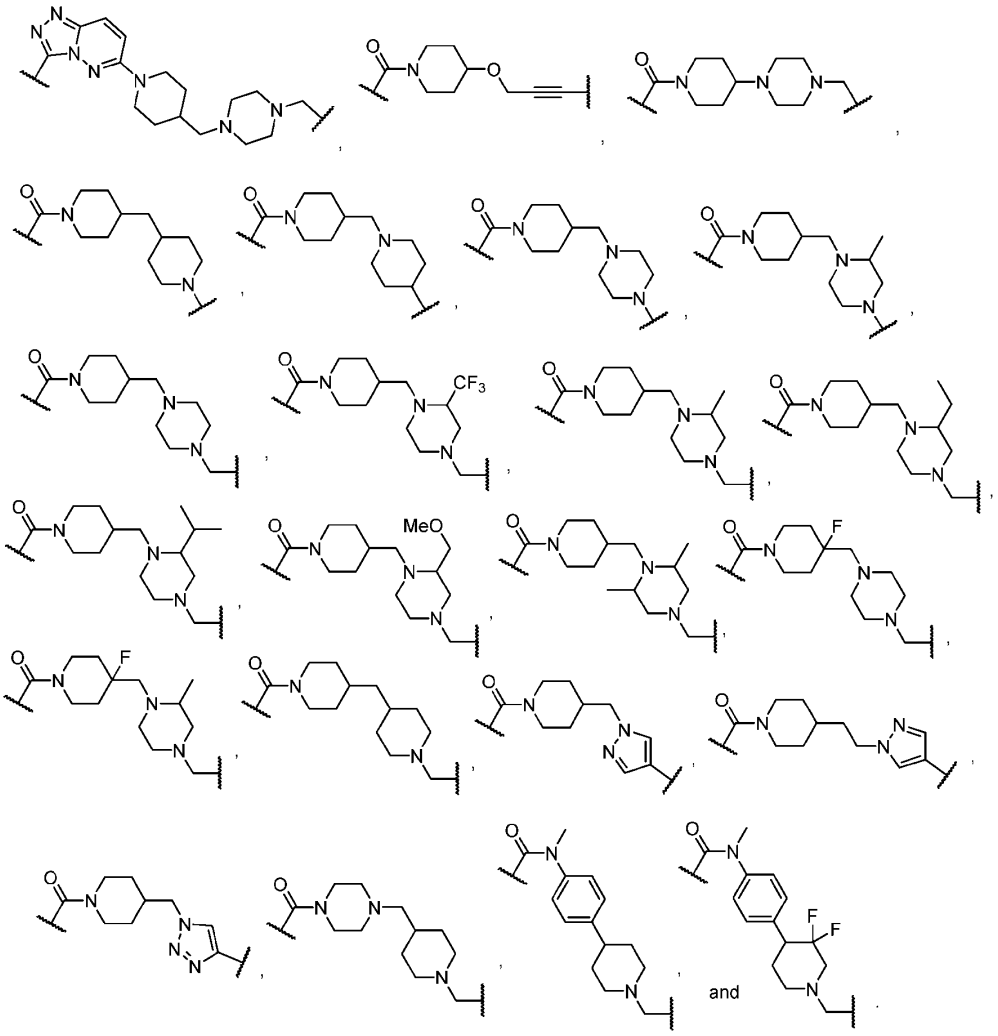
In some embodiments, L is .

In some embodiments, L is .

In some embodiments, at least one of the R^{17}, R^{18}, R^{19}, and R^{20} of L moiety is not hydrogen.

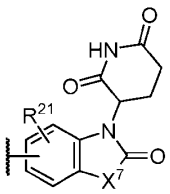
In some embodiments, R^{17} is hydrogen and at least one of the R^{18}, R^{19}, and R^{20} of L moiety is not hydrogen.

In some embodiments, A-L is selected from:



Moiety LBM

In some embodiments, LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl; and

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from C_{1-4}alkyl and C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22} and R^{22} is methyl.

In some embodiments, X^7 is NR^{22} and R^{22} is cyclopropyl.

In some embodiments, X^7 is $CR^{23}R^{23}$; each R^{23} is independently selected from halogen and C_{1-4}alkyl; or both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O.

In some embodiments, X^7 is $CR^{23}R^{23}$; each R^{23} is independently selected from hydrogen and C_{1-4}alkyl.

In some embodiments, X^7 is $CR^{23}R^{23}$, and both R^{23} are methyl or both R^{23} are fluoro.

In some embodiments, X^7 is $CR^{23}R^{23}$, and both R^{23} are methyl.

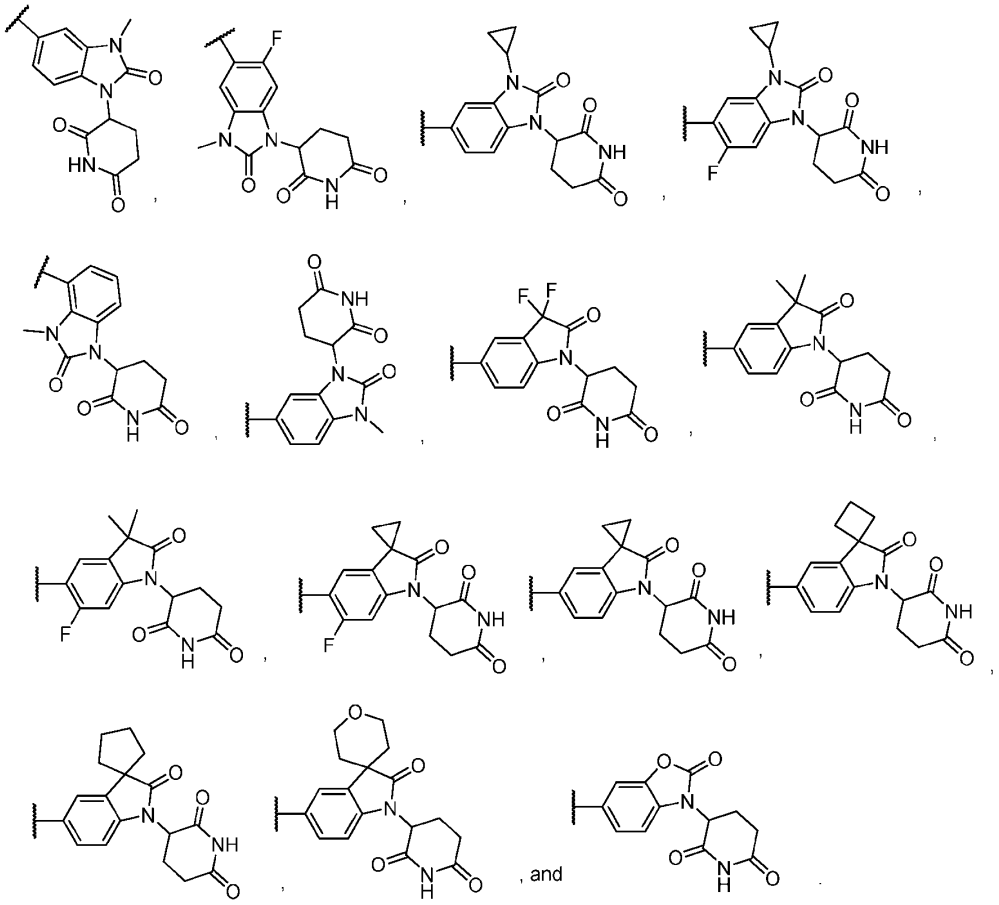
In some embodiments, X^7 is $CR^{23}R^{23}$; both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O.

In some embodiments, X^7 is $CR^{23}R^{23}$, and both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl.

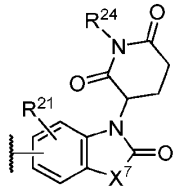
In some embodiments, X^7 is $CR^{23}R^{23}$, and both R^{23} together with the carbon they are attached to form a 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one heteroatom that is O.

In some embodiments, R^{21} is hydrogen or fluoro.

In some embodiments, LBM is selected from:



In some embodiments, LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen and C_{1-4}alkyl, or both instances of R^{23} together with the atom to which they are attached form a 3 or 4 membered carbocyclic ring which may be optionally substituted one or more times with a C_{1-4}alkyl, fluoro, or hydroxy; and

R^{24} is selected from hydrogen and C_{1-4}alkyl.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl; and wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl; and wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22}; R^{22} is selected from C_{1-4}alkyl and deuterated C_{1-4}alkyl; and wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl.

In some embodiments, X^7 is NR^{22}; and R^{22} is C_{3-4} cycloalkyl.

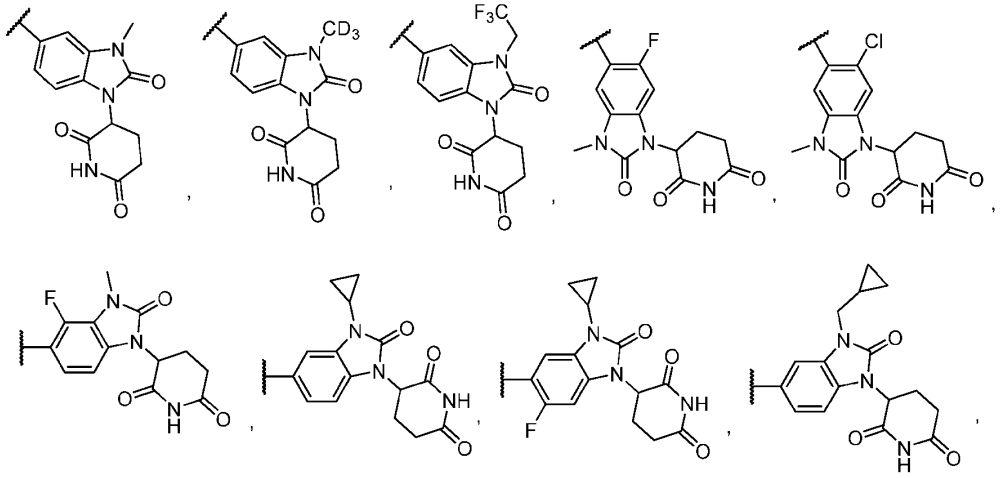
In some embodiments, X^7 is $CR^{23}R^{23}$; both R^{23} are C_{1-4}alkyl; or two R^{23} together with the atom to which they are attached form a 3 or 4 membered carbocyclic ring which may be optionally substituted one or more times with a C_{1-4}alkyl, fluoro, or hydroxy. In some embodiments, X^7 is $CR^{23}R^{23}$; each R^{23} is independently selected from hydrogen and C_{1-4}alkyl.

In some embodiments, X^7 is $CR^{23}R^{23}$; two R^{23} together with the atom to which they are attached form a 3 or 4 membered carbocyclic ring which may be optionally substituted one or more times with a C_{1-4}alkyl, fluoro, or hydroxy.

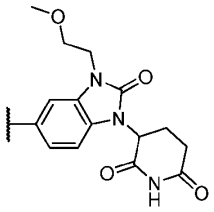
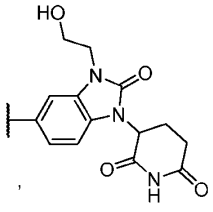
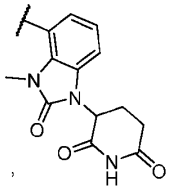
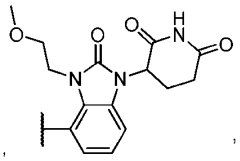
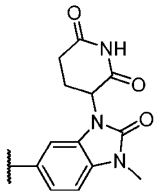
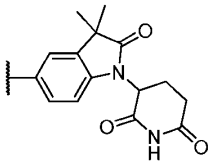
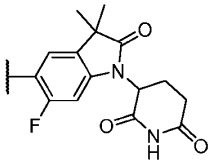
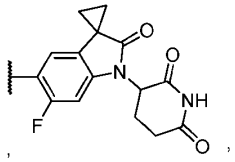
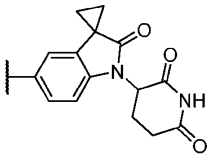
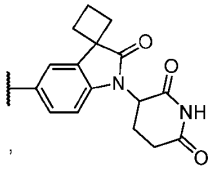
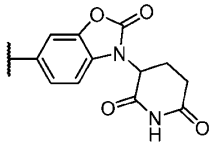
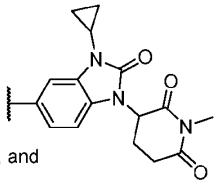
In some embodiments, R^{24} is hydrogen.

In some embodiments, R^{21} is hydrogen, chloro, or fluoro.

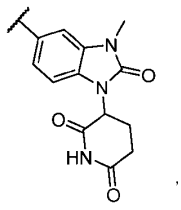
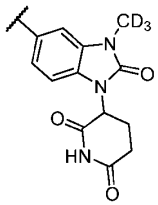
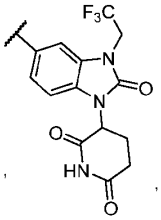
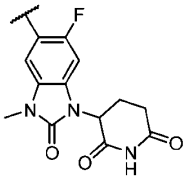
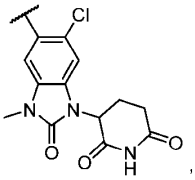
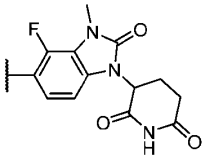
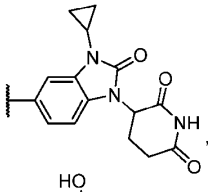
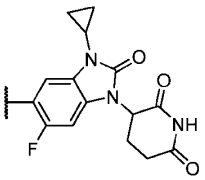
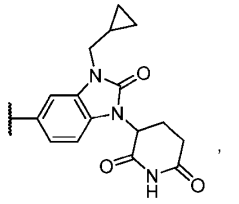
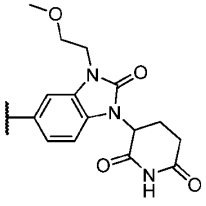
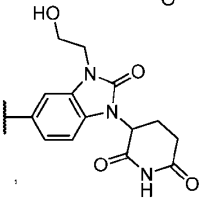
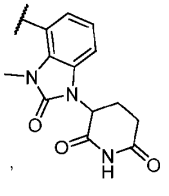
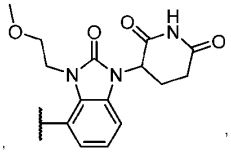
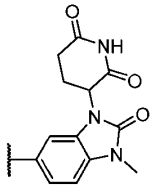
In some embodiments, R^{21} is hydrogen or fluoro.



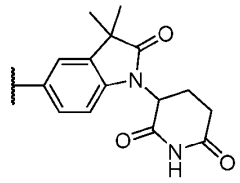
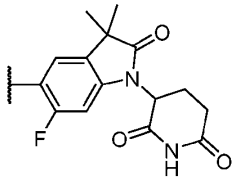
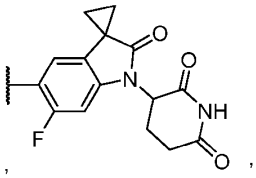
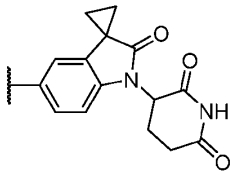
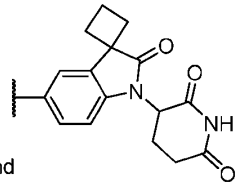
In some embodiments, LBM is selected from:

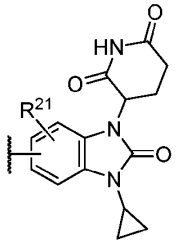

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In some embodiments, LBM is selected from:


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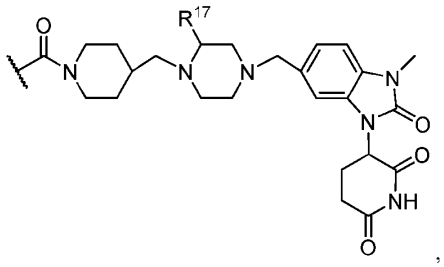
In some embodiments, LBM is selected from:


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, and

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In some embodiments, LBM is of the formula:

, wherein R^{21} is hydrogen or fluoro.

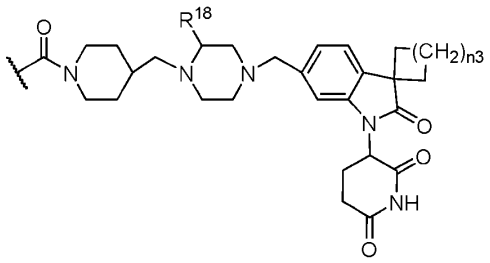
Moiety A-L-LAM

In some embodiments, A-L-LBM is


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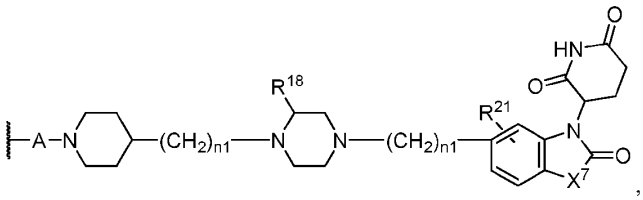
wherein R^{17} is as defined anywhere herein.

In some embodiments, A-L-LBM is



wherein R^{17} is as defined anywhere herein, and n3 is 0, 1, 2 or 3.

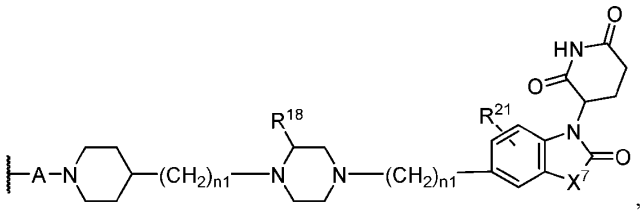
In some embodiments, A-L-LBM is of the formula:



,

and wherein A is CO, n1 is 1, and R^{18} and R^{21} are as defined anywhere herein.

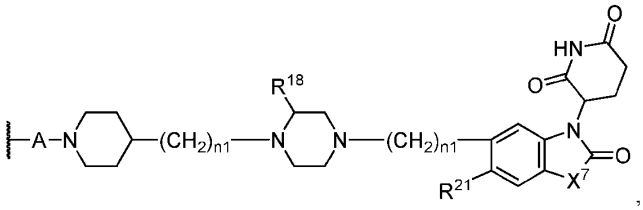
In some embodiments, A-L-LBM is of the formula:



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and wherein A is CO, n1 is 1, and X^7, R^{18}, and R^{21} are as defined anywhere herein.

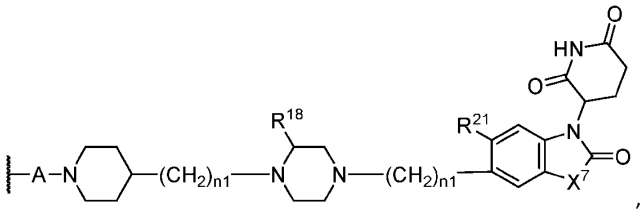
In some embodiments, A-L-LBM is of the formula:



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and wherein A is CO, n is 1, R^{18} is hydrogen or C_{1-4}alkyl, and R^{21} is hydrogen and fluoro.

In some embodiments, A-L-LBM is of the formula:

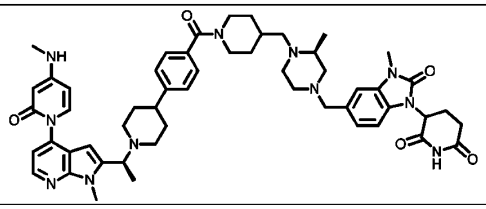
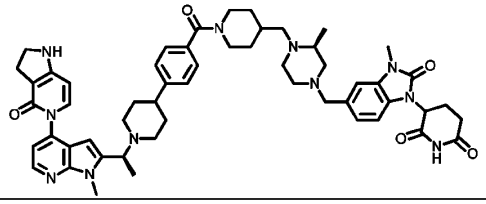
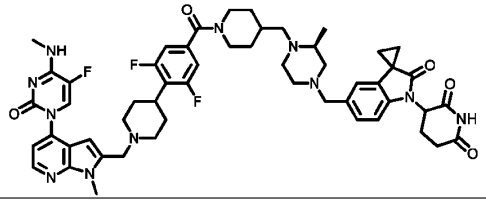
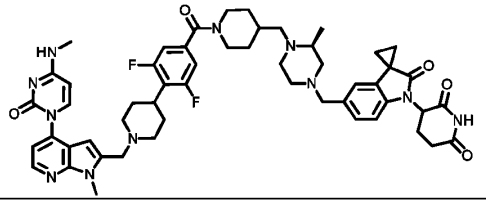
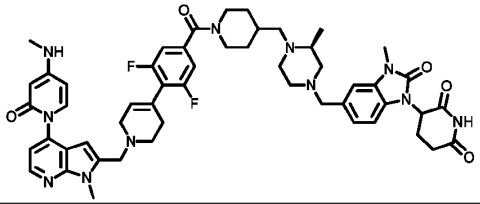
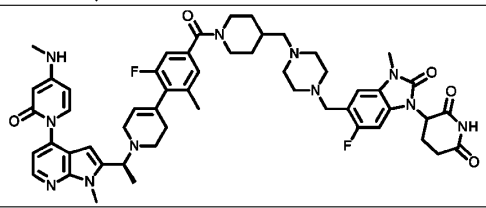


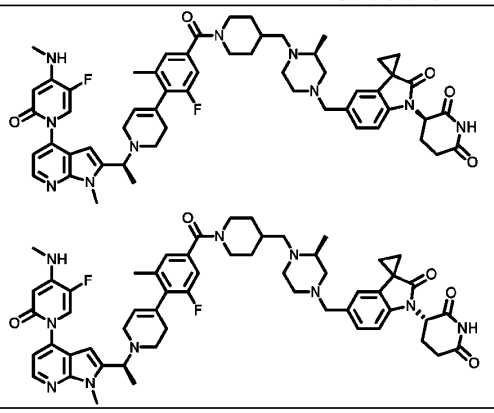
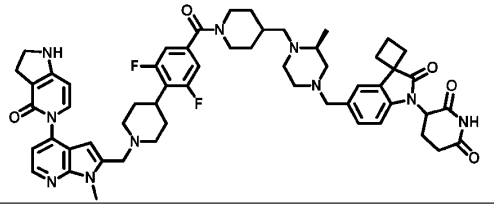
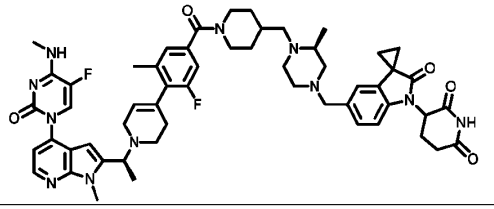
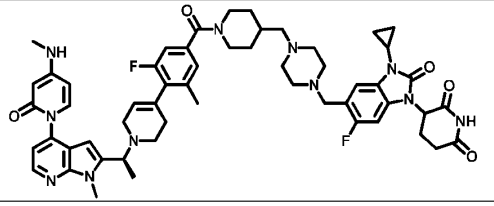
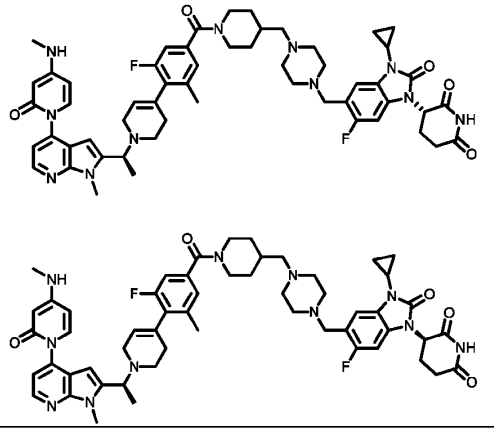
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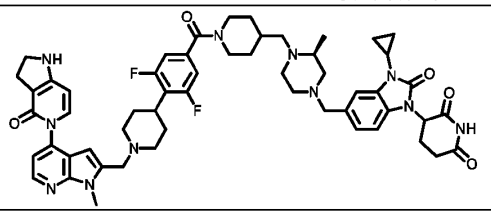
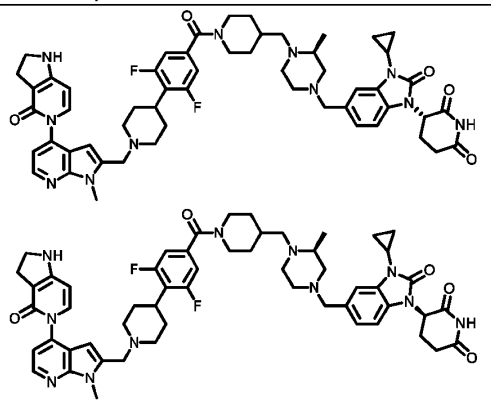
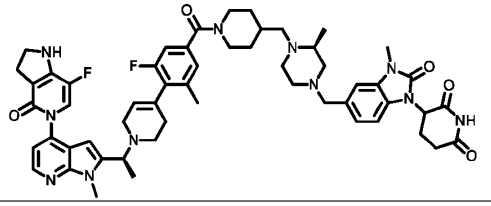
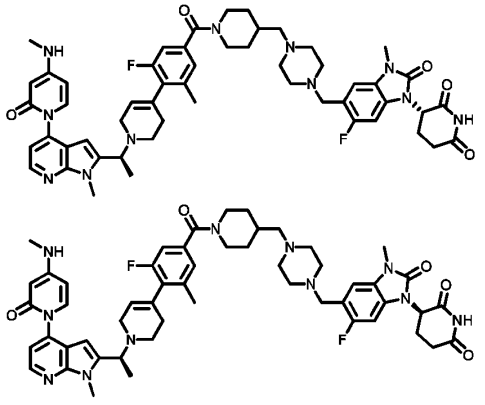
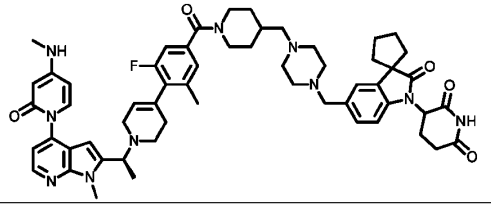
and wherein A is CO, n is 1, R^{18} is hydrogen or C_{1-4}alkyl, R^{17} is hydrogen, chloro, or fluoro, and X^1 is as defined anywhere herein.

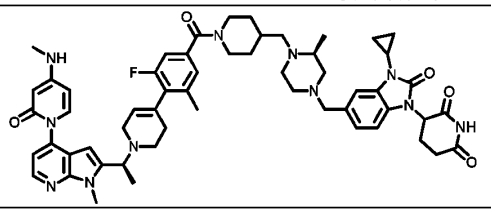
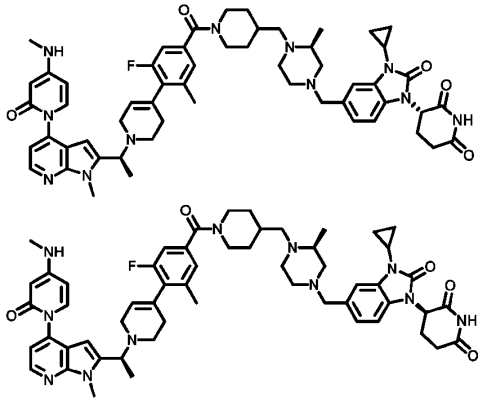
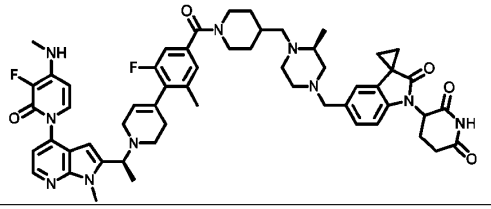
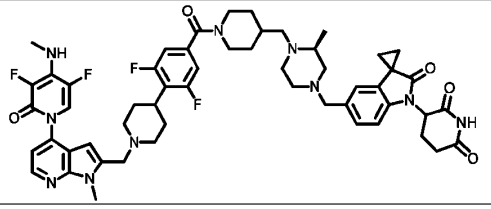
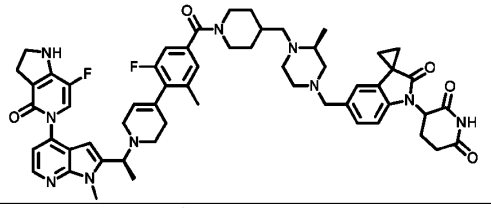
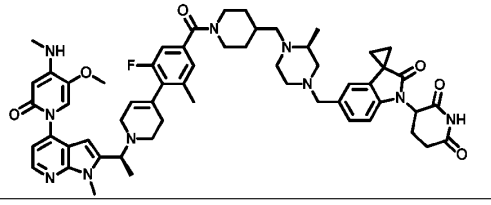
In some embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

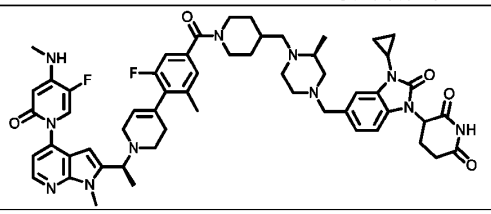
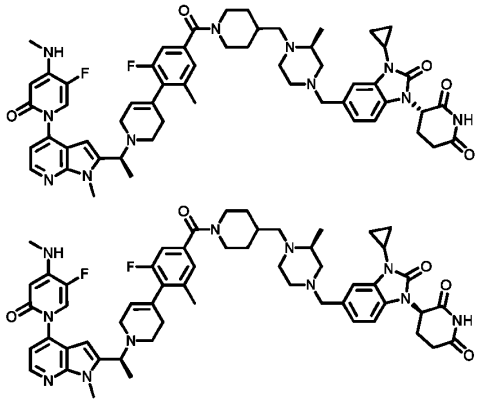
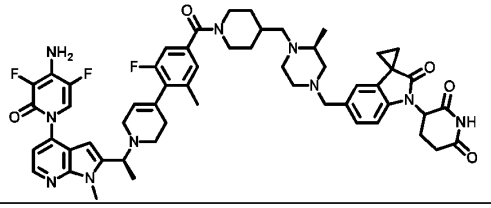
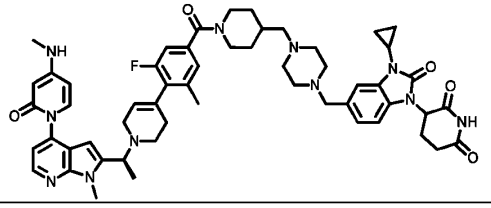
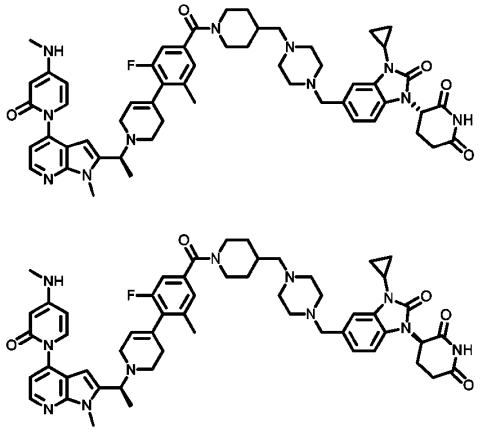
Table 1

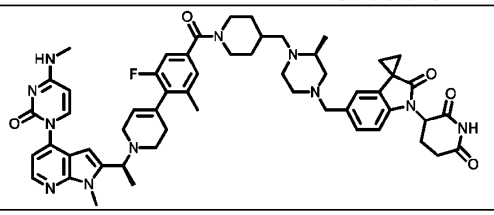
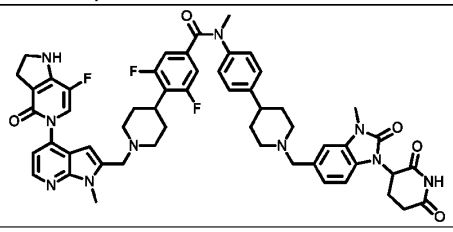
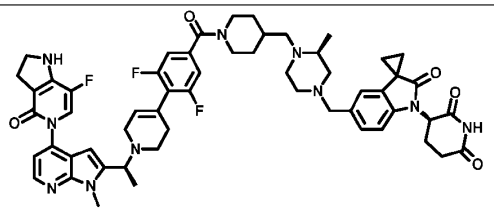
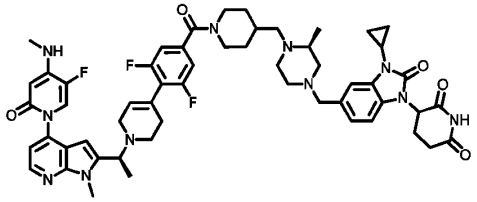
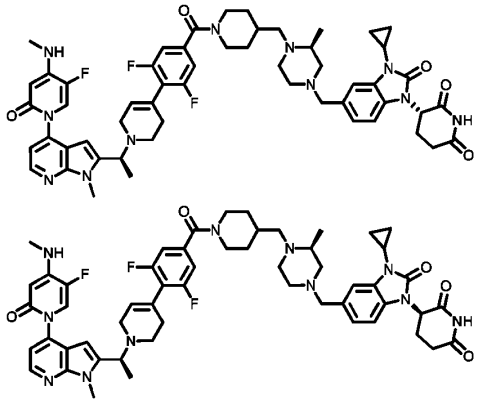
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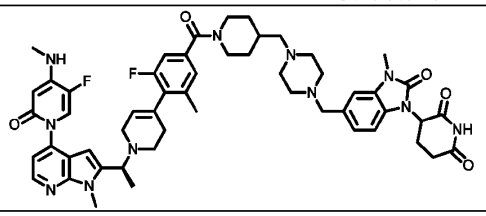
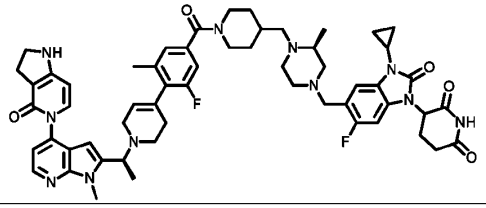
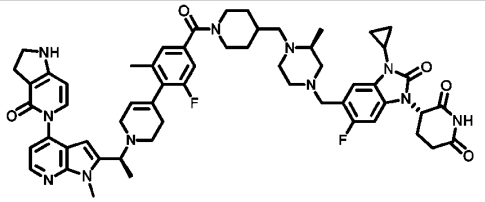
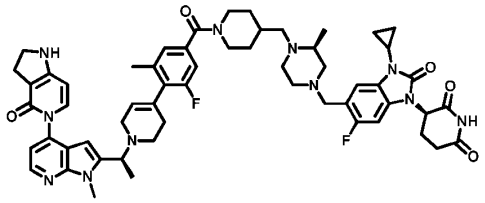
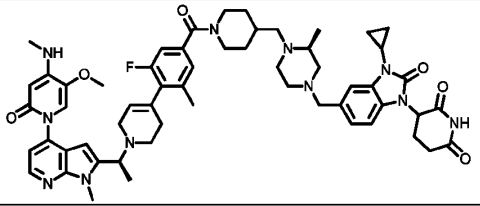
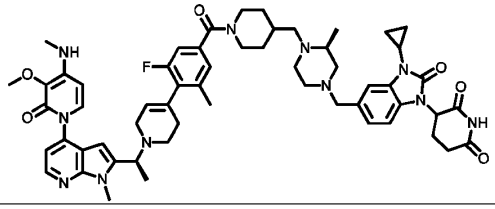
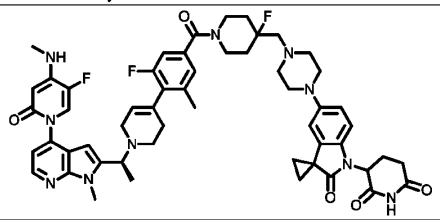
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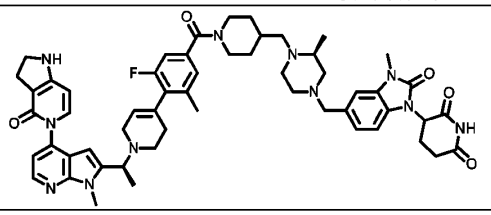
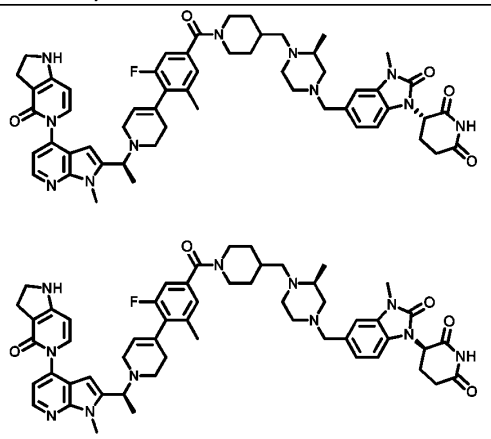
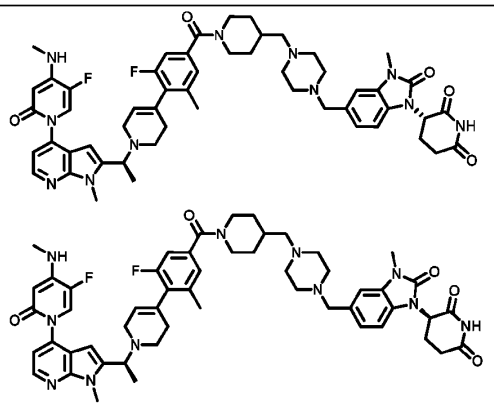
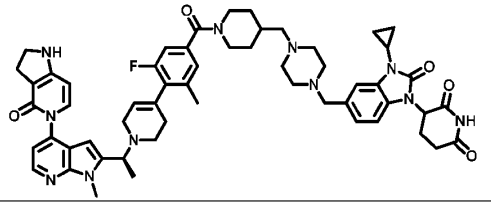
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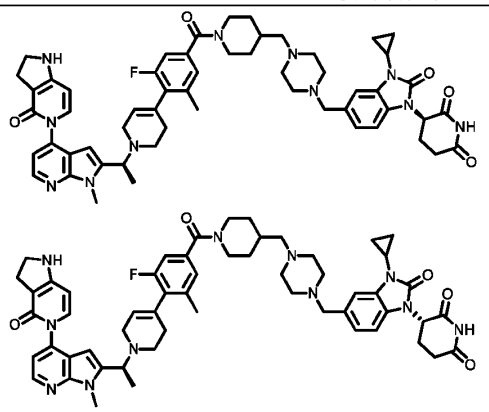
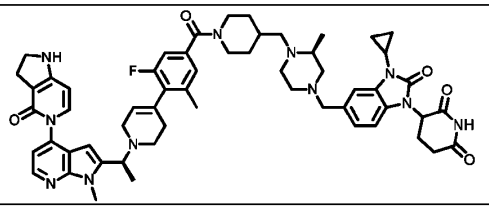
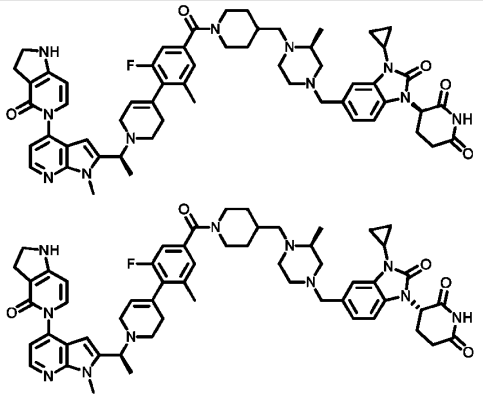
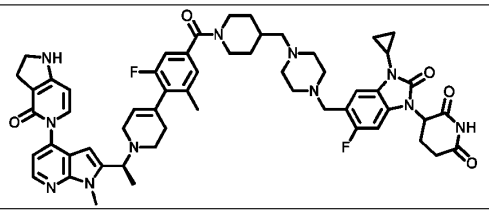
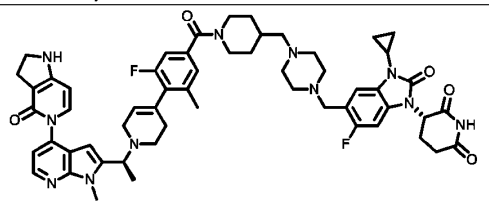
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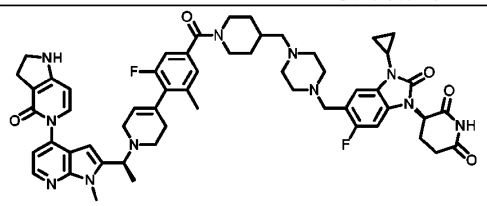
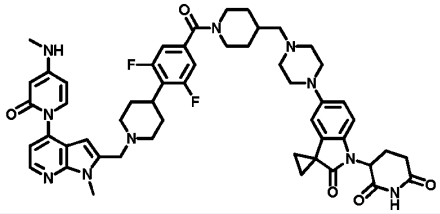
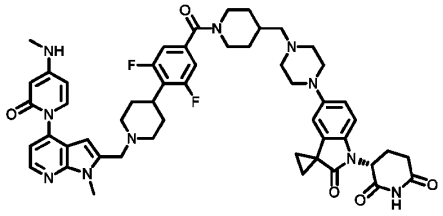
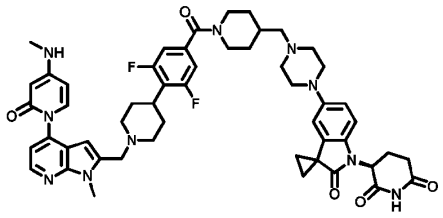
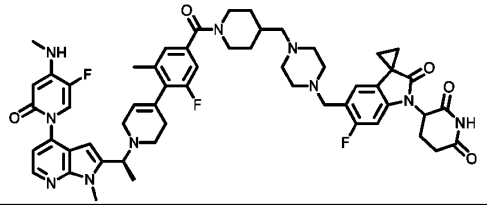
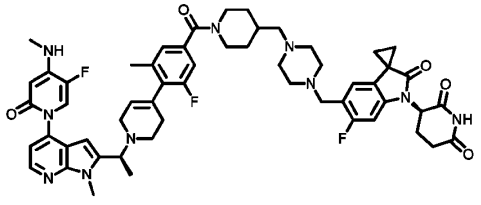
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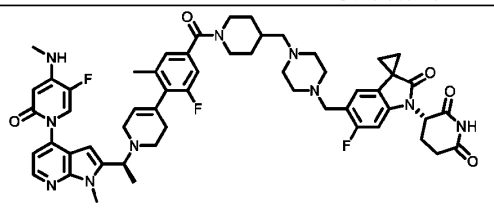
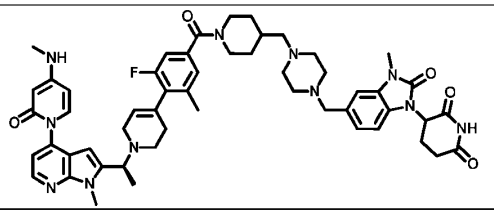
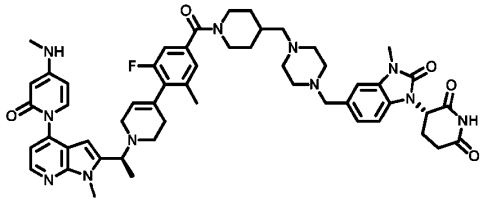
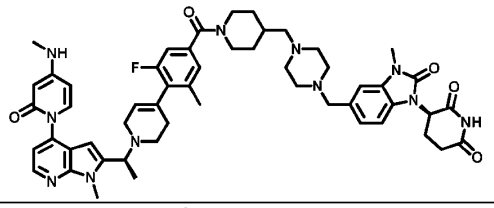
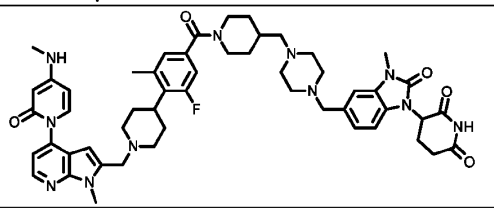
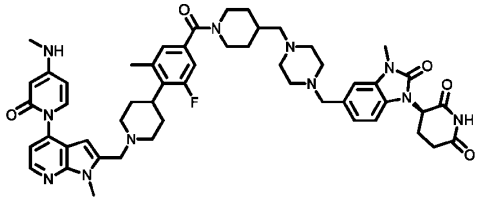
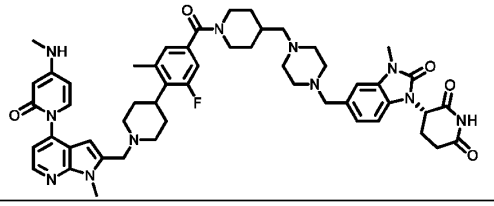
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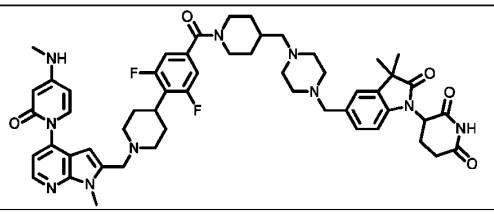
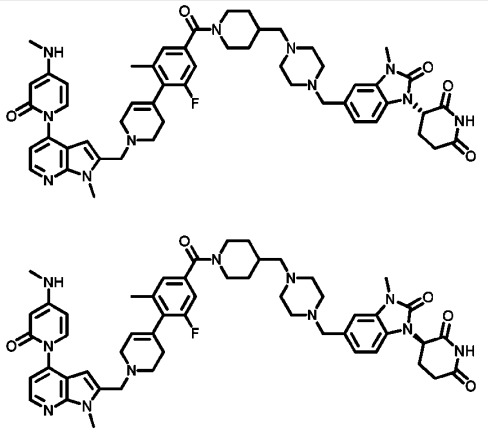
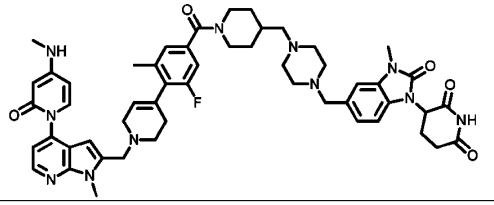
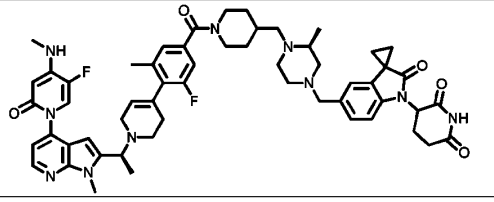
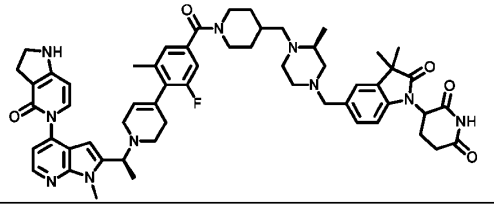
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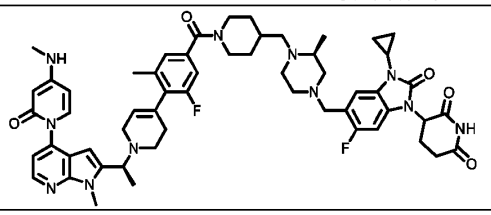
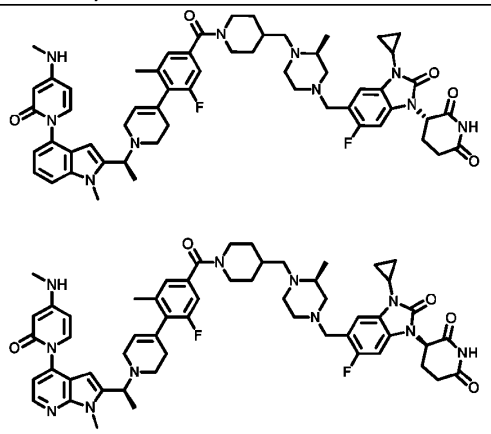
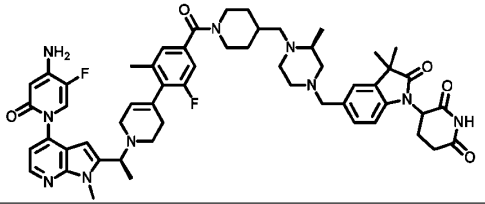
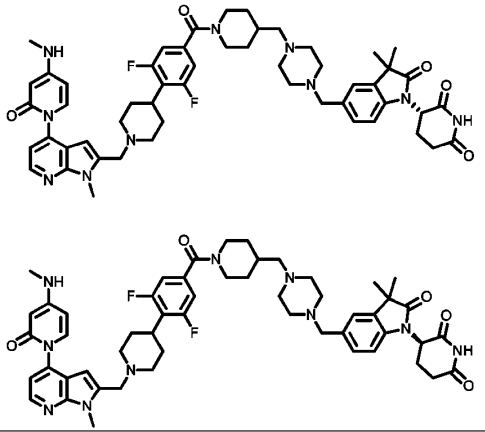
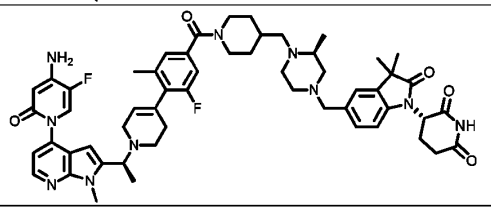
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3u140	

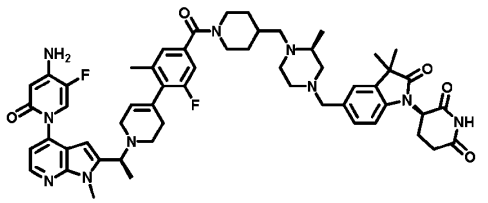
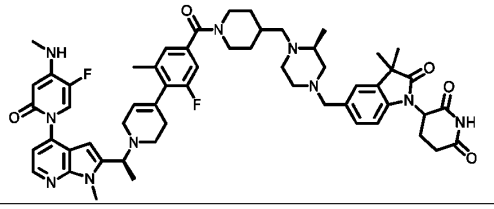
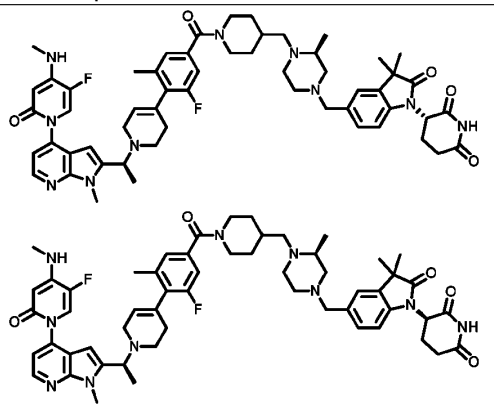
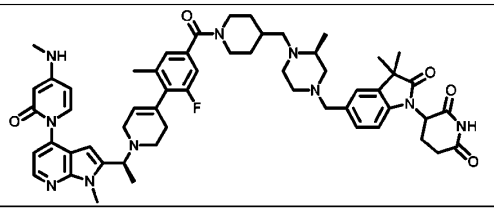
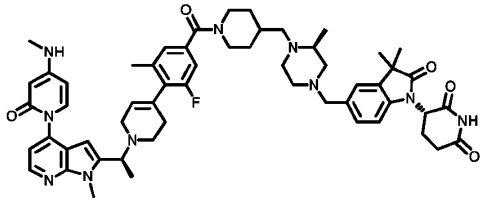
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3u146	
3u147 and 3u148	

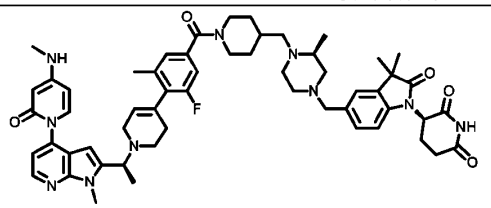
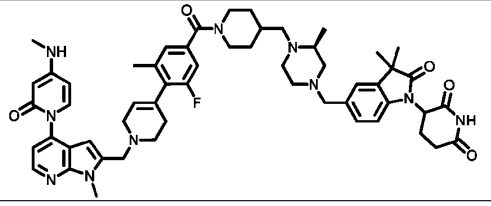
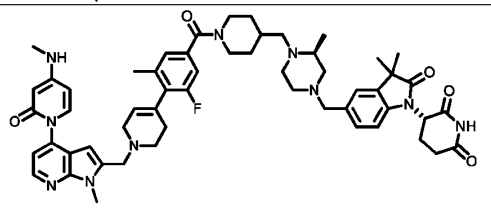
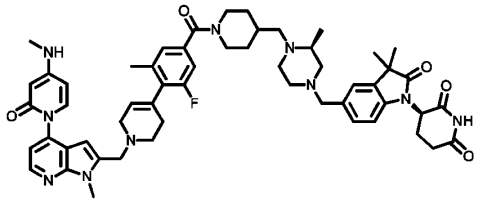
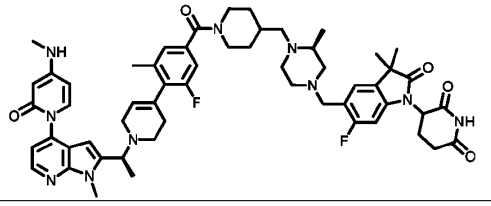
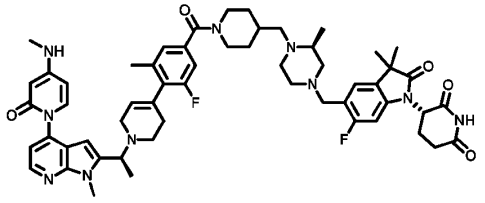
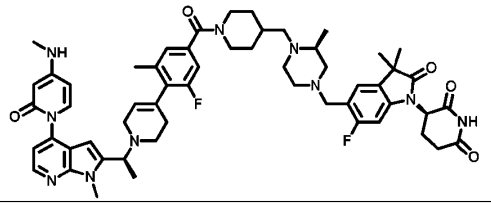
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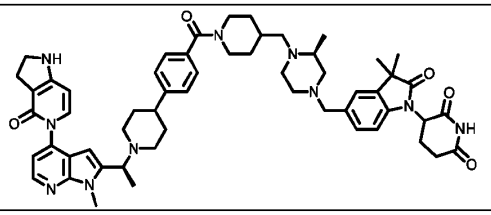
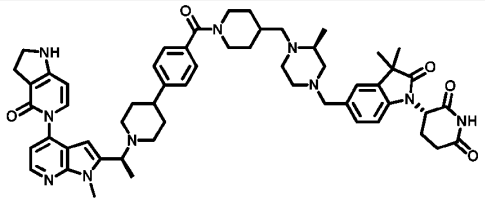
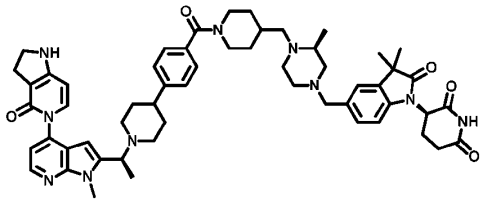
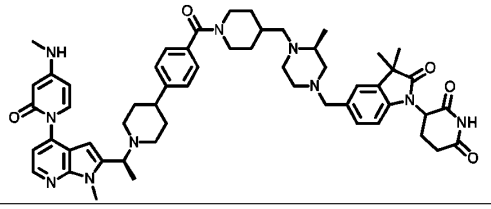
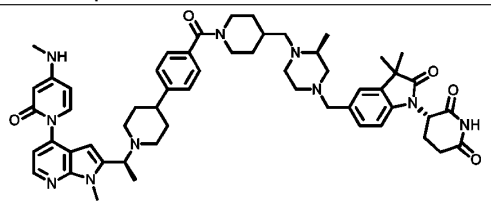
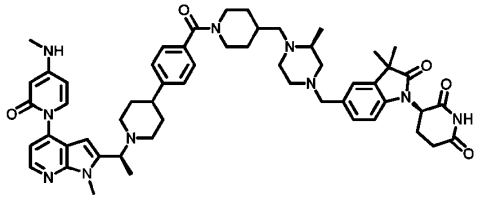
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3u159 and 3u160	 

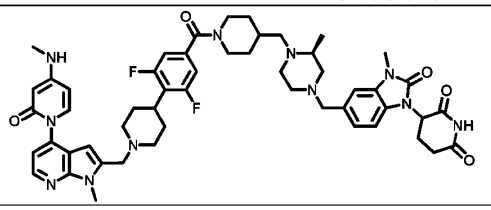
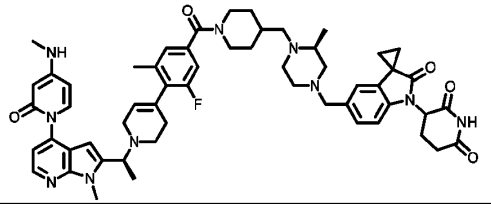
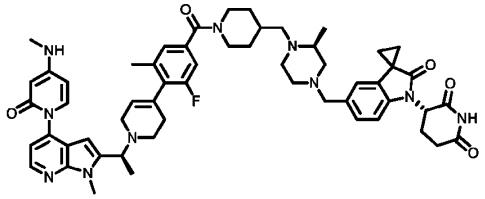
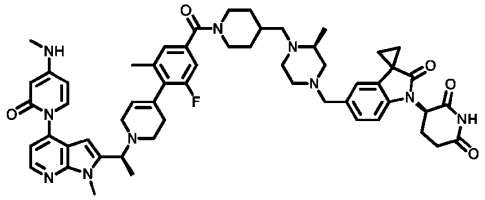
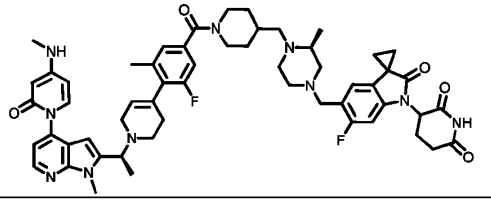
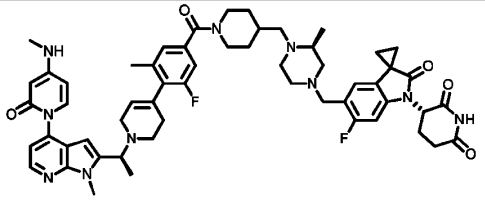
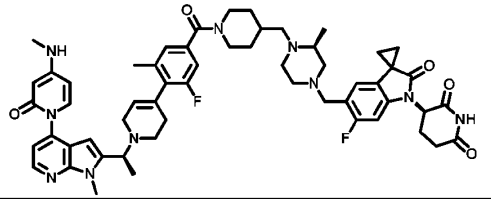
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3u165	

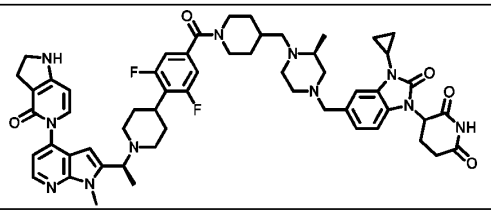
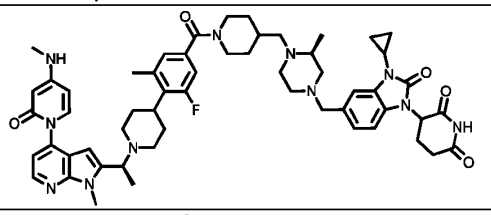
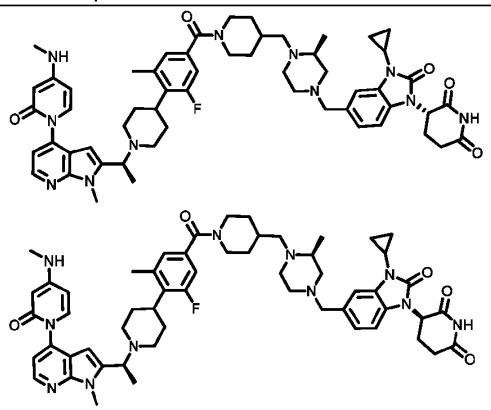
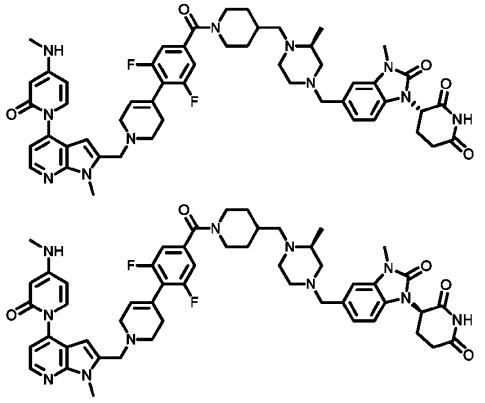
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3u169	
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3u170 and 3u171	

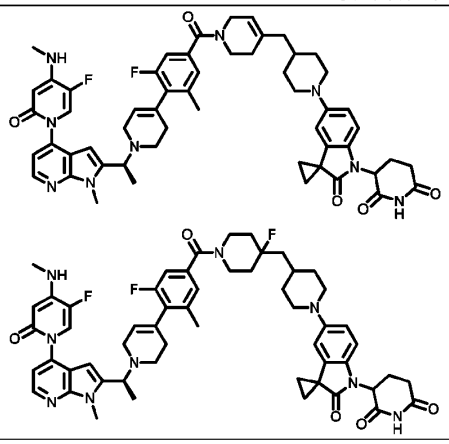
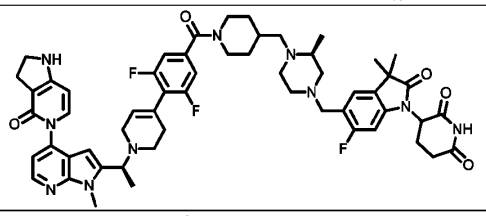
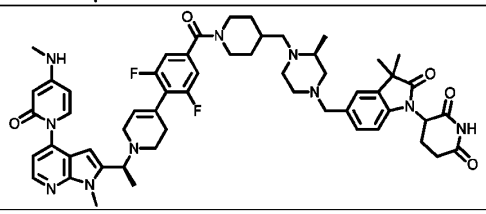
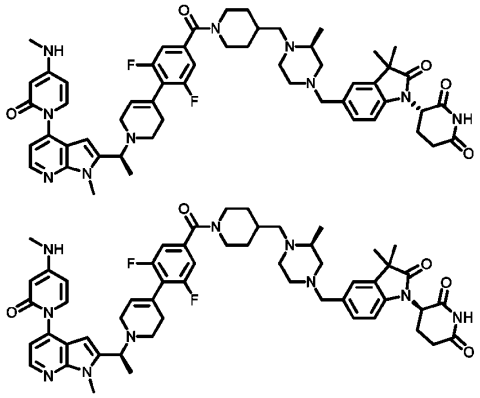
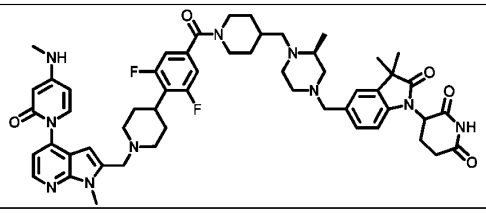
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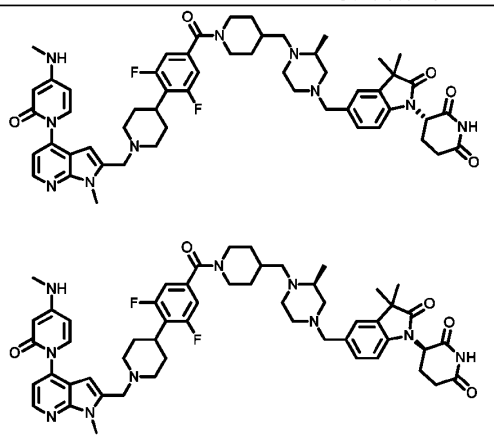
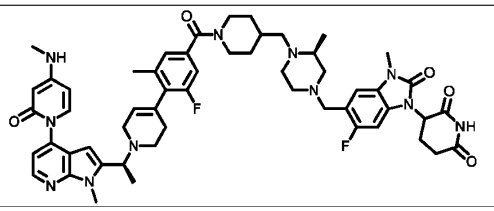
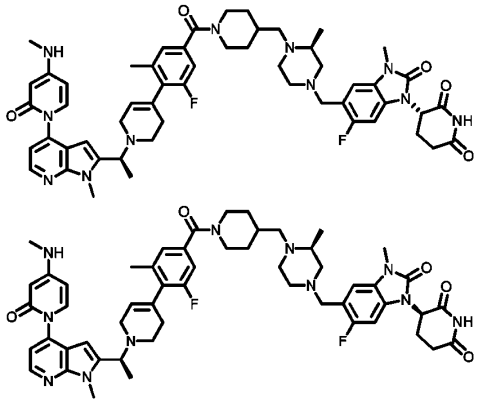
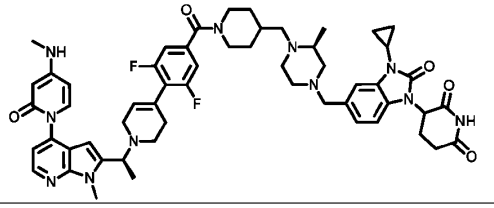
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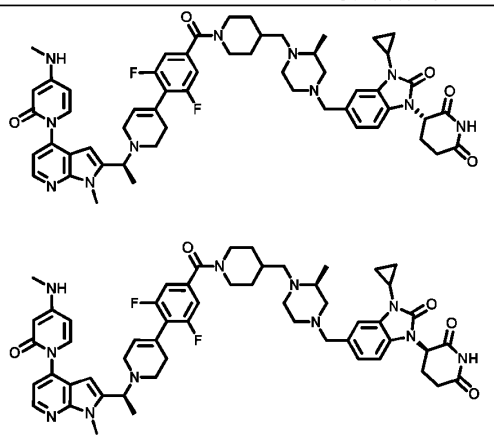
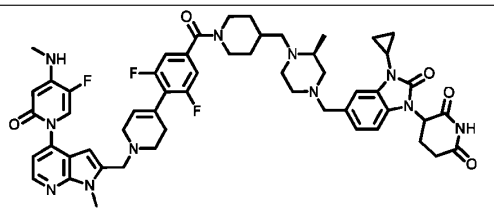
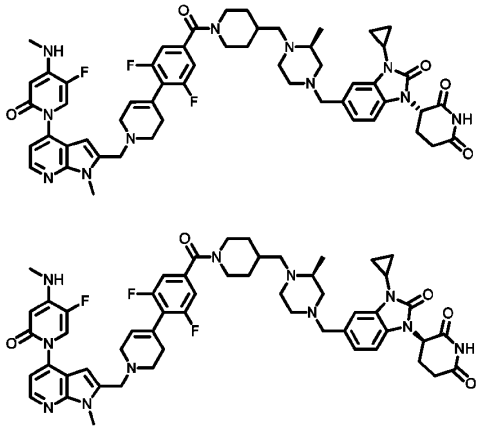
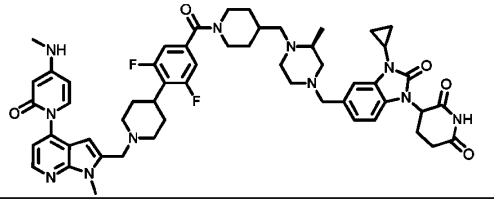
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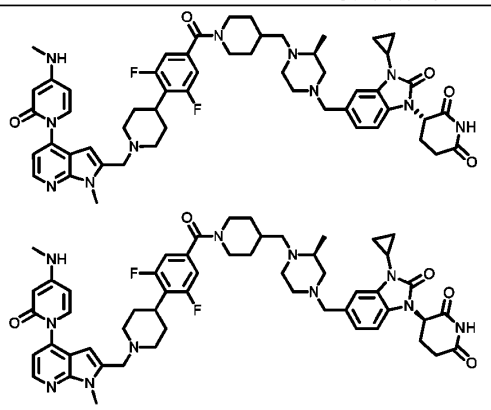
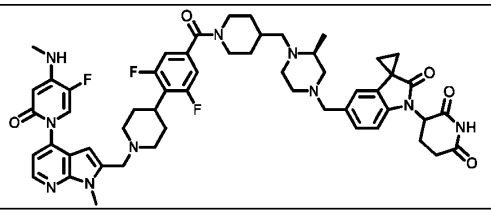
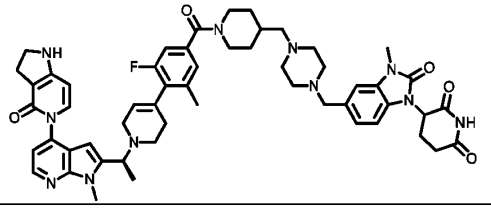
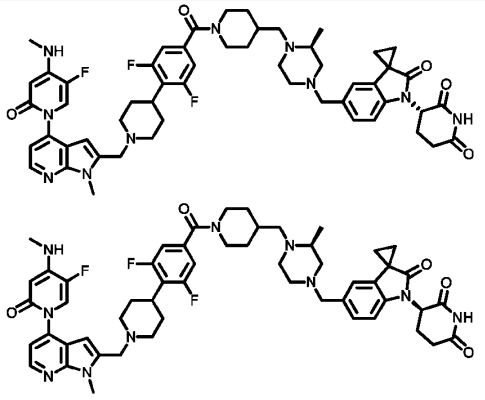
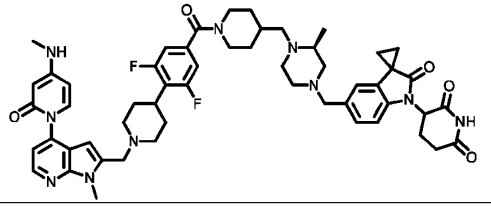
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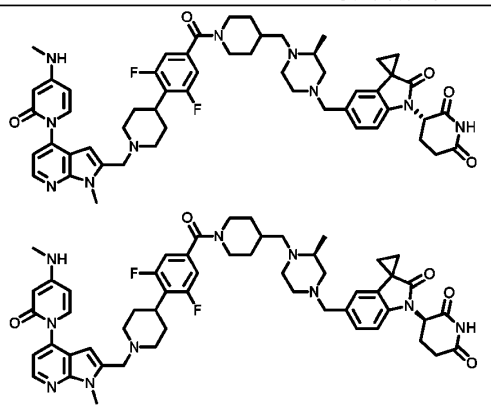
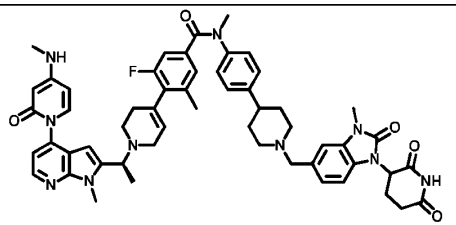
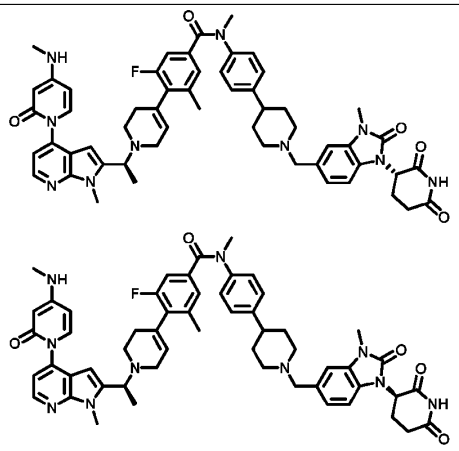
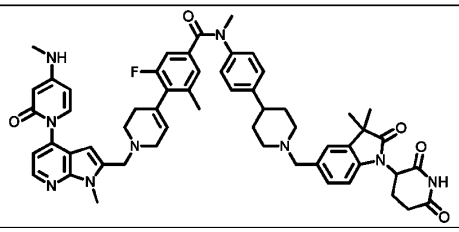
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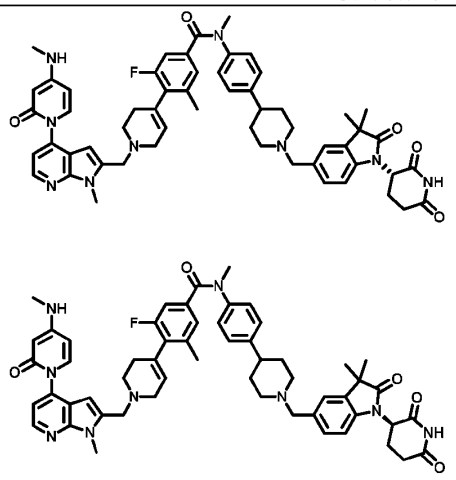
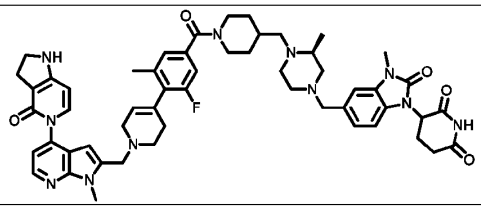
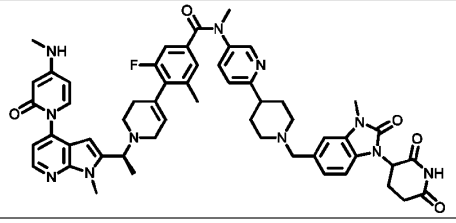
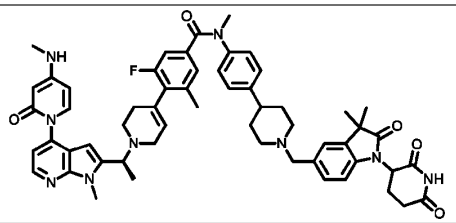
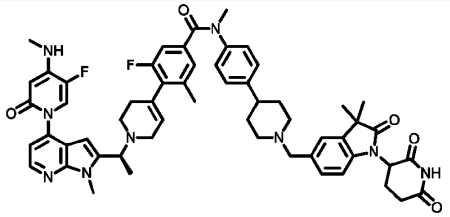
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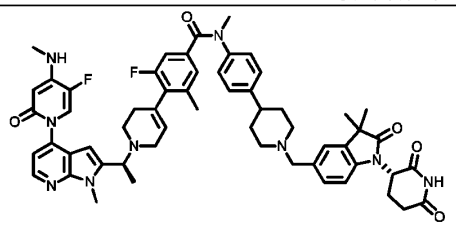
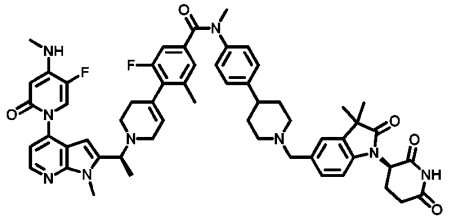
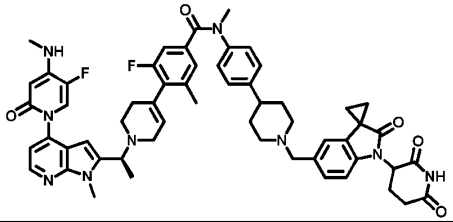
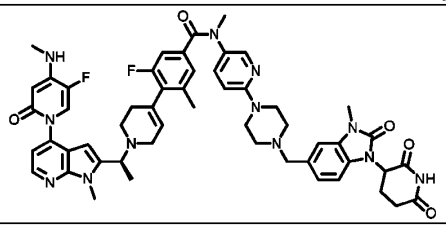
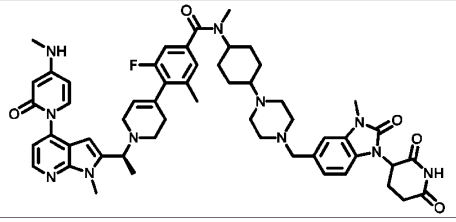
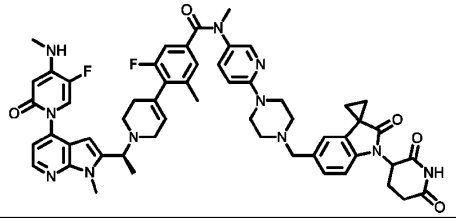
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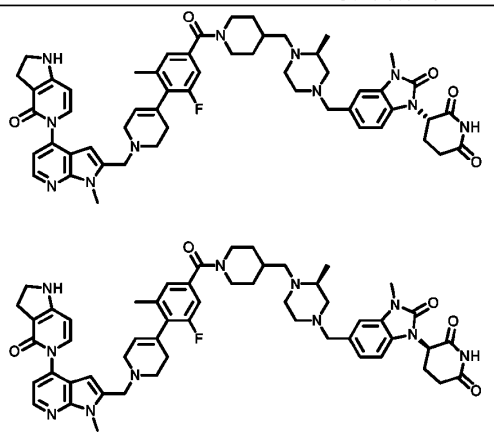
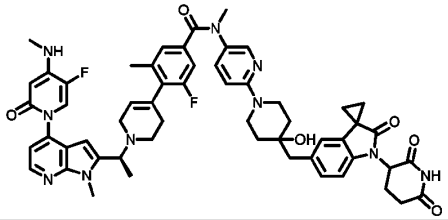
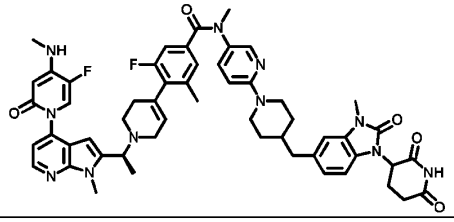
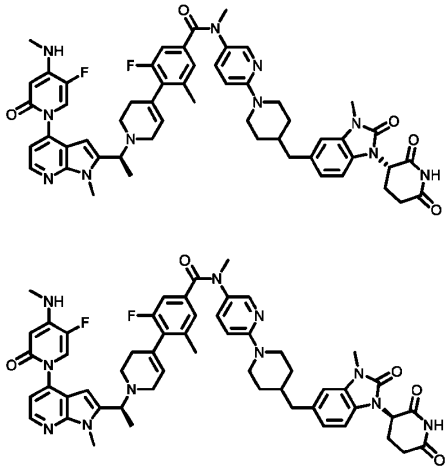
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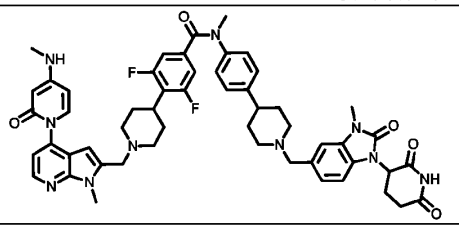
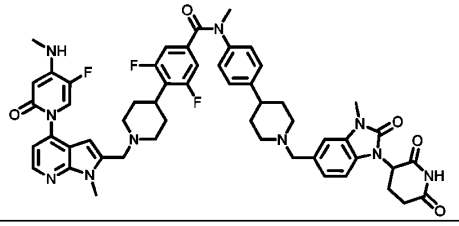
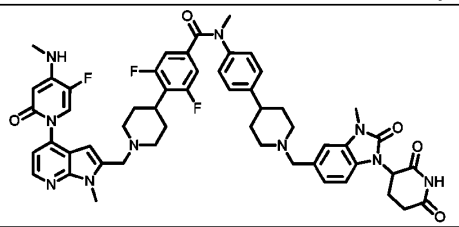
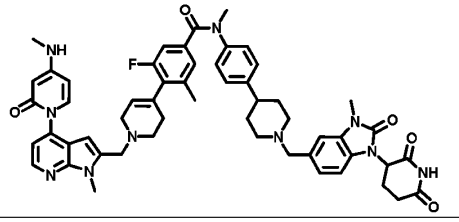
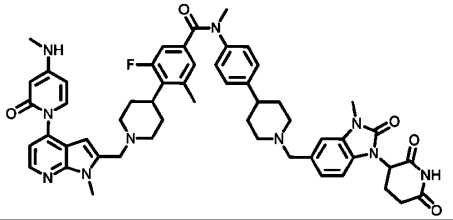
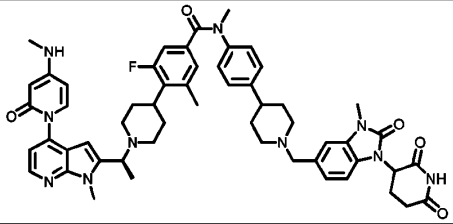
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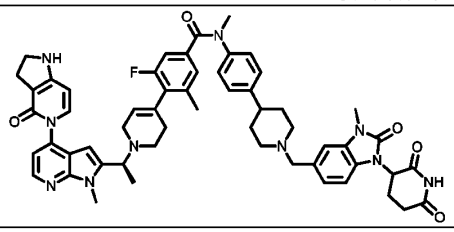
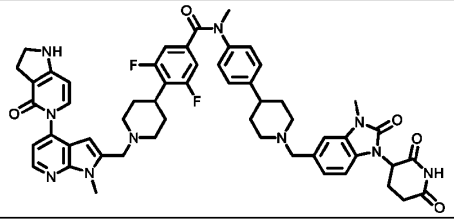
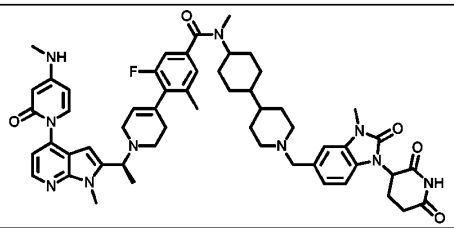
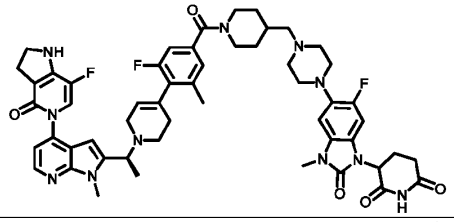
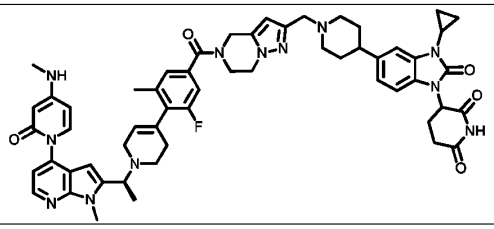
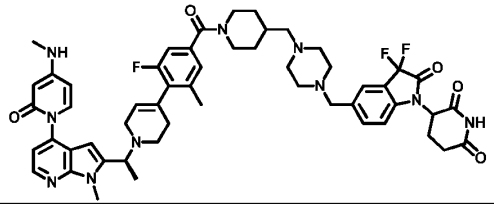
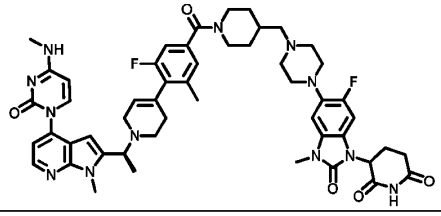
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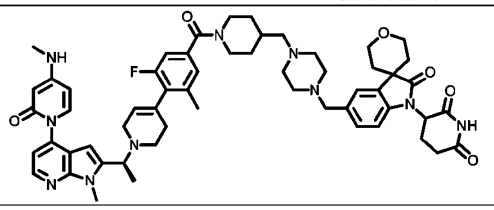
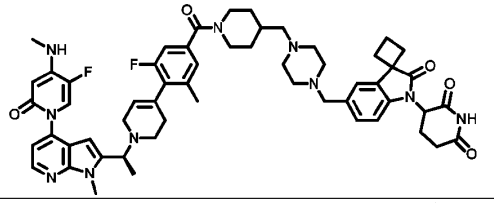
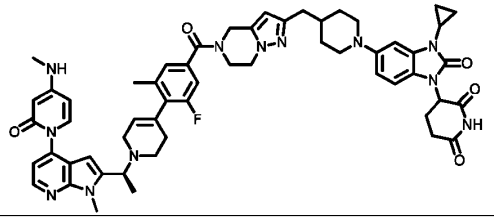
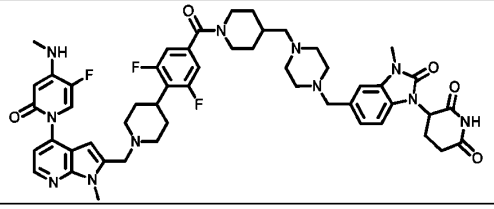
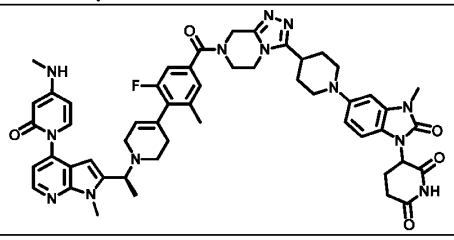
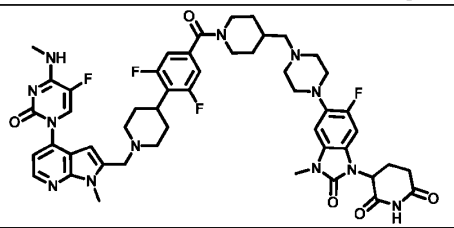
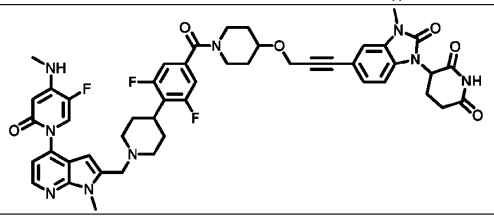
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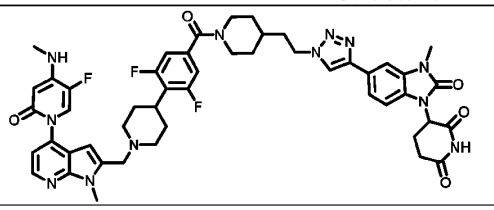
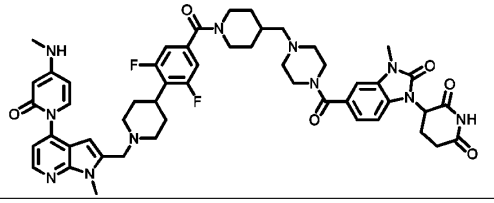
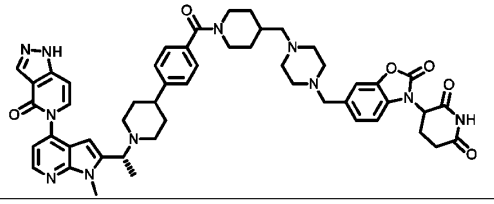
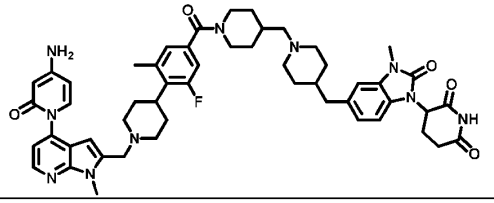
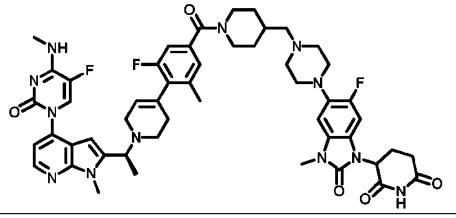
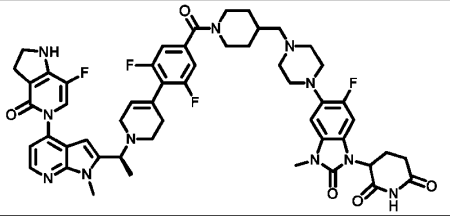
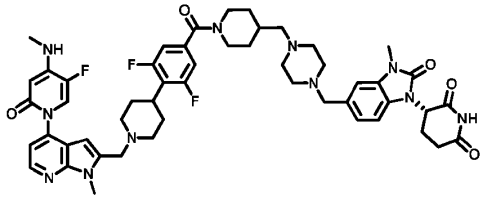
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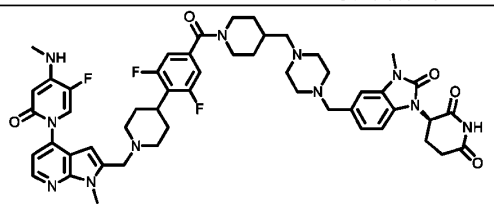
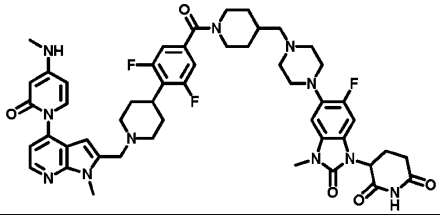
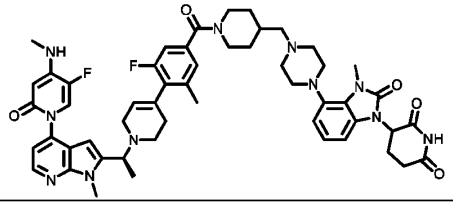
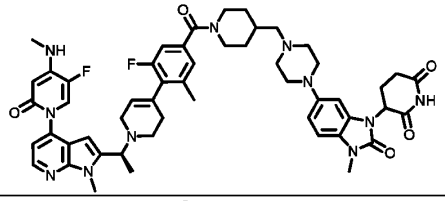
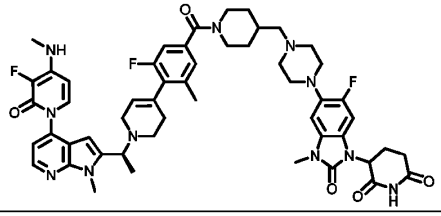
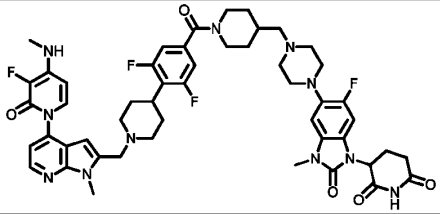
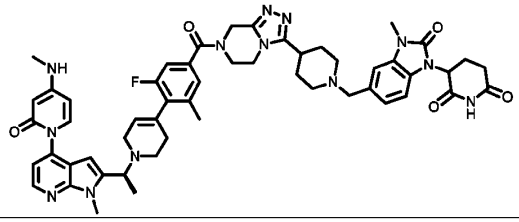
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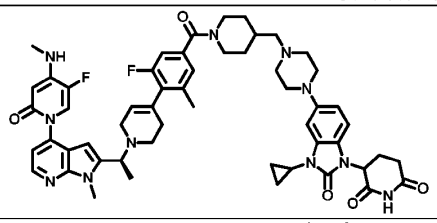
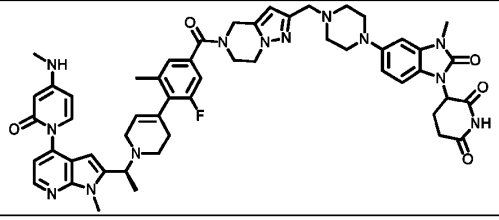
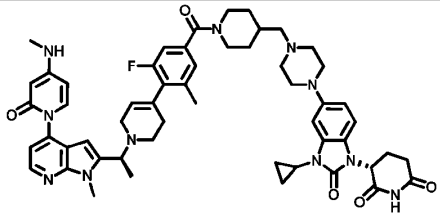
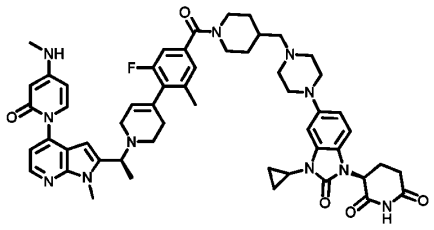
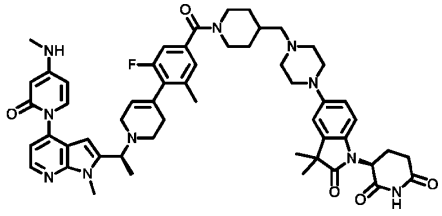
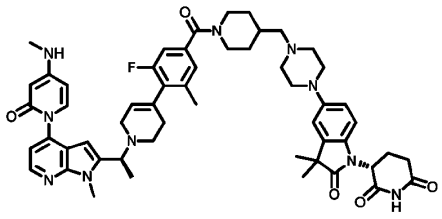
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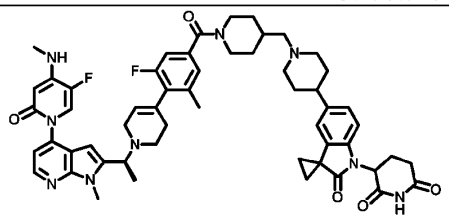
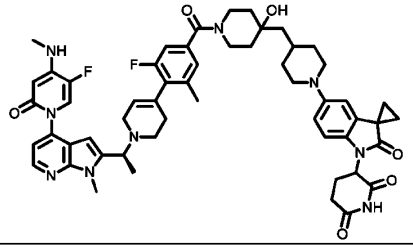
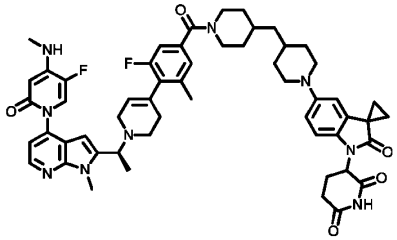
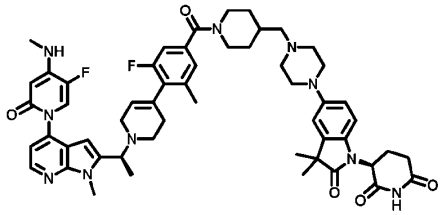
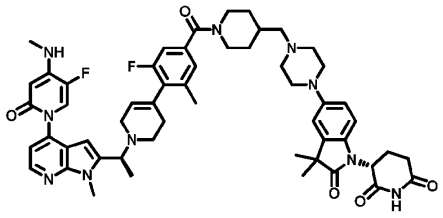
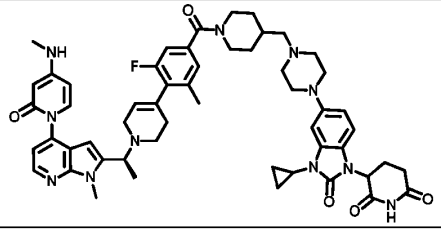
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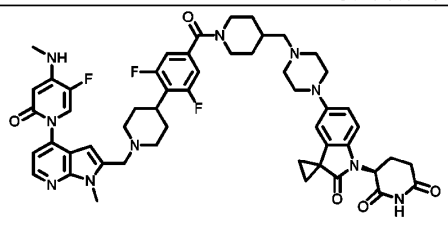
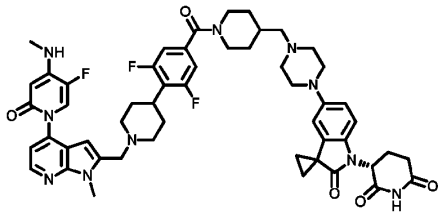
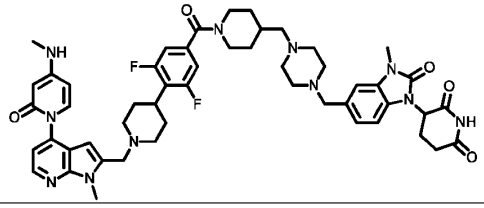
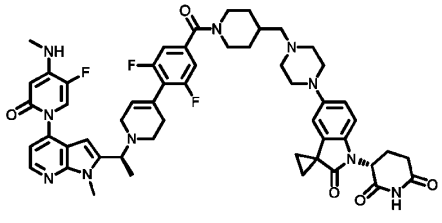
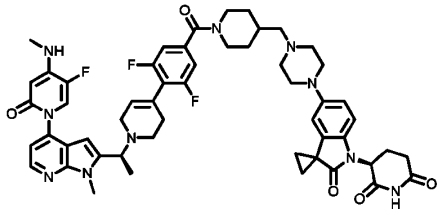
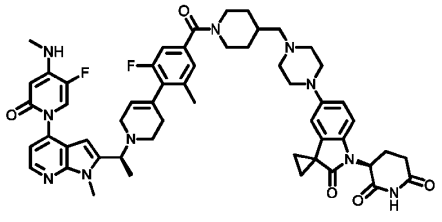
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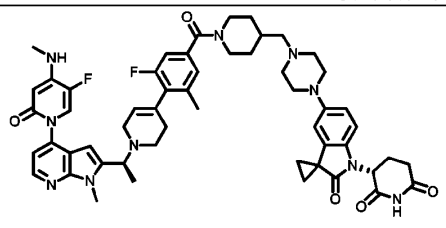
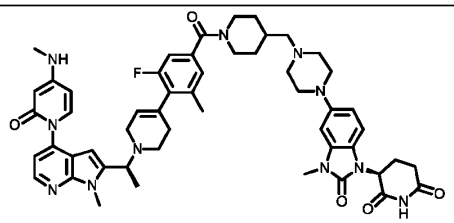
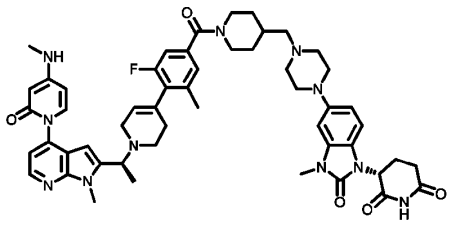
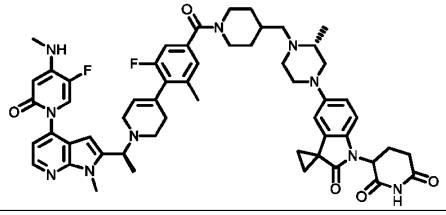
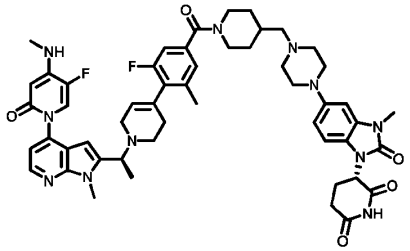
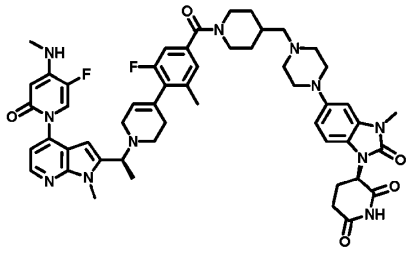
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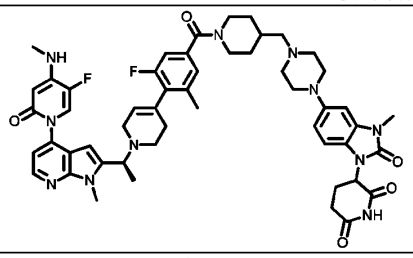
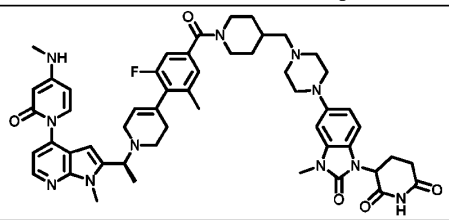
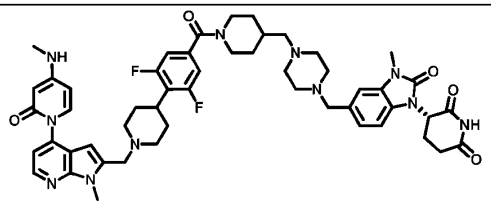
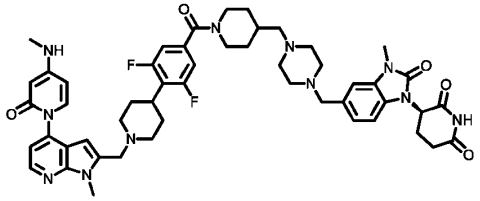
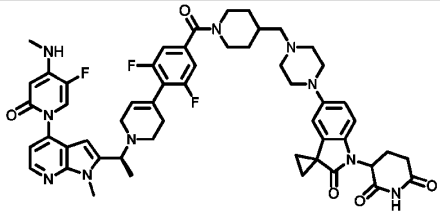
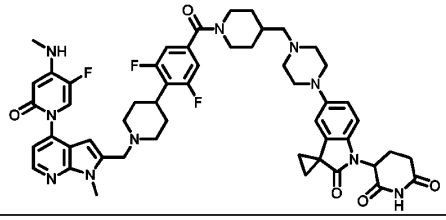
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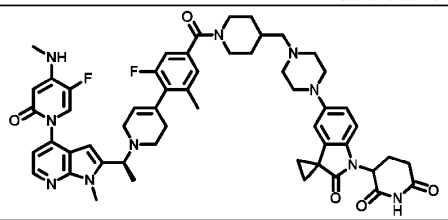
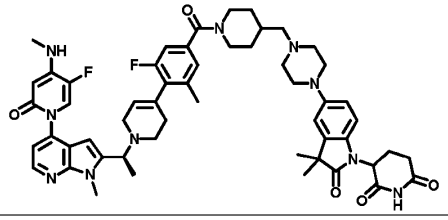
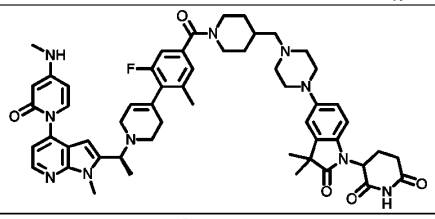
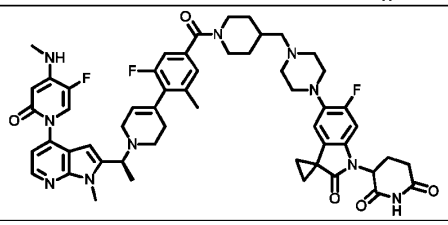
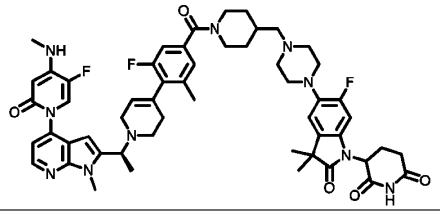
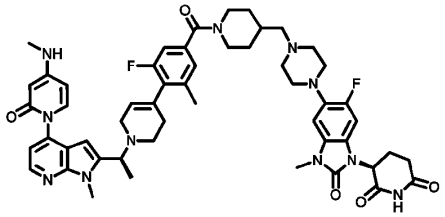
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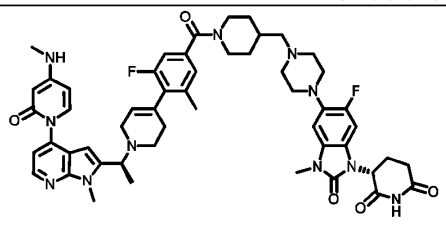
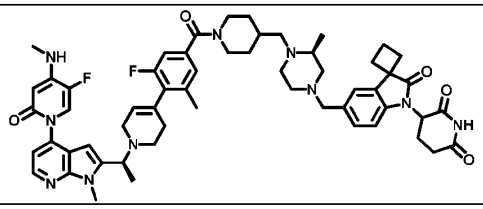
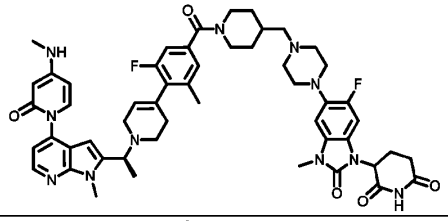
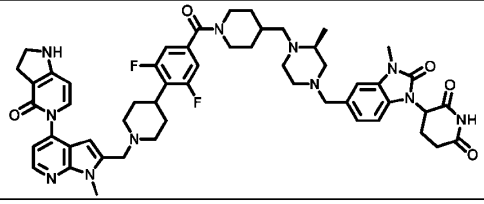
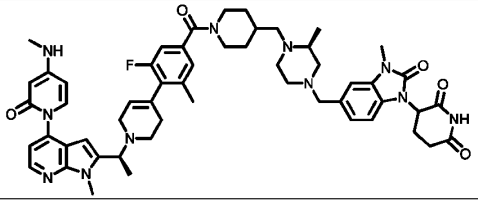
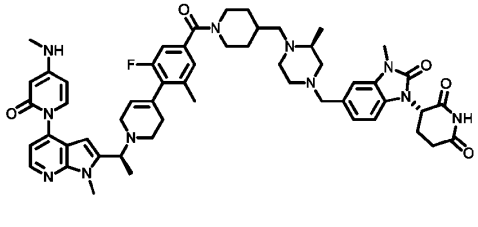
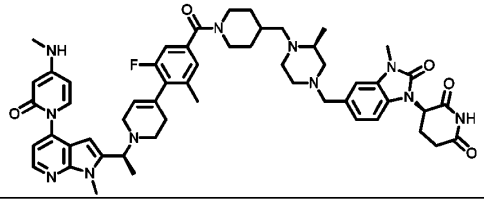
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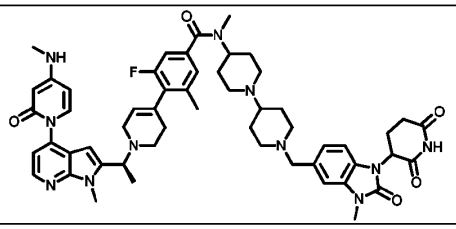
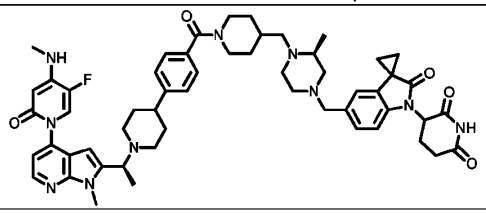
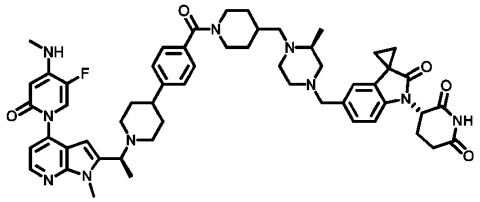
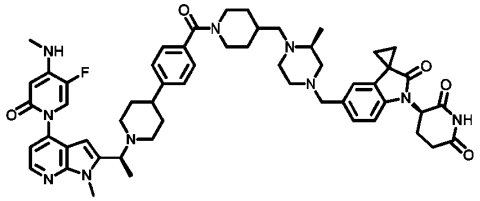
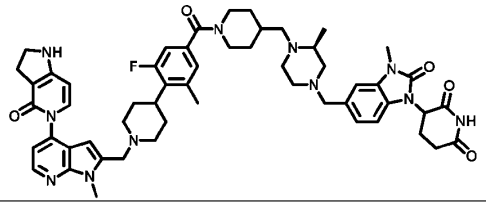
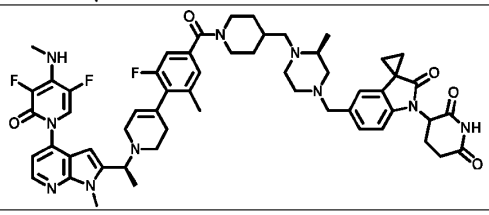
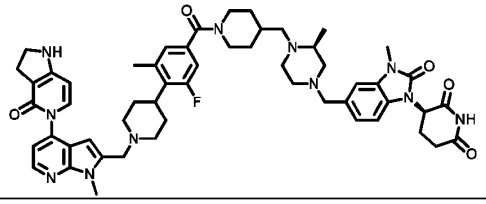
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3u291 and 3u292	

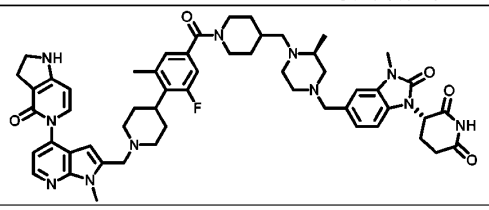
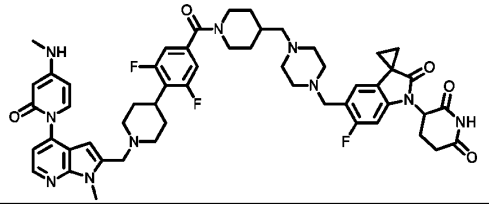
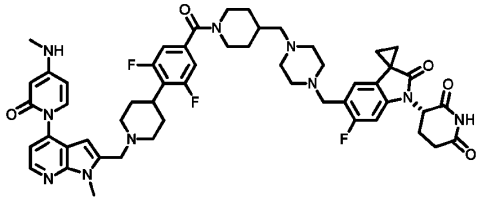
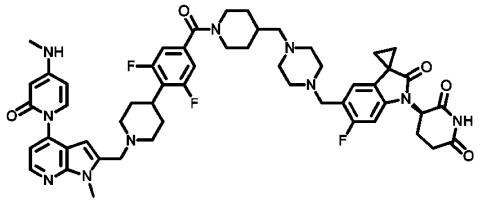
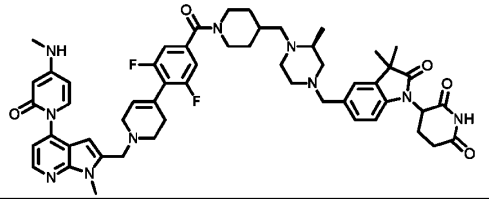
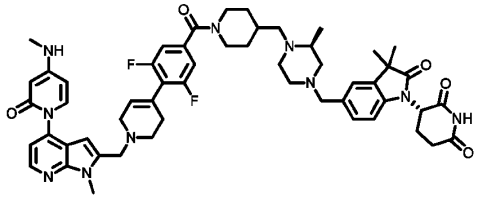
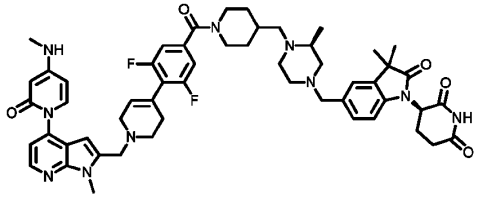
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3u296 and 3u297	 

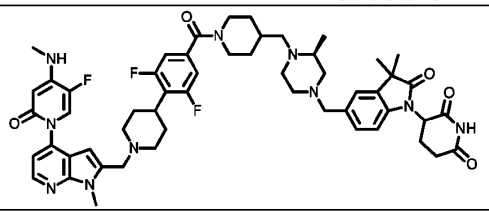
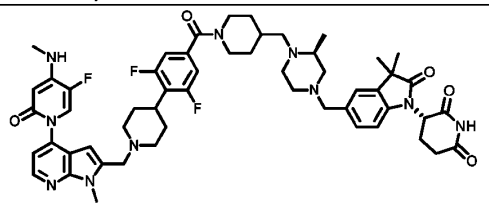
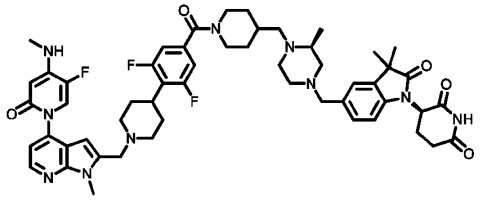
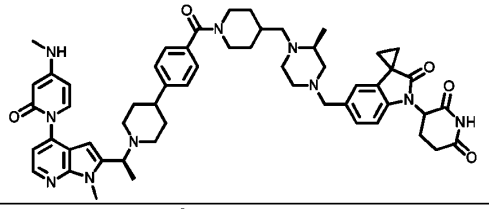
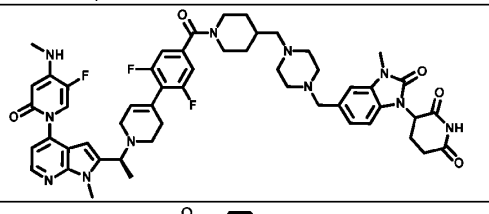
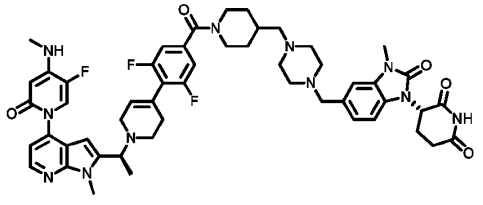
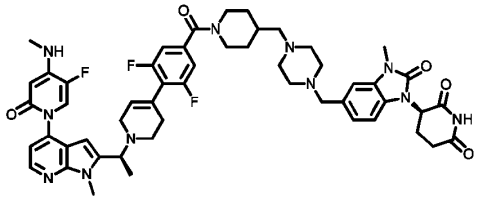
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3u301	

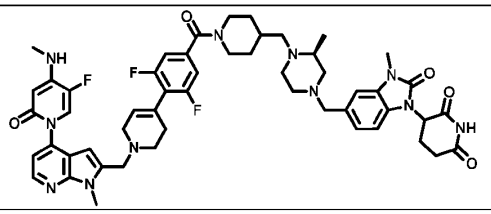
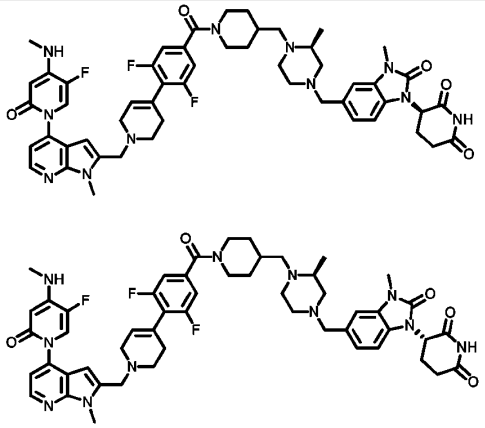
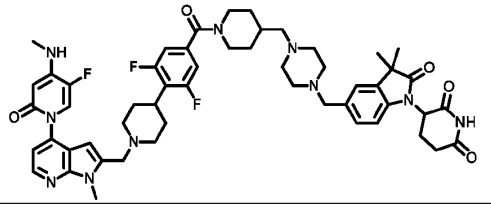
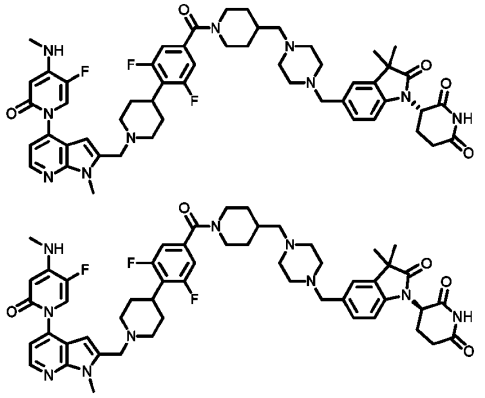
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3u305	
3u306	
3u307 and 3u308	

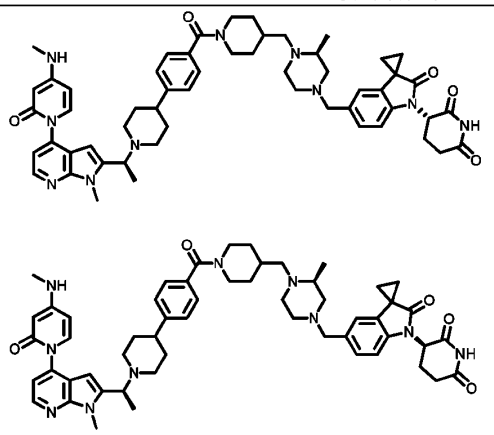
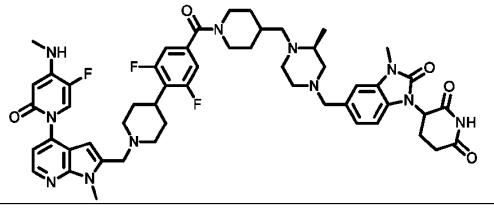
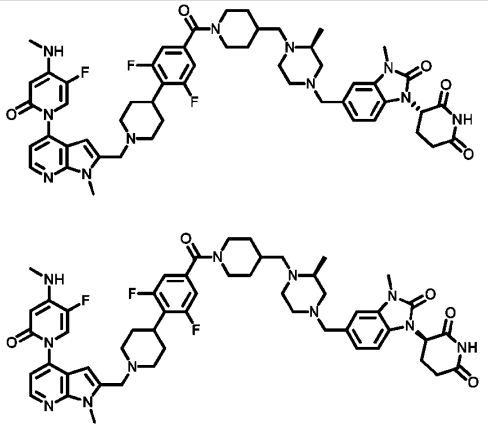
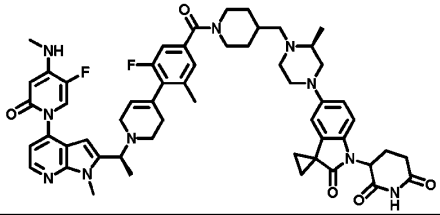
No.	Structure
	
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3u311	
3u32	
3u33 and 3u34	 

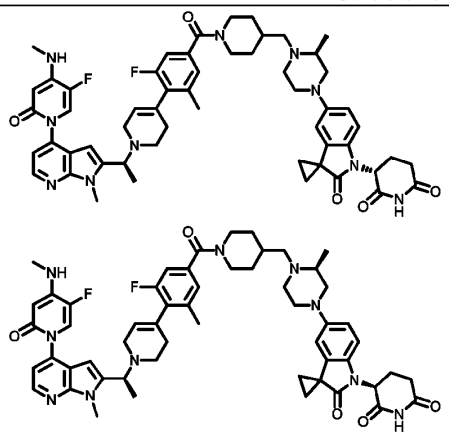
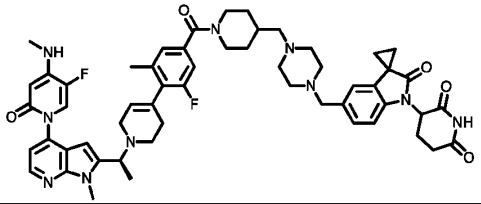
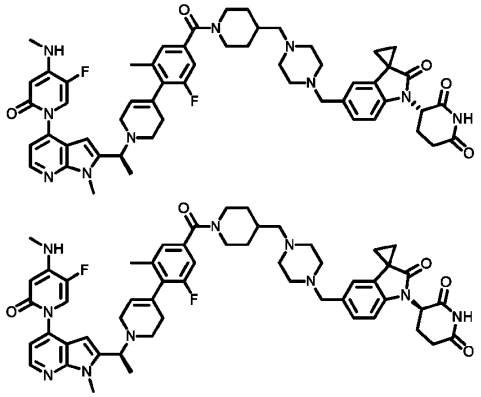
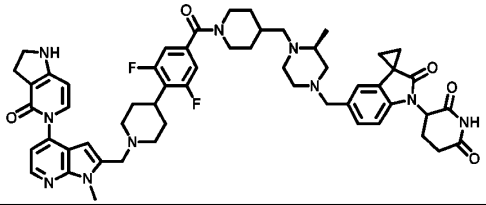
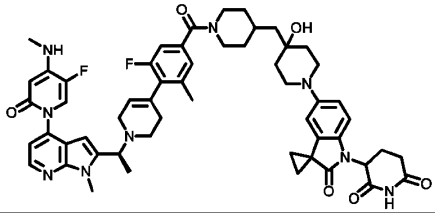
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3u40 and 3u41	

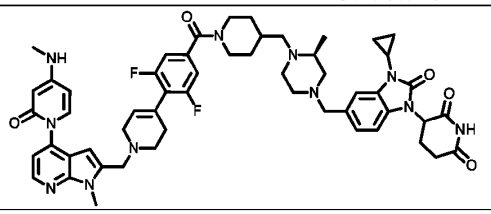
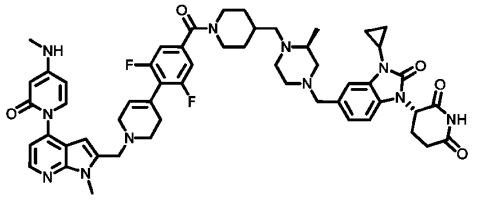
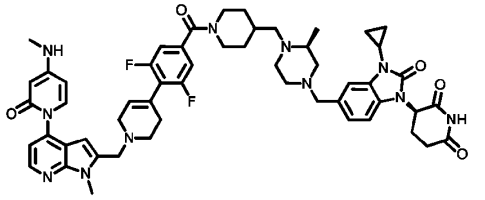
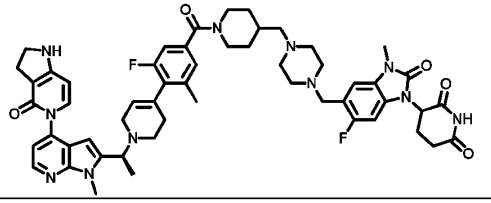
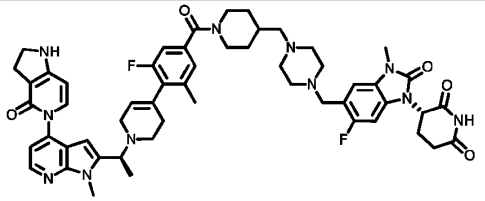
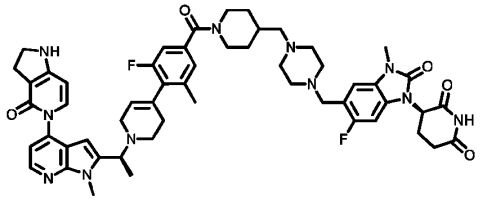
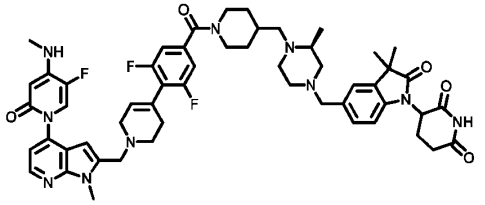
No.	Structure
	
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3u45	
3u46 and 3u47	 

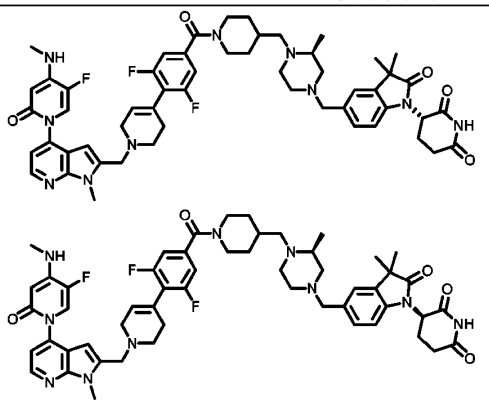
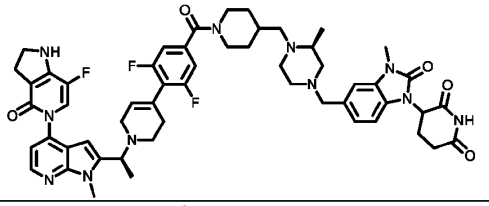
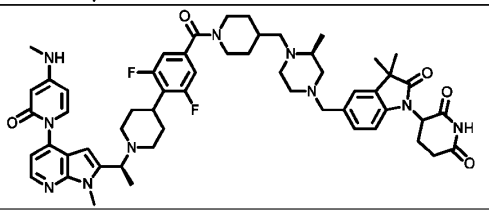
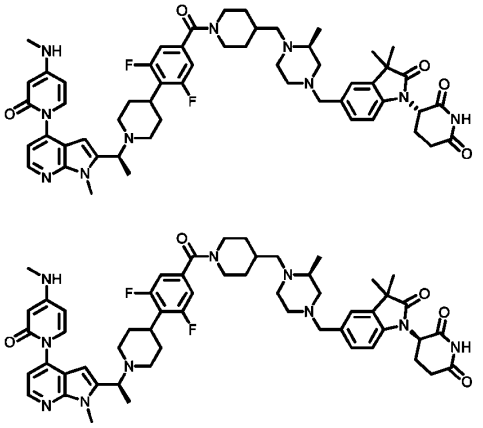
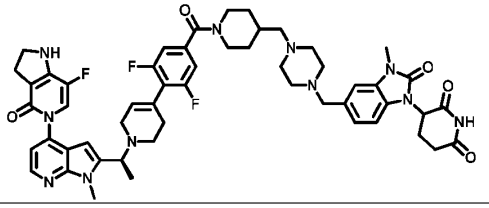
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3u51	
3u52 and 3u53	 

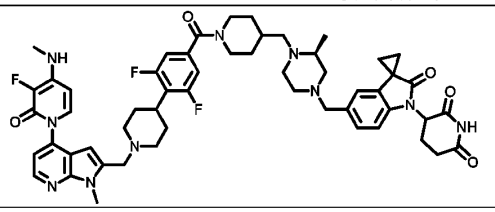
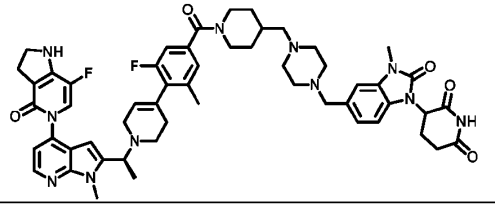
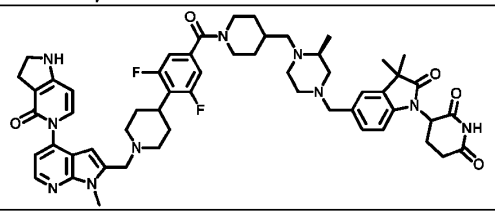
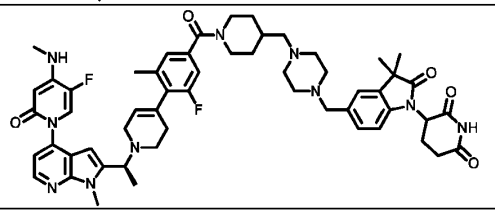
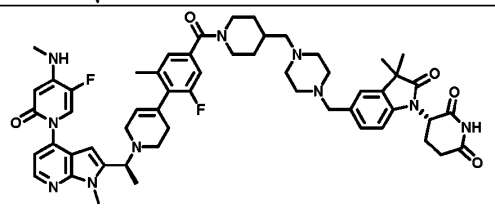
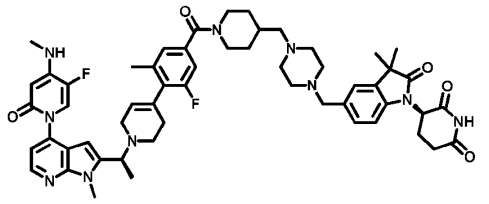
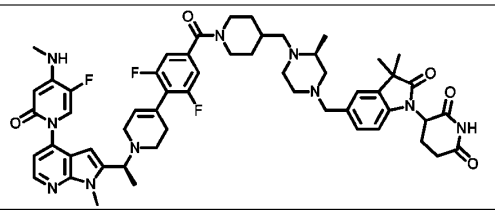
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3u57	
3u58 and 3u59	

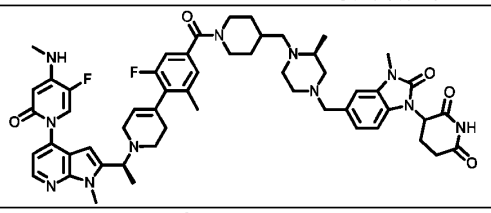
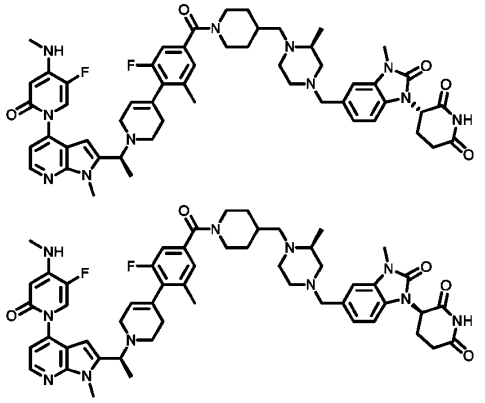
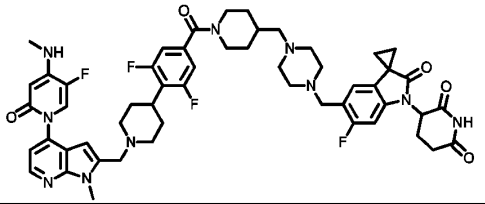
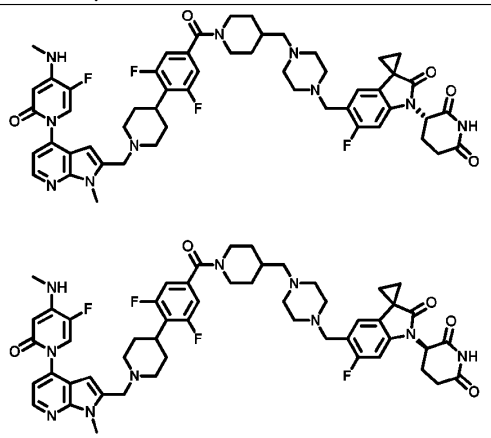
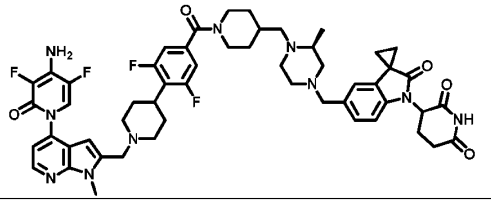
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3u60	
3u61 and 3u62	
3u63	

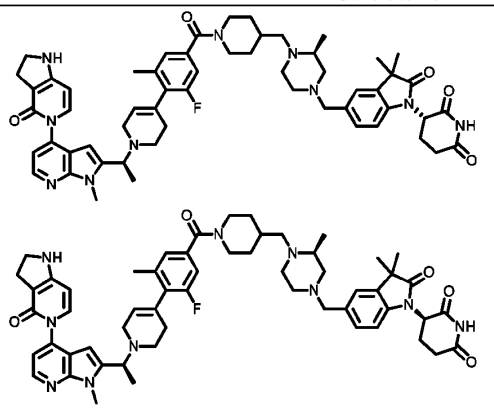
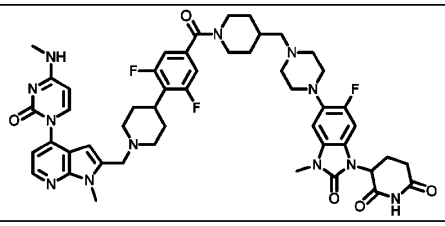
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3u66	
3u67 and 3u68	
3u69	
3u70	

No.	Structure
3u71	
3u72 and 3u73	 
3u74	
3u75 and 3u76	 
3u77	

No.	Structure
3u78 and 3u79	
3u8	
3u80	
3u81 and 3u82	
3u83	

No.	Structure
3u84	
3u85	
3u86	
3u87	
3u88 and 3u89	 
3u9	

No.	Structure
3u90	
3u91 and 3u92	
3u93	
3u94 and 3u95	
3u96	

No.	Structure
3u97 and 3u98	
3h43	

In one or more embodiments of the present disclosure, the compounds of formula (I) have an (EC_{50}) value in the Eotaxin-3 release assay of less than 100 micromolar, or of less than 10 micromolar, or less than 100 nanomolar, or less than 10 nanomolar.

In one or more embodiments of the present disclosure, the compounds of formula (I) have an (DC_{50}) value in the STAT6 assay describe below of less than 100 micromolar, or of less than 10 micromolar, or less than 100 nanomolar, or less than 10 nanomolar.

The compounds of formula (I) may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a co-solvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The disclosure also provides crystalline forms of compounds of the disclosure, such as polymorphs and pseudopolymorphs, and also mixtures thereof.

Compounds of formula (I) may comprise asymmetrically substituted (chiral) carbon atoms which give rise to the existence of isomeric forms, e.g. enantiomers diastereomers, and other steroisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present disclosure provides all such isomers, either in optically pure form or as mixtures thereof (e.g. racemic mixtures or partially purified optical mixtures). Pure stereoisomeric forms of the compounds and the intermediates of this disclosure may be obtained by the application of procedures known in the art. The various isomeric forms may be separated by physical separation methods such as selective crystallization and

chromatographic techniques, e.g. high pressure liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by selective crystallization of their diastereomeric salts which may be formed with optically active amines, or with optically active acids. Optically purified compounds may subsequently be liberated from said purified diastereomeric salts. Enantiomers may also be resolved by the formation of diastereomeric derivatives. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chiral pure starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. Any geometric isomer, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

"Racemates" refers to a mixture of enantiomers. The mixture can comprise equal or unequal amounts of each enantiomer.

"STAT6 modulator" refers to compounds of the present disclosure that inhibit or reduce some or all of the activity of the Signal transducer and activator of transcription 6 (STAT6), including STAT6 degraders.

"STAT6 degrader" refers to compounds of the present disclosure that bind to and/or inhibit both STAT6 protein and an E3 ligase with measurable affinity, resulting in the ubiquitination and subsequent degradation of the STAT6 protein. In certain embodiments, a STAT6 degrader has an DC50 of less than about 50 pM, less than about 1 pM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM. As used herein, the term "monovalent" refers to a degrader compound without an appended E3 ligase binding moiety.

STAT6-mediated disorders, diseases, and/or conditions refers to any disease or other deleterious condition in which STAT6 or a mutant thereof, are known to play a role.

A "subject" or "patient" is meant to describe a human or vertebrate animal, including a dog, cat, horse, cow, mouse, or the like.

"Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results, such as inhibiting the disease or condition (e.g., decreasing one or more symptoms

resulting from the disease or condition, and/or diminishing the extent of the disease or condition), slowing or arresting the development of one or more clinical symptoms associated with the disease or condition, and/or relieving the disease, enhancing the effect of another medication, delaying the progression of the disease, increasing quality of life, and/or prolonging survival.

In the compounds of formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number found in nature. The present disclosure includes all suitable isotopic variations of the compounds of formula (I). For example, different isotopic forms of hydrogen include ^{1}H, ^{2}H and ^{3}H, different isotopic forms of carbon include ^{12}C, ^{13}C and ^{14}C and different isotopic forms of nitrogen include ^{14}N and ^{15}N. Enriching for deuterium (^{2}H) may for example increase *in-vivo* half-life or reduce dosage regimens, or may provide a compound useful as a standard for characterization of biological samples. Isotopically enriched compounds within formula (I) can be prepared by conventional techniques well known to a person skilled in the art or by processes analogous to those described in the procedures and examples herein using appropriate isotopically enriched reagents and/or intermediates.

In some embodiments, compounds described herein, or pharmaceutically acceptable salts, isomers, or a mixture thereof, have from 1 to n hydrogen atoms attached to a carbon atom replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds can increase resistance to metabolism, and thus can be useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," TRENDS PHARMACOL. SCI., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

In some embodiments, a compound of the disclosure is a solvate or a hydrate.

In one embodiment the disclosure provides a compound as above for use in therapy.

In one embodiment the disclosure provides a compound as above for use in the treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of STAT-6.

In one embodiment the disclosure provides a compound as above for use in the treatment of autoimmune diseases.

The compounds of the present disclosure may be useful for preventing, treating or ameliorating diseases characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors.

In an embodiment the disclosure provides the use of a compound of formula (I) as defined above, in the manufacture of a medicament for the prophylaxis, treatment or amelioration of any of the following diseases characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors.

In an embodiment the disclosure provides a method of preventing, treating or ameliorating diseases characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors, the method comprising administering to a person suffering from at least one of said diseases an effective amount of one or more compounds according to formula (I), optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination with other therapeutically active compounds.

In an embodiment the disclosure provides a method of preventing, treating or ameliorating autoimmune diseases, conditions characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors the method comprising administering to a person suffering from at least one of said diseases an effective amount of one or more compounds according to formula (I), optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination with other therapeutically active compounds.

Besides being useful for human treatment, the compounds of the present disclosure may also be useful for veterinary treatment of animals including mammals such as horses, cattle, sheep, pigs, dogs, and cats.

Pharmaceutical Compositions and Modes of Administration

For use in therapy, compounds of the present disclosure are typically in the form of a pharmaceutical composition. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of Formula (I), optionally together with one or more other therapeutically active compound(s), together with a pharmaceutically acceptable excipient, vehicle or carrier(s). In some embodiments, the excipient is "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

In some embodiments, the compound of the disclosure is provided in an amount of 0.0001 99.9% by weight of a formulation.

In the form of a dosage unit, a compound of the disclosure may be administered one or more times a day at appropriate intervals. In some embodiments, a dosage unit of a formulation contain between 0.001 mg and 1000 mg, such as between 0.01 mg and 300 mg of a compound of Formula (I).

A suitable dosage of the compound of the disclosure may depend, *inter alia*, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound may be administered either orally, parenterally, topically, transdermally or intradermally and other routes according to different dosing schedules, e.g. daily, weekly or with monthly intervals. In some embodiments, a single dose comprising a compound of the disclosure may provide an amount of the compound in the range from 0.001 to 400 mg/kg body weight.

In some embodiment, a compound of the disclosure is provided in combination with one or more therapeutically active compounds. If the treatment involves administration of another therapeutically active compound *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, may be consulted for useful dosages of said compounds.

The administration of a compound of the present disclosure with one or more other active compounds may be either concomitantly or sequentially.

The formulations include e.g. those in a form suitable for oral, rectal, parenteral transdermal, intradermal, ophthalmic, topical, nasal, sublingual or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by but not restricted to any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, *The Science and Practice of Pharmacy*, 21ed ed., 2005. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations may be prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier, semisolid carrier or a finely divided solid carrier or combinations of these, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present disclosure suitable for oral and buccal administration may be in the form of discrete units as capsules, sachets, tablets, chewing gum or lozenges, each containing a predetermined amount of the active ingredient.

A tablet may be made by compressing, moulding or freeze drying the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form; for example with a lubricant; a disintegrating agent or a dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier. Freeze dried tablets may be formed in a freeze-dryer from a solution of the drug substance.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient,

e.g. isotonic saline, isotonic glucose solution or buffer solution. Liposomal formulations are also suitable for parenteral administration.

Transdermal formulations may be in the form of a plaster, patch, microneedles, liposomal or nanoparticulate delivery systems or other cutaneous formulations applied to the skin.

Formulations suitable for ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for ophthalmic administration.

Formulations suitable for topical, such as dermal, intradermal or ophthalmic administration include liquid or semi-solid preparations, solutions or suspensions.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers.

In some embodiments, administration can be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery).

In some embodiments, pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient.

In some embodiments, one or more compounds as disclosed herein or a pharmaceutical composition thereof is formulated for topical administration to the skin or mucosa (e.g., dermally or transdermally).

In some embodiments, topical compositions can include ointments and creams. In some embodiments, ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. In some embodiments, creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. For example, cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. For example, the oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. In some embodiments, the emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. In some embodiments, as with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually

and specifically indicated to be incorporated by reference, regardless of any separately provided incorporation of particular documents made elsewhere herein.

Combination Therapies

In one embodiment, the compounds disclosed herein may be used in combination with one or more additional therapeutic agents. In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, can be combined with the therapeutically effective amount of one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents.

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of an inflammatory, and/or dermatologic disease or disorder, such as atopic dermatitis (AD). Non-limiting examples of such agents include topical corticosteroids (TCS) (e.g., desonid, hydrocortisone, fluocinolone, triamcinolone, betamethasone diproprionate), topical calcineurin inhibitors (TCI) (e.g., tacrolimus, pimecrolimus), cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, interferon gamma, phosphodiesterase 4 (PDE4) inhibitor such as crisaborole, JAK inhibitor (e.g., ruxolitinib, upadacitinib, abrocitinib, baricitinib), dupilumab, and anti-IL-13 antibody (e.g., tralokinumab).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as acne. Non-limiting examples of such agents include topical therapies such as benzoyl peroxide, topical retinoids, topical antibiotic, clascoterone, salicylic acid and azelaic acid; and systemic therapies such as doxycycline, minocycline, sarecycline, combined oral contraceptives, spironolactone, and isotretinoin.

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as alopecia areata. Non-limiting examples of such agents include topical therapies such as systemic corticosteroids (such as prednisolone), cyclosporine, azathioprine, methotrexate, sulfasalazine, simvastatin/exetimibe, inosiplex, antihistamines (such as fexofenadine), and oral JAK inhibitors (such as ritlecitinib or brepocitinib).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as asthma. Non-limiting examples of such agents include inhaled ICS-formoterol (such as budesonide-formoterol), short-acting beta2 agonists (such as albuterol sulfate), leukotriene receptor antagonists (such as montelukast), immunoglobulin E antibodies (such as omalizumab) and long-acting muscarinic antagonists (such as tiotropium).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as chronic obstructive pulmonary disease (COPD). Non-

limiting examples of such agents include short-acting beta2 agonists (such as albuterol sulfate), short acting muscarinic antagonists (such as aiprtropium), long-acting beta2 agonists (such as olodaterol), and long-acting muscarinic antagonists (such as tiotropium).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as chronic rhinosinusitis with polyps. Non-limiting examples of such agents include intranasal corticosteroid, or biologics such as benralizumab (targets IL-5), dupilumab (targets IL-13), omalizumab (targets IgE).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as contact dermatitis. Non-limiting examples of such agents include topical corticosteroids, topical calcineurin inhibitors (such as pimecrolimus, tacrolimus), topical phosphodiesterase 4 inhibitors, such as crisaborole, systemic immunosuppressants and modulators, such as systemic corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine or dupilumab.

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as dermatomyositis. Non-limiting examples of such agents include topical corticosteroids, topical calcineurin inhibitors (such as pimecrolimus, tacrolimus), systemic corticosteroids (such as prednisone), antimalarials (such as hydroxychloroquine, cholorquine, quinacrine), methotrexate, mycophenolate mofetil, intravenous immunoglobulin, rituximab, and JAK inhibitors (such as tofacitinib).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as esophageal eosinophilia. Non-limiting examples of such agents include systemic corticosteroids (such as budesonide, fluticasone, prednisone), topical corticosteroids, and proton pump inhibitors (such as omeprazole, esomeprazole, pantoprazole and lansoprazole).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as psoriasis. Non-limiting examples of such agents include topical treatments such as topical corticosteroids (such as betamethasone dipropionate, clobetasol propionate, desoximetasone, diflorasone diacetate, fluocinonide, flurandrenolide, halobetasol propionate, amcinonide, mometasone furoate, triamcinolone acetonide, fluticasone propionate, hydrocortisone valerate, clocortolone pivalate), topical calcineurin inhibitors (such as pimecrolimus, tacrolimus), topical vitamin D analogues (such as calcipotriene, calcitriol, tacalcitol or mazacalcitol), topical retinoids (such as tazarotene); systemic nonbiologic therapies such as methotrexate, phosphodiesterase 4 inhibitors (such as apremilast), immunosuppressants (such as cyclosporine), oral retinoids (such as acitretin), oral Janus

kinase inhibitors (such as tofacitinib), fumaric acid esters (such as dimethyl fumarate), systemic immunosuppressants and antimetabolites (such as hydroxyurea, mycophenolate mofetil, azathioprine, leflunomide, tacrolimus and thioguanine); and biologic therapies such as TNF-a inhibitors (such as etanercept, infliximab, adalimumab, certolizumab), IL-12/IL-23 inhibitors (such as ustekinumab), IL-17 inhibitors (such as secukinumab, ixekizumab, brodalumab), and IL-23 inhibitors (such as guselkumab, tildrakizumab, risankizumab).

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as scleroderma. Non-limiting examples of such agents include immunosuppressive treatments (such as methotrexate, mycophenolate mofetil, cyclophosphamide, tocilizumab, and rituximab), and autologous haematopoietic stem cell transplantation.

In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or stereoisomer thereof, is co-administered with one or more agents useful for the treatment and/or prophylaxis of a dermatologic condition, such as vitiligo. Non-limiting examples of such agents include topical treatments such as topical corticosteroids, topical calcineurin inhibitors (such as pimecrolimus, tacrolimus), topical vitamin D analogues (such as calcipotriene); and systemic therapies such as oral corticosteroids (such as betamethasone).

In some embodiments, an additional therapeutic agent includes one or more of 608, 610, 611, clindamycin phosphate + benzoyl peroxide, 101BHG-D01, 1-H-11, 4P-022, 5-OXO-ETE receptor antagonists, 9MW-1911, AB-1000, AB-101a, abatacept, ABBV-712, ABCL-575, Ab-IPL-IL-17, ABM-125, abrocitinib, ABY-035/AFO2, ABY-062, AC-201, ACE-1334, acitretin, aclidinium bromide, aclidinium bromide + formoterol fumarate, acumapimod, AD-17002, adakitug, adalimumab, adapalene, adapalene + benzoyl peroxide, adapalene + clindamycin hydrochloride, adapalene + clindamycin phosphate, aderamastat, Adi, ADi-100, Adipocell, adipose tissue-derived mesenchymal stem cell-derived exosomes, adipose-derived stem cell therapy, AD-MSC-CM, ADSTEM, ADX-246, aerosolized hydroxychloroquine, afamelanotide, AJ-101, AJ-303, AK-101, AK-119, AKP-08, albuterol sulfate, ALD-R491, alefacept, Allergovac depot , allogeneic adipose-derived mesenchymal stem cell therapy, allogeneic adult pluripotent stem cells , allogeneic mesenchymal stem cell therapy, allogeneic UC-MSC therapy, allogeneic umbilical cord mesenchymal stem cell therapy , AlloRx, alprazolam, AM-1476, ambroxol hydrochloride, AMG-0101, Amilo-5MER, aminolevulinic acid, aminolevulinic acid hydrochloride, aminopterin, amlitelimab, AMTX-100, AMTX-100 CF, Anapsos, ANB-032, ANB-101, anifrolumab, anti-CD19 CAR T cell therapy , anti-CD7 CAR T-cell therapy , anti-EMAP II fully humanized antibodies, anti-IL-4/IL-13 vaccine, anti-P2X7 monoclonal antibody humanized , anti-PAR2 therapeutics, antroquinonol, APD-588, APG-222, APG-777, APG-808, APG-990, APGT-001, APIRx-1603, apremilast, aprepitant, APT-101, AQ-001S, AQ-280, AR-100DP1, AR-110, arformoterol, ARG-201, ARGX-118, ARN-4079, ARO-MUC5AC, ARO-RAGE, ARO-TSLP, ARQ-234, arsenic trioxide, ARTS-011, AS-012, asengeprast, asivatrep, ASN-008, astegolimab, AT-004, AT-005, AT-0287, AT-

193, ATB-1606, ATI-2138, ATL-105, ATR-006, ATR-01, [illegible], auranofin, AUR 101, auremolimab, autologous leukocyte cell therapy, avenciguat, AVI-3307, AVID-200, AVX-001, AWEPO-003, AX-158, AX-202, AZD-0284, AZD-0449, AZD-8630, azelaic acid, azelastine, azithromycin, B-244, Bacmune, bambuterol, baricitinib, barzolvolimab, BAT-6026, bazlitoran, BB-1511, BBACN, BBI-03, BBI-6000, BCG polysaccharide + nucleic acid , BCI-332, beclometasone dipropionate + formoterol fumarate, beclomethasone dipropionate, beclomethasone dipropionate + formoterol fumarate + glycopyrronium bromide , bedoradrine, begelomab, belimumab, belumosudil, bempikibart, bencycloquidium bromide, benralizumab, benzoyl peroxide, benzoyl peroxide + tretinoin , berdazimer sodium, bermekimab, bersiporocin dihydrochloride, bertilimumab, betamethasone, betamethasone dipropionate, betamethasone valerate, bexotegrast, BFP-002, BFP-102, BGB-23339, BI-1291583, BI-1323495, BI-765250, bilastine, bimekizumab, bimiralisib, BIO-11006 Inhalation Solution, BioLexa, BITT-CD4D11, BITT-CD4F10, BLR-200, BLU-808, BMS-986313, BMS-986322, BMS-986326, BMX-010, boningmycin, BOS-475, Bosakitug, bosentan, bovhyaluronidase azoximer, Box-5, BR-201, branebrutinib, BRE-AD01, brensocatib, brentuximab vedotin, brepocitinib, brilacidin, brilaroxazine hydrochloride, briquilimab, brodalumab, BSI-056T, BSI-502, BTX-1204, BTX-1308, BTX-1503, budesonide, budesonide + arformoterol, budesonide + formoterol, budesonide + formoterol fumarate, budesonide + procaterol hydrochloride, budesonide + salbutamol, budesonide + salmeterol, buloxibutid, BV-200 series, BVX-20, BZ-371, BZ-371B, C4X-6746, C-867, CABA-201, CAL-4, calcipotriol, calcipotriol + betamethasone , calcipotriol + betamethasone dipropionate, calcipotriol + cortisone, calcitriol, CALY-002, camoteskimab, CAN-10, cannabidiol, cannabidiol + dronabinol, cannabinoid CB2 receptor agonist antibody , carbon dioxide + perfluorooctyl bromide, cavosonstat, CB-06-01, CB2 receptor agonists, CB5138-3, CC-90006, CC-92252, CCI-15106, CCX-624, CD19-CAR-DNT, CEE-321, cendakimab, certolizumab pegol, CG-459, Chanllergen, CHF-6333, CHF-6366, CHF-6550, ciclesonide, ciclosporin, ciprofloxacin hydrochloride, CIT-013, CJRB-402, CKBA, clascoterone, CLBS-03, clindamycin, clindamycin phosphate + benzoyl peroxide, clindamycin phosphate + tretinoin, clobetasol propionate, clobetasol propionate + tretinoin, CM-101, CM-326, CMK-389, CMR-316, CMS-D001, ColiFin, COPD vaccine, cord blood derived stem cells, corticotropin, COYA-204, CPL-409116, crisaborole, CS-12192, CS-32582, CS-43001, CSJ-117, CSPCHA-115, CT-05, CT-303, CT-P55, CTX-101, CTXT-102, cudetaxestat sodium, CUR-N399, Cutaquig, CVXL-0074, CXF-11, CXG-86, CXG-87, cyproterone acetate + ethinyl estradiol, D-2570, D4-103-01, D4-103-02, D4-103-03, D4-103-04, daniluromer, dapansutrile, dapsone, daridorexant hydrochloride, daxdilimab, dazukibart, DB-007-4, DBI-001, DBM-1152A, DC-806, DC-853, deflazacort, delgocitinib, denifanstat, depemokimab, dersimelagon, desloratadine, desogestrel + ethinylestradiol, desonide, deucravacitinib, deuruxolitinib phosphate, dexamethasone sodium phosphate, dexpramipexole, difamilast, dimethyl fumarate, dimethyl fumarate + ethyl hydrogen fumarate calcium + ethyl hydrogen fumarate magnesium + ethyl hydrogen fumarate zinc, diroleuton, dithranol cream, divozilimab, DLQ-02, DLX-105, DLX-2323, DMT-210, DMT-310, DMX-700, DMXD-011, DNX-114, doxofylline, doxofylline (bronchiectasis), Alitair Pharmaceuticals, doxycycline hyclate, doxycycline hyclate (delayed release), Mayne, doxycycline hyclate (easy-to-

swallow, acne, bacterial infection), Aqua Pharmaceuticals, DFV-0210, drospirenone + ethinylestradiol, dual alpha-V/beta-1 and alpha-5/beta-1 integrin inhibitors, dual AMCase/CHIT1 inhibitors, dual anti-CD19/anti-BAFF CAR T-cell therapy, dual JAK3/TEC inhibitor, dupilumab, dust mite vaccine, DW-2008S, DYV-024, DZ-2002, EB-005, EB-06, EBI-H, eblasakimab, efzofitimod, EI-001, elapegademase, elarekibep, emedastine, empasiprubart, ENA-002, ENB-109, endonuclease modulators, ENERGI-F708, enpatoran, ensifentrine, ensifentrine + glycopyrrolate, EP-104-GI, EP-262, epeleuton, Epi-13, epinastine hydrochloride, epinephrine, EpiTight, EPM-301, EQ-101, erdosteine, erlotinib, ESK-001, etanercept, EtanerRel, ETD-001, ETH-47, etrasimod, etrinabdione, EVX-B4, EYD-001, F-200, F-528, factor D inhibitor, farudodstat, FB-102, FB-401, FB-704A, FB-825, FB-918, FCR-001, FCX-013, fevipiprant, filgotinib maleate, fipaxalparant, flunisolide, fluocinonide, fluticasone, fluticasone + formoterol, fluticasone furoate, fluticasone furoate + umeclidinium + vilanterol, fluticasone furoate + vilanterol trifenatate, fluticasone propionate, fluticasone propionate + formoterol fumarate, fluticasone propionate + salbutamol sulfate, fluticasone propionate + salmeterol, fluticasone propionate + salmeterol xinafoate, formoterol, formoterol fumarate, formoterol fumarate + fluticasone propionate, formoterol fumarate + glycopyrronium bromide, FPP-003, FPP-005, froniglutide, FRTX-02, FTC-001, FWB-1313, FZ-007, FZJ-003, GABAA receptor agonists, Gamunex, GB-001, GB-0895, GD-134, GD-iExo-001, gefurulimab, GEN-501, GL-7190, GLPG-3667, glutathione + ascorbic acid + bicarbonate, glycopyrrolate + formoterol fumarate + budesonide, glycopyrronium + formoterol fumarate + fluticasone propionate, glycopyrronium + vilanterol, glycopyrronium bromide, glycopyrronium bromide + indacaterol maleate, GMDP, GM-XANTHO, GN-037, GNKS-356, GNR-068, GPCR antagonists, GR-010, GR-1501, GR-1802, GR-2002, GR-2301, Grastek, GRC-39815, GRT-6015, GSK-1070806, GSK-2831781, GSK-3862995B, GSK-3923868, GT-20029, gumokimab, gusacitinib, guselkumab, GZ-21T, H-018, halobetasol propionate, halobetasol propionate + tazarotene, halogenated xanthene, halometasone, HB00-17, HB-0034, HB-0043, HB-1734, HBM-9001, HBM-9378, HCW-9302, HDM-3010, HECB-1800301, HEMP-001, HI-1640V, histamine human immunoglobulin, Hizentra, HJ-787, HL-231, HLA-open conformer-specific monoclonal antibody, HLK-6002, house dust mite allergen, house dust mites immunotherapy, HP-1901, Hpb glutamate dehydrogenase modulator, HPP-737, HpVac-R13, HRG-2005, HRS-9821, HS-10374, HS-401, HT-004, HuL-001, human adipose-derived mesenchymal stem cells, human umbilical cord-derived mesenchymal stem cell therapy, HY-07170702, HY-072808, HY-1770, HY-209, hypericin, hypochlorous acid, HZ-J001, IBI-3002, IBI-356, IBIO-100, IBL-101, icanbelimod, ICP-332, ICP-488, iCP-NI, ifetroban, IFNalpha kinoide, IgE inhibitors, IHL-675A, IL-17 NanoAb, IL-25 targeted therapeutic, IL-4R alpha antagonist, IL-4Ra targeted therapeutic, ILB-2107, iloprost, IMB-101, IMG-007, IMG-008, IMG-036, immune globulin intravenous, imsidolimab, IMX-120, IN-A002, inaticabtagene autoleucel, INCB-054707, indacaterol, indacaterol acetate + glycopyrronium bromide + mometasone furoate, Indamet, inebilizumab, infliximab, Integrin alpha-2/beta-1 inhibitor, Integrin alpha-5/beta-1 inhibitor, Interleukin IL-17A inhibitor, INV-007, INV-103, INV-17, IPG-1094, IPG-7236, ipratropium + fenoterol, ipratropium bromide, ipratropium bromide + salbutamol sulfate, IR-444, IRL-201104, IRX-4204, isotretinoin, itepekimab, itolizumab, ivacaftor, ivarmacitinib sulfate, ivermectin,

ixekizumab, izokibep, JadiCell therapy, JAK inhibitors, JAK 909, jaktinib dihydrochloride monohydrate, jaktinib hydrochloride, JK-0001, JK-0002, JNJ-1459, JNJ-2113, JNJ-3534, JNJ-67484703, JRF-106, JRF-401, JRP-878, JS-005, JTE-051, JTE-451, JW-1601, JW-202232, JW-2202, JYB-1904, JYP-0061, JYP-0066, K-1032, KB-5XX, KBL-693, KBL-697, KI-696, KINE-201, KITCL-27, KN-002, KP-470, KT-294, KT-474, KT-621, KX-826, KYV-101, L-608, LABA + LAMA therapy, Langopept, larsucosterol, LAS-200019, LBG-1600M, LCK inhibitor, lebrikizumab, lepzacitinib, levalbuterol, levalbuterol hydrochloride, levonorgestrel + ethinylestradiol, LG-283, LGM-1506, LGM-2605, LH-8, LIT-00505, lithium succinate, LMY-920, LNK-01001, LNK-01004, LNP-1955, LNR-653.1, londamocitinib, long acting beta agonist/long acting muscarinic agonist, long-acting aerosolized peptide-based therapy, lonodelestat acetate, lp-003, LP-0200, LQ-036, LQ-041, LQ-043, LR-19019, LR-20016, LT-002-158, lucinactant, lunsekimig, LUT-014, LW-104, LY-3509754, LY-3872386, LY-3972406, LYS-006, lysophospholipase inhibitor, LZM-012, M-119102, M3 muscarinic receptor antagonists, M-605110, M-610101, manfidokimab, masitinib, MAX-40070, maxacalcitol, maxacalcitol + betamethasone, MCM-001, MDI-1228, MDNA-413, MDPK-67b, ME-3183, Melgain, mepolizumab, mesalazine, Mesenchymal stem/stromal cell therapy , mesenchymoangioblast-derived mesenchymal stem cell therapy, metenkefalin acetate + tridecactide acetate, methotrexate, methyl aminolevulinate hydrochloride, methylprednisolone suleptanate, MG-01, MG-K10, MG-S-2525, MGY-1838, MG-ZG122, MH-004, MH-080, minocycline, minocycline + adapalene, minocycline hydrochloride, MIT-001, mitiperstat, Mitizax, MM-09, mometasone, mometasone + formoterol, mometasone furoate, mometasone furoate + indacaterol acetate, monlunabant, montelukast, montelukast sodium, montelukast sodium + levocetirizine dihydrochloride, mosedipimod, mouse monoclonal antibody against human interleukin-8 , MP-1032, MSB-01, MSB-03, MSB-3163, MSM-605, MT-5562, MTC-896, mucosa-associated lymphoid tissue lymphoma translocation protein 1 inhibitors, mufemilast, MufroSyn, mugwort pollen allergen vaccine, muscarinic M3 receptor antagonist, MYJ-1633, nacystelyn, nadifloxacin, nadolol, nalfurafine, NBL-012, NCP-111, NCP-112, ND-003, NDX-3315, NDX-3324, nedocromil, nemolizumab, netakimab, nibrozetone, niclosamide, NIK inhibitors, nitric oxide, nitroglycerin, NLP-91, NM26-2198, nomacopan, norethindrone acetate + ethinylestradiol, noscapine/noscapine analogs, NP-339, nrf2 activator, NS-402, NTR-441, NVS-451, NX-73, OATD-01, OB-756, obefazimod, OC-701, OCR-4715, Octagam 10%, olodaterol, olodaterol hydrochloride + tiotropium bromide monohydrate l, olopatadine, OLX-103, OM-001, omalizumab, omiganan pentahydrochloride, omilancor, OMN-71, ONO-4685, OP-2101, opinercept, OpSCF, ordesekimab, ORI-001, orismilast, ORKA-001, ORKA-002, orticumab, ozagrel hydrochloride, ozenoxacin, PA-9159, paridiprubart, PBF-680, PBI-100, PC-114, PDC-APB, PDE4 inhibitor, pegtarazimod, pemirolast, peresolimab, PF-07264660, PF-07275315, PG-011, PG-102, Viromed, phimelanotide, PHP-1212, PI3K-delta inhibitor, picankibart, piclidenoson, pimecrolimus, PIPE-791, pirfenidone, pitavastatin, PKC theta inhibitors, PLM-301, PNV-5032, POLB-002, ponesimod, potassium dobesilate, PR-023, pranlukast, pranlukast hydrate, PRCL-02, PrEP-001, prostaglandin D2 synthase inhibitors, Prozumab, PRP-PBMC autologous cellular therapy, PS-35, psoriasis therapeutics, PT-101, P-TET, PUL-042, PUR-0110, PUR-1800, PX-128, PX-130, PZ-07/2024,

Q-1804, Q-301, QBKPN, QLM-3003, QN-02, QP-CO1, QRX 003, quisovalimab, QX 002 N, QX 004 N, QX-005-N, QX-007-N, QX-008-N, QX-009-N, QX-010-N, QY-101, QY-201, QY-211, R-187, R-552, rademikibart, rare phytocannabinoids, ravulizumab, RAY-121, RB-1000, RBM-009, RBN-012759, RBO-0987, RC-1416, RCD-405, recombinant midismase, reformulated calcipotriol + betamethasone, REGEND-001, REGN-1908-1909, remetinostat, remibrutinib, renzapride, repirinast, repurposed aldesleukin, Repurposed azeliragon, repurposed lenabasum, reslizumab, RESP-1000 series, RESP-2000 series, RESP-X, retinoic acid, revefenacin, REX-7117, rezpegaldesleukin, RG-6151, RG-6244, RG-6314, RG-6315, RG-6341, RG-6421, RGRN-305, rilzabrutinib, riociguat, risankizumab, ritlecitinib, rituximab, RLS-1496, RLV-102, rocatinlimab, roflumilast, ropsacitinib, ROR gamma T inverse agonists, ROR-gamma inverse agonists, rose bengal sodium, RP-3128, RSBT-001, RSS-0393, R-TPR-022, rupatadine + montelukast, RUTI, ruxolitinib, RYSW-01, S1P1 agonist, salbutamol, salmeterol, salmeterol xinafoate + fluticasone propionate, SAMiRNA program, SAR-441566, SAR-443726, sarecycline, SB-010, SB-011, SCD-044, SCD-153, SCT-640A, SCT-650-C, SDC-1801, secukinumab, SEGRA, seletalisib, SEL-K2, selnoflast, seratrodast, SFA-002, SFA-004, SG-100, SGT-510, SH2 domain inhibitor program targeting STAT6, SHR-1703, SHR-1819, SHR-1905, SHR-4597, si-544, SIG-1322, SIG-1451, SIG-1456, SIM-0278, SIM-335, sitaxentan, SKI-O-703, SKL-XYZ, SLS-008, SM-17, small mobile stem cell therapy, SMET-D1, SNC-103, SNG-001, SNG-100, SNK-01, sodium chromoglycate, sodium pyruvate, sonelokimab, soquelitinib, sovleplenib, spesolimab, SPL84-23, SSGJ-621, SSS-07, ST-1830, stapokibart, STAR-0310, STAT3 inhibitor, STMC-103H, STS-01, STSA-1201, SUDO-286, SUL-238, SuperMApo, suplatast tosilate, SYHX-1901, SYX-5219, T-517, tacalcitol, tacrolimus, TAF-001, tagraxofusp, TAGX-0003, TAKC-02, tanimilast, TAP-1502, TAP-1503, tapinarof, Tavo-101, tazarotene, tazarotene + betamethasone dipropionate, tazarotene + clindamycin, TD-8236, TDM-180935, TDM-Atop01, TDM-Psor01, TDM-Scar01, telazorlimab, Tempol, temtokibart, teprotumumab, TER-101, terbutalin, terguride, tesnatilimab, TEV-48574, TEV-53275, tezepelumab, TFF-HMW-HA, Thalassophryne nattereri peptide, THB-001, theophylline, THOR-809, TI-520, TI-620, tibulizumab, tildrakizumab, timolumab, tiotropium, tiotropium bromide, tipelukast, tirbanibulin, TLL-018, TLY-012, TO-210, tofacitinib, tofacitinib + fingolimod, tofacitinib citrate, tonabacase, TOP-N44, TOP-N53, torudokimab, tosufloxacin, tozorakimab, TP-317, TQC-2731, TQC-2938, TQC-3564, TQC-3721, TQC-3927, TQH-2722, TQH-2929, TQH-3906, TQH-3910, trabikibart, tralokinumab, tranilast, transcription factor pathway inhibitor , tregalizumab, treprostinil, treprostinil diolamine, tretinoin, tretinoin + benzoyl peroxide, trifarotene, TRIV-509, TRN-157, TRPA1 antagonists, TS-0001, TT-01, TT-01688, tulinercept, tulobuterol, TVB-3567, UA-021, UB-221, UCB-1381, UCB-9741, ucenprubart, UHE-101, UHE-105, UI-009, UI-010, UI-031, UI-033, UI-034, ulobetasol, umbilical cord blood-derived stem cell therapy , UMC119-06, umeclidinium bromide, umeclidinium bromide + vilanterol trifenatate, upadacitinib, USP-4 inhibitors, ustekinumab, UTAA-09, VALERGEN-DS, vamorolone, vapendavir, vardenafil, VB-1953, VC-005, VDAA, VDAD, VDJ-006, VEGFR targeted DK4/10 , venanprubart, VENT-03, verekitug, vilanterol + fluticasone furoate + glycopyrronium bromide, vipoglanstat hydrogensulfate, VISTA agonist, vixarelimab, VLRX-001, VM-AD, VNLG-152, vonifimod, voriconazole, votucalis, VRN-04, VS-105,

VSG-158, VSTM-1 agonist, VT-014, VTH-212, vunakizumab, [illegible], WM-1R3, WNT inhibitor, WNT pathway agonist antibodies, wnt pathway stimulator, WXFL-10203614, WXSH-0150, XCUR-17, XKH-001, XmAb-564, XT-0528, XZ.700, YH-25487, YH-35324, YKRH-00020, YR-001, Yso3, zabedosertib, zafirlukast, zasocitinib, ZB-168, Zemaira, ZeP-3, zetomipzomib, zevaquenabant, ZHB-107-108, zibotentan, zileuton, zirconium zr 89 crefmirlimab berdoxam, ZL-1102, ZPL-521, and/or bi-specific antibodies targeting one or more targets referenced herein.

In some embodiments a compound of the disclosure provided herein, or pharmaceutically acceptable salt or stereoisomer thereof, is administered with one or more therapeutic agents selected from a PPARd inhibitor, IRAK4 inhibitor, TPL2 inhibitor, α4β7 inhibitor, BTLA agonist, PD1 agonist, or an FXR agonist.

In some embodiments a compound of the disclosure provided herein, or pharmaceutically acceptable salt or stereoisomer thereof, is administered with one or more therapeutic agents selected from seladelpar, edecesertib, tilpisertib fosmecarbil, GS-1427, GS-0272, GS-0151, or cilofexor.

The benefit of combination may be increased efficacy and/or reduced side effects for a component as the dose of that component may be adjusted down to reduce its side effects while benefiting from its efficacy augmented by the efficacy of the compound of the present disclosure.

In some embodiments, the additional therapeutic agent includes an agent useful for modulating, treating, or preventing inflammation, such as a 4-1BB ligand, 5-Alpha-reductase inhibitor, 5-HT 1a receptor antagonist, 5-HT 1a receptor partial agonist, 5-HT 2a receptor antagonist, 5-HT 2a receptor partial agonist, 5-HT 2b receptor antagonist, 5-HT 3 receptor antagonist, 5-HT 4 receptor agonist, 5-HT 6 receptor antagonist, 5-HT 7 receptor antagonist, 5-Lipoxygenase activating protein inhibitor, 5-Lipoxygenase inhibitor, Accessory gene regulator A inhibitor, Acetaldehyde dehydrogenase modulator, Acetylcholine receptor agonist, Acetylcholine receptor antagonist, Acetylcholinesterase inhibitor, Acidic mammalian chitinase inhibitor, ACTH receptor agonist, Activity-dependent neuroprotector modulator, ADAM-33 inhibitor, ADAM-9 inhibitor, Adenosine A1 receptor antagonist, Adenosine A1 receptor modulator, Adenosine A2b receptor antagonist, Adenosine A3 receptor agonist, Adenosine A3 receptor antagonist, Adenosine deaminase stimulator, Adenosylhomocysteinase inhibitor, Adenylate cyclase stimulator, Adrenergic receptor agonist, Adrenocorticotrophic hormone ligand, Advanced glycosylation product receptor antagonist, AGER gene inhibitor, AIMP multisynthetase complex protein 1 inhibitor, Albumin antagonist, Alcohol dehydrogenase 5 inhibitor, Aldose reductase inhibitor, Alk-5 protein kinase inhibitor, Alpha 1 antitrypsin modulator, Alpha 1 antitrypsin stimulator, Alpha 1 proteinase inhibitor, Alpha 2 adrenoceptor agonist, Amiloride sensitive sodium channel inhibitor, AMP activated protein kinase alpha 2 stimulator, AMP activated protein kinase stimulator, Amyloid protein deposition inhibitor, Androgen receptor antagonist, Angiotensin II AT-1 receptor antagonist, Angiotensin II AT-2 receptor agonist, Anoctamin 1 stimulator, Aortic smooth muscle actin inhibitor, AP1 transcription factor modulator, Apelin receptor agonist, Apolipoprotein A antagonist, Apolipoprotein A5 stimulator, Apolipoprotein B modulator, Apolipoprotein E modulator, Apoptosis regulator Bcl X inhibitor,

Apoptosis regulator Bcl w inhibitor, APRIL receptor modulator, Aryl hydrocarbon receptor agonist, Aryl hydrocarbon receptor modulator, B and T lymphocyte attenuator stimulator, B-lymphocyte antigen CD19 inhibitor, B-lymphocyte antigen CD19 modulator, B-lymphocyte antigen CD20 inhibitor, B-lymphocyte stimulator ligand inhibitor, B-lymphocyte stimulator ligand modulator, Bcl-2 protein inhibitor, Beta 1 adrenoceptor antagonist, Beta 2 adrenoceptor agonist, Beta 2 adrenoceptor antagonist, Beta 2 adrenoceptor modulator, Beta adrenoceptor agonist, Beta amyloid antagonist, Beta-catenin inhibitor, Beta-catenin modulator, Bifunctional aminoacyl tRNA synthetase inhibitor, BMP10 gene inhibitor, BMP15 gene inhibitor, Bone marrow proteoglycan modulator, Botulinum toxin A stimulator, Bromodomain containing protein 1 inhibitor, Bromodomain containing protein inhibitor, Btk tyrosine kinase inhibitor, C-myc binding protein inhibitor, C-type lectin domain protein 4C inhibitor, Ca2+ release activated Ca2+ channel 1 inhibitor, Calcineurin inhibitor, Calcium channel inhibitor, Cannabinoid CB1 receptor antagonist, Cannabinoid CB1 receptor inverse agonist, Cannabinoid CB2 receptor agonist, Cannabinoid CB2 receptor modulator, Cannabinoid receptor agonist, Cannabinoid receptor antagonist, Cannabinoid receptor modulator, Catalase stimulator, CCL26 gene inhibitor, CCR3 chemokine modulator, CCR5 chemokine antagonist, CCR6 chemokine antagonist, CCR8 chemokine antagonist, CD11b antagonist, CD122 agonist, CD122 modulator, CD19 modulator, CD2 antagonist, CD223 modulator, CD3 modulator, CD30 modulator, CD4 antagonist, CD40 ligand receptor antagonist, CD47 antagonist, CDw123 modulator, Cell adhesion molecule inhibitor, Cell surface glycoprotein CD200R agonist, Cell surface glycoprotein MUC18 inhibitor, CFTR modulator, CFTR stimulator, Chaperonin stimulator, Chemokine receptor antagonist, Chitinase inhibitor, Collagen I agonist, Collagen I antagonist, Collagen modulator, Collagen VII antagonist, Complement C1q subcomponent inhibitor, Complement C1s subcomponent inhibitor, Complement C5 factor inhibitor, Complement factor C2 inhibitor, Complement factor D inhibitor, COVID19 spike glycoprotein modulator, CSF-1 antagonist, CXC10 chemokine ligand inhibitor, CXCR2 chemokine antagonist, cyclic GMP AMP synthase inhibitor, Cyclooxygenase inhibitor, Cytokine receptor agonist, Cytokine receptor antagonist, Cytokine receptor common beta chain inhibitor, Cytoplasmic protein NCK inhibitor, Cytosolic phospholipase A2 inhibitor, Cytotoxic T-lymphocyte protein-4 stimulator, Deoxyribonuclease gamma stimulator, DHFR inhibitor, Diacylglycerol O acyltransferase 1 inhibitor, Dihydroorotate dehydrogenase inhibitor, Dipeptidyl peptidase I inhibitor, Dipeptidyl peptidase IV inhibitor, DNA gyrase inhibitor, DNA methyltransferase inhibitor, Dopamine D2 receptor partial agonist, Dopamine D3 receptor agonist, Dopamine D3 receptor partial agonist, Dopamine D4 receptor partial agonist, DYRK-1 alpha protein kinase inhibitor, Ectonucleotide pyrophosphatase-PDE-2 inhibitor, EGF like module receptor 1 antagonist, EGFR family tyrosine kinase receptor inhibitor, Elastase inhibitor, Endonuclease modulator, Endostatin modulator, Endothelin ET-A receptor antagonist, Endothelin ET-B receptor antagonist, Enolase 1 inhibitor, Eosinophil peroxidase inhibitor, Eotaxin 2 ligand inhibitor, Eotaxin ligand inhibitor, EP4 prostanoid receptor antagonist, Epidermal growth factor receptor antagonist, Epidermal growth factor receptor modulator, Estradiol agonist, Estrogen receptor agonist, Extracellular signal related kinase-2 inhibitor, Facilitated glucose transporter-1 modulator, Fatty acid synthase inhibitor, FGF receptor antagonist, FGF-

2 ligand, FGF-4 ligand, FGF3 receptor antagonist, Filaggrin stimulator, FLT3 tyrosine kinase inhibitor, FMLP related receptor I agonist, FMLP related receptor II agonist, Free fatty acid receptor 2 agonist, Free fatty acid receptor 3 agonist, Fyn tyrosine kinase inhibitor, FXR agonist, G-protein coupled bile acid receptor 1 agonist, G-protein coupled receptor-44 antagonist, G-protein coupled receptor-44 modulator, GABA A receptor agonist, GABA A receptor alpha-2 subunit modulator, GABA A receptor alpha-3 subunit modulator, GABA A receptor alpha-5 subunit modulator, Galectin-10 modulator, GATA 3 transcription factor inhibitor, Glucagon-like peptide 1 receptor agonist, Glucocorticoid receptor agonist, Glutamate dehydrogenase modulator, Glutamate receptor modulator, Glutathione dependent PGD synthase inhibitor, Glutathione independent PGD synthase inhibitor, Glutathione reductase inhibitor, GroEL protein 2 inhibitor, Guanylate cyclase stimulator, H+ K+ ATPase inhibitor, Heat shock protein inhibitor, Heme oxygenase 1 modulator, Heparin agonist, High mobility group protein B1 inhibitor, Histamine H1 receptor antagonist, Histamine H4 receptor antagonist, Histamine receptor antagonist, Histone deacetylase-1 inhibitor, Histone deacetylase-2 inhibitor, Histone deacetylase-2 stimulator, Histone deacetylase-3 inhibitor, Histone deacetylase-6 inhibitor, Histone H2A modulator, Histone H4 modulator, HMG CoA reductase inhibitor, Hsp 90 inhibitor, Hsp70 binding protein 1 inhibitor, Hyaluronidase stimulator, Hypoxia inducible factor stimulator, I-kappa B kinase beta inhibitor, I-kappa B kinase epsilon inhibitor, IgG receptor FcRn large subunit p51 modulator, IL-1 receptor accessory protein inhibitor, IL-1 receptor antagonist, IL-10 receptor agonist, IL-10 receptor antagonist, IL-12 receptor antagonist, IL-13 receptor antagonist, IL-13 receptor modulator, IL-15 receptor antagonist, IL-17 antagonist, IL-18 antagonist, IL-2 receptor alpha subunit stimulator, IL-2 receptor antagonist, IL-2 receptor modulator, IL-22 antagonist, IL-23 antagonist, IL-3 receptor modulator, IL-4 receptor antagonist, IL-4 receptor modulator, IL-5 receptor antagonist, IL-6 receptor antagonist, IL-7 receptor antagonist, IL-8 receptor antagonist, IL17RA gene inhibitor, IL2 gene stimulator, Immunoglobulin E antagonist, Immunoglobulin E modulator, Immunoglobulin G agonist, Immunoglobulin G1 modulator, Immunoglobulin agonist, Immunoglobulin kappa modulator, Immunoglobulin modulator, Inducible nitric oxide synthase inhibitor, Insulin receptor substrate-1 inhibitor, Insulin-like growth factor 1 receptor antagonist, Integrin alpha-2/beta-1 antagonist, Integrin alpha-4/beta-1 antagonist, Integrin alpha-4/beta-7 antagonist, Integrin alpha-5/beta-1 antagonist, Integrin alpha-5/beta-3 modulator, Integrin alpha-V/beta-1 antagonist, Integrin beta 1 binding protein modulator, Interferon alpha 14 ligand, Interferon alpha ligand inhibitor, Interferon beta ligand, Interferon beta ligand inhibitor, Interferon gamma ligand inhibitor, Interferon gamma receptor antagonist, Interferon type I receptor antagonist, Interleukin 1 delta ligand inhibitor, Interleukin 1 like receptor (IL33R) antagonist, Interleukin 1 like receptor 1 modulator, Interleukin 1 like receptor 2 inhibitor, Interleukin 13 ligand inhibitor, Interleukin 13 receptor alpha 1 antagonist, Interleukin 15 ligand inhibitor, Interleukin 17 ligand inhibitor, Interleukin 17A ligand inhibitor, Interleukin 17A ligand modulator, Interleukin 17E ligand inhibitor, Interleukin 17E ligand modulator, Interleukin 17F ligand inhibitor, Interleukin 17F ligand modulator, Interleukin 18 ligand inhibitor, Interleukin 23A inhibitor, Interleukin 31 ligand inhibitor, Interleukin 31 ligand modulator, Interleukin 33 ligand inhibitor, Interleukin 33 ligand modulator, Interleukin receptor 17A antagonist,

Interleukin receptor 17B antagonist, Interleukin-1 alpha ligand inhibitor, Interleukin-1 beta ligand modulator, Interleukin-1 ligand inhibitor, Interleukin-2 ligand, Interleukin-2 ligand inhibitor, Interleukin-31 receptor modulator, Interleukin-4 ligand inhibitor, Interleukin-5 ligand inhibitor, Interleukin-6 ligand inhibitor, Interleukin-8 ligand inhibitor, Interleukin-9 ligand inhibitor, IRAK-4 protein kinase inhibitor, IRAK-4 protein kinase degrader, Itk tyrosine kinase inhibitor, JAK tyrosine kinase inhibitor, Jak1 tyrosine kinase inhibitor, Jak2 tyrosine kinase inhibitor, Jak3 tyrosine kinase inhibitor, Jun N terminal kinase inhibitor, Kallikrein 2 inhibitor, Kallikrein 5 modulator, Kallikrein 7 inhibitor, Kallikrein 7 modulator, Kallikrein inhibitor, KCNA voltage-gated potassium channel-3 inhibitor, Kelch like ECH associated protein 1 inhibitor, Kelch like ECH associated protein 1 modulator, Kit tyrosine kinase inhibitor, LanC like protein 2 stimulator, Lanosterol-14 demethylase inhibitor, Lck tyrosine kinase inhibitor, Lectin mannose binding protein inhibitor, Leukocyte Ig like receptor A4 modulator, Leukocyte elastase inhibitor, Leukotriene A4 hydrolase inhibitor, Leukotriene BLT receptor antagonist, Leukotriene C4 antagonist, Leukotriene C4 synthase inhibitor, Leukotriene D4 agonist, Leukotriene D4 antagonist, Leukotriene E4 antagonist, Leukotriene receptor antagonist, Liver X receptor agonist, LOXL2 gene inhibitor, Lung surfactant associated protein D stimulator, Lyn tyrosine kinase inhibitor, Lysophosphatidate-1 receptor antagonist, Lysophospholipase inhibitor, Macrophage migration inhibitory factor inhibitor, Major allergen I polypeptide chain 2 inhibitor, Major allergen inhibitor, MALT protein 1 inhibitor, Mannan-binding lectin serine protease inhibitor, MAP kinase modulator, MAPKAPK2 inhibitor, MARCKS protein inhibitor, Mas-related G-protein receptor X2 antagonist, Mas-related G-protein receptor X2 inhibitor, MEK protein kinase inhibitor, MEK-1 protein kinase inhibitor, Melanocortin MC1 receptor agonist, Melanocortin MC5 receptor antagonist, Melanocortin receptor agonist, Melanocyte stimulating hormone ligand, Membrane copper amine oxidase inhibitor, Metalloprotease-12 inhibitor, MEX3B gene inhibitor, Mineralocorticoid receptor antagonist, MIP 3 alpha ligand inhibitor, Mite allergen modulator, Mitochondrial 10 kDa heat shock protein stimulator, MKL myocardin like protein inhibitor, MMP1 gene stimulator, MNK protein kinase inhibitor, Monocyte chemotactic protein 1 ligand inhibitor, MS4A2 gene modulator, mTOR complex 1 inhibitor, mTOR complex 2 inhibitor, MUC5AC gene inhibitor, Muscarinic M1 receptor antagonist, Muscarinic M2 receptor antagonist, Muscarinic M3 receptor antagonist, Muscarinic M4 receptor antagonist, Muscarinic M5 receptor antagonist, Muscarinic receptor agonist, Muscarinic receptor antagonist, Muscarinic receptor modulator, Myeloperoxidase inhibitor, Myosin heavy chain inhibitor, NACHT LRR PYD domain protein 3 inhibitor, NEDD4 family interacting protein 1 stimulator, Neuropilin 2 modulator, Neutral endopeptidase inhibitor, NFE2L2 gene stimulator, Nicotinic ACh receptor alpha 7 subunit stimulator, Nicotinic acetylcholine receptor agonist, NK1 receptor antagonist, NKG2 D activating NK receptor antagonist, NLR family member X1 stimulator, Non receptor tyrosine kinase TYK2 antagonist, Nuclear erythroid 2-related factor 1 stimulator, Nuclear erythroid 2-related factor 2 stimulator, Nuclear erythroid 2-related factor inhibitor, Nuclear factor kappa B gene inhibitor, Nuclear factor kappa B inducing kinase inhibitor, Nuclear factor kappa B inhibitor, Nuclear factor kappa B modulator, Oncostatin M receptor subunit beta inhibitor, Opioid growth factor receptor agonist, Opioid receptor

delta antagonist, Opioid receptor kappa agonist, Orexin 1 receptor antagonist, Orexin 2 receptor antagonist, Orphan nuclear receptor antagonist, Outer membrane protein modulator, OX-40 receptor agonist, OX-40 receptor antagonist, OX40 ligand inhibitor, OX40 ligand modulator, Oxoeicosanoid receptor 1 antagonist, P-Glycoprotein inhibitor, P-selectin glycoprotein ligand-1 inhibitor, P2X2 purinoceptor antagonist, P2X3 purinoceptor antagonist, P2X7 purinoceptor modulator, P2Y6 purinoceptor modulator, p38 MAP kinase inhibitor, p53 tumor suppressor protein stimulator, PcrV protein type III inhibitor, PDE 3 inhibitor, PDE 4 inhibitor, PDE 4b inhibitor, PDE 4d inhibitor, PDE 5 inhibitor, PDGF receptor antagonist, Peptidase 1 inhibitor, PGD2 antagonist, PGI2 agonist, Phosphatidylinositol 4 kinase beta inhibitor, Phosphoinositide 3-kinase inhibitor, Phosphoinositide-3 kinase delta inhibitor, Phospholipase A2 inhibitor, Phospholipase C inhibitor, PIM-1 protein kinase inhibitor, PIM-2 protein kinase inhibitor, PIM-3 protein kinase inhibitor, Placenta growth factor ligand inhibitor, Plasminogen activator inhibitor 1 inhibitor, Platelet activating factor receptor antagonist, Poly ADP ribose polymerase 14 inhibitor, PPAR gamma agonist, PPAR gene modulator, Progesterone receptor agonist, Programmed cell death ligand 1 modulator, Programmed cell death protein 1 modulator, Programmed cell death protein 1 stimulator, Prostaglandin E synthase inhibitor, Prostaglandin E synthase-1 inhibitor, Protease inhibitor, Protease-activated receptor-2 antagonist, Proteasome beta-8 subunit modulator, Proteasome inhibitor, Protein kinase C theta inhibitor, Protein kinase inhibitor, Protein NOV homolog modulator, Protein tyrosine kinase inhibitor, Protoporphyrinogen oxidase modulator, Pyruvate kinase muscle isozyme stimulator, Raf B protein kinase inhibitor, Ras gene inhibitor, Reactive oxygen species modulator inhibitor, Ret tyrosine kinase receptor inhibitor, Retinoic acid receptor agonist, Retinoic acid receptor antagonist, Retinoic acid receptor gamma agonist, Retinoic acid receptor gamma antagonist, Retinoic acid receptor gamma inverse agonist, Retinoic acid receptor modulator, Retinoid receptor agonist, Retinoid X receptor agonist, Retinoid X receptor modulator, Retinoid Z receptor gamma antagonist, Retinoid Z receptor gamma inverse agonist, Rev protein modulator, Rho associated protein kinase 1 inhibitor, Rho associated protein kinase 2 inhibitor, Ribonuclease P inhibitor, Ribonuclease stimulator, RIP-1 kinase inhibitor, S100 calcium binding protein A4 inhibitor, S100A8 gene inhibitor, S100A9 gene inhibitor, SARS coronavirus 3C protease like inhibitor, Secretory phospholipase A2 receptor antagonist, Serine protease inhibitor, Serine threonine protein kinase TBK1 inhibitor, Serum amyloid A protein modulator, SH2 domain containing protein inhibitor, Sialic acid-binding Ig-like lectin 8 inhibitor, SIRT3 gene stimulator, SMAD inhibitor, SNAI1 transcription factor inhibitor, SOD3 gene stimulator, Sodium channel inhibitor, Sphingosine 1 phosphate phosphatase 1 stimulator, Sphingosine-1-phosphate receptor-1 agonist, Sphingosine-1-phosphate receptor-1 antagonist, Sphingosine-1-phosphate receptor-1 modulator, Sphingosine-1-phosphate receptor-3 modulator, Sphingosine-1-phosphate receptor-4 antagonist, Sphingosine-1-phosphate receptor-4 modulator, Sphingosine-1-phosphate receptor-5 modulator, Sphingosylphosphorylcholine receptor antagonist, Src tyrosine kinase inhibitor, STAT inhibitor, STAT-1 modulator, STAT-3 inhibitor, STAT-5 inhibitor, STAT-6 inhibitor, STAT-6 degrader, Stearoyl CoA desaturase-1 inhibitor, Stress induced secreted protein 1 stimulator, Superoxide dismutase modulator, Superoxide dismutase

stimulator, Syk tyrosine kinase inhibitor, Synuclein alpha inhibitor, T cell receptor antagonist, T cell receptor modulator, T cell surface glycoprotein CD28 inhibitor, T-cell antigen CD7 modulator, T-cell differentiation antigen CD6 inhibitor, T-cell surface glycoprotein CD8 inhibitor, T-cell transcription factor NFAT modulator, Tau aggregation inhibitor, Tau deposition inhibitor, Tec tyrosine kinase inhibitor, TGF beta 1 ligand inhibitor, TGF beta 3 ligand inhibitor, TGF beta 3 ligand modulator, TGF beta ligand inhibitor, TGF beta receptor agonist, TGF beta receptor antagonist, TGF-beta activated kinase-1 inhibitor, TGF-beta type II receptor antagonist, TGF-beta type II receptor modulator, TGF-beta type III receptor antagonist, Thromboxane A2 antagonist, Thromboxane synthetase inhibitor, Thymic stromal lymphopoietin ligand, Thymic stromal lymphopoietin ligand inhibitor, Thymic stromal lymphopoietin ligand modulator, Thymic stromal lymphopoietin receptor antagonist, Thymic stromal lymphopoietin receptor modulator, TLR agonist, TLR modulator, TLR-2 agonist, TLR-2 antagonist, TLR-4 antagonist, TLR-6 agonist, TLR-7 antagonist, TLR-8 antagonist, TLR-9 agonist, TLR-9 antagonist, TNF agonist, TNF alpha ligand inhibitor, TNF alpha ligand modulator, TNF antagonist, TNF binding agent, TNF related apoptosis inducing ligand, TNF-like receptor-2 modulator, Tumor necrosis factor 15 ligand inhibitor, Topoisomerase IV inhibitor, TRAIL receptor agonist, Transcription factor inhibitor, Transcription factor modulator, Transthyretin modulator, Trk tyrosine kinase receptor inhibitor, TRP cation channel A1 inhibitor, TRP cation channel A1 modulator, TRP cation channel C1 inhibitor, TRP cation channel V1 antagonist, TRP cation channel V1 modulator, TRP cation channel V2 modulator, Tsl protein kinase inhibitor, Tubulin binding agent, Tubulin receptor antagonist, Tumor necrosis factor 13B receptor modulator, Tumor necrosis factor 13C receptor modulator, Tumor necrosis factor 14 ligand inhibitor, Tumor necrosis factor 15 ligand modulator, Tumor necrosis factor ligand inhibitor, Txk tyrosine kinase inhibitor, Tyk2 tyrosine kinase inhibitor, Tyk2 tyrosine kinase modulator, Type I IL-1 receptor antagonist, Type I TNF receptor antagonist, Type II TNF receptor modulator, Tyrosine phosphatase substrate 1 inhibitor, Ubiquitin inhibitor, Ubiquitin ligase modulator, Ubiquitin ligase stimulator, Ubiquitin thioesterase-4 inhibitor, Unspecified GPCR antagonist, Unspecified GPCR modulator, Unspecified ion channel inhibitor, Uteroglobin stimulator, V-set transmembrane domain protein 1 stimulator, Vascular cell adhesion protein 1 antagonist, VEGF ligand inhibitor, VEGF receptor modulator, VEGF-2 receptor modulator, Vimentin inhibitor, Vitamin D3 receptor agonist, Wnt 5A ligand inhibitor, Wnt ligand modulator or YSK-4 protein kinase inhibitor.

Kits

Provided herein are also kits that include a compound described herein, or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof, and suitable packaging. In one embodiment, a kit further includes instructions for use. In one aspect, a kit includes a compound of Formula I (or any other Formula described herein), or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, and intravenous bag.

EXAMPLES

Experimental procedures

Reactions were performed at room temperature unless stated otherwise. When a compound whose synthesis is described herein was used at a larger scale than its reported synthesis, it is to be implicitly understood that more material had been prepared similarly.

Microwave reactions were performed in dedicated MW instruments in closed vials.

^{1}H NMR spectra were recorded at 250-600 MHz in d_6-DMSO unless stated otherwise.

Reactions performed above the boiling point of the solvent took place in sealed tubes or screw-cap vials.

"Dried" refers to drying an organic solution over Na_2SO_4, $MgSO_4$, or $CaCl_2$ and filtering off the drying agent.

"Degassed" refers to air-sensitive reactions being flushed with inert atmosphere via evacuation and back-filling or by bubbling inert atmosphere through the mixture for several minutes.

NaH was used as a 60% oil dispersion.

"Filtration" of mixtures refers to the removal/isolation of solid material from mixture by filtration through a paper filter, PFTE septum, or through a pad of celite. Additional solvent was used to wash the solid.

"Purification by SCX" refers to the loading of the material onto a SCX column, washing with MeOH, eluting with NH_3 in MeOH, and concentrating the fractions containing the product.

"Partitioned (A/B)" refers to the partitioning of a mixture between solvents A and B. OL (A/B) refers to the organic layer after partitioning the mixture between solvents A and B. AL (A/B) refers to the aq. layer after partitioning the mixture between solvents A and B.

Crude reaction mixtures after reductions with iron/zinc power and AcOH/NH_4Cl were typically filtered through celite before work-up of the filtrate.

Catalytic hydrogenations were performed using a catalyst such as 10% Pd/C and a H_2 balloon unless stated otherwise. The mixture after the reaction was typically filtered through celite to remove the catalyst.

Intermediates were obtained sufficiently pure for the next step from the procedures outlined in the specification.

Some of the final compounds (Examples) were obtained in pure form and the yield provided accordingly while others were obtained as DMSO solutions for which the concentration and volume are specified.

HPLC Methods

Several Intermediates and final compounds (Examples) were purified using the HPLC methods listed below.

Column	Eluent	Flow rate
XBridge Prep C18 OBD, 150x19 mm 5 µm	A: 50 mM aq. NH_4HCO_2, B: ACN, 10-100% ACN	30 mL/min
XTerra® RP-18 OBD, 150x19 mm 5 µm	A: 0.1% aq. NH_4HCO_2, B: ACN, 10-100% ACN	30 mL/min
PRINCETONE ULTIMA C18 250x20 mm, 5 µm	A: 0.05% aq. HCO_2H, B: ACN 0 min 20% B, 1 min 20% B, 10 min 70% B, 10.1 min 99% B, 12 min 99% B, 12.1 min, 20% B, 15 min 20% B 12.1/20,15/20	16 mL/min
PRINCETONE ULTIMA C18 250x20 mm, 5 µm	A: 0.1% aq. HCO_2H, B: ACN 0 min 20% B, 2 min 20% B, 10 min 50% B	16 mL/min
LUNA OMEGA C18 250x21.2 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 40% B, 1 min 40% B, 10 min 85% B, 10.1 min 99% B, 12 min 99% B, 12.1 min 40% B, 15min 40% B	18 mL/min
COGENT C18 250x21.2 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 30% B, 2 min 30% B, 10 min 50% B	16 mL/min
COGENT C18 250x21.2 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 30% B, 1 min 30% B, 10 min 80% B, 10.1 min 99% B, 12 min 99% B, 12.1 min 30% B, 15 min 30% B	20 mL/min
LUNA C18 150x21.2 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 40% B, 1 min 40% B, 10 min 80% B, 10.1 min 99% B, 12 min 99% B, 12.1 min 40% B, 15 min 40% B	18 mL/min
X-SELECT PHENYL HEXYL 250x19 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 30% B, 1 min 30% B, 10 min 55% B	16 mL/min
X-SELECT PHENYL HEXYL 250x19 mm, 5 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 55% B, 1 min 55% B, 10 min 70% B, 15 min 90% B, 15.1 min 100% B, 19 min 100% B, 19.1 min 55% B	18 mL/min
AZZOTA 250x20mm, 10 µm	A: 10 mM aq. NH_4HCO_2, B: ACN 0 min 40% B, 1 min 40% B, 10 min 85% B, 10.1 min 99% B, 12 min 99% B, 12.1 min 40% B, 15 min 40% B	18 mL/min

AZZOTA 250x20 mm, 5 µm	A: 10 mM aq. ABC, B: ACN 0 min 30% B 1 min 30% B, 10 min 85% B	17 mL/min
PRINCETONE ULTIMA C18 250x20 mm, 10 µm	A: 0.1% aq. HCO_2H, B: ACN 0 min 10% B, 1 min 10% B, 10 min 90% B, 10.1 min 99% B, 13 min 99% B, 13.1 min 10% B, 16 min 10% B	17 mL/min
XSELECT CSH C18 250x19 mm 5 µm	A: 0.1% aq. HCO_2H, B: ACN 0 min 10% B, 1 min 10% B, 10 min 90% B, 10.1 min 99% B, 13 min 99% B, 13.1 min 10 % B, 16 min 10% B	17 mL/min
YMC-PACK-ODS-AQ C18 250x20 mm 5 µm	A: 0.1% aq. HCO_2H, B: ACN 0 min 25% B, 2 min 25% B, 10 min 35% B	15 mL/min
HICHROME C18 250x20 mm 5 µm	A: 10 mM aq. ABC, B: ACN 0 min 40% B, 2 min 40% B, 10 min 80% B	18 mL/min
X SELECTC18 250x19 mm 5 µm	A: 10 mM aq. ABC, B: ACN 0 min 40% B, 1 min 40% B, 10 min 80% B, 11 min 80% B, 11.1 min 99% B, 15 min 99% B, 15.1 min 40% B, 19 min 40% B	16 mL/min

LC/MS Methods

The compounds of the disclosure (Examples) were characterized by the LC/MS methods listed below.

Method	**Column and eluent**	**Gradient**	**Flow rate**
1	Agilent Poroshell 120 SB-C18 4.6x30 mm 2.7 µm operated at 60 °C A: 0.1% aq. HCO_2H B: 0.1% HCO_2H in ACN	0 min 1% B, 1.5 min 100% B, 1.73 min 100% B	3 mL/min
2	Acquity BEH C18 50x2.1 mm 1.7 µm operated at 35 °C A: 0.05% aq. HCO_2H B: 0.05% HCO_2H in ACN	0 min 3% B, 0.4 min 3% B, 2.5 min 98% B, 3.5 min 98%, 3.6 min 3% B, 4 min 3% B	0.6 mL/min
3	Acquity BEH C18 50x2.1 mm 1.7 µm operated at 35 °C A: 0.05% aq. HCO_2H B: 0.05% HCO_2H in ACN	0 min 3% B, 2.5 min 3% B, 7.5 min 98% B, 9.6 min 3% B, 10 min 3% B	0.6 mL/min

4	Acquity BEH C18 100x2.1 mm 1.7 µm operated at 50 °C A: 0.05% aq. HCO_2H B: 0.05% HCO_2H in ACN	0 min 3% B, 8.5 min 100% B, 9 min 100% B, 9.5 min 3% B, 10 min 3% B	0.55 mL/min
5	Acquity BEH C18 50x2.1 mm 1.7 µm operated at 35 °C A: 0.05% aq. TFA B: 0.05% TFA in ACN	0 min 3% B, 0.4 min 3% B, 2.5 min 98% B, 3.5 min 98% B, 3.6 min 3% B, 4 min 3% B	0.6 mL/min
6	Acquity BEH C18 50x2.1 mm 1.7 µm operated at 35 °C A: 0.05% aq. TFA B: 0.05% TFA in ACN	0 min 3% B, 2.5 min 3% B, 7.5 min 98% B, 9.5 min 98% B, 9.6 min 3% B, 10 min 3% B	0.6 mL/min
7	Acquity BEH C18 100x2.1 mm 1.7 µm operated at 50 °C A: 0.05% aq. TFA B: 0.05% TFA in ACN	0 min 3% B, 16 min 100% B, 18 min 100% B, 18.5 min 3% B, 20 min 3% B	0.45 mL/min
8	Xbridge C18 75x4.6 mm 3.5 µm operated at 35 °C A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B, 1 min 15% B, 4 min 98% B, 7 min 98% B, 7.5 min 5% B, 8 min 5% B	1.3 mL/min
9	X Bridge C18 150x4.6 mm 3.5µm operated at 35 °C A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 1 min 5% B, 3 min 15% B, 7 min 55% B, 11 min 98% B, 16 min 98% B, 16.1 min 5% B, 20 min 5% B	1.0 mL/min
10	X SELECT C18 150x4.6 mm 3.5µm operated at RT A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 1 min 5% B, 3 min 15% B, 7 min 55% B, 11 min 98% B, 16 min 98% B, 16.1 min 5% B, 20 min 5% B	1.0 mL/min
11	Acquity UPLC HSS T3 50x2.1 mm 1.8 µm operated at 30 °C	0 min 1% B, 0.5 min 6% B, 1 min 6% B, 2.6 min 95% B, 3.8	0.7 mL/min

	A: 10 mM aq. NH_4OAc + 0.1% HCO_2H B: 0.1% HCO_2H in ACN	min 95% B, 9.81 min 1% B, 4.8 min 1% B	
12	Acquity UPLC HSS T3 50x2.1 mm 1.8 µm operated at 60 °C A: 10 mM aq. NH_4OAc + 0.1% HCO_2H B: 0.1% HCO_2H in ACN	0 min 5% B, 0.9 min 95% B, 1.2 min 95% B, 1.4 min 5% B	1.2-1.3 mL/min
13	X Brigde BEH C18 (3x100) mm, 2.5µm operated at 35 °C A: 0.05 % TFA in ACN B: 0.05% aq. TFA	0 min 5% A, 5 min 98% A, 9 min 98% A, 9.01 min 5% A, 12 min 5% A	1 mL/min
14	ACQUITY UPLC BEH C18 (2.1x100) mm, 1.7µm operated at 60 °C A: 0.05 % TFA in ACN B: 0.05 % aq. TFA	0 min 10% A, 2.5 min 10% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 10% A, 10 min 10% A	0.4mL/min
15	YMC-Triart C18 ExRS (75x4.6mm, 3µm) operated at 45 °C A: 10mM aq. NH_4HCO_3 B: 100% ACN	0 min 5% B, 0.8 min 5% B, 2 min 25% B, 5 min 90% B, 7 min 95% B, 8.5 min 95% B, 8.6 min 5% B, 10 min 5% B	1.0mL/min
16	X-BRIDGE C8 (4.6X75mm) 3.5µm operated at 50 °C A: 0.05% aq. HCO_2H B: 0.05% HCO_2H in ACN	0 min 5% B, 3 min 98% B, 5 min 98% B, 5.5 min 5% B, 6 min 5% B	1.0mL/min
17	Xbridge C18 (75x4.6mm, 3 µm) operated at 50 °C A: 10mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B, 1 min 15% B, 4 min 98% B, 7 min 98% B, 7.5 min 5% B, 8 min 5% B	1.0 mL/min
18	Acquity BEH C18 (50mmx2.1mm, 1.7um) operated at 35 °C A: 0.05% aq. HCO_2H B: 0.05 % TFA in ACN	0 min 5% B, 5 min 98% B, 9 min 98% B, 9.01 min 5% D, 12 min 5% B	0.6 mL/min

19	ACQUITY UPLC BEH C18 (2.1x100) mm, 1.7µm operated at 45 °C A: 0.05 % TFA in ACN B: 0.05 % aq. TFA	0 min 10% A, 2.5 min 10% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 10% A, 10 min 10% A	0.4mL/min
20	ACQUITY UPLC BEH C18 (2.1x100) mm, 1.7µm operated at 35 °C A: 0.05 % TFA in ACN B: 0.05 % aq. TFA	0 min 10% A, 2.5 min 10% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 10% A, 10 min 10% A	0.4mL/min
21	ACQUITY UPLC BEH C18 (2.1x100) mm, 1.7µm operated at 50 °C A: 0.05 % TFA in ACN B: 0.05 % aq. TFA	0 min 10% A, 2.5 min 10% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 10% A, 10 min 10% A	0.55mL/min
22	ACQUITY UPLC BEH C18 (2.1x100) mm, 1.7µm operated at 35 °C A: 0.05 % TFA in ACN B: 0.05 % aq. TFA	0 min 10% A, 2.5 min 10% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 10% A, 10 min 10% A	0.65mL/min
23	X Bridge C18 (50mmx4.6mm, 3.5 µm) operated at 45 °C A: 10mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B , 5 min 98% B, 7.5 min 98% B, 7.6 min 5% B, 9 min 5% B	0.8 mL/min
24	YMC-Triart C18 ExRS (50x2.1mm, 1.9µm) operated at 35 °C A: 0.05% aq. TFA B: 0.05 % TFA in ACN	0 min 5% B, 5 min 98% B, 9 min 98% B, 9.01 min 5% B, 12 min 5% B	0.6 mL/min
25	X Bridge C18 50x4.6 mm 3.5µm operated at 35 °C A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 2% B, 0.5 min 2% B, 3 min 98% B, 6 min 98%B, 8 min 2% B	0.8 mL/min
26	X Bridge C18 50x4.6 mm 3.5µm operated at 30 °C A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B, 1.0 min 15% B, 4.0 min 98% B, 7.0 min 98% B, 7.5 min 5% B, 8.0 min 5% B	1.3 mL/min

27	X Bridge C18 50x4.6 mm 3.5µm operated at 45 °C A: 10 mM aq. NH_4HCO_3 B: ACN	0 min 2% B, 0.5 min 2% B, 2.5 min 98% B, 5 min 98% B, 5.1 min 2% B, 6 min 2% B	1.0 mL/min
28	YMC Triart C18 (75x4.6mm, 3 um) operated at 45 °C A: 5mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B, 1 min 15% B, 6 min 55% B, 9 min 95% B, 12 min 95% B, 13 min 5% B, 14 min 5% B	1.3 mL/min
29	YMC Triart C18 (75x2.1mm, 1.9 um) operated at 35 °C A: 0.05 % aq. TFA B: 0.05 % TFA in ACN	0 min 3% B, 0.4 min 3% B, 2.5 min 98% B, 3.5 min 98% B, 3.6 min 3% B, 4 min 3% B	0.6 mL/min
30	YMC Triart C18 (50x2.1mm, 1.9 um) operated at 60 °C A: 0.05 % aq. TFA B: 0.05 % TFA in ACN	0 min 3% A, 2.5 min 3% A, 7.5 min 98% A, 9.5 min 98% A, 9.6 min 3% A, 10 min 3% A	0.6 mL/min
31	YMC Triart C18 (50x2.1mm, 1.9 um) operated at 60 °C A: 0.05 % aq. TFA B: 0.05 % TFA in ACN	0 min 3% A, 0.4 min 3% A, 2.5 min 98% A, 3.5 min 98% A, 3.6 min 3% A, 4 min 3% A	0.6 mL/min
32	YMC Triart C18 (50x4.6mm, 1.9 um) operated at 60 °C A: 0.05 % TFA in ACN B: 0.05% aq. TFA	0 min 5% A, 0.5 min 5% A, 3 min 95% A, 6 min 95% A, 6.1 min 5% A, 8 min 5% A	1.0 mL/min
33	X Bridge C18 75x4.6 mm 3.5µm operated at 45 °C A: 5 mM aq. NH_4HCO_3 B: ACN	0 min 5% B, 0.5 min 5% B, 1 min 15% B, 6 min 55% B, 9 min 95% B, 12 min 95% B, 13 min 5% B, 14 min 5% B	1.0 mL/min
34	X Bridge C18 75x4.6 mm 3.5µm operated at 35 °C A: 10mM aq. NH_4HCO_3	0 min 5% B, 0.5 min 5 % B, 1.0 min 15% B, 4.0 min 98% B, 7.0	1.3 mL/min

	B: ACN	min 98% B, 7.5 min 5% B, 8.0 min 5% B	
35	X Brigde BEH C18 (3x100) mm, 2.5µm operated at 35 °C A: 0.05 % TFA in ACN B: 0.05% aq. TFA	0 min 3% A, 4 min 98% A, 5 min 98% A, 5.01 min 3% A, 6 min 3% A	1 mL/min
36	X Bridge C18 (100mmx3mm, 2.5 µm) operated at 50 °C A: 0.05 % aq. TFA B: 0.05 % TFA in ACN	0 min 3% A, 4 min 98% A, 5 min 98% A, 5.01 min 3% A, 6 min 3% A	1.0mL/min
37	X Bridge C18 (75mmx4.6mm, 3.5 µm) operated at 45 °C A: 10 mM aq. NH_4HCO_3 B: 100% ACN	0 min 5% B, 0.8 min 5% B, 2 min 25% B, 5 min 90% B, 7 min 95% B, 8.6 min 5% B, 10 min 5% B	1.0mL/min
38	Acquity BEH C18 100x2.1 mm 1.7 µm operated at 60 °C A: 0.05 % TFA in ACN B: 0.05% aq. TFA	0 min 3% A, 1 min 10% A, 8.5 min 100% A, 9 min 100% A, 9.5 min 3% A, 10 min 3% A	0.55 mL/min
39	Acquity BEH C18 100x2.1 mm 1.7 µm operated at 60 °C A: 0.05 % aq. TFA B: 0.05 % TFA in ACN	0 min 3% A, 8 min 100% A, 9 min 100% A, 9.5 min 3% A, 10 min 3% A	0.45 mL/min
40	Acquity BEH C18 100x2.1 mm 1.7 µm operated at 45 °C A: 0.05% aq. TFA B: 0.05% TFA in ACN	0 min 10% B, 2.5 min 10% B, 7.5 min 98% B, 9.5 min 98% B, 9.6 min 10% B, 10 min 10% B	0.4mL/min
41	Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm operated at 45 °C A: 0.1% aq HCO_2H B 0.1% HCO_2H in ACN	0 min 1% B, 1.5 min 100% B, 2.2 min 100% B	3 mL/min
42	Waters HSS T3 1.8µm ,1.0x 50mm column operated at 50 °C A: 0.01% aq HCO_2H B 0.01% HCO_2H in AC	0 min 10%B, 0.1 min 10% B, 0.6 min 95% B, 1.5 min 95% B, 1.51 min 10% B	0.475 mL/min

Abbreviations

ABPR = automated back pressure regulator

ACN = acetonitrile

AcOH = acetic acid

AdBrettPhos Pd G3 = [2-(di-1-adamantyl-phosphino)-2',4',6'-tri-*iso*-propyl-3,6-dimethoxybiphenyl][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

aq = aqueous

Boc = *tert*-butoxycarbonyl

Boc_2O = di-*tert*-butyl dicarbonate

BOP = (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate

B_2Pin_2 = 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)

Brettphos Pd G3 = [(2-Di-*cyclo*-hexylphosphino-3,6-dimethoxy-2',4',6'- tri-*iso*-propyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate methanesulfonate

BrettPhos Pd G4 = [2'-(methylamino)-[1,1'-biphenyl]-2-yl]palladio methanesulfonate di-*cyclo*-hexyl[3,6-dimethoxy-2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane

brine = saturated aqueous sodium chloride

cataCXium Pd G4 = [di(adamantan-1-yl)(butyl)phosphine](methanesulfonato- κO)[2'-(methylamino)-2-biphenylyl]palladium

CBz = benzyloxycarbonyl

CBz-Cl = benzyl chloroformate

CDI = 1,1'-carbonyldiimidazole

DAST = diethylaminosulfur trifluoride

dba = dibenzylideneacetone

DCC = di-*cyclo*-hexylcarbodiimide

DCE = 1,2-dichloroethane

DCM = dichloromethane

DEA =diethylamine

DEAD = diethyl azodicarboxylate

Deoxo-Fluor = bis(2-methoxyethyl)aminosulfur trifluoride

DIAD = di-*iso*-propyl azodicarboxylate

DIPEA = di-*iso*-propyl ethyl amine

DMAP = 4-(dimethylamino)pyridine

DME = 1,2-dimethoxyethane

DMF = dimethyl formamide

DMDCH = *trans-N,N'*-dimethyl-*cyclo*-hexane-1,2-diamine

DMEDA = *N1,N2*-dimethylethane-1,2-diamine

DMP = Dess–Martin periodinane

DMS = dimethyl sulfide

DMSO = dimethyl sulfoxide

DPPF = 1,1'-bis(diphenylphosphino)ferrocene

EDC = N-(3-dimethylaminopropyl)-N'-ethylcarbodi-imide

EtOAc = ethyl acetate

EtOH = ethanol

FC = flash chromatography on silica gel unless stated otherwise from the eluent described in the brackets

h = hour(s)

HATU = (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HBTU = N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate

HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol

HOBt = hydroxybenzotriazole

HPLC = high performance liquid chromatography

Int./Ints. = intermediate/intermediates

IPA = *iso*-propyl alcohol

KOAc = potassium acetate

KOtBu = potassium *tert*-butoxide

LCMS = liquid chromatography–mass spectrometry
LDA = lithium di-*iso*-propylamide
LiHMDS = lithium bis(trimethylsilyl)amide
mCPBA = *m*-chloro-perbenzoic acid
MeOH = methanol
2MeTHF = 2-methyl-tetrahydrofuran
MHz = megahertz
MS = molecular sieves
MsCl = methanesulfonyl chloride (mesyl chloride)
MTBE = methyl *tert*-butyl ether
MW = microwave
NaOtBu = sodium *tert*-butoxide
NBS = *N*-bromosuccinimide
NMP = *N*-methyl-2-pyrrolidon
NMR = nuclear magnetic resonance
ON = overnight
Pd_2dba_3 = tris(dibenzylideneacetone)dipalladium(0)
PdDPPFCl$_2$-DCM = [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) DCM complex
Pd G3 SPhos = (2-Di-*cyclo*-hexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
Pd G3 *tert*-butyl-Xphos = methanesulfonato (di-*tert*-butyl) phenylphosphino (2'-amino-1,1'-biphenyl-2-yl) palladium(II)
ppm = parts per million
PyBOP = (benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate
RT = room temperature
RU = response units
RuPhos = 2-di-*cyclo*-hexylphosphino-2',6'-di-*iso*-propoxybiphenyl
Ruphos Pd-G2 = Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
sat. = saturated
SCX = strong cation exchange
SEM = 2-(trimethylsilyl)ethoxymethyl
SFC = supercritical fluid chromatography
SPR = Surface plasmon resonance
STAB = sodium triacetoxy borohydride
TBAF = tetra *n*-butyl ammonium fluoride
TBAI = tetra *n*-butyl ammonium iodide
TFA = trifluoro acetic acid
Tf_2O = trifluoromethanesulfonic anhydride
THF = tetrahydrofuran
TLC = thin layer chromatography
TMEDA = tetramethylethylenediamine
Ts = tosyl
TsOH = p-toluenesulfonic acid
T3P = propanephosphonic acid anhydride
VCD = Vibrational circular dichroism
XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos = 2-di-*cyclo*-hexylphosphino-2′,4′,6′-tri-*iso*-propylbiphenyl

Synthesis Methods

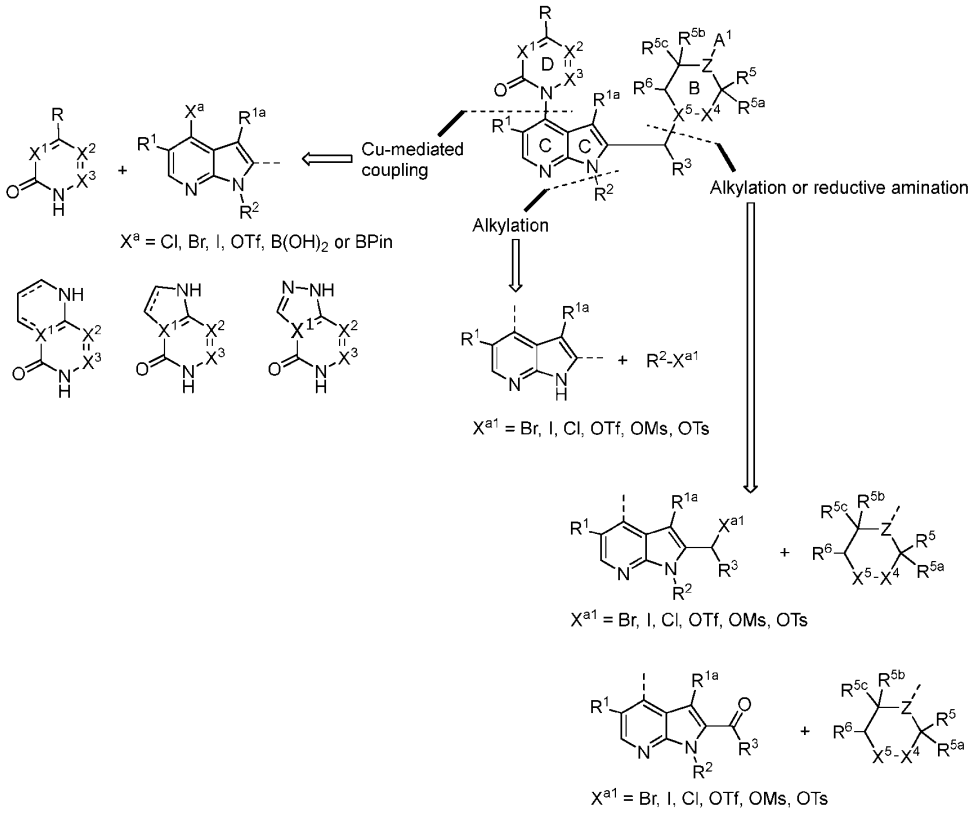
The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of synthesis. The compounds of the disclosure could for example be prepared using the reactions and techniques outlined below together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are carried out in solvents appropriate to the reagents and materials employed and suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognized by one skilled in the art. Not all compounds falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used.

The compounds of the present disclosure or any intermediate could be purified, if required, using standard methods well known to a synthetic organist chemist, e.g. methods described in "Purification of Laboratory Chemicals", 6th ed. 2009, W. Amarego and C. Chai, Butterworth-Heinemann.

Starting materials are either known or commercially available compounds, or may be prepared by routine synthetic methods well known to a person skilled in the art.

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. The organic solvents used were usually anhydrous. The solvent ratios indicated refer to vol:vol unless otherwise noted. Thin layer chromatography was performed using Merck 6OF254 silica-gel TLC plates. Visualization of TLC plates was performed using UV light (254 nm) or by an appropriate staining technique.

The compounds of the disclosure can be prepared according to the key bond formations as outlined below.



Linking A = CO to L-LBM (i.e. of R^9) via an amide bond can be performed from the corresponding acid, an appropriate amine, and a suitable coupling agent for example under the conditions used to prepare Int. **1AF84**.

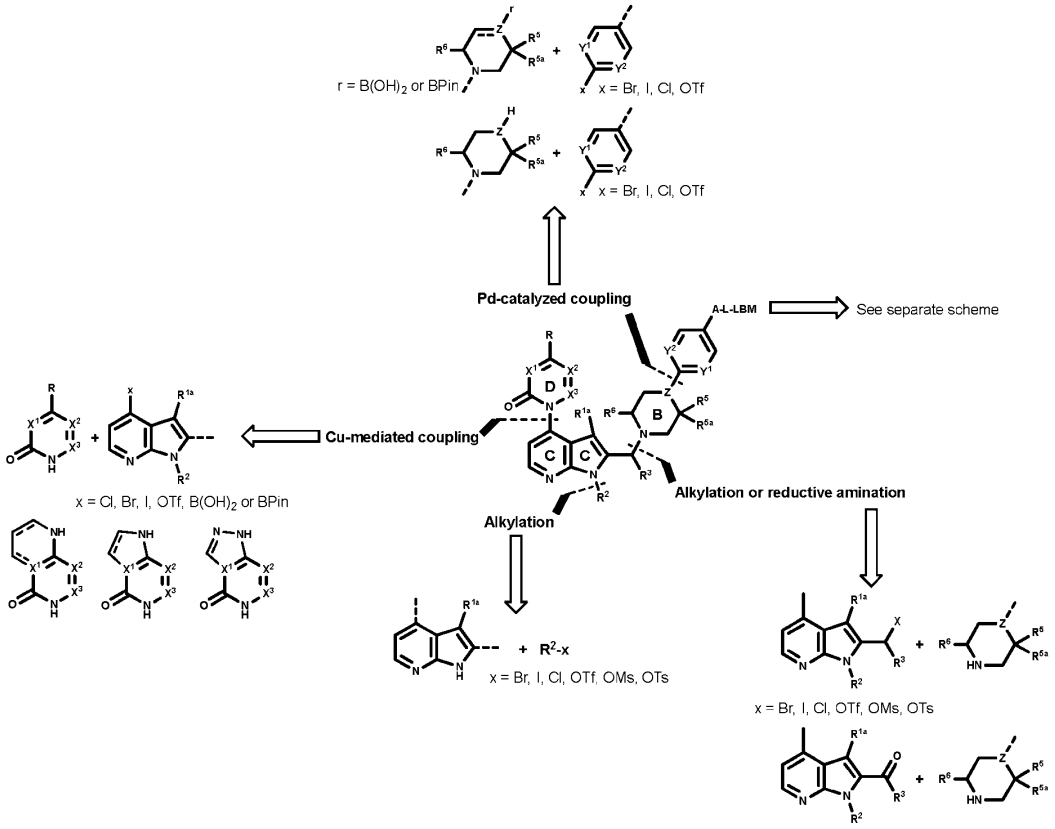
Linking the $\mathbf{A^1}$ and **B** rings can be achieved in palladium-mediated couplings reactions wherein either an amine (Z=N) is reacted with an aryl (pseudo)halide based on ring $\mathbf{A^1}$ or by coupling ring **B** in which Z is a carbon atom linked to a boronic acid or boronate to aryl (pseudo)halide based on ring $\mathbf{A^1}$. Such reactions can be performed as described for the syntheses of Ints. **1M51** and **1S3**.

The bond connecting the **B** ring to the azaindole core (**C-C**) can be formed either by alkylation of the **B** ring amine or lactam with an alkyl (pseudo)halide linked to the azaindole core (**C-C**) or by reductive amination of the **B** ring amine to the ketone/aldehyde linked to the azaindole core (**C-C**). Such reactions can be performed as described for the synthesis of Examples **1d40/1d41** from Int. **1T1** or Examples **1m6** from Int. **1M1**.

R^2 can be attached to the parent azaindole core (**C-C**) by alkylation with a suitable alkylation agent. Such reactions can be performed as described for the syntheses of Int. **1K3**.

Attaching ring **D** to the azaindole core (**C-C**) can be done either by copper-mediated coupling of a boronic acid or boronate linked to the azaindole (**C-C**) core and the heteroaromatic ring **D** or by copper-mediated Ullmann reaction between an aryl (pseudo)halide derivative of the azaindole core (**C-C**) and the heteroaromatic ring **D**. Such reactions can be performed as described for the synthesis of Example **1af63** from Int. **1AF1** or Example **1ab4** from **1AB4**.

Additionally or alternatively, the compounds of the disclosure can be prepared according to the key bond formations as outlined below.



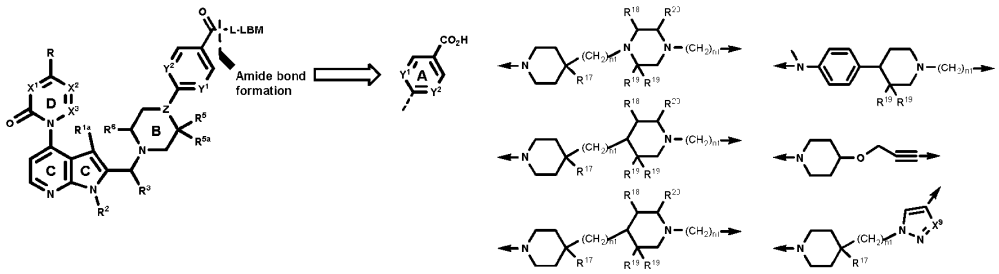
Linking A = CO to L-LBM via an amide bond can be performed from the corresponding acid, an appropriate amine, and a suitable coupling agent for example under the conditions used to prepare Int. **1AF84**.

The bond connecting the **B** ring to the azaindole core (**C-C**) can be formed either by alkylation of the **B** ring amine or lactam with an alkyl (pseudo)halide liked to the azaindole core (**C-C**) or by reductive amination of the **B** ring amine to the ketone/aldehyde liked to the azaindole core (**C-C**). Such reactions can be performed as described for the synthesis of Examples **1d40/1d41** from Int. **1T1** or Examples **1m6** from Int. **1M1**.

The bond connecting the **B** ring to the azaindole core (**C-C**) can be formed either by alkylation of the **B** ring amine or lactam with an alkyl (pseudo)halide liked to the azaindole core (**C-C**) or by reductive amination of the **B** ring amine to the ketone/aldehyde liked to the azaindole core (**C-C**). Such reactions can be performed as described for the synthesis of Examples **1d40/1d41** from Int. **1T1** or Examples **1m6** from Int. **1M1**.

R^2 can be attached to the parent azaindole core (**C-C**) by alkylation with a suitable alkylation agent. Such reactions can be performed as described for the syntheses of Int. **1K3**.

Attaching ring **D** to the azaindole core (**C-C**) can be done either by copper-mediated coupling of a boronic acid or boronate linked to the azaindole (**C-C**) core and the heteroaromatic ring **D** or by copper-mediated Ullmann reaction between an aryl (pseudo)halide derivative of the azaindole core (**C-C**) and the heteroaromatic ring **D**. Such reactions can be performed as described for the synthesis of Example **1af63** from Int. **1AF1** or Example **1ab4** from **1AB4**.



Compounds in which A = CO the -L- fragment can be introduced via amide bond formation. The prerequisite acids can for example be prepared as described herein for Int. **1M60** from Example **1m56**.

The synthesis Int. **3E274** exemplifies a precursor in which the amide bond linking CO to L-LBM is formed from the prerequisite substrates Ints. **3E275/1AC4**. The specification exemplifies L-LBM fragments such as Int. **3E68** and their coupling to give the compounds of the disclosure such as described for the reaction of Ints. **3E171/3E68** to give Example **3e39**.

Compounds in which the LBM motif is linked to the rest of the molecule via a triple bond or a C-C to a five-membered aromatic ring can be prepared via cross-coupling reactions from precursors like Ints. **3E240/3B1**.

Compounds in which the LBM motif is linked to the rest of the molecule via a methylene linker can be prepared by reductive amination such as described herein for Int. **3E2**. Compounds in which the LBM is linked to the rest of the molecule via the 4-position of a piperidine ring can be prepared from Ints. like **3D1**.

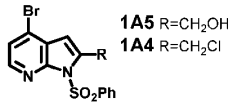
The LBM motif can be functionalized with Cl or F atoms such as in Ints. **3E50**, **3E61**, and **3E131**.

The LBM motif can be functionalized on the benzimidazolone nitrogen atom not bearing the piperidine-2,6-dione unit by functionalized alkyl groups such as $(CH_2)_2OH$, $(CH_2)_2OMe$, or CH_2CF_3

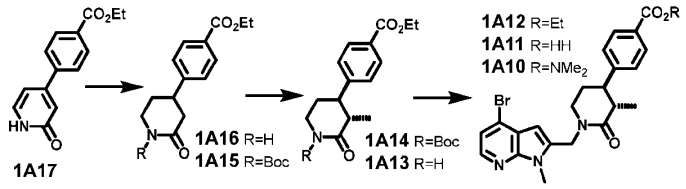
as in Ints. **3E13**, **3E159**, and **3E106**. The LBM motif can be functionalized on the benzimidazolone nitrogen atom not bearing the piperidine-2,6-dione unit by alkyl groups like methyl or *cyclo*-propyl as in Ints. **3E3**, and **3E20**.

Compounds in which the LBM motif is an oxindole or benzoxazole can be prepared from Ints. **3E288** and **3E257**.

Example 1 – Preparation of Intermediates

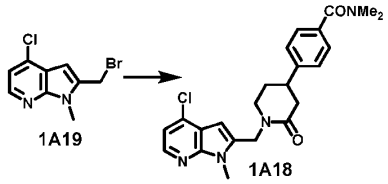


4-Bromo-1-(phenyl-sulfonyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.27 g) and $NaBH_4$ (33 mg) were stirred 0.5h in THF/ MeOH (9:1, 5 mL) at 0 °C. The OL (water/EtOAc) was washed with brine, dried, and concentrated to give Int. **1A5** (4-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methanol (281 mg). Int. **1A5** (0.24 g) and MsCl (0.052 mL) was stirred 0.5h in DCM/Et_3N (29:1, 5.2 mL). MsCl (0.014 mL) was added and stirring continued 0.5h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 1:1) to give Int. **1A4** 4-bromo-2-(chloromethyl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (0.15 g).

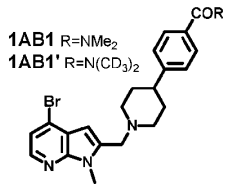


4-Bromopyridin-2(1H)-one (1.0 g), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3.17 g), $PdDPPFCl_2$-DCM (0.42 g), and K_3PO_4 (3.66 g) were degassed in dioxane/water (10:1, 11 mL) and stirred 2h at 110 °C under MW conditions. The mixture was filtered, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **1A17** ethyl 4-(2-oxo-1H-pyridin-4-yl)benzoate (0.50 g). Int. **1A17** (3.5 g) was hydrogenated 48h using 10% Pd/C (1.5 g) in EtOH/AcOH (4:1, 50 mL), filtered, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **1A16** ethyl 4-(2-oxopiperidin-4-yl)-benzoate (2.5 g). Int. **1A16** (0.50 g), Boc_2O (0.61 g), and DMAP (23 mg) were stirred ON in DCM/Et_3N (25:1, 21 mL) at 0 °C to RT ON. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **1A15** *tert*-butyl 4-(4-ethoxy-carbonylphenyl)-2-oxo-piperidine-1-carboxylate (0.40 g). Int. **1A15** (0.30 g) was stirred 0.5h in 0.1M LiHMDS in THF (11 mL) at -78 °C. CH_3I (0.16 mL) was added and stirring continued 2h at -25 to -30 °C. The OL (sat. aq. NH_4Cl / EtOAc) was washed with water and brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **1A14** *tert*-butyl *trans*-4-(4-ethoxycarbonylphenyl)-3-methyl-2-oxo-piperidine-1-carboxylate (0.18 g). Int. **1A14** (0.60 g) was

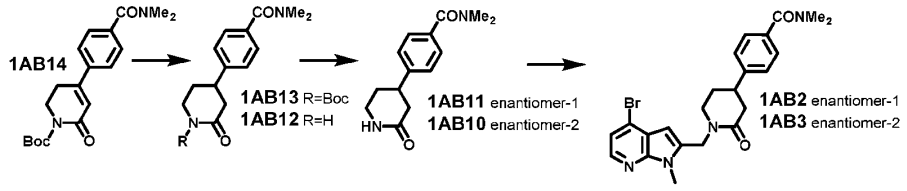
stirred ON in DCM/TFA (32:1, 20.6 mL) at 0 °C to RT and concentrated. The OL (10% MeOH in DCM/sat. aq. $NaHCO_3$) was dried, and concentrated to give Int. **1A13** ethyl 4-[*trans*-3-methyl-2-oxo-4-piperidyl]benzoate (0.38 g). Int. **1A13** (0.20 g) and NaH (28 mg) were stirred 0.5h in THF (10 mL) at 0 °C to RT. Int. **1J1** (0.22 g) and TBAI (25 mg) were added and stirring continued ON. The OL (aq. citric acid/EtOAc) was dried and concentrated to give Ints. **1A12/1A11** ethyl 4-[*trans*-1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3-methyl-2-oxo-4-piperidyl]benzoate and 4-[*trans*-1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3-methyl-2-oxo-4-piperidyl]benzoic acid (0.30 g). 20 mg of this mixture, $HNMe_2$ (0.11 g, HCl salt), and HATU (0.25 g) were stirred ON in DMF/DIPEA (28.6:1, 10.4 mL). The mixture was combined with another batch prepared similarly on 30 mg scale, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **1A10** *N*,*N*-Dimethyl-4-[*trans*-1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3-methyl-2-oxo-4-piperidyl]benzamide (0.20 g).



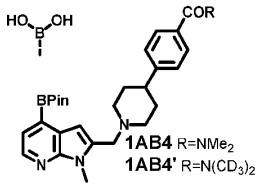
Int. **1A18** 4-[1-[(4-Chloro-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-2-oxo-4-piperidyl]-*N*,*N*-dimethyl-benzamide was prepared similarly to Int. **1A10** from Int. **1A16** and 4-chloro-2-(chloromethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine (prepared similarly to Int. **1J1**).



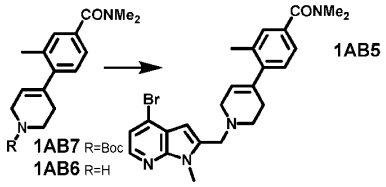
Int. **1J1** (8 g) and *N*,*N*-dimethyl-4-(4-piperidyl)benzamide (9.9 g, HCl salt) were stirred ON in DMF/DIPEA (0.7:1, 47 mL) at 0°C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 1:3) to give Int. **1AB1** 4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*,*N*-dimethylbenzamide (9 g). Int. **1AB1'** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide was prepared similarly from $HN(CD_3)_2$.



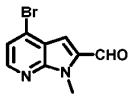
Na_2CO_3 (9.2 g), 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methane-sulfonamide (10 g), and (4-(dimethylcarbamoyl)phenyl)boronic acid (5.5 g) were degassed in toluene/water (4:1, 250 mL) and stirred 3h at 100 °C. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 2:3) to give Int. **1AB14** *tert*-butyl 4-[4-(dimethylcarbamoyl)phenyl]-6-oxo-2,3-dihydropyridine-1-carboxylate (5.1 g). Int. **1AB14** (4.4 g) was hydrogenated ON using 10% Pd/C (0.45 g) in MeOH (100 mL), filtered, and concentrated to give Int. **1AB13** *tert*-butyl 4-(4-(dimethylcarbamoyl)-phenyl)-2-oxopiperidine-1-carboxylate (3.9 g). Int. **1AB13** (8.1 g) was stirred ON in DCM/4M HCl in dioxane (4.2:1, 124 mL) and concentrated. The OL (sat. aq. $NaHCO_3$/10% MeOH in DCM) was dried and concentrated to give Int. **1AB12** *N*,*N*-dimethyl-4-(2-oxo-piperidin-4-yl)-benzamide (2.9 g). This material was resolved by SFC using a Chiralpak IG 250x25 5µm column operated at 30 °C and an eluent of 50% CO_2 and 50% MeOH (100 g/min) and a back pressure of 100 bar to give Int. **1AB11** (0.93 g, first peak) and Int. **1AB12** (0.91 g, second peak). The absolute configurations of these compounds were not determined. Int. **1AB12** (95 mg) and NaH (20 mg) were stirred 0.25h in DMF (1 mL). Int. **1J1** (0.10 g) was added and stirring continued 0.5h. The OL (DCM/water) was washed with water and brine, dried, concentrated, and triturated in ACN to give Int. **1AB3** (S)-4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-2-oxopiperidin-4-yl)-*N*,*N*-dimethylbenzamide or (R)-4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-2-oxopiperidin-4-yl)-*N*,*N*-dimethyl-benzamide (31 mg). Int. **1AB2** (S)-4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-2-oxopiperidin-4-yl)-*N*,*N*-dimethylbenzamide or (R)-4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-2-oxopiperidin-4-yl)-*N*,*N*-dimethyl-benzamide (35 mg) was prepared similarly from Ints. **1AB11/1J1** (95 mg/0.10 g). The absolute configurations of these compounds were not determined.



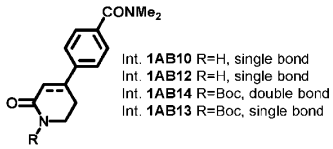
Int. **1AB1** (0.15 g), B_2Pin_2 (0.13 g), KOAc (81 mg), and $PdDPPFCl_2$-DCM (27 mg) were degassed in dioxane (3 mL) and stirred at 90 °C, filtered and concentrated to give Ints. **1AB4/1AB4'** *N*,*N*-Dimethyl-4-[1-[[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]benzamide and [2-[[4-[4-(dimethylcarbamoyl)phenyl]-1-piperidyl]methyl]-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]boronic acid and *N*,*N*-bis(methyl-d_3)-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzamide and (2-((4-(4-(bis-(methyl-d_3)carbamoyl)phenyl)piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid.



4-Bromo-*N*,*N*,3-trimethylbenzamide (9.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (15.2 g), $PdDPPFCl_2$-DCM (0.67 g), and Na_2CO_3 (9.62 g) were degassed in dioxane (180 mL) and stirred ON at 90 °C. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 2:3) to give Int. **1AB7** *tert*-butyl 4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (11.0 g). Int. **1AB7** (0.6 g) was stirred ON in DCM/TFA (30:1, 15.5 mL), concentrated, and triturated in Et_2O to give Int. **1AB6** *N*,*N*,3-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (TFA salt). Ints. **1AB6/1AB8** (0.23 g, TFA salt/0.1 g) were stirred ON in DCE/DIPEA (11.4:1, 5.4 mL) at 0 °C to RT. STAB (26 mg) was added and stirring continued 2h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (MeOH/DCM 1:9) to give Int. **1AB5** 4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-*N*,*N*,3-trimethylbenzamide (0.10 g).

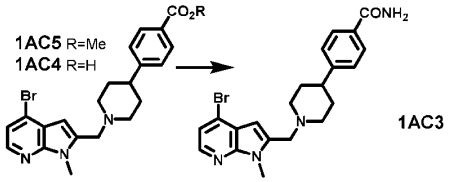


4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine (5.0 g) was stirred 2h in 1.1M LDA in THF (33 mL) at -78 °C. DMF (3.46 g in THF (20 mL)) was added and stirring continued ON at -78 °C to RT ON. The OL (sat. aq. NH_4Cl/EtOAc) was washed with water, brine, dried, concentrated, and triturated in EtOAc / pentane to give Int. **1AB8** 4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (3.1 g).

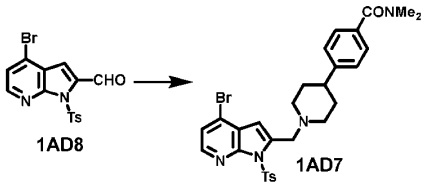


$PdDPPFCl_2$-DCM (1.1 g), *tert*-Butyl 6-oxo-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (10.2 g), (4-(dimethylcarbamoyl)phenyl)boronic acid (5.7 g), and Na_2CO_3 (9.4 g) were stirred 3h in toluene/water (150/40 mL) at 100 °C. The mixture was filtered. The filtrate was concentrated and purified by FC (EtOAc/Hexane 3:2) to give Int. **1AB14** *tert*-butyl 4-(4-(dimethyl-carbamoyl)-phenyl)-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (5.2 g). Int. **1AB14** (5 g) and 10% Pd/C (2.5 g) were hydrogenated 48h under a hydrogen pressure of 60 psi in EtOAc (100 mL). The mixture was filtered and concentration to give Int. **1AB13** *tert*-butyl 4-(4-(dimethylcarbamoyl)phenyl)-2-oxopiperidine-1-carboxylate (4.0 g). Int. **1AB13** (0.1 g) was stirred

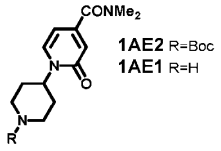
12h in DCM/4M HCl in dioxane (5/0.4 mL). The residue after concentration was triturated in Et_2O to give Int. **1AB10/1AB12** N,N-dimethyl-4-(2-oxopiperidin-4-yl)benzamide (78 mg).



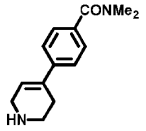
Int. **1AB8** (6.0 g) and methyl 4-(1-piperidin-4-yl)benzoate (7.1 g, HCl salt) were stirred 4h in DCE/DIPEA (7.7:1, 113 mL). STAB (11.0 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and triturated in EtOAc/MeOH give Int. **1AC5** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate. Int. **1AC5** (0.4 g) and NaOH (0.18 g) were stirred ON in THF/MeOH (2:1, 9 mL), concentrated, and triturated in dilute aq. HCl to give Int. **1AC4** 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-benzoic acid (0.38 g). Int. **1AC4** (0.5 g) and CDI (0.7 g) were stirred 2h in DMF/Et_3N (30:1, 7.2 mL). 25% aq. NH_3 (1.51 mL) was added followed by water to precipitate a solid that was stirred ON in 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (10 mL) to afford Int. **1AC3** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzamide (0.35 g).



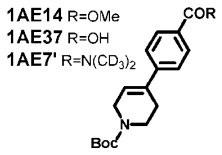
4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g) was stirred 1h in 0.6M LDA in THF (14.2 mL) at -78 °C. DMF (1.3 mL) was added and stirring continued 2h at -78 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 1:0 to 9:1) to give Int. **1AD8** 4-bromo-1-(*p*-tolylsulfonyl)-pyrrolo[2,3-b]-pyridine-2-carbaldehyde (0.6 g). *N*,*N*-Dimethyl-4-(4-piperidinyl)-benzamide (1.4 g, HCl salt) and Int. **1AD8** (1.3 g) were stirred ON in DCE/DIPEA (20:1, 21 mL) at 0 °C to RT. STAB (1.1 g) was stirring continued 2h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **1AD7** 4-[1-[[4-bromo-1-(*p*-tolyl-sulfonyl)-pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]-N,N-dimethyl-benzamide (2.3 g).



KOtBu (37 mg), *tert*-butyl 4-(*p*-tolylsulfonyloxy)piperidine-1-carboxylate (0.16 g), K_2CO_3 (83 mg), and *N*,*N*-dimethyl-2-oxo-1H-pyridine-4-carboxamide (50 mg) were degassed in DME (5 mL) and stirred ON at 120 °C. The OL (water/MeOH/DCM) was dried and concentrated to give Int. **1AE2** *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-oxo-1-pyridyl]-piperidine-1-carboxylate. Int. **1AE2** (0.25 g) was stirred in DCM/TFA (8.6:1, 5.6 mL). The mixture was concentrated to give Int. **1AE1** *N*,*N*-Dimethyl-2-oxo-1-(piperidin-4-yl)-1,2-dihydropyridine-4-carboxamide (0.15 mg, TFA salt).

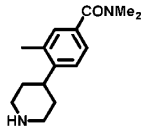


4-Bromo-*N*,*N*-dimethylbenzamide (25 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (40.7 g), Na_2CO_3 (34.5 g), and $PdDPPFCl_2$-DCM (2.24 g) were degassed in dioxane/water (7.7:1, 260 mL) and stirred at 90 °C ON and filtered. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 55:45) to give *tert*-butyl 4-(4-(dimethyl-carbamoyl)-phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (36.0 g). 5.0 g of this material was stirred ON in DCM/TFA (6.9:1, 46 mL) and concentrated. The OL (sat. aq. $NaHCO_3$/10% MeOH in DCM) was washed with brine, dried, concentrated, and triturated in Et_2O to give Int. **1AE7** 4-(3,6-dihydro-2H-pyridin-4-yl)-*N*,*N*-dimethyl-benzamide (2.80 g).

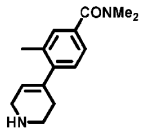


Methyl 4-bromobenzoic acid ester (10 g) *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14.4 g), $NaHCO_3$ (11.7 g), and $PdDPPFCl_2$-DCM (1.2 g) were degassed in dioxane (300 mL) and stirred at 100 °C ON. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **1AE14** *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (11 g). 4.5 g of this material and LiOH-H_2O (3.0 g) were stirred 4h in MeOH/THF/water (4:2:1, 35 mL) at 0 °C to RT. The mixture was partially concentrated and diluted with aq. citric acid to precipitate Int. **1AE37** 4-(1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (3.9 g). Int. **1AE37** (4.0 g), HATU 7.52 g), and $HN(CD_3)_2$ (1.73 g, HCl salt) were stirred ON in DMF/DIPEA (2.5:1, 42 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give *tert*-butyl 4-[4-[bis-(trideuteriomethyl)-carbamoyl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (3.5 g). 2.5 g of this material was stirred ON in DCM/TFA (1:1, 30 mL) at 0 °C to RT and concentrated. The OL (aq. $NaHCO_3$/10% MeOH in DCM) was dried, concentrated, and triturated

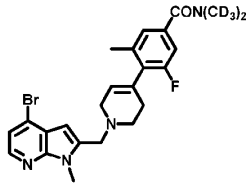
in Et_2O/pentane to give Int. **1AE7'** *N*,*N*-Bis(methyl-d_3)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (1.7 g).



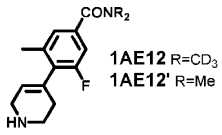
tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (33.7 g), 4-bromo-*N*,*N*,3-trimethylbenzamide (20.0 g), Na_2CO_3 (21.4 g), and $PdDPPFCl_2$-DCM (1.48 g) were degassed in dioxane/water (9:1, 200 mL) and stirred ON at 110 °C. The mixture was filtered, concentrated, and purified by FC (heptane/EtOAc 1:1) to give *tert*-butyl 4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (25 g). 15 g of this material was hydrogenated ON using 10% Pd/C (5.0 g) in MeOH (200 mL), filtered, and concentrated to give *tert*-butyl 4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-piperidine-1-carboxylate (14.0 g). 10 g of this material was stirred ON in DCM/TFA (1:1, 200 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **1AE8** *N*,*N*,3-trimethyl-(4-piperidin-4-yl)benzamide (9.2 g, TFA salt).



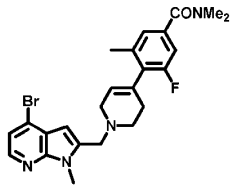
tert-Butyl 4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (4.0 g) was stirred 0.5h in 4M HCl in dioxane (40 mL), concentrated, and triturated in Et_2O to give Int. **1AE8'** *N*,*N*,3-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (1.06 g, HCl salt).



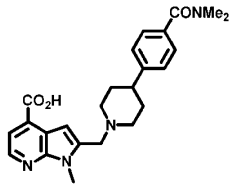
Ints. **1J1/1** (0.70 g/0.49 g, HCl salt) and KI (0.11 g) were stirred ON in DMF / DIPEA (8.3:1, 11.2 mL) at 0 °C to RT. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (EtOAc/hexane 7:3) to give Int. **1AE9** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methyl-*N*,*N*-bis(methyl-d_3)benzamide (0.45 g).



Methyl 4-bromo-3-fluoro-5-methyl-benzoate (20 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (27.5 g), K_2CO_3 (44.8 g), and $PdDPPFCl_2$-DCM (3.31 g) were degassed in dioxane/water (4:1, 0.5 L) and stirred at 100 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane to EtOAc) to give *tert*-butyl 4-(2-fluoro-4-methoxy-carbonyl-6-methyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (15.5 g). This material and LiOH-H_2O (3.72 g) were stirred ON in MeOH/water (1:1, 0.3 L) and acidified to precipitate 4-(1-*tert*-butoxycarbonyl-3,6-dihydro-2H-pyridin-4-yl)-3-fluoro-5-methyl-benzoic acid (11.8 g). 5.0 g of this material, $HN(CD_3)_2$ (1.44 g, HCl salt), and HATU (6.8 g) were stirred ON in DMF/DIPEA (6.4:1, 58 mL), concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[4-[bis(trideuterio-methyl)carbamoyl]-2-fluoro-6-methyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (5.1 g). This material was stirred 1h in HFIP/10M aq. HCl (31:1, 52 mL) and diluted with MTBE to precipitate Int. **1AE12** 3-Fluoro-5-methyl-*N*,*N*-bis(methyl-d_3)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (3.45 g, HCl salt). Int. **1AE12'** 3-fluoro-5-methyl-*N*,*N*-bis(methyl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide was prepared in a similar manner from $HN(CH_3)_2$.

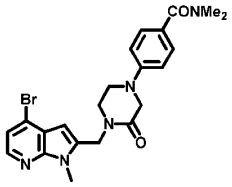


Int. **1J3** (0.50 g) was stirred 1h in DCM (20 mL) and MsCl (0.8 mL) at 0 °C. The OL (water/DCM) was washed with sat. aq. $NaHCO_3$ and concentrated to give (4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl methanesulfonate (0.52 g). 0.5 g of this material, KI (0.13 g), and Int. **1AE12'** (0.51 g) were stirred ON in DMF/DIPEA (14:1, 21.5 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane to EtOAc) to give Int. **1AE13** 4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-*N*,*N*,5-trimethyl-benzamide (0.52 g).

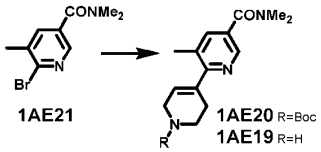


Int. **1AB1** (0.15 g), $Mo(CO)_6$ (87 mg), Pd_2dba_3 (8 mg), and XantPhos (10 mg) were degassed in EtOH (5 mL) and stirred 0.5h at 120 °C under MW conditions. The mixture was filtered and HPLC-purified give ethyl 2-((4-(4-(dimethylcarbamoyl)phenyl)piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (0.25 g). This material and LiOH (69 mg) were stirred in water/EtOH (2:1, 1.5 mL), concentrated, and HPLC-purified to give Int. **1AE15** 2-((4-(4-

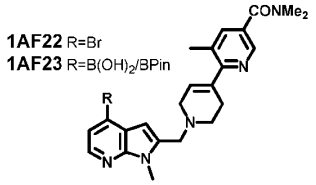
(Dimethylcarbamoyl)phenyl)piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid (0.15 g).



Piperazin-2-one (1.0 g), 4-bromo-*N*,*N*-dimethylbenzamide (1.14 g), K_3PO_4 (6.4 g), $Pd(OAc)_2$ (0.22 g), and RuPhos (0.93 g) were degassed in *tert*-butyl alcohol (15 mL) and stirred ON at 80-90 °C. The mixture was filtered, concentrated, and purified by FC (DCM/MeOH 9:1) to give *N*,*N*-dimethyl-4-(3-oxopiperazin-1-yl)benzamide (0.70 g). 0.25 g of this material and NaH (81 mg) were stirred 1h in THF/DMF (10:1, 5.5 mL) at 0 °C to RT. Int. **1J1** (0.25 g) was added and stirring continued ON at 0 °C to RT. The OL (10% MeOH in DCM/water) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **1AE16** 4-(4-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3-oxopiperazin-1-yl)-*N*,*N*-dimethylbenzamide (0.20 g).

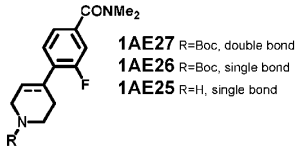


6-Bromo-5-methyl-pyridine-3-carboxylic acid (4.5 g), HATU (9.5 g), and $HN(CH_3)_2$ (8.4 g, HCl salt) were stirred ON in DMF/DIPEA (2.5:1, 45 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated and purified by FC (hexane/EtOAc 3:7) to give Int. **1AE21** 6-bromo-*N*,*N*,5-trimethylnicotinamide (4.2 g). 3.2 g of this material, $NaHCO_3$ (3.9 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (6.1 g), and $PdDPPFCl_2$-DCM (0.27 g) were degassed in dioxane/water (3.7:1, 14 mL) and stirred ON at 110 °C. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **1AE20** *tert*-butyl 5-(dimethylcarbamoyl)-3-methyl-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (4.0 g). 0.25 g of this material was stirred ON in DCM/TFA (8.4:1, 5.6 mL) at 0 °C to RT, concentrated, and triturated in Et_2O/pentane to give Int. **1AE19** *N*,*N*,5-trimethyl-6-(1,2,3,6-tetrahydro-pyridin-4-yl)pyridine-3-carboxamide (0.28 g, TFA salt).



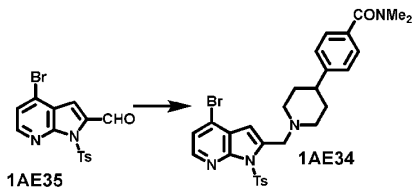
Ints. **1AE19/1J1** (0.5 g/0.5 g) were stirred ON ACN/Et_3N (18:1, 26 mL), concentrated, and HPLC-purified to give Int. **1AE22** 6-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3,6-

dihydro-2H-pyridin-4-yl]-*N*,*N*,5-trimethyl-pyridine-3-carboxamide (0.3 g). Int. **1AE22** (3 g), B_2Pin_2 (5.0 g), KOAc (5.0 g), and $PdDPPFCl_2$-DCM (0.05 g) were degassed in dioxane (25 mL) and stirred ON at 80 °C. The OL (water/EtOAc) was dried and concentrated to give Int. **1AE23** (2-((5-(dimethylcarbamoyl)-3-methyl-3',6'-dihydro-[2,4'-bipyridin]-1'(2'H)-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid/*N*,*N*,3-trimethyl-1'-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide (1.0 g).

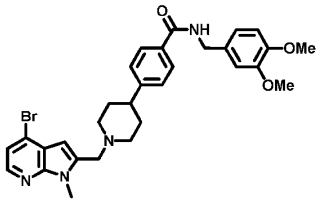


1AE27 R=Boc, double bond
1AE26 R=Boc, single bond
1AE25 R=H, single bond

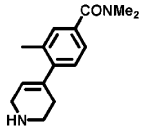
4-Bromo-3-fluoro-*N*,*N*-dimethyl-benzamide (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.51 g), Na_2CO_3 (1.72 g), and $PdDPPFCl_2$-DCM (0.17 g) were degassed in dioxane/water (4:1, 10 mL) and stirred at 100 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give Int. **1AE27** *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.2 g). This material was hydrogenated ON using 10% Pd/C (40 mg) in MeOH (10 mL) under an atmosphere of H_2 in a sealed tube, filtered, and concentrated to give Int. **1AE26** *tert*-butyl 4-[4-(dimethylcarba-moyl)-2-fluoro-phenyl]piperidine-1-carboxylate (0.60 g) that was stirred in 4M HCl in dioxane (10 mL) ON, concentrated, and HPLC-purified to give Int. **1AE25** 3-fluoro-*N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (63 mg).



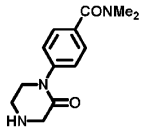
4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g) was stirred 1h in 0.6 M LDA in THF (14 mL) at -78 °C. DMF (1.3 mL) was added and stirring continued 2h at -78 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **1AE35** 4-bromo-1-(*p*-tolyl-sulfonyl)pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.6 g). Int. **1A35** (1.5 g) and *N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (1.6 g, HCl salt) were stirred ON in DCM/DIPEA (5:1, 24 mL). STAB (2.5 g) was added and stirring continued 2h at 0 °C to RT. The OL (DCM/water) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **1AE34** 4-[1-[[4-bromo-1-(*p*-tolylsulfonyl)-pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]-*N*,*N*-dimethyl-benzamide (1.0 g).



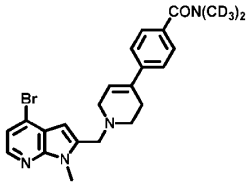
Int. **1AC4** (0.10 g), HATU (164 mg), and (3,4-dimethoxybenzyl)(methyl)-amine (58 mg) were stirred 3h in DMF/DIPEA (25:1, 3.1 mL). The OL (sat. aq. $NaHCO_3$/DCM) was dried, concentrated, and purified by FC (DCM to DCM/MeOH 93:7) to give Int. **1AE36** 4-(1-((4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*-(3,4-dimethoxybenzyl)-*N*-methylbenzamide (0.12 g).



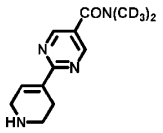
tert-Butyl 4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (4.0 g) was stirred 0.5h in 4M HCl in dioxane (40 mL), concentrated, and triturated in Et_2O to give Int. **1AE38** *N*,*N*,3-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (1.06 g, HCl salt).



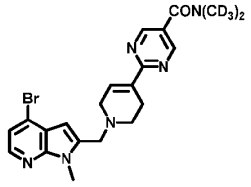
tert-Butyl 3-oxopiperazine-1-carboxylate (0.50 g), 4-bromo-*N*,*N*-dimethylbenzamide (0.68 g), K_3PO_4 (1.06 g), CuI (71 mg), DMDCH (36 mg), were degassed in dioxane (10 mL) and was stirred at 100 °C ON. The OL (water/EtOAc) was dried, concentrated, and purified by FC (EtOAc/MeOH 1:0 to 9:1) to give *tert*-butyl 4-(4-(dimethylcarbamoyl)-phenyl)-3-oxopiperazine-1-carboxylate (0.80 g). 0.23 g of this material was stirred 1h in DCM/TFA (1:1, 6 mL) and concentrated to give Int. **1AE39** *N*,*N*-Dimethyl-4-(2-oxo-piperazin-1-yl)benzamide (0.24 g, TFA salt).



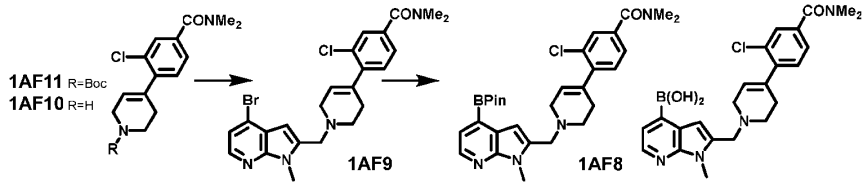
Int. **1J1/1AE7'** (0.33 g/0.30 g), and KI (21 mg) were stirred ON in DMF/DIPEA (7.3:1, 9 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane to EtOAc) to give Int. **1AF1** 4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide (0.20 g).



Methyl 2-bromopyrimidine-5-carboxylate (10.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (15.6 g), K_2CO_3 (25.5 g), and $PdDPPFCl_2$-DCM (1.88 g) were degassed in dioxane/water (4:1, 0.25 L) and stirred ON at 100 °C. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give methyl 2-(1-*tert*-butoxycarbonyl-3,6-dihydro-2H-pyridin-4-yl)pyrimidine-5-carboxylate (14.7 g). This material and LiOH-H_2O (2.15 g) were stirred ON in MeOH/water (1:1, 200 mL) and acidified to precipitate 2-(1-*tert*-butoxy-carbonyl-3,6-dihydro-2H-pyridin-4-yl)pyrimidine-5-carboxylic acid (8.0 g). 4.0 g of this material, $HN(CD_3)_2$ (1.21 g, HCl salt), and HATU (5.27 g) were stirred in DMF/DIPEA (3:1, 27 mL), concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[5-[bis(tri-deuteriomethyl)carbamoyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (2.20 g). This material was stirred in 1h HFIP/10M aq. HCl (30:1, 23 mL), concentrated, and triturated in MTBE to give Int. **1AF2** *N*,*N*-bis(methyl-d_3)-2-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-5-carboxamide (1.40 g, HCl salt).

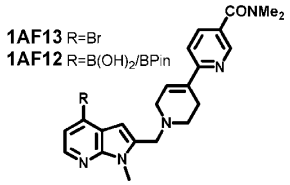


Ints. **1AF2/1J1** (0.5 g/0.5 g) were stirred in ACN/Et_3N (19:1, 26 mL), concentrated, and HPLC-purified to give Int. **1AF3** 2-[1-[(4-Bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*-bis(trideuteriomethyl)pyrimidine-5-carboxamide (0.3 g).

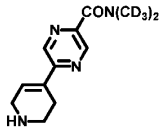


4-Bromo-3-fluoro-*N*,*N*-dimethyl-benzamide (1 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.5 g), Na_2CO_3 (1.7 g), $PdPDDFCl_2$-DCM (0.17 g) were deassed in dioxane/water (4:1, 10 mL) and stirred ON at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give Int. **1AF11** *tert*-butyl 4-[4-(dimethylcarbamoyl)-2-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.2 g). Int. **1AF11** (0.6 g) was stirred ON in 4M HCl in dioxane (10 mL). The residue after concentration was HPLC-purified to give Int. **1AF10** 3-fluoro-*N*,*N*-dimethyl-4-(1,2,3,6-

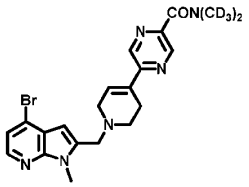
tetrahydropyridin-4-yl)benzamide (0.22 g). Ints. **1AF10/1J1** (0.5 g/0.5 g) were stirred ON in ACN/Et_3N (19:1, 26 mL), concentrated, and HPLC-purified to give Int. **1AF9** 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)-methyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*,3,5-tetramethyl-benzamide (0.3 g). Int. **1AF9** (3 g), B_2pin_2 (5 g), KOAc (5 g), and $PdDPPFCl_2$-DCM (50 mg) were degassed in dioxane and stirred ON at 80 °C. The OL (EtOAc/water) was dried and concentrated to give Int. **1AF8** 3-chloro-*N*,*N*-dimethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide / (2-((4-(2-chloro-4-(dimethylcarbamoyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (1 g).



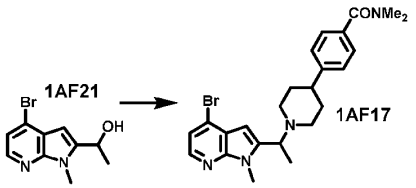
Ints. **1S5/1J1** (0.5 g/0.5g, as the HCl salt) were stirred ON in ACN/Et_3N (19:1, 26 mL), concentrated, and HPLC-purified to give Int. **1AF13** 6-[1-[(4-bromo-1-methyl-pyrrolo-[2,3-b]pyridin-2-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*-dimethyl-pyridine-3-carboxamide (0.3 g). Int. **1AF13** (3.0 g), KOAc (5.0 g), B_2Pin_2 (5.0 g), and $PdDPPFCl_2$-DCM (50 mg) were degassed in dioxane (25 mL) and stirred at 80 °C ON. The OL (water/EtOAc) was concentrated to give Example **1AF12** *N*,*N*-Dimethyl-1'-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide / (2-((5-(dimethylcarbamoyl)-3',6'-dihydro-[2,4'-bipyridin]-1'(2'H)-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (1.0 g).



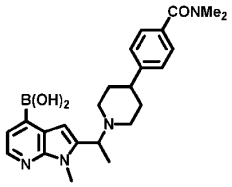
Methyl 5-bromopyrazine-2-carboxylate (11.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (17.2 g), K_2CO_3 (28.0 g), $PdPDDFCl_2$-DCM (2.07 g) were deassed in dioxane/ water (5:1, 250 mL) and stirred ON at 100 °C. The aq. layer (water/EtOAc) was acidified to precipitate 5-(1-*tert*-butoxy-carbonyl-3,6-dihydro-2H-pyridin-4-yl)pyrazine-2-carboxylic acid (12.0 g). 4.5 g of this material, $HN(CD_3)_2$ (1.40 g, HCl salt), and HATU (6.20 g) were stirred ON in DMF/DIPEA (2.6:1, 28 mL), concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[5-[bis(trideuteriomethyl)-carbamoyl]pyrazin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (2.0 g). This material was stirred in 1h HFIP/10M aq. HCl (29:1, 21 mL), concentrated, and triturated in MTBE to give Int. **1AF14** 5-(1,2,3,6-Tetrahydropyridin-4-yl)-*N*,*N*-bis(trideuteriomethyl)pyrazine-2-carboxamide (0.88 g, HCl salt).



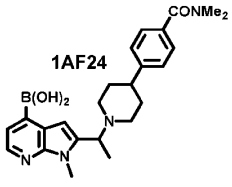
Ints. **1AF14/1J1** (0.5 g/0.5 g), and Et_3N (1.2 mL) were stirred ON in ACN (25 mL), concentrated, and HPLC-purified to give Int. **1AF15** 5-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-*N*,*N*-bis(methyl-d_3)pyrazine-2-carboxamide (0.3 g).



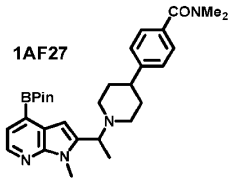
1.0M MeMgBr in THF (185 mL) was added to a solution of Int. **1AB8** (29.5 g) in THF (1.2 L) at 0 °C and stirring continued 3h. The OL (sat. aq. NH_4Cl/EtOAc) was washed with brine, dried, concentrated and purified by FC (pentane/EtOAc 3:1) to give Int. **1AF21** 1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethan-1-ol (25.5 g). 0.30 g of this material was stirred in toluene/$SOCl_2$ (12.5:1, 10.8 mL) at 0 °C before stirring 0.5h at 110 °C. The mixture was concentrated. The residue, Cs_2CO_3 (1.15 g), KI (0.98 g), and *N*,*N*-dimethyl-4-(4-piperidyl)-benzamide (0.41 g) were stirred ON in ACN (10 mL) at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM / MeOH 95:5) to give Int. **1AF17** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-piperidin-4-yl)-*N*,*N*-dimethylbenzamide (0.28 g).



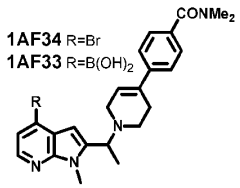
Int. **1AF17** (0.70 g), B_2Pin_2 (0.51 g), KOAc (0.4 g), and $Pd(PPh_3)_2Cl_2$ (0.1 g) were degassed in THF (50 mL) and stirred ON at 100 °C, filtered, concentrated, and triturated in pentane to give Int. **1AF24** (2-(1-(4-(4-(dimethyl-carbamoyl)phenyl)piperidin-1-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (0.85 g).



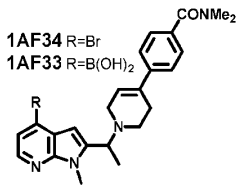
Int. **1AF17** (0.70 g), B_2Pin_2 (0.51 g), KOAc (0.4 g), and $Pd(PPh_3)_2Cl_2$ (0.1 g) were degassed in THF (50 mL) and stirred ON at 100 °C, filtered, concentrated, and triturated in pentane to give Int. **1AF24** (2-(1-(4-(4-(dimethyl-carbamoyl)phenyl)piperidin-1-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (0.85 g).



Int. **1AF17** (0.70 g), B_2Pin_2 (38 mg), KOAc (45 mg), and $PdDPPFCl_2$-DCM (25 mg) were degassed in dioxane (10 mL) and stirred ON at 110 °C. The mixture was filtered, concentrated, and purified by FC (pentane/EtOAc 95:5) to give Int. **1AF27** *N,N*-dimethyl-4-(1-(1-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo-[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzamide (0.85 g).

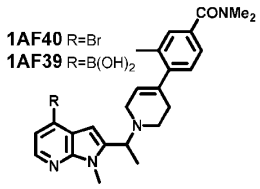


1-(4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethan-1-ol (0.20 g) was stirred 1.5h in toluene/$SOCl_2$ (29:1, 5.2 mL) at 0 °C to 110 °C and concentrated. The residue, KI (10 mg), and Int. **1AF5** (0.23 g) were stirred ON in DMF/DIPEA (2.5:1, 2.8 mL) at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1 to 85:15) to give Int. **1AF34** 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-*N,N*-dimethyl-benzamide (80 mg). Int. **1AF34** (0.32 g), B_2Pin_2 (24 mg), KOAc (25 mg), and $PdCl_2(PPh_3)_2$ (48 mg) were degassed in THF (5 mL) and stirred ON at 90 °C. The mixture was filtered, concentrated, and purified by FC (pentane/EtOAc 95:5) to give Int. **1AF33** (2-(1-(4-(4-(dimethylcarbamoyl)-phenyl)-3,6-dihydropyridin-1(2H)-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-boronic acid (0.50 g).

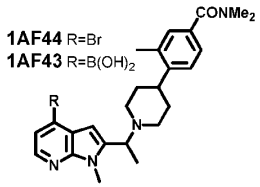


1-(4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethan-1-ol (0.20 g) was stirred 1.5h in toluene / $SOCl_2$ (29:1, 5.2 mL) at 0 °C to 110 °C and concentrated. The residue, KI (10 mg), and Int. **1AF5** (0.23 g) were stirred ON in DMF/DIPEA (2.5:1, 2.8 mL) at 0 °C to RT. The OL (water/EtOAc)

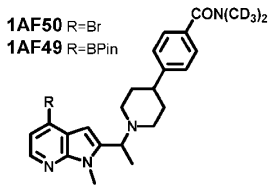
was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1 to 85:15) to give Int. **1AF34** 4-[1-[1-(4-bromo-1-methyl-pyrrolo-[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*-dimethyl-benzamide (80 mg). Int. **1AF34** (0.32 g), B_2Pin_2 (24 mg), KOAc (25 mg), and $PdCl_2(PPh_3)_2$ (48 mg) were degassed in THF (5 mL) and stirred ON at 90 °C. The mixture was filtered, concentrated, and purified by FC (pentane/EtOAc 95:5) to give Int. **1AF33** (2-(1-(4-(4-(dimethyl-carbamoyl)-phenyl)-3,6-dihydropyridin-1(2H)-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-boronic acid (0.50 g).



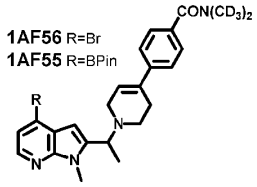
Int. **1AF40** 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*,3-trimethyl-benzamide (0.15 g) was prepared similarly to Int. **1AF17** from Int. **1AF21** (0.20 g) and Int. **1AE38** (0.37 g, TFA salt). Int. **1AF39** (2-(1-(4-(4-(dimethylcarbamoyl)-2-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)-ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (40 mg) was prepared similarly to Int. **1AF33** from Int. **1AF40** (50 mg).



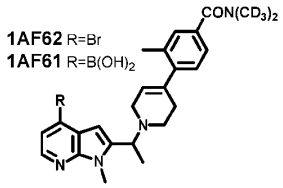
Int. **1AF44** 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-4-piperidyl]-*N*,*N*,3-trimethyl-benzamide (0.15 g) was prepared similarly to Int. **1AF17** from Ints. **1AF24/1AE38** (0.20 g/0.42 g, TFA salt). Int. **1AF43** (2-(1-(4-(4-(dimethylcarbamoyl)-2-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]-pyridin-4-yl)boronic acid (0.60 g) was prepared similarly to Int. **1AF39** from Int. **1AF44** (0.50 g).



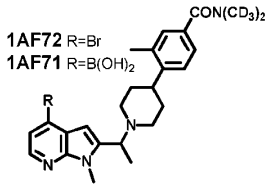
Int. **1AF50** 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-4-piperidyl]-*N*,*N*-bis(trideuterio-methyl)benzamid (0.65 g) was prepared similarly to Int. **1AF17** from Ints. **1AF21/1D7** (0.35 g/0.53 g, TFA salt). Int. **1AF49** [2-[1-[4-[4-[bis(trideuterio-methyl)carbamoyl]phenyl]-1-piperidyl]ethyl]-1-methyl-pyrrolo[2,3-b]-pyridin-4-yl]-boronic acid (0.41 g) was prepared similarly to Int. **1AF25** from Int. **1AF50** (0.32 g) and B_2Pin_2 (0.34 g).



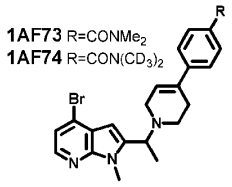
Int. **1AF56** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide (0.60 g) was prepared similarly to Int. **1AF34** from Int. **1AF21** (0.50 g) and Int. 1**AE7'** (0.69 g). Int. **1AF55** [2-[1-[4-[4-[bis(trideuteriomethyl)carbamoyl]phenyl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]boronic acid (0.55 g) was prepared similarly to Int. **1AF39** from Int. **1AF56** (0.50 g).



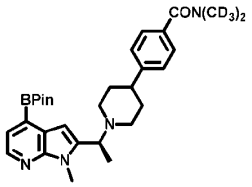
Int. **1AF62** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-3-methyl-*N*,*N*-bis(methyl-d_3)benzamide (0.46 g) was prepared similarly to Int. **1AF17** from Ints. **1AF24/1S20** (0.50 g/0.70 g). Int. **1AF61** (2-(1-(4-(4-(bis(methyl-d_3)carbamoyl)-2-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (0.75 g) was prepared similarly to Int. **1AF55** from B_2Pin_2 (0.52 g) and Int. **1AF62** (0.5 g).



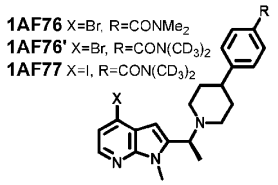
Int. **1AF72** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-3-methyl-*N*,*N*-bis-(methyl-d_3)benzamide (90 mg) was prepared similarly to Int. **1AF17** from Ints. **1AF24/1S22** (0.10 g/0.19 g, TFA salt). Int. **1AF71** (2-(1-(4-(4-(bis(methyl-d_3)carbamoyl)-2-methylphenyl)piperidin-1-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (0.10 g) was prepared similarly to Int. **1AF55** from Int. **1AF72** (90 mg) and B_2Pin_2 (0.12 g).



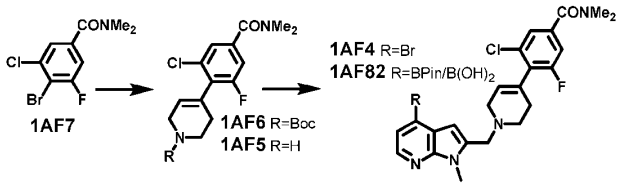
Int. **1AF21** (1.20 g) was stirred 1h in toluene/$SOCl_2$ (5.9:1, 23.5 mL) at 0 °C to 110 °C and concentrated. The residue, Cs_2CO_3 (4.60 g), KI (0.39 g), and Int. **1AE7** (1.30 g) were stirred ON in ACN (30 mL) at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1 to 85:15) to give Int. **1AF73** 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*-dimethyl-benzamide (1.0 g). Int. **1AF74** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide (0.60 g) was prepared similarly from Ints. **1AE7'/1AF21** (0.69 g/0.50 g).



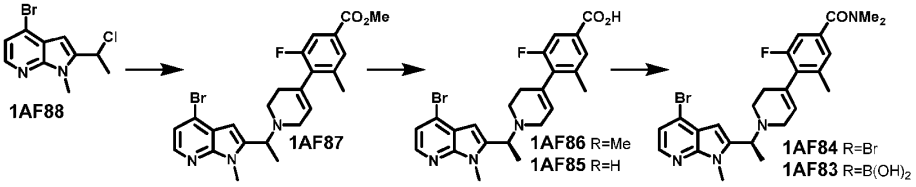
Int. **1AF76** (1.50 g), B_2Pin_2 (1.60 g), KOAc (0.93 g), and PdPDDFCl$_2$-DCM (0.26 g) were degassed in dioxane (30 mL) and stirred 6h at 90 °C, filtered, concentrated, and triturated in Et_2O to give Int. **1AF75** (S)-*N*,*N*-bis(methyl-d_3)-4-(1-(1-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-piperidin-4-yl)benzamide (1.30 g).



Int. **2C36** (0.35 g), HATU (0.3 g), and $HN(CD_3)_2$ (77 mg, HCl salt) were stirred ON in DMF/DIPEA (14.7:1, 10.7 mL) at 0 °C to RT and diluted with water to precipitate Int. **1AF76** (0.30 g). Int. **1AF76'** (3.5 g) was prepared similarly from Int. **2C36** (4.5 g). Int. **1AF76'** (0.10 g), CuI (20 mg), NaI (63 mg), and DMDCH (30 mg) were degassed in dioxane (5 mL) and stirred at 110 °C ON and filtered. The OL (DCM/aq. NH_3) was dried, concentrated, and purified by FC (DCM/MeOH 97:3) to give Int. **1AF77** (S)-4-(1-(1-(4-iodo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-*N*,*N*-bis(methyl-d_3)-benzamide (50 mg). The absolute configuration of **1AF76** (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)-ethyl)piperidin-4-yl)-*N*,*N*-dimethylbenzamide and **1AF76'** (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)ethyl)-piperidin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide was determined to S by VCD.

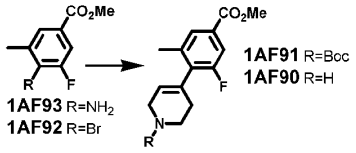


CDI (7.04 g) was added to a solution of 4-bromo-3-fluoro-5-methyl-benzoyl chloride (11.0 g) in DCM (50 mL) at 0 °C and stirring continued 0.5h. $HN(CH_3)_2$ (7.1 g, HCl salt) was added before refluxing 5h. The mixture was washed with water, dried, and concentrated to give Int. **1AF7** 4-bromo-3-fluoro-*N*,*N*,5-trimethyl-benzamide (12.4 g). This material, *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (15.0 g), K_2CO_3 (18.3 g), and $PdDPPFCl_2$-DCM (0.73 g) were degassed in dioxane (100 mL) and stirred 48h at 90 °C. The OL (water/MTBE) was dried and concentrated to give Int. **1AF6** *tert*-butyl 4-(2-chloro-4-(dimethylcarbamoyl)-6-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (11.0 g). Int. **1AF6** (0.6 g) was stirred 0.5h in THF/4M HCl in dioxane (1:1, 2 mL). The OL (water/EtOAc) was dried and concentrated to give Int. **1AF5** 3-chloro-5-fluoro-*N*,*N*-dimethyl-4-(1,2,3,6-tetrahydro-pyridin-4-yl)benzamide (0.25 g, HCl salt). This material, K_2CO_3 (0.37 g), and Int. **1J1** (0.23 g) were stirred in DMF (5 mL) ON. The OL (water/MTBE) was layer was dried and concentrated to give Int. **1AF4** 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)-methyl]-3,6-dihydro-2H-pyridin-4-yl]-3-chloro-5-fluoro-*N*,*N*-dimethyl-benzamide (0.17 g). This material, B_2Pin_2 (0.17 g), KOAc (0.10 g), and $PdDPPFCl_2$-DCM (6 mg) were degassed in dioxane (5 mL) and stirred 48h at 100 °C. The OL (water/MTBE) was layer was dried and concentrated to give Int. **1AF82** 3-Chloro-5-fluoro-*N*,*N*-dimethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide/(2-((4-(2-chloro-4-(dimethyl-carbamoyl)-6-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-boronic acid (0.19 g).

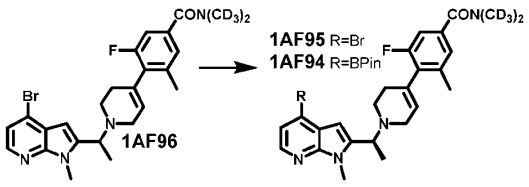


Int. **1AF21** (8 g) was stirred 0.5h in toluene/$SOCl_2$ (4:1, 123 mL) at 0 °C to 80 °C and concentrated to give Int. **1AF88** (7.5 g). Ints. **1AF88/1AF90** (7.5 g, 7.8 g, HCl salt), Cs_2CO_3 (31 g), and KI (23 g) were stirred ON in ACN (100 mL) at 0 °C to RT. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 41:9) to give Int. **1AF87** methyl 4-[1-[1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-3-fluoro-5-methyl-benzoate (3.9 g). Int. **1AF87** (0.2 g) was resolved by SFC using a Chiralpak AD-H 250x21 mm 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% MeOH (70 g/min) and a back pressure of 100 bar to give Int. **1AF86** methyl (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoate (70 mg, second peak). The absolute configuration was determined by VCD for Int. **1AF86**. Int. **1AF86** (2.5 g) and LiOH (1.1 g) were stirred 1h in THF/MeOH/water (2:1:1, 20 mL) at 0 °C to RT. The mixture was concentrated and triturated in aq. citric acid to precipitate Int. **1AF85** 4-[1-[(1S)-1-(4-bromo-1-methyl-pyrrolo[2,3-

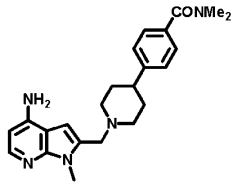
b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-3-fluoro-5-methyl-benzoic acid (2.3 g). 4-[1-[(1S)-1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-3-fluoro-5-methyl-benzoic acid (1.8 g), HATU (2.2 g), and $HNMe_2$ (0.93 g, HCl salt) were stirred ON in DMF/DIPEA (6.1:1, 23.3 mL) at 0 °C to RT. The mixture was diluted with water to precipitate Int. **1AF84** 4-[1-[(1S)-1-(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-3-fluoro-*N*,*N*,5-trimethyl-benzamide (1.5 g). Int. **1AF84'** (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methyl-*N*,*N*-bis(methyl-d_3)benzamide was prepared similarly using the HCl salt of $HN(CD_3)_2$. Int. **1AF84** (1.1 g), KOAc (0.86 g), B_2Pin_2 (1.1 g), and $PdDPPFCl_2$-DCM (0.18 g) stirred 1h in dioxane (10 mL) at 110 °C under MW conditions. The mixture was filtered, concentrated, and triturated in pentane to give Int. **1AF83** [2-[(1S)-1-[4-[4-(dimethylcarbamoyl)-2-fluoro-6-methyl-phenyl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]boronic acid (1.3 g).



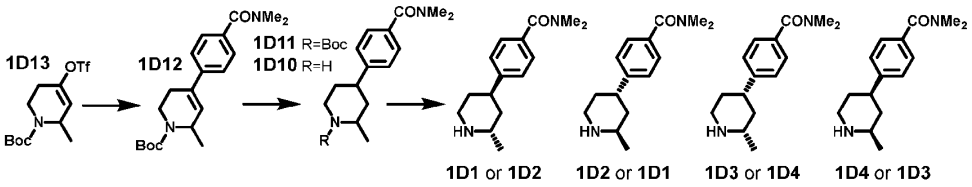
2-Fluoro-4-iodo-6-methyl-aniline (20 g) and $PdDPPFCl_2$-DCM were stirred ON in $MeOH/Et_3N$ (23:1, 522 mL) under an atmosphere of CO (200 psi) at 80 °C. The mixture was filtered. The OL (EtOAc/10% aq. EDTA) was dried and concentrated to afford Int. **1AF93** methyl 4-amino-3-fluoro-5-methyl-benzoate (14 g). Int. **1AF93** (25 g), *tert*-butyl nitrite (21.1 g), and $CuBr_2$ (152 g) were stirred ON in ACN (500 mL) at 0 °C to 80 °C. The mixture was cooled to 0 °C, diluted with sat. aq. $NaHCO_3$, and filtered. The OL (EtOAc/10% aq. NH_3) was concentrated and purified by FC (hexane/EtOAc 9:1) to give Int. **1AF92** methyl 4-bromo-3-fluoro-5-methyl-benzoate (21 g). Int. **1AF92** (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.9 g), $NaHCO_3$ (1.29 g), and $PdDPPFCl_2$-DCM (0.33 g) were degassed in dioxane/water (5:1, 18 mL) and stirred ON at 110 °C. The mixture was filtered. The OL (EtOAc/water) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **1AF91** *tert*-butyl 4-(2-fluoro-4-(methoxycarbonyl)-6-methyl-phenyl)-3,6-dihydro-pyridine-1(2H)-carboxylate (0.65 g). Int. **1AF91** (10 g) was stirred in 1.5 M HCl in dioxane (160 mL) at 0 °C to RT. The residue after concentration was triturated in Et_2O to give Int. **1AF90** methyl 3-fluoro-5-methyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzoate (13 g, HCl salt).



Ints. **1AF88/1AE12** (4.5 g, 5.5 g, HCl salt), Cs_2CO_3 (27 g), and KI (1.4 g) were stirred ON in ACN (50 mL) at 0 °C to RT. The mixture was diluted with water, filtered, and concentrated. The OL (EtOAc/water) was dried and concentrated. The residue was mixed with another batch prepared similarly on 1.5 g scale and purified by FC (pentane/EtOAc 3:7) to give Int. **1AF96** (4.8 g). Int. **1AF96** (5.0 g) was resolved by SFC using a Lux Cellulose.2 250x30 mm 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% IPA (90 g/min) and a back pressure of 120 bar to give Int. **1AF95** (1.5 g, peak 2). Int. **1AF95** (0.5 g), B_2Pin_2 (0.38 g), KOAc (0.29 g), and $PdDPPFCl_2$-DCM (81 mg) were degassed in dioxane (5 mL) and stirred 1h at 120°C under MW conditions. The mixture was concentrated and triturated in pentane/Et_2O to give Int. **1AF94** 3-fluoro-5-methyl-4-[1-[(1S)-1-[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]-pyridin-2-yl]ethyl]-3,6-dihydro-2H-pyridin-4-yl]-*N*,*N*-bis(trideuteriomethyl)benzamide (0.6 g).

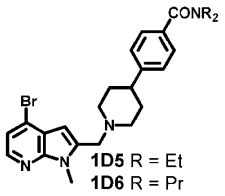


Int. **1AB1** (0.29 g), CuI (0.12 g), and NaN_3 (83 mg) were degassed in DMSO/DMEDA (14.4:1, 1.4 mL) and stirred at 100 °C. The OL (sat. aq. NH_4Cl/EtOAc) was washed with water, brine, dried, concentrated, HPLC-purified, and triturated in MTBE to give Int. **1C1** 4-[1-[(4-Amino-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*,*N*-dimethyl-benzamide (0.22 g).

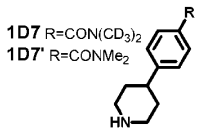


2.0M LDA in THF (28.1 mL) was added to a solution of *tert*-butyl 2-methyl-4-oxo-piperidine-1-carboxylate (10.0 g) in THF (200 mL) -78 °C. The mixture was stirred for 0.3h at -78 °C. 1,1,1-Trifluoro-*N*-phenyl-*N*-((trifluoro-methyl)sulfonyl)methane-sulfonamide (20 g in THF (10 mL)) was added and stirring continued 3h at -78 °C to RT. The OL (aq. NH_4Cl/EtOAc) was washed with water and brine, dried, and concentrated to give Int. **1D13** *tert*-butyl 6-methyl-4-(trifluoromethyl-sulfonyloxy)-3,6-dihydro-2H-pyridine-1-carboxylate (18.0 g). Int. **1D13** (10 g), Na_2CO_3 (7.67 g), (4-(dimethyl-carbamoyl)phenyl)boronic acid (8.38 g), and $PdDPPFCl_2$-DCM (1.20 g) were degassed in toluene/water (5:1, 120 mL) and refluxed ON. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **1D12** *tert*-butyl 4-[4-(dimethyl-carbamoyl)phenyl]-6-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (5.2 g). 5.0 g of this material was hydrogenated ON using 10% Pd/C (2.50 g) and H_2 (50-60 psi) in EtOH (75 mL), filtered, concentrated, and purified by FC (hexane/EtOAc 35:65) to give Int. **1D11** *tert*-butyl 4-[4-(dimethylcarbamoyl)phenyl]-2-methyl-

piperidine-1-carboxylate (4.0 g). 5.0 g of this material was stirred ON in DCM/TFA (3.6:1, 26 mL) at 0 °C to RT, concentrated, and triturated in Et_2O/pentane to give Int. **1D10** *N,N*-dimethyl-4-(2-methyl-4-piperidyl)benzamide (4.0 g, TFA salt). Int. **1D10** (10.8 g) was separated into the racemic *cis* and *trans* diastereomers by SFC using a Chiral Art Cellulose SC 250x30 5µm column operated at 30 °C and an eluent of 60% CO_2 and 40% MeOH containing 0.5% $HNEt_2$ (90 g/min) and a back pressure of 120 bar to give the *cis* racemate (first two peaks; 3.0 g) and the *trans* racemate (last two peaks; 7.0 g). The *trans* racemate (7.0 g) was resolved by SFC on a Sepiatec instrument fitted with a Chiralpak IK 250X30 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% MeOH containing 0.5% NH_3 at a (90 g/min) and a back pressure of 100 bar to give Int. **1D1** *N,N*-dimethyl-4-((2S,4R)-2-methylpiperidin-4-yl)benzamide (0.95 g, first peak) and Int. **1D2** *N,N*-dimethyl-4-((2R,4S)-2-methylpiperidin-4-yl)benzamide (1.2 g, second peak). The absolute configuration was determined by VCD for Int. **1D1** and **1D2**. The *cis* racemate (3.0 g) was resolved by SFC using a Chiralpak IGK 250x30 5µm column operated at 30 °C and an eluent MeOH containing 0.5% NH_3 (30 mL/min) and a back pressure of 100 bar to give Int. **1D3** *N,N*-dimethyl-4-((2R,4R)-2-methylpiperidin-4-yl)benzamide (0.70 g, first peak) and Int. **1D4** *N,N*-dimethyl-4-((2S,4S)-2-methyl-piperidin-4-yl)benzamide (0.90 g, second peak). The absolute configuration was determined by VCD for Int. **1D3** and **1D4**.

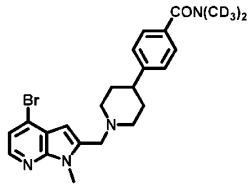


Int. **1CA4** (20 mg), $HNEt_2$ (24 µL), and HATU (27 mg) were stirred 0.25h in DMF (1 mL). The OL (sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, and concentrated to give Int. **1D5** 4-(1-((4-Bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N,N*-diethylbenzamide (30 mg). Int. **1D6** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N,N*-dipropyl-benzamide (37 mg, was prepared similarly from $HNPr_2$.

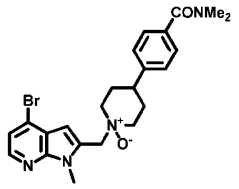


1-(1,1-Dimethylethyl) 4-(4-carboxyphenyl)-1-piperidinecarboxylate (5.1 g), HATU (13 g), and $HN(CD_3)_2$ (2.5 g, HCl salt) were stirred ON in DMF/DIPEA (1.8:1, 47 mL). Water was added to precipitate solid that was dissolved in DCM/MeOH (9:1), dried, concentrated, and purified by FC (hexane/EtOAc 2:3) to give *tert*-butyl 4-[4-[bis-(trideuteriomethyl)carbamoyl]phenyl]piperidine-1-carboxylate (4.8 g). 1.1 g of this material was stirred ON in DCM/TFA (3.6:1, 26 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **1D7** *N,N*-Bis(methyl-d_3)-4-(1l2-piperidin-4-yl)-

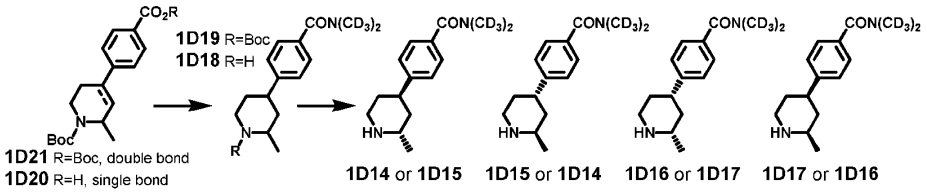
benzamide (0.81 g, TFA salt). Int. **1D7'** *N*,*N*-dimethyl-4-(4-piperidyl)benzamide (9 g, HCl salt) was prepared similarly from 1-(1,1-dimethylethyl) 4-(4-carboxyphenyl)-1-piperidine-carboxylate (17 g) and $HN(CH_3)_2$ (13.6 g, HCl salt).



Int. **1AC4** (4.0 g), EDC (4.7 g, HCl salt), HOBt (2.5 g), and $HN(CD_3)_2$ (1.4 g, HCl salt) were stirred ON in DMF/DIPEA (8.2:1, 89 mL). The residue after concentration was purified by FC (EtOAc/hexane) to give Int. **1D8** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*,*N*-bis(methyl-d_3)benzamide (2.7 g).

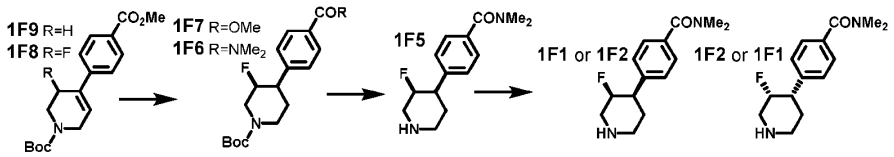


Int. **1AB1** (1 g) mCPBA (0.59 g) were stirred 2h in DCM (10 mL) at 0 °C. The OL (sat. aq. $NaHCO_3$/DCM) was dried and concentrated. The residue was stirred 1h in TFA, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **1D9** 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-1-oxido-piperidin-1-ium-4-yl]-*N*,*N*-dimethyl-benzamide (0.77 g).



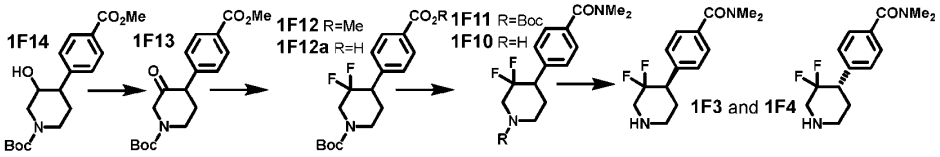
Int. **1D21** *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)-6-methyl-3,6-dihydropyridine-1(2H)-carboxylate (5.20 g) was prepared similarly to Int. **1D12** from Int. **1D13** (10.0 g) and (4-(methoxycarbonyl)phenyl)boronic acid (7.82 g). Int. **1D20** *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)-2-methylpiperidine-1-carboxylate (3.0 g) was prepared similarly to Int. **1D11** from Int. **1D21** (3.5 g). Int. **1D20** (3.0 g) and $LiOH{\cdot}H_2O$ (1.50 g) were stirred 4h in THF/MeOH/water (1.3:1:1, 50 mL) at 0 °C to RT and concentrated. The OL (aq. citric acid/EtOAc) was dried and concentrated to give 4-(1-*tert*-butoxy-carbonyl-2-methyl-4-piperidyl)benzoic acid (1.50 g) 6.0 g of this material, $HN(CD)_3)_2$ (2.47 g, HCl salt), HOBt (1.90 g), and EDC-HCl (2.70 g) were stirred ON in DMF/DIPEA (1.9:1, 46 mL) at 0 °C to RT. The OL (water/EtOAc) was dried and concentrated to give Int. **1D19** *tert*-butyl 4-(4-(bis(methyl-d_3)carbamoyl)-phenyl)-2-methylpiperidine-1-carboxylate (4.50 g). 3.5 g of this material was stirred 4h in DCM/ TFA (2.5:1, 70 mL) at 0 °C to RT, concentrated, and triturated in

Et_2O/pentane to give Int. **1D18** 4-(2-methyl-4-piperidyl)-*N*,*N*-bis(trideuteriomethyl)benzamide (3.50 g, TFA salt). Int. **1D18** was separated into Ints. **1D14** *N*,*N*-bis(methyl-d_3)-4-((2S,4R)-2-methylpiperidin-4-yl)benzamide, Int. **1D15** *N*,*N*-bis-(methyl-d_3)-4-((2R,4S)-2-methylpiperidin-4-yl)benzamide, Int. **1D16** *N*,*N*-bis(methyl-d_3)-4-((2R,4R)-2-methylpiperidin-4-yl)benzamide, and Int. **1D17** *N*,*N*-bis(methyl-d_3)-4-((2S,4S)-2-methyl-piperidin-4-yl)benzamide as described for Ints. **1D1-1D4**. The absolute configurations of these compounds were not determined. The absolute configurations of these compounds were determined by comparison to RT on chiral chromatography *vs.* Int. **1D1-1D4**.

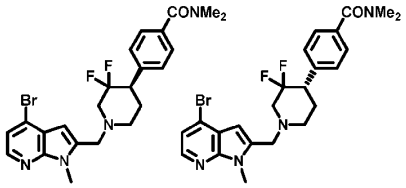


Methyl 4-bromobenzoate (25 g), $PdDPPFCl_2$-DCM (4.7 g), $NaHCO_3$ (49 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (39 g) were degassed in 1,4-dioxane/water (5:1, 0.6 L) and stirred ON at 110 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 99:1) to give Int. **1F9** *tert*-butyl 4-(4-(methoxycarbonyl)-phenyl)-3,6-dihydro-pyridine-1(2H)-carboxylate (18 g). Int. **1F9** (38 g) and SelectFluor (7.2 g) were stirred 1h in ACN/water (3:1, 0.64 L). SelectFluor (2.1 g) was added and stirring continued 1h. The OL (EtOAc/sat. aq. $NaHCO_3$) was dried, concentrated, and purified by FC (hexane/EtOAc 85:15) to give Int. **1F8** *tert*-butyl-3-fluoro-4-(4-methoxy-carbonylphenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (6.0 g). Int. **1F8** (4.8 g) was hydrogenated ON using 10% Pd/C (0.48 g) in EtOAc (200 mL), filtered, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **1F7** *tert*-butyl-3-fluoro-4-(4-methoxycarbonylphenyl)piperidine-1-carboxylate (3.2 g). Int. **1F7** (3.5 g) and $LiOH\text{-}H_2O$ (1.4 g) were stirred ON in $MeOH/THF/H_2O$ (3:2:1; 25 mL) at 0 °C to RT and concentrated. The OL (10% MeOH in DCM/aq. citric acid) was dried and concentrated to give *cis*-4-(1-(*tert*-butoxycarbonyl)-3-fluoro-piperidin-4-yl)benzoic acid (2.1 g). 2.5 of this compound, HATU (4.4 g), and $HN(CH_3)_2$ (1.9 g, HCl salt) were stirred ON in DMF/DIPEA (2.4:1, 35 mL) at 0 °C to RT. The OL (water/5% MeOH in DCM) was dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **1F6** *cis-tert*-butyl-4-[4-(dimethylcarbamoyl)-phenyl]-3-fluoro-piperidine-1-carboxylate (2.4 g). Int. **1F6** (1.5 g) was stirred ON in DCM/TFA (3,8:1, 13 mL) at 0 °C to RT and concentrated. The OL (aq. $NaHCO_3/Et_2O$ and 10% MeOH in DCM) was dried and concentrated to give Int. **1F5** *N*,*N*-dimethyl-4-[*cis*-3-fluoro-4-piperidyl]-benzamide (1.19 g). This material was resolved by SFC using a Lux Cellulose-4 250x30 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% 0.5% *iso*-propyl amine in IPA (100 g/min) and a back pressure of 100 bar to give Int. **1F1** (0.47 g) and Int. **1F2** (0.50 g) 4-((3S,4R)-

3-Fluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide and 4-((3R,4S)-3-fluoropiperidin-4-yl)-*N*,*N*-dimethyl-benzamide. The absolute configurations of these compounds were not determined.

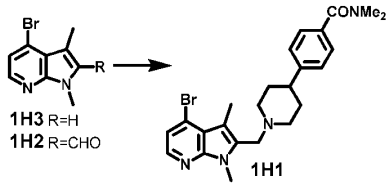


Int. **1F9** (10 g) was stirred ON in THF/2M BH_3-DMS in THF (11.6:1, 217 mL) at 0 °C to RT. 2M aq. NaOH (38 mL) and 30% aq. H_2O_2 (5.9 mL) were added and stirring was continued at 0 °C to RT over 1h. The OL (sat. aq. NaS_2O_3/EtOAc) was washed with water and brine, dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **1F14** *tert*-butyl 3-hydroxy-4-(4-(methoxy-carbonyl)phenyl)piperidine-1-carboxylate (7.4 g). Int. **1F14** (8.0 g) and DMP (5.1 g) were stirred ON in DCM (200 mL) at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **1F13** *tert*-butyl 4-(4-methoxy-carbonyl-phenyl)-3-oxo-piperidine-1-carboxylate (5.2 g). Int. **1F13** (5.0 g) was stirred ON in DCM/50% Deoxo-Fluor in THF (12.2:1, 108 mL) at -78 °C to RT ON. The OL (aq. $NaHCO_3$/DCM) was washed with sat. aq. citric acid, dried, concentrated, and purified by FC (hexane) to give Int. **1F12** *tert*-butyl 3,3-difluoro-4-(4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (2.5 g). This material and LiOH-H_2O (1.5 g) were stirred in MeOH/THF/H_2O (3:3:1; 60 mL) at 0 °C to RT over 4h, concentrated, and triturated in dilute aq. citric acid to give Int. **1F12a** 4-(1-*tert*-butoxycarbonyl-3,3-difluoro-4-piperidyl)benzoic acid (2.3 g). Int. **1F12a** (4.8 g), HATU (6.4 g), and $HN(CH_3)_2$ (2.3 g, HCl salt) were stirred ON in DMF/DIPEA (13.2:1, 108 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane / EtOAc 1:4) to give Int. **1F11** *tert*-butyl 4-(4-(dimethylcarbamoyl)-phenyl)-3,3-difluoro-piperidine-1-carboxylate (4.5 g). Int. **1F11** (4.2 g) was stirred ON in DCM/TFA (27:1, 83 mL) at 0 °C to RT and concentrated. The OL (5% MeOH in DCM/sat. aq. $NaHCO_3$) was dried and concentrated to give Int. **1F10** 4-(3,3-difluoro-4-piperidyl)-*N*,*N*-dimethyl-benzamide (3 g). This material was resolved by SFC using a Chiralpak IG 250x30 5µm column operated at 30 °C and an eluent of 60% CO_2 and 40% MeOH (80 g/min) and a back pressure of 60 bar to give Int. **1F3** (1.1 g) and Int. **1F4** (1.0 g) (R)-4-(3,3-Difluoropiperidin-4-yl)- *N*,*N*-dimethylbenzamide and (S)-4-(3,3-difluoropiperidin-4-yl)- *N*,*N*-dimethylbenzamide. The absolute configurations of these compounds were not determined.

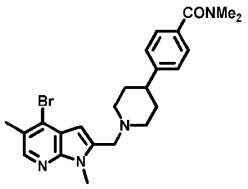


Ints. **1J1/1F3** (45 mg/60 mg), Cs_2CO_3 (169 mg), NaI (26 mg) were stirred in DMF (1 mL) for 0.5 h and HPLC-purified to give Int. **1F15** (48 mg). Int. **1F16** was prepared similarly from Int. **1F4**.

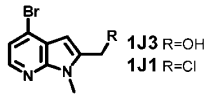
Ints. **1F15** and **1F16** (R)-4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3,3-difluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide and (S)-4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3,3-difluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide. The absolute configurations were not determined for these compounds.



4-Bromo-3-methyl-1H-pyrrolo[2,3-b]pyridine (0.51 g) and NaH (0.12 g) were stirred 1h in DMF (5 mL) at 0 °C before MeI (0.3 mL) was added and stirring continued for 0.3h. The OL (water/EtOAc/Et_2O) was washed with brine, dried, concentrated to give Int. **1H3** 4-bromo-1,3-dimethyl-pyrrolo[2,3-b]pyridine (0.53 g). This material was stirred 2h in THF/1.0 M LDA in THF (2.9:1, 13.5 mL) -78 °C before DMF (1 mL) was added and stirring continued 2h at -78 °C to RT. The OL (sat. aq. NH_4Cl / EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 1:1) to give Int. **1H2** 4-bromo-1,3-dimethyl-pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.17 g). Int. **1H2** (30 mg) and *N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (42 mg) were stirred 0.5h in DCE (2 mL) . STAB (57 mg) was added and stirring continued ON. The OL (sat. aq. $NaHCO_3$/DCM.) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **1H1** 4-[1-[(4-bromo-1,3-dimethyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*,*N*-dimethyl-benzamide (30 mg).

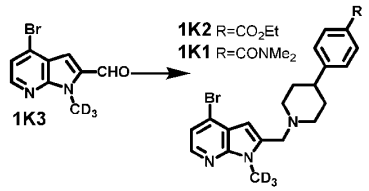


Int. **1I1** 4-(1-((4-bromo-1,5-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*,*N*-dimethylbenzamide (0.16 g) as prepared similarly to Int. **1H1** from 4-bromo-5-methyl-1H-pyrrolo[2,3-b]pyridine (0.51 g) and *N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (0.18 g).

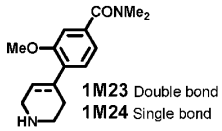


Int. **1AB8** (30 g) and $NaBH_4$ (19 g) were stirred 2h in MeOH (300 mL) at 0 °C to RT. The OL (aq. $Na_2S_2O_3$/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **1J3** (4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methanol. Int. **1J3** (2.5 g) was stirred ON in DCM/Et_3N/MsCl (21.4:5.2:1, 39 mL) at 0 °C to RT and filtered. The OL layer (EtOAc/water) was

washed with brine, dried, and concentrated to give Int. **1J1** 4-bromo-2-(chloromethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine (2.0 g).

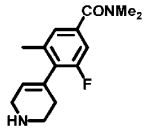


4-Bromo-1-(trideuteriomethyl)pyrrolo[2,3-b]pyridine (0.40 g) was stirred 2h in THF/2M LDA in THF (7.1:1, 11.4 mL) at -78 °C. DMF (0.7 mL) was added and stirring continued 2h at -78 °C to RT and diluted with water to precipitate Int. **1K3** 4-bromo-1-(trideuterio-methyl)pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.35 g). Int. **1K3** (0.17 g) and methyl 4-(piperidin-4-yl)benzoate (0.16 g) were stirred 3h in DCE/DIPEA (28.3:1, 15.5 mL). STAB (0.26 g) was added and stirring continued ON. The OL (water/DCM) was washed brine, dried, concentrated, and purified by FC (pentane/EtOAc 4:1) to give Int. **1K2** methyl 4-[1-[[4-bromo-1-(trideuteriomethyl)pyrrolo-[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]-benzoate (0.14 g). Int. **1K2** (50 mg) was stirred 0.25h in THF/MeOH/2M aq. NaOH (7.1:3.6:1, 3.3 mL). pH was adjusted to 5 with 1M aq. HCl. The mixture was concentrated. The residue and HATU (85 mg) were dissolved in DMF/DIPEA (25.6:1, 2.1 mL) before $HN(CH_3)_2$ (14 mg; HCl salt) was added and stirring continued 72h. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM / MeOH 1: to 9:1) to give Int. **1K1** 4-[1-[[4-bromo-1-(trideuteriomethyl)pyrrolo[2,3-b]pyridin-2-yl]-methyl]-4-piperidyl]- *N,N*-dimethyl-benzamide (39 mg).

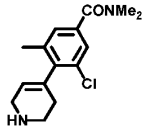


4-Bromo-3-methoxybenzoic acid (3.0 g), $HN(CH_3)_2$ (1.6 g, HCl salt), and HATU (5.92 g) were stirred ON in DCM/DIPEA (7.4:1, 57 mL), concentrated, and HPLC-purified to give 4-bromo-3-methoxy-*N,N*-dimethyl-benzamide (2.5 g). 1.0 g of this material, *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.44 g), K_2CO_3 (2.14 g), and $PdDPPFCl_2$-DCM (0.16 g) were degassed in dioxane/water (4:1, 10 mL) and stirred at 100 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-(4-(dimethylcarbamoyl)-2-methoxy-phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (1.10 g). 0.6 g of this material was hydrogenated ON using 10% Pd/C (0.2 g) in MeOH (10 mL), filtered, concentrated, stirred in 4M HCl in dioxane (10 mL) ON, concentrated, and HPLC-purified to give Int. **1M24** 3-methoxy-*N,N*-dimethyl-4-(piperidin-4-yl)benzamide (0.23 g). *tert*-Butyl 4-(4-(dimethylcarba-moyl)-2-methoxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (0.50 g) was

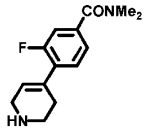
stirred ON in 4M HCl in dioxane (10 mL), concentrated, and HPLC-purified to give Int. **1M23** 3-methoxy-*N*,*N*-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.17 g).



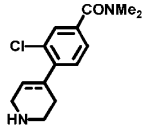
$NaNO_2$ (6.1 g) and 4-amino-3-fluoro-5-methyl-benzoic acid (15.0 g) were stirred 0.3h in 48% aq. HBr (150 mL) at 0 °C. CuBr (13.0 g) was added and stirring continued 4h. The OL (aq. $NaHCO_3$/MTBE) was washed with water and concentrated to give 4-bromo-3-fluoro-5-methyl-benzoic acid (8.50 g). 4-Bromo-3-fluoro-5-methyl-benzoic acid (15.0 g) was stirred 5h in DCM/$SOCl_2$ (83:1, 150 mL), and concentrated. The residue and $HNMe_2$ (3.1 g, HCl salt) were stirred 5h DCM/Et_3N (13.6:1, 160 mL) The OL (water/DCM) was concentrated. The residue, K_2CO_3 (7.3 g), PdPDPPFCl_2-DCM (0.15 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (6.0 g) were degassed dioxane (150 mL) and stirred 48h at 90 °C. The OL (water/ dioxane) was concentrated, stirred 0.5h in THF/4M HCl in dioxane (1:1, 100 mL), concentrated, and HPLC-purified to give Int. **1M25** 3-fluoro-*N*,*N*,5-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.22 g).



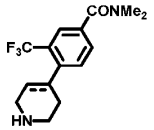
Int. **1M26** 3-chloro-*N*,*N*,5-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.11 g) was prepared similarly to Int. **1M25** from 4-bromo-3-chloro-5-methyl-benzoic acid (15 g).



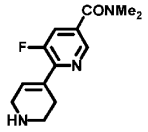
4-Bromo-3-fluoro-*N*,*N*-dimethyl-benzamide (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.41 g), Na_2CO_3 (1.61 g), and PdDPPFCl_2-DCM (0.16 g) were degassed in dioxane/water (4:1, 10 mL) and stirred ON at 100 °C. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[4-(dimethylcarbamo-yl)-2-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.20 g). 0.6 g of this material was stirred ON in 4M HCl in dioxane (10 mL). The mixture was concentrated and HPLC-purified to give Int. **1M29** 3-fluoro-*N*,*N*-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)-benzamide (0.22 g).



4-Bromo-3-chloro-*N*,*N*-dimethyl-benzamide (5.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.71 g), Na_2CO_3 (8.1 g), and $PdDPPFCl_2$-DCM (0.78 g) were degassed in dioxane/water (4:1, 10 mL) and stirred at 100 °C ON. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[2-chloro-4-(dimethylcarbamoyl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.10 g). This material was hydrogenated ON using 10% Pt/C (1.1 g) in MeOH (10 mL), filtered, and concentrated to give *tert*-butyl 4-[2-chloro-4-(dimethylcarbamoyl)phenyl]-piperidine-1-carboxylate (0.60 g). This material was stirred ON in 4M HCl in dioxane (10 mL), concentrated, and HPLC-purified to give Int. **1M44** 3-chloro-*N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (0.15 g). *tert*-Butyl 4-[2-chloro-4-(dimethyl-carbamoyl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.60 g) was stirred ON in 4M HCl in dioxane (10 mL), concentrated, and HPLC-purified to give Int. **1M43** 3-chloro-*N*,*N*-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.22 g).

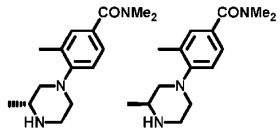


4-Bromo-3-(trifluoromethyl)benzoic acid (3.0 g), $HN(CH_3)_2$ (1.36 g, HCl salt) and HATU (5.1 g) stirred ON in DCM/DIPEA (8.6:1, 56 mL), concentrated, and HPLC-purified to give 4-bromo-*N*,*N*-dimethyl-3-(trifluoro-methyl)benzamide (2.40 g). 1.0 g of this material, *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (1.25 g), K_2CO_3 (1.87 g), and $PdDPPFCl_2$-DCM (0.14 g) were degassed in dioxane/water (4:1, 10 mL) and stirred ON at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to obtain *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-(trifluoromethyl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.04 g). 0.50 g of this material was stirred ON in 4M HCl in dioxane (10 mL), filtered, and HPLC-purified to give Int. **1M45** *N*,*N*-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoro-methyl)benzamide (0.14 g). *tert*-Butyl 4-[4-(dimethyl-carbamoyl)-2-(trifluoromethyl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.50 g) was hydrogenated ON using 10% Pd/C (0.5 g) in MeOH (10 mL). The mixture was filtered. The residue after concentration was stirred ON in 4M HCl in dioxane (10 mL), concentrated, and HPLC-purified to give Int. **1M46** *N*,*N*-dimethyl-4-(piperidin-4-yl)-3-(trifluoromethyl)benzamide (0.23 g).

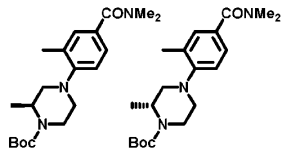


6-Chloro-5-fluoro-pyridine-3-carboxylic acid (3.0 g), $HN(CH_3)_2$ (1.53 g, HCl salt), and HATU (7.15 g) were stirred ON in DCM/DIPEA (5.6:1, 59 mL), concentrated, and purified by FC (hexane to EtOAc) to give 6-chloro-5-fluoro-*N*,*N*-dimethyl-pyridine-3-carboxamide (3.1 g). This material, *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-3,6-dihydropyridine-1(2H)-

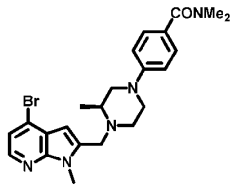
carboxylate (5.20 g), K_3CO_3 (8.50 g), and $PdDPPFCl_2$-DCM (0.62 g) were degassed in dioxane/water (4:1, 50 mL) and stirred ON at 100 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-Butyl 4-[5-(dimethylcarbamoyl)-3-fluoro-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (3.10 g). 0.13 g of this material was stirred 1.5h in DCM/4M HCl in dioxane (3.6:1, 6.4 mL) and concentrated. The OL (DCM/aq. $NaHCO_3$) was dried, concentrated, and HPLC-purified to give Int. **1M47** 5-fluoro-*N*,*N*-dimethyl-6-(1,2,3,6-tetrahydropyridin-4-yl)pyridine-3-carboxamide (20 mg).



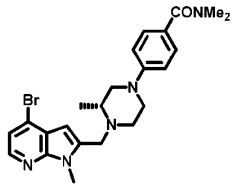
tert-Butyl (S)-2-methylpiperazine-1-carboxylate (1.0 g), ethyl 4-bromo-3-methyl-benzoate (1.46 g), Cs_2CO_3 (4.88 g), Pd_2dba_3 (0.23 g), and XPhos (0.24 g) were degassed in dioxane (20 mL) and stirred at 110 °C ON. The OL (EtOAc/water) was concentrated and purified by FC (hexane to EtOAc) to give *tert*-butyl (2R)-4-(4-ethoxy-carbonyl-2-methyl-phenyl)-2-methyl-piperazine-1-carboxylate (0.85 g). 0.70 g of this material and LiOH-H2O (0.22 g) were stirred 6h in THF/water/MeOH (10 mL), concentrated, and triturated in dilute aq. citric acid to give 4-[(3R)-4-*tert*-butoxy-carbonyl-3-methyl-piperazin-1-yl]-3-methyl-benzoic acid (0.45 g). 4-[(3R)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]-3-methyl-benzoic acid (0.70 g), $HNMe_2$ (0.26 g, HCl salt), HOBt (0.42 g), and EDC (0.60 g, HCl salt) were stirred ON in DCM/DIPEA (10:1, 11 mL) at 0 °C to RT. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 3:2) to give *tert*-butyl (2R)-4-[4-(dimethylcarbamoyl)-2-methyl-phenyl]-2-methyl-piperazine-1-carboxylate (0.45 g). This material was stirred 6h in DCM/TFA (6:1, 7 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **1M49** (R)-*N*,*N*,3-trimethyl-4-(3-methylpiperazin-1-yl)-benzamide (0.20 g). Int. **1M59** (S)-*N*,*N*,3-trimethyl-4-(3-methylpiperazin-1-yl)-benzamide was prepared similarly from *tert*-butyl (R)-2-methylpiperazine-1-carboxylate.



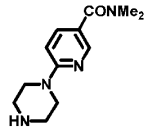
tert-Butyl (S)-2-methylpiperazine-1-carboxylate (2.5 g), NaOtBu (2.4 g), Pd_2dba_3 (0.57 g), Xphos (0.59 g), and 4-bromo-*N*,*N*-dimethylbenzamide (3.1 g) were degassed in dioxane (30 mL) and stirred ON at 100 °C. The OL (Et_2O/ water) was washed with brine, dried, concentrated, and purified by FC (hexane / EtOAc 1:4) to give Int. **1M50** *tert*-butyl (S)-4-(4-(dimethylcarbamoyl)phenyl)-2-methyl-piperazine-1-carboxylate and *tert*-butyl (2.4 g). Int. **1M52** (R)-4-(4-(dimethylcarbamoyl)phenyl)-2-methyl-piperazine-1-carboxylate (0.46 g) was prepared similarly from *tert*-butyl (R)-2-methylpiperazine-1-carboxylate (0.50 g).



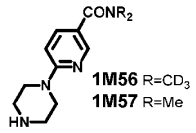
Int. **1M50** (46 mg) was stirred 1h in DCM/TFA (1:1, 1 mL) and concentrated. The residue and 4Å MS were stirred ON in DCM/DIPEA (19.5:1, 1.6 mL). Int. **1J1** (23 mg) was added and stirring was continued ON. The OL (DCM/sat. aq. $NaHCO_3$) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 95:5) to give Int. **1M51** (S)-4-(4-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3-methylpiperazin-1-yl)-*N*,*N*-dimethylbenzamide (40 mg).



Int. **1M52** (46 mg) was stirred 1h in DCM/TFA (1:1, 1 mL) and concentrated. The residue, Int. **1AB8** (21 mg), and 4Å MS were stirred 2h in DCM/DIPEA (19.5:1, 1.6 mL). STAB (56 mg) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 95:5) to give Int. **1M53** (R)-4-(4-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3-methylpiperazin-1-yl)-*N*,*N*-dimethylbenzamide (30 mg).

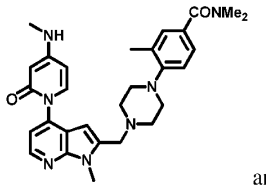


Boc-piperazine (0.40 g), 6-bromo-*N*,*N*-dimethylnicotinamide (0.59 g), NaOtBu (0.41 g), Xphos (0.10 g), and Pd_2dba_3 (0.1 g) were degassed in dioxane (4 mL) and stirred at 110 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1) to give 0.30 g of *tert*-butyl 4-(5-(dimethylcarbamoyl)pyridin-2-yl)-piperazine-1-carboxylate. 0.26 g of this material was stirred 1h in 3M HCl in dioxane (3 mL) at 0 °C to RT and concentrated to give Int. **1M55** *N*,*N*-dimethyl-6-(piperazin-1-yl)nicotinamide (0.14 g, HCl salt).

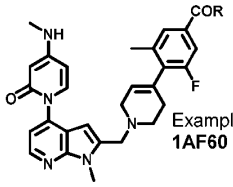


4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)benzoic acid (1.0 g), $HN(CD_3)_2$ (0.43 g, HCl salt), HOBt (0.66 g), and EDC (0.94 g, HCl salt) were stirred ON in DCM/DIPEA (15.4:1, 21 mL). The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1) to give *tert*-butyl 4-(5-(bis(methyl-d_3)carbamoyl)-pyridin-2-yl)piperazine-1-carboxylate (0.95 g). This

material was stirred in DCM/TFA (6.7:1, 35 mL), concentrated, and triturated in Et_2O to give Int. **1M56** *N,N*-bis(methyl-d_3)-6-(piperazin-1-yl)nicotinamide (0.85 g). Int. **1AE20** (14 g) was hydrogenated ON using 10% Pd/C (3.5 g) in MeOH (200 mL), filtered, and concentrated to give *tert*-butyl 4-[5-(dimethyl-carbamoyl)-2-pyridyl]piperidine-1-carboxylate (11 g). 0.9 g of this material was stirred in DCM/TFA (10:1, 11 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **1M57** *N,N*-dimethyl-6-(piperidin-4-yl)nicotinamide (0.50 g, TFA salt).

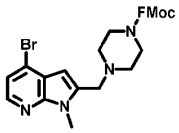


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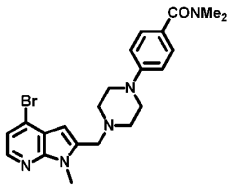


Example **1m56** R=NMe_2
1AF60 R=OH

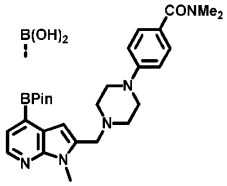
Ints. **1M1/1S7** (15 mg/22 mg, HCl salt) were stirred 0.5h in DCE (0.5 mL). STAB (25 mg) was added and stirring was continued ON. The mixture was filtered. The filtrate was stirred 0.5h in TFA (0.5 mL), concentrated, and purified by HPLC to give Example **1m6** *N,N*,3-Trimethyl-4-(4-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperazin-1-yl)benzamide (6.6 mM in DMSO (0.70 mL). Example **1m56** 3-Fluoro-*N,N*,5-trimethyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (10 mM in DMSO (1.2 mL)) was prepared similarly to Example **1m6** from Int. **1M25** (17 mg). Example **1m56** (2.4 g) and LiOH-H_2O (1.1 g) were stirred 3h in THF/water (2.5:1, 28 mL) at 0 °C to 60 °C. The residue after concentration was triturated in aq. HCl to give Int. **1M60** 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (2.4 g).



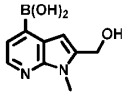
Int. **1AB8** (0.25 g) and 9H-fluoren-9-ylmethyl piperazine-1-carboxylate (0.48 g) were stirred 2h in DCE/AcOH (100:1, 10 mL). STAB (0.44 g) was added and stirring continued 2h at 0 °C to RT. The OL (sat. aq. $NaHCO_3$/DCM) was washed with brine, dried, and concentrated to give Int. **1N2** 9H-fluoren-9-ylmethyl 4-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]piperazine-1-carboxylate (0.20 g).



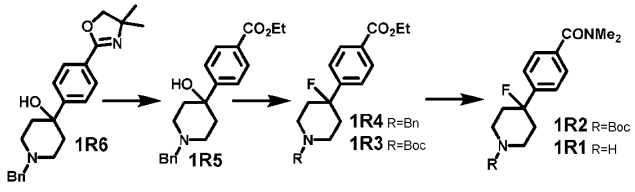
Int. **1AB8** (0.35 g) and *N,N*-dimethyl-4-(piperazin-1-yl)benzamide (0.40 g, HCl salt) were stirred 4h in DCE/DIPEA (6.5:1, 11.6 mL). STAB (0.94 g) was added and stirring continued ON. The OL (water / DCM) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **1N4** 4-(4-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperazin-1-yl)-*N,N*-dimethyl-benzamide (0.44 g).



Int. **1N4** (25 mg), KOAc (11 mg), $PdDPPFCl_2$-DCM (4 mg), and B_2Pin_2 (15 mg) were degassed in dioxane (3 mL) and stirred 4h at 70 °Ch. KOAc (11 mg), and B_2Pin_2 (15 mg), and $PdDPPFCl_2$-DCM (4 mg) were added and stirring continued 4h at 70 °C and ON at RT. KOAc (11 mg), B_2Pin_2 (15 mg), and $PdDPPFCl_2$-DCM (4 mg) were added and stirring continued 6h at 90 °C. The mixture was filtered and HPLC-purified to give Int. **1N5** *N,N*-dimethyl-4-[4-[[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)pyrrolo[2,3-b]pyridin-2-yl]methyl]piperazin-1-yl]benzamide and (2-((4-(4-(dimethyl-carbamoyl)-phenyl)piperazin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid.

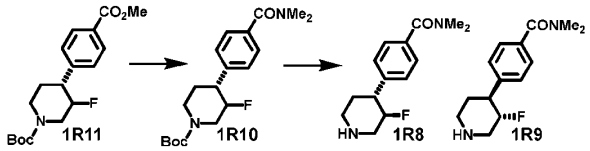


Int. **1J3** (1.0 g), B_2Pin_2 (1.58 g), $Pd(PPh_3)_2Cl_2$ (0.29 g), and KOAc (1.02 g) were degassed dioxane (10 mL) and stirred 3h at 100 °C and concentrated. The residue decanted with pentane and concentrated to give Int. **1O3** [2-(hydroxymethyl)-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]boronic acid (0.8 g).



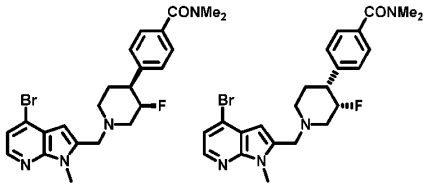
2-(4-Bromophenyl)-4,4-dimethyl-4,5-dihydrooxazole (10 g) and Mg turnings (1.1 g) and I_2 (50 mg) were refluxed 1h in THF (50 mL). 1-Benzylpiperidin-4-one (8.0 mL) was added before refluxing 3h. The OL (sat. aq. NH_4Cl/MTBE) was washed with water, brine, dried, and concentrated to give Int. **1R6** 1-benzyl-4-(4-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)phenyl)piperidin-4-ol. Int. **1R6** (7.0 g) was stirred ON in EtOH/96% H_2SO_4 (10:1, 400 mL) at 90 °C and concentrated. The OL (sat. aq. $NaHCO_3$/DCM) was dried, concentrated, and purified by FC (DCM/2M NH_3 in MeOH 1:0 to 4:1) to give Int. **1R5** ethyl 4-(1-benzyl-4-hydroxypiperidin-4-yl)-benzoate. Int. **1R5** (0.06 g) was dissolved

in DCM (10 mL) at -78 °C. DAST (0.28 mL) was added and stirring continued 2h at -78 °C to RT over 2h. The OL (DCM/water) was washed with brine, dried, concentrated, and HPLC-purified to give Int. **1R4** ethyl 4-(1-benzyl-4-fluoro-piperidin-4-yl)benzoate. Int. **1R4** (2.0 g) was stirred 3h in DCM (40 mL) and 1-chloroethyl carbono-chloridate (0.76 mL) at 0 °C to RT and concentrated. The residue was refluxed 0.5h in MeOH (20 mL) and concentrated. The residue and Boc_2O (1.56 g) were stirred ON in DCM/Et_3N (14.7:1, 27 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 1:1) to give 4-(1-(*tert*-butoxycarbonyl)-4-fluoropiperidin-4-yl)benzoic acid. 0.77 g of this material, HATU (1.18 g), and $HN(CH_3)_2$ (0.29 g, HCl salt) were stirred 1h in DMF/DIPEA (5:1, 10 mL). The OL (EtOAc/water) was dried, concentrated, and purified by FC (heptane to EtOAc / MeOH 95:5) to give Int. **1R2** *tert*-butyl 4-(4-(dimethylcarbamoyl)-phenyl)-4-fluoropiperidine-1-carboxylate. Int. **1R2** (0.55 g) was stirred 1h in MeOH/4M HCl in dioxane (1:1, 20 mL), concentrated, and purified by SCX and HPLC to give Int. **1R1** 4-(4-fluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide (62 mg).

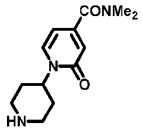


Int. **1AE14** (10.0 g) was stirred ON in THF/2.0 M BH_3-Me_2S in THF (11:6:1, 218 mL) at 0 °C to RT. 2.0 M aq. NaOH (38 mL) and 30% aq. H_2O_2 (5.9 mL) were added and stirring continued 1h. The OL (sat. aq. $Na_2S_2O_3$/ EtOAc) was washed with water and brine, dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give *tert*-butyl 3-hydroxy-4-(4-(methoxycarbonyl)-phenyl)piperidine-1-carboxylate (7.4 g). 7.0 g of this material was dissolved in DCM (140 mL) at -78 °C. 50% Deoxo-Fluor in THF (4.5 mL) was added and stirring continued 6h at -78 °C to RT. The OL (sat. aq. $NaHCO_3$/DCM) were washed with sat. aq. citric acid, dried, concentrated, and purified by FC (hexane/EtOAc 85:15) to give Int. **1R11** *tert*-butyl 3-fluoro-4-(4-(methoxycarbonyl)phenyl)-piperidine-1-carboxylate (4.8 g). Int. **1R11** (10.0 g) and LiOH-H_2O (6.1 g) were stirred ON in MeOH/THF/water (2:4:1, 230 mL) at 0 °C to RT and concentrated. The OL (aq. citric acid/10% MeOH in DCM) was dried and concentrated to give 4-(1-(*tert*-butoxy-carbonyl)-3-fluoropiperidin-4-yl)benzoic acid (8.0 g). 22 g of this material, HATU (39 g), and $HN(CH_3)_2$ (16.5 g, HCl salt) were stirred ON in DMF/DIPEA (6:7:1, 0.46 L) at 0 °C to RT. The OL (water / MeOH / DCM (5:95)) was dried, concentrated, and purified by FC (hexane/EtOAc 2:3) to give *tert*-butyl 4-(4-(dimethylcarbamoyl)phenyl)-3-fluoropiperidine-1-carboxylate (20 g). This material was stirred ON in DCM/TFA (37:1, 513 mL) at 0 °C to RT ON and concentrated. The aq. layer (water/Et_2O) was basified with sat. aq. $NaHCO_3$ and extracted with MeOH / DCM (5:95). The OLs were dried and concentrated to give 4-(3-fluoropiperidin-4-yl)-*N*,*N*-dimethyl-benzamide (14.5 g). This material was resolved by SFC using a Chiralpak IG 250x25 5µm column operated at 30 °C using an eluent of 70% CO_2 and 30% MeOH containing 0.5% $HNEt_2$ (100 g/min) and a back pressure of 100 bar to give Int.

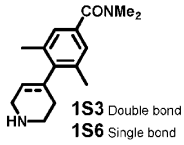
1R8 (5.3 g, first peak) and Int. **1R9** (5.1 g, second peak) 4-((3R,4R)-3-fluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide and 4-((3S,4S)-3-fluoropiperidin-4-yl)-*N*,*N*-dimethylbenzamide. The absolute configurations of these compounds were not determined.



Int. **1F1** (0.10 g), DIPEA (0.21 mL), KI (20 mg), and Int. **1J1** were stirred ON in DMF (5 mL). The OL (EtOAc/ water) was dried, concentrated, and purified by FC (hexane/EtOAc 3:7) to give Int. **1R12** *N*,*N*-Dimethyl-4-[(3R,4S)-1-[(4-bromo-1-methyl-pyrrolo[2,3-b]-pyridin-2-yl)methyl]-3-fluoro-4-piperidyl]benzamide (0.12 g). Int. **1R13** *N*,*N*-dimethyl-4-[(3S,4R)-1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3-fluoro-4-piperidyl]benzamide (0.12 g) was prepared similarly from Ints. **1F2/1J1** (0.10 g/0.16 g).

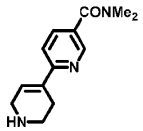


KOtBu (74 mg), K_2CO_3 (0.17 g), *N*,*N*-dimethyl-2-oxo-1H-pyridine-4-carboxamide (0.10 g), and *tert*-butyl 4-(*p*-tolylsulfonyloxy)piperidine-1-carboxylate (0.24 g) were stirred ON in DME (5 mL) at 110 °C ON. The OL (EtOAc/water) was dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-oxo-1-pyridyl]piperidine-1-carboxylate (70 mg). *tert*-Butyl 4-[4-(dimethylcarbamoyl)-2-oxo-1-pyridyl]piperidine-1-carboxylate (0.20 g) was stirred in DCM/TFA (10:1, 5.5 mL) and concentrated to give Int. **1S2** *N*,*N*-Dimethyl-2-oxo-1-(4-piperidyl)pyridine-4-carbox-amide and Int. **1S2'** N,N-dimethyl-2-(4-piperidyloxy)pyridine-4-carboxamide (0.15 g, TFA salt).

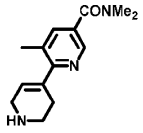


4-Bromo-*N*,*N*,3,5-tetramethylbenzamide (5.5 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7.3 g), $PdDPPFCl_2$-DCM (0.88 g), and $NaHCO_3$ (5.4 g) were degassed in dioxane/water (3:1, 47 mL) and stirred ON at 100 °C. The OL (EtOAc/water) was dried, concentrated, and purified by FC (pentane/EtOAc 1:1) to give *tert*-butyl 4-[4-(dimethylcarbamoyl)-2,6-dimethyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (4.5 g). 0.3 g of this material was stirred ON in 2.9M HCl in dioxane (7 mL) at 0 °C to R, concentrated, and triturated in Et_2O. The solid was treated with sat. aq. $NaHCO_3$ and concentrated. The residue was

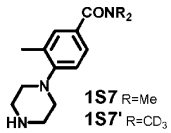
dissolved in DCM, dried, and concentrated to give Int. **1S3** *N*,*N*,3,5-tetramethyl-4-(1,2,3,6-tetrahydro-pyridin-4-yl)benzamide (0.15 g). *tert*-Butyl 4-[4-(dimethylcarbamoyl)-2,6-dimethyl-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (50 mg) was hydrogenated 48h using PtO_2 (15 mg) in AcOH (3 mL), filtered, and concentrated to give Int. **1S6** *N*,*N*,3,5-tetramethyl-4-(piperidin-4-yl)benzamide (35 mg).



6-Bromo-*N*,*N*-dimethylnicotinamide 20.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (27.0 g), $NaHCO_3$ (25.7 g), and $PdDPPFCl_2$-DCM (0.71 g) were degassed in dioxane/water (4:1, 0.5 L), refluxed ON, and filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 45:55) to give *tert*-butyl 4-[5-(dimethyl-carbamoyl)-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (17 g). 1.0 g of this material was stirred ON in DCM/4M HCl in dioxane (2.6:1, 14 mL) at 0 °C to RT. The mixture was combined with another two batches prepared on 0.1 g scale and concentrated. The residue was stirred in water at pH 8 (adjusted with $NaHCO_3$). The mixture was purified by FC (reverse-phase C18 column; 8% ACN in 0.001% aq. formic acid) to give Int. **1S4** *N*,*N*-dimethyl-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide (0.60 g).

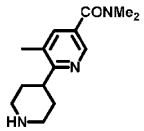


6-Bromo-*N*,*N*,5-trimethyl-pyridine-3-carboxamide (3.2 g), $NaHCO_3$ (3.9 g), $PdDPPFCl_2$-DCM (0.27 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (6.1 g) were degassed in dioxane/water (4:1, 13 mL) and stirred ON at 110 °C. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 1:4) to give *tert*-butyl 4-[5-(dimethyl-carba-moyl)-3-methyl-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (4.0 g). 0.35 g of this material was stirred ON in DCM/TFA (10:1, 9 mL) at 0 °C to RT, concentrated, and triturated in Et_2O/pentane to give Int. **1S5** *N*,*N*,3-trimethyl-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide (0.35 g, TFA salt).

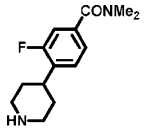


tert-Butyl piperazine-1-carboxylate (5.0 g), 4-bromo-*N*,*N*,3-trimethylbenzamide (7.1 g), Pd_2dba_3 (1.19 g), XPhos (1.29 g), and NaOtBu (5.19 g) were degassed in dioxane (50 mL) and stirred ON at 100 °C and filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC

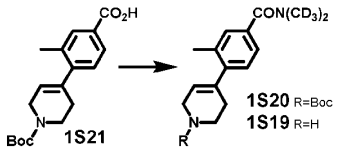
(pentane/EtOAc 3:7) to give *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-methyl-phenyl]piperazine-1-carboxylate (6.1 g). 7.2 g of this material was stirred ON in 4M HCl in dioxane/DCM (1.8:1, 55 mL) at 0 °C to RT, concentrated, and triturated in Et_2O/pentane to give Int. **1S7** *N*,*N*,3-trimethyl-4-(piperazin-1-yl)benzamide (5.0 g, HCl salt). Int. **1S7'** 3-methyl-N,N-bis(methyl-d_3)-4-(piperazin-1-yl)benzamide was prepared similarly from 4-bromo-3-methyl-N,N-bis(methyl-d_3)benzamide.



6-Bromo-*N*,*N*,5-trimethyl-pyridine-3-carboxamide (3.2 g), $NaHCO_3$ (3.9 g), and PdDPPFCl_2-DCM (0.27 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (6.1 g) were degassed in dioxane/water (4:1, 14 mL) and stirred ON at 110 °C. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 1:4) to give *tert*-butyl 4-[5-(dimethylcarba-moyl)-3-methyl-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (4.0 g). 4.2 g of this material was hydrogenated ON using 10% Pd/C (2.0 g) in MeOH (100 mL), filtered, concentrated, and purified by FC (hexane/EtOAc 1:9) to give *tert*-butyl 4-[5-(dimethyl-carbamoyl)-3-methyl-2-pyridyl]piperidine-1-carboxylate (3.5 g). 4.3 g of this material was stirred ON in DCM/TFA (1.5:1, 25 mL) at 0 °C to RT, concentrated, and triturated in pentane/Et_2O to give Int. **1S8** *N*,*N*,5-Trimethyl-6-(piperidin-4-yl)nicotinamide (5.0 g, TFA salt).

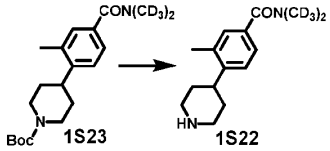


4-Bromo-3-fluoro-*N*,*N*-dimethyl-benzamide (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.51 g), Na_2CO_3 (1.72 g), and PdDPPFCl_2-DCM (0.17 g) were degassed in dioxane/water (4:1, 10 mL) and stirred ON at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane to EtOAc) to give *tert*-butyl 4-[4-(dimethyl-carbamoyl)-2-fluoro-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (1.20 g). This material was hydrogenated ON using 10% Pd/C (45 mg) in MeOH (2 mL), filtered, concentrated, stirred ON in 4M HCl in dioxane (10 mL), concentrated, and HPLC-purified to give Int. **1S18** 3-fluoro-*N*,*N*-dimethyl-4-(piperidin-4-yl)benzamide (63 mg).

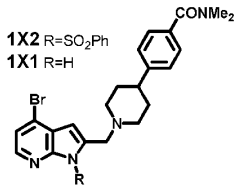


96% aq. H_2SO_4 (2.5 mL) was added to a solution of 4-bromo-3-methyl-benzoic acid (20 g) in MeOH (300 mL). The mixture was stirred at 90 °C ON and concentrated. The organic layer (sat. aq. $NaHCO_3$/EtOAc) was dried and concentrated to give methyl 4-bromo-3-methyl-benzoate (20 g). 10g

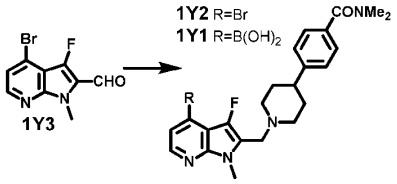
of this material, *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14.8 g), Na_2CO_3 (13.8 g), and $PdDPPFCl_2$-DCM (0.84 g) were degassed in dioxane/water (2.3:1, 100 mL), stirred ON at 90 °C, filtered, concentrated, and purified by FC (hexane/EtOAc 95:5) to give *tert*-butyl 4-(4-methoxycarbonyl-2-methyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (7.0 g). 2.5 g of this material and LiOH-H_2O (2.0 g) were stirred ON in EtOH/THF/water (2:1:1, 24 mL) at 0 °C to RT, concentrated, and triturated in dilute aq. citric acid to give Int. **1S21** 4-(1-*tert*-butoxycarbonyl-3,6-dihydro-2H-pyridin-4-yl)-3-methyl-benzoic acid (2.0 g). Int. **1S20** (0.70 g) was prepared similarly to Int. **1D8** from Int. **1S21** (2.0 g). Int. **1S19** 3-methyl-*N*,*N*-bis(methyl-d_3)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.31 g) was prepared similarly to Int. **1S7** from Int. **1S20** (0.80 g).



Int. **1S20** (0.35 g) was hydrogenated ON using 10% Pd/C (50 mg) in MeOH (10 mL), filtered, and concentrated to give Int. **1S23** (0.21 g). Int. **1S22** 3-methyl-*N*,*N*-bis-(methyl-d_3)-4-(piperidin-4-yl)benzamide (0.45 g) was prepared similarly to Int. **1S7** from Int. **1S23** (0.90 g).

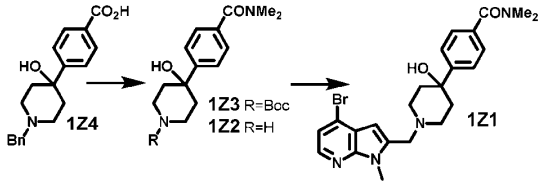


Int. **1A6** (0.30 g), *N*,*N*-dimethyl-4-(4-piperidyl)benzamide (0.34 g), and 4Å MS were stirred 0.3h in DCM (5 mL). STAB (0.52 g) was added and stirring was continued ON. The mixture was filtered, concentrated, and purified by FC (heptane to EtOAc/MeOH 1:4) to give Int. **1X2** 4-[1-[[1-(benzenesulfonyl)-4-bromo-pyrrolo-[2,3-b]-pyridin-2-yl]-methyl]-4-piperidyl]-*N*,*N*-dimethyl-benzamide (0.22 g). Int. **1X2** (0.12 g) was stirred 2.5h in EtOH/4M aq. NaOH (2.5:1, 2.8 mL) at 80 °C and concentrated. The OL (water/DCM) was concentrated to give Int. **1X1** 4-[1-[(4-bromo-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*,*N*-dimethyl-benzamide (94 mg).

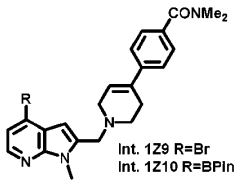


4-Bromo-3-fluoro-1-methyl-pyrrolo[2,3-b]pyridine (1.9 g) was stirred 2h in THF/2.0 M LDA in THF (5:1, 24 mL) at -78 °C. DMF (1.6 mL in THF (5 mL)) was added and stirring continued 2h at -78 °C to RT. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC

(pentane/EtOAc 1:4) to give Int. **1Y3** 4-bromo-3-fluoro-1-methyl-pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.4 g). Int. **1Y3** (0.39 g) and *N,N*-dimethyl-4-(4-piperidyl)benzamide trifluoro acetate (0.38 g) were stirred ON in DCE/DIPEA (3.8:1, 6.3 mL) at 0 °C to RT. STAB (0.64 g) was added and stirring continued ON at 0 °C to RT. The OL (EtOAc/water) was washed brine, dried, concentrated, and purified by FC (pentane to EtOAc) to give Int. **1Y2** 4-[1-[(4-bromo-3-fluoro-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N,N*-dimethyl-benzamide (0.38 g). Int. **1Y2** (0.25 g), B_2Pin_2 (0.17 g), KOAc (0.16 g), and $PdDPPFCl_2$-DCM (37 mg) were degassed in THF (20 mL) and ON at 100 °C, concentrated, and triturated in pentane to give Int. **1Y1** (2-((4-(4-(dimethylcarbamoyl)phenyl)-piperidin-1-yl)methyl)-3-fluoro-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid (0.2 g).

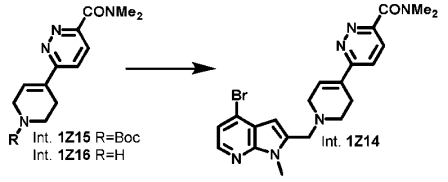


Int. **1R5** (0.5 g) and LiOH (181 mg) were stirred ON in MeOH/THF/water (3:5:1, 9 mL) and concentrated to give Int. **1Z4** 4-(1-benzyl-4-hydroxypiperidin-4-yl)benzoic acid (0.40 g). Int. **1Z4** (0.40 g), $HN(CH_3)_2$ (0.31 g, HCl salt), and HATU (636 mg) were stirred ON in DMF/DIPEA (7:3:1, 9.1 mL). The OL (EtOAc/water) was concentrated, and purified by FC (heptane/EtOAc 5:3 to 3:7) to give Int. 1**Z3** 4-(1-benzyl-4-hydroxy-piperidin-4-yl)-*N,N*-dimethyl-benzamide. Int. **1Z3** (1.0 g) was hydrogenated 32h using 10% Pd/C (0.5 g) in MeOH (20 mL), filtered, and concentrated to give Int. **1Z2** 4-(4-hydroxypiperidin-4-yl)-*N,N*-dimethylbenzamide. Int. **1Z2** (0.20 g) and 4-bromo-1H-pyrrolo[2,3-b]pyridine-2-carboxaldehyde (0.19 g) were stirred 4h in DCE/DIPEA (10:1, 3.3 mL). STAB (0.51 g) was added and stirring continued 32h. The OL (water/DCM) was concentrated and purified by FC (hexane/EtOAc 1:0 to 4:1) to give Int. **1Z1** 4-[1-[(4-Bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-hydroxy-4-piperidyl]-*N,N*-dimethyl-benzamide (0.15 g).

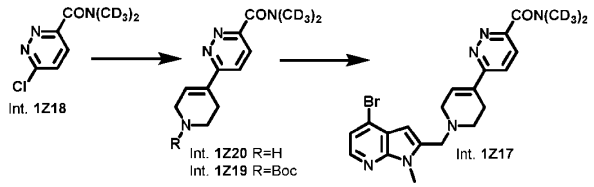


Int. **1J1** (0.97 g), KI (12 mg), Int. **1AE7** (1 g), and K_2CO_3 (1.6 g) were stirred 11h in DMF (10 mL). The OL (water/MTBE) was concentrated to give Int. **1Z9** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N-dimethylbenzamide (0.67 g). Int. **1Z9** (0.67 g), KOAc (0.44 g), $PdDPPFCl_2$-DCM (24 mg), and bis(pinacolato)diboron (0.75 g) were stirred 48h in dioxane (10 mL) at 90 °C under an inert atmosphere. The OL (water/MTBE) was concentrated to give Int. **1Z10** N,N-dimethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-1H-pyrrolo-[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.72 g). 6-bromopyridazin-3-amine (0.25 g) and di-*tert*-butyl dicarbonate (0.38 g) were stirred ON in 1M LiHMDs in THF (1.9 mL) and THF (5 mL) at 0 °C to RT under an inert atmosphere. The OL (sat. aq. NH_4Cl/EtOAc) was dried, and concentrated to give Int. **1Z11** *tert*-butyl (6-bromopyridazin-3-yl)carbamate (0.15 g).

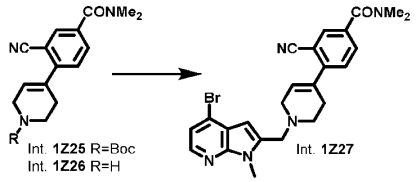


6-Chloro-N,N-dimethylpyridazine-3-carboxamide (0.85 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.6 g), K_2CO_3 (2.5 g), and $PdDPPFCl_2$-DCM (0.19 g) were stirred ON in dioxane/H_2O (4:1, 25 mL) at 100 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC ($CHCl_3$/MTBE 1:0 to 0:1) to give Int. **1Z15** *tert*-butyl 4-(6-(dimethylcarbamoyl)pyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1 g). Int. **1Z15** (1 g) was stirred 1h in 1,1,1,3,3,3-hexafluoro-2-propanol /10M HCl (19:1, 10.5 mL). The mixture was diluted with MTBE to precipitate Int. **1Z16** N,N-dimethyl-6-(1,2,3,6-tetrahydro-pyridin-4-yl)pyridazine-3-carboxamide (0.8 g, HCl salt). Ints. **1J1/1Z16** (0.2 g/0.3 g) were stirred 12h in ACN/Et_3N (48:1, 20.4 mL). The mixture was concentrated and HPLC-purified to give Int. **1Z14** 6-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N-dimethylpyridazine-3-carboxamide (70 mg).

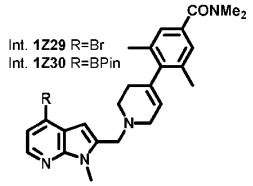


6-Chloropyridazine-3-carboxylic acid (1 g) was stirred in DCM/$SOCl_2$ (40:1, 20.5 mL) for 2h at 40 °C and concentrated. Bis(methyl-d_3)amine hydrochloride (0.61 g) in DCM (20 mL) and Et_3N (2.6 mL) were added and the mixture was stirred ON. The mixture was concentrated and purified by FC ($CHCl_3$/ACN 1:0 to 1:1) to give Int. **1Z18** 6-chloro-N,N-bis(methyl-d_3)pyridazine-3-carboxamide (1.2 g). Int. **1Z18** (1.2 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.1 g), K_2CO_3 (3.5 g), and $PdDPPFCl_2$-DCM (0.26 g) were stirred ON in dioxane/H_2O (4:1, 25 mL) at 100 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC ($CHCl_3$/MTBE 1:0 to 0:1) to give Int. **1Z19** *tert*-butyl 4-(6-(bis-(methyl-d_3)carbamoyl)-pyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.55 g). Int. **1Z19** (0.55 g) was stirred 1h in 1,1,1,3,3,3-hexafluoro-2-propanol/10M HCl (26:1, 5.2 mL). The mixture was diluted with MTBE to precipitate Int. **1Z20** N,N-bis(methyl-d_3)-6-(1,2,3,6-

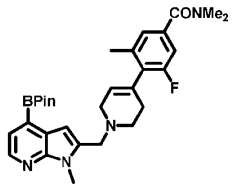
tetrahydropyridin-4-yl)-pyridazine-3-carboxamide (0.2 g, HCl salt). Ints. **1J1/1Z20** (0.2 g/0.2 g) were stirred 12h in ACN/Et_3N (48:1, 20.4 mL). The mixture was concentrated and HPLC-purified to give Int. **1Z17** 6-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]-pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N-bis(methyl-d_3)pyridazine-3-carboxamide (50 mg).



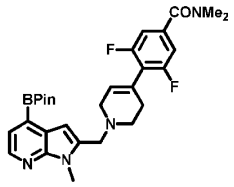
4-Chloro-3-cyanobenzoic acid (3.4 g) and di(1H-imidazol-1-yl)methanone (3.0 g) were refluxed 0.3h in dioxane (50 mL). Dimethylamine hydrochloride (1.5 g) was added and stirring continued 10h. The mixture was concentrated. The OL (aq. $NaHSO_4$/$CHCl_3$) was concentrated to give Int. **1Z24** 4-chloro-3-cyano-N,N-dimethyl-benzamide (0.87 g). Int. **1Z24** (1 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.6 g), K_2CO_3 (2.0 g), and $PdDPPFCl_2$-DCM (0.20 g) were stirred in dioxane/H_2O (4:1, 20 mL) ON at 100 °C under an inert atmosphere. The mixture was filtered, concentrated, and purified by FC ($CHCl_3$/ACN 1:0 to 4:1) to give Int. **1Z25** *tert*-butyl 4-(2-cyano-4-(dimethyl-carbamoyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (0.44 g). Int. **1Z25** (0.44 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The mixture was concentrated to give Int. **1Z26** 3-cyano-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.3 g, HCl salt). Ints. **1J1/1Z26** (0.3 g/0.3 g) and K_2CO_3 (0.5 g) were stirred 11h in DMF (10 mL). The mixture was diluted with water to precipitate Int. **1Z27** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-cyano-N,N-dimethylbenzamide (0.12 g).



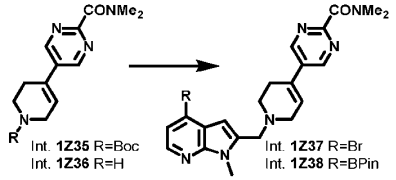
Ints. **1J1/RR44** (0.3 g/0.3 g) were stirred 12h in ACN/Et_3N (29:2, 10.7 mL). The mixture was concentrated and HPLC-purified to give Int. **1Z29** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,3,5-tetramethylbenzamide (0.3 g). Int. **1Z29** (0.3 g), bis(pinacolato)diboron (0.4 g), KOAc (0.5 g), and $PdDPPFCl_2$-DCM (50 mg) were stirred 12h in dioxane (10 mL) at 80 °C under an inert atmosphere. The OL (water/EtOAc) was concentrated to give Int. **1Z30** N,N,3,5-tetramethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.3 g).



Int. **1Z50** (0.75 g), bis(pinacolato)diboron (0.78 g), PdDPPFCl$_2$-DCM (0.13 g), and KOAc (0.45 g) were stirred 1.3h in dioxane (10 mL) at 110 °C under an inert atmosphere under MW conditions. The mixture was filtered through celite and concentrated to give Int. **1Z31** 3-fluoro-N,N,5-trimethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.85 g).

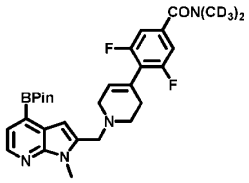


Int. **1Z65** (0.50 g), bis(pinacolato)diboron (0.52 g), PdDPPFCl$_2$-DCM (83 mg), and KOAc (0.30 g) were stirred 1h in dioxane (10 mL) at 110 °C under an inert atmosphere under MW conditions. The mixture was filtered through celite, concentrated, and washed with pentane to give Int. **1Z33** 3,5-difluoro-N,N-dimethyl-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.50 g).

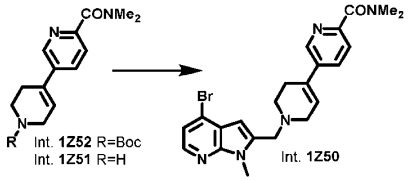


5-Bromo-N,N-dimethylpyrimidine-2-carboxamide (1.3 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.9 g), K_2CO_3 (2.3 g), and PdDPPFCl$_2$-DCM (0.22 g) were stirred ON in dioxane/H_2O (4:1, 20 mL) at 100 °C under an inert atmosphere. The mixture was concentrated and purified by FC (MTBE/MeOH) to give Int. **1Z35** *tert*-butyl 4-(2-(dimethylcarbamoyl)pyrimidin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.9 g). Int. **1Z35** (0.9 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The mixture was concentrated to give Int. **1Z36** N,N-dimethyl-5-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2-carboxamide (0.65 g, HCl salt). Ints. **1J1/1Z36** (0.3 g/0.3 g) and K_2CO_3 (0.5 g) were stirred 11h in DMF (10 mL). The mixture was diluted with water to precipitate Int. **1Z37** 5-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N-dimethylpyrimidine-2-carboxamide (0.35 g). Int. **1Z37** (0.35 g), bis(pinacolato)diboron (0.70 g), PdDPPFCl$_2$-DCM (10 mg), and KOAc (0.40 g) were stirred 14h in dioxane (10 mL) at 90 °C under an inert atmosphere. The OL (water/chloroform) was

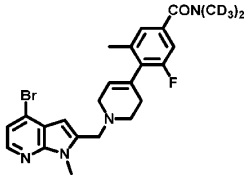
concentrated and HPLC-purified to give Int. **1Z38** N,N-dimethyl-5-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2-carboxamide (90 mg).



Int. **1Z65** (0.50 g), bis(pinacolato)diboron (0.52 g), PdDPPFCl$_2$-DCM (82 mg), and KOAc (0.30 g) were stirred 1h in dioxane (6 mL) at 120 °C under MW conditions. The mixture was filtered through celite and concentrated to give Int. **1Z40** 3,5-difluoro-N,N-bis(methyl-d_3)-4-(1-((1-methyl-4-(4,4,5,5-tetra-methyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.60 g).

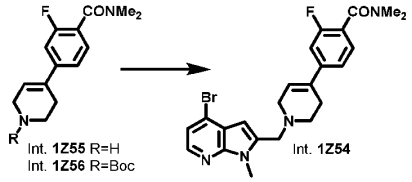


5-Bromo-N,N-dimethylpicolinamide (1.5 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.2 g), K_2CO_3 (2.7 g), and PdDPPFCl$_2$-DCM (0.27 g) were stirred ON in dioxane/H_2O (4:1, 20 mL) ON 100 °C under an inert atmosphere. The mixture was concentrated and purified by FC (hexane/MTBE 1:0 to 0:1) to give Int. **1Z52** *tert*-butyl 6-(dimethyl-carbamoyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (1 g). Int. **1Z51** (1 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The mixture was concentrated to give Int. **1Z52** N,N-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxamide (0.5 g, HCl salt). Ints. **1J1/1Z52** (0.6 g/0.5 g) and K_2CO_3 (0.9 g) were stirred 11h in DMF (10 mL). The mixture was diluted with water to precipitate Int. **1Z50** 1'-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-N,N-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxamide (0.4 g).

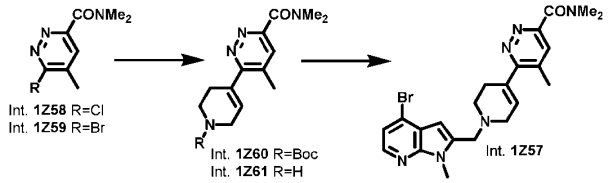


Int. **1AE9** (0.45 g), bis(pinacolato)diboron (0.35 g), PdDPPFCl$_2$-DCM (75 mg), and KOAc (0.27 g) were stirred 1h in dioxane (5 mL) for 1h at 110 °C under MW conditions. The mixture was filtered through celite and concentrated to give Int. **1Z53** 3-fluoro-5-methyl-N,N-bis(methyl-d_3)-4-(1-

((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.40 g).

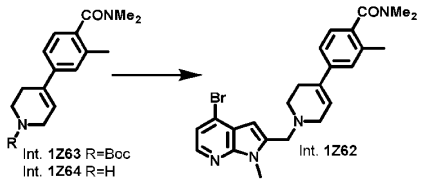


PdDPPFCl$_2$-DCM (0.25 g), 4-bromo-2-fluoro-N,N-dimethylbenzamide (1.5 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.1 g), and K_2CO_3 (2.5 g) were stirred ON in dioxane/H_2O (4:1, 20 mL) at 100 ° C under an inert atmosphere. The mixture was concentrated and purified by FC (hexane/MTBE 3:2 to 0:1) to give Int. **1Z55** *tert*-butyl 4-(4-(dimethyl-carbamoyl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (1 g). Int. **1Z55** (1 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The mixture was concentrated to give Int. **1Z56** 2-fluoro-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.5 g, HCl salt). Ints. **1J1/PP60** (0.5 g/0.5 g) and K_2CO_3 (0.8 g) were stirred 11h in DMF (10 mL). The mixture was diluted with water to precipitate Int. **1Z54** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetra-hydropyridin-4-yl)-2-fluoro-N,N-dimethylbenzamide (0.4 g).

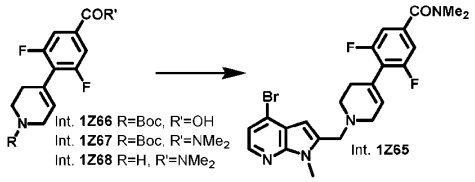


CDI (2.6 g) in THF (175 mL) was added dropwise to a mixture of 6-chloro-5-methylpyridazine-3-carboxylic acid (2 g) in THF (175 mL). The mixture was refluxed 3.5h. Dimethylamine hydrochloride (2.8 g) and Et_3N (5.2 mL) were added and stirring continued 16h at RT. The OL (brine/EtOAc) was concentrated to give Int. **1Z58** 6-chloro-N,N,5-trimethylpyridazine-3-carboxamide (0.8 g). Int. **1Z58** was refluxed ON in bromotrimethylsilane (10 mL). The mixture was concentrated and purified by preparative TLC (hexane/EtOAc, 3:1) to give Int. **1Z59** 6-bromo-N,N,5-trimethylpyridazine-3-carbox-amide (0.9 g). PdDPPFCl$_2$-DCM (0.3 g), Int. **1Z59** (0.9 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.0 g), and K_2CO_3 (2.0 g) were refluxed ON in dioxane/H_2O (15:4, 190 mL) under an inert atmosphere. The OL (aq. $NaHCO_3$/EtOAc) was dried, and concentrated to give Int. **1Z60** *tert*-butyl 4-(6-(dimethylcarbamoyl)-4-methylpyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.3 g). Int. **1Z60** (1.3 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The residue after concentration was triturated in EtOAc to give Int. **1Z61** N,N,5-trimethyl-6-(1,2,3,6-tetrahydropyridin-4-yl)pyridazine-3-carboxamide (0.9, HCl salt). STAB (0.30 g) and Ints. **1AB8/1Z61** (0.1 g/0.1 g) were stirred ON in DCE/Et_3N (73:1, 10.1 mL) at 0 °C to RT. The residue after concentration was dissolved in THF,

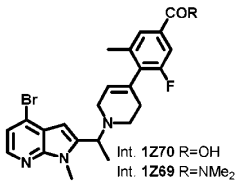
filtered through silica, and concentrated to give Int. **1Z57** 6-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,5-trimethylpyridazine-3-carboxamide (0.19 g).



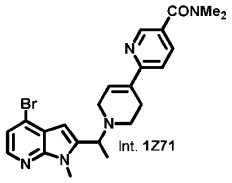
PdDPPFCl$_2$-DCM (1.1 g), 4-bromo-N,N,2-trimethylbenzamide (3.3 g), K_2CO_3 (5.7 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5.9 g) were refluxed ON in dioxane/H_2O (15:4, 190 mL) under an inert atmosphere. The OL (aq. $NaHCO_3$/EtOAc) was dried and concentrated to give Int. **1Z63** *tert*-butyl 4-(4-(dimethylcarbamoyl)-3-methyl-phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (4.1 g). Int. **1Z63** (4.1 g) was stirred ON in 2.8M HCl in dioxane (30 mL). The residue after concentration was triturated in EtOAc to give Int. **1Z64** N,N,2-trimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (2.3 g, HCl salt). STAB (0.30 g) and Ints. **1AB8/1Z64** (0.1 g/0.1 g) were stirred ON in DCE/Et_3N (73:1, 10.1 mL) at 0 °C to RT. The residue after concentration was dissolved in THF, filtered through silica, and concentrated to give Int. **1Z62** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,2-trimethylbenzamide (0.19 g).



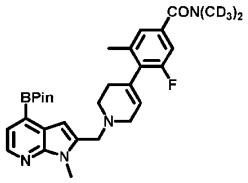
LiOH·H_2O (9.5 g) and Int. **3C18** (16 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 300 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **1Z66** 4-(1-(*tert*-butoxy-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoic acid (10 g). Int. **1Z66** (5 g), HATU (8.4 g), and dimethylamine hydrochloride (1.8 g) were stirred 16h in DMF (40 mL) and DIPEA (13 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:1) to give Int. **1Z67** *tert*-butyl 4-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (3.7 g). Int. **1Z67** (3.7 g) was stirred 16h in 2M HCl in dioxane (60 mL) at 0 °C to RT. The mixture was concentrated to give Int. **1Z68** 3,5-difluoro-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (2.9 g, HCl salt). Ints. **1J1/1Z68** (0.35 g/0.49 g), KI (22 mg), and K_2CO_3 (0.56 g) were stirred 16h in ACN (20 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 3:7) to give Int. **1Z65** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluoro-N,N-dimethylbenzamide (0.35 g).



$LiOH{\cdot}H_2O$ (33 g) and Int. **1AF87** (76 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 1.5 L) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid at 0 °C to precipitate Int. **1Z70** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoic acid (68 g). Int. **1Z70** (70 g), dimethylamine hydrochloride (36 g), and HATU (84 g) were stirred 12h in DMF (300 mL) and DIPEA (180 mL) at 0 °C to RT. The mixture was diluted with water to precipitate a solid that was dried to give Int. **1Z69** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (63 g).

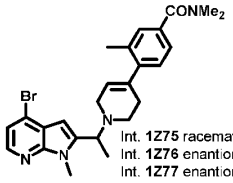


Ints. **1AF88/1S4** (1.5 g/1.5 g), KI (91 mg), and Cs_2CO_3 (8.9 g) were stirred 16h in ACN (15 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **1Z71** 1'-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-N,N-dimethyl-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide (0.50 g).

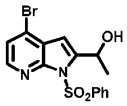


3-fluoro-5-methyl-N,N-bis(methyl-d_3)-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

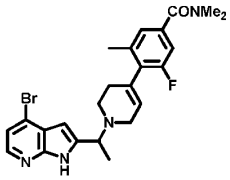
Int. **1AE9** (0.45 g), bis(pinacolato)diboron (0.35 g), PdDPPFCl$_2$-DCM (75 mg), and KOAc (0.27 g) were stirred 1h in dioxane (5 mL) at 110 °C under MW conditions. The mixture was filtered through celite and concentrated to give Int. **1Z73** 3-fluoro-5-methyl-N,N-bis(methyl-d_3)-4-(1-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.40 g).



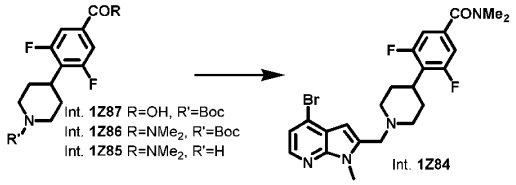
Int. **1AE38** (3.2 g) and Cs_2CO_3 (18 g) were stirred 0.3h in ACN (20 mL). Int. **1AF88** (3 g) and KI (0.91 g) were added and stirring continued 12h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 1:9) to give Int. **1Z75** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,3-trimethylbenzamide (0.90 g). Int. **1Z75** (0.90 g) was resolved by SFC on a SFC-150-022 instrument fitted with a Chiral ART Amylose-C NEO 250x30 mm 5µm column operated at 30 °C and an eluent of 80% CO_2 and 20% MeOH at a (100 g/min) and a back pressure of 100 bar to give Int. **1Z76** (0.15 g, first peak) and Int. **1Z77** (0.15 g, second peak) (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,3-trimethylbenzamide and (R)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N,3-trimethylbenzamide. The absolute configurations of these compounds were not determined.



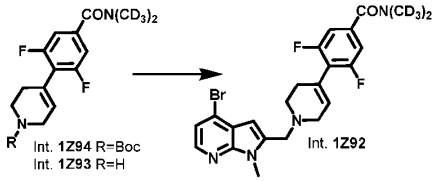
3M CH_3MgCl in THF (32 mL) was added slowly to a solution of Int. **1A6** (11.5 g) in THF (310 mL) at -78 °C. The mixture was stirred 0.5h at -78 °C to RT. The OL (aq. NH_4Cl/EtOAc) was dried, and concentrated to give Int. **1Z79** 1-(4-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethan-1-ol (12 g).



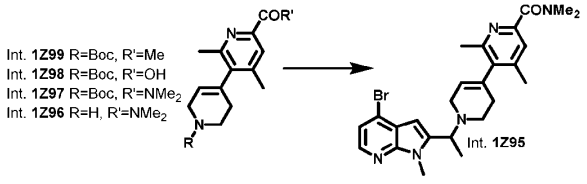
$SOCl_2$ (0.18 mL) was added to a solution of Int. **1Z79** (0.1 g) in toluene (3 mL). The mixture was stirred 0.5h and concentrated. Int. **1AE12'** (90 mg), KI (20 mg), and Cs_2CO_3 (0.40 g) were stirred ON in a solution of the residue in ACN (5 mL). The mixture was HPLC-purified to give Int. **1Z80** 4-(1-(1-(4-bromo-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (13 mg).



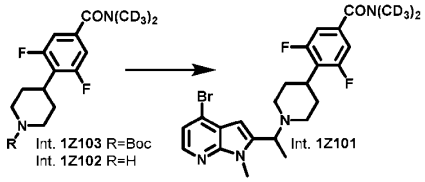
$LiOH{\cdot}H_2O$ (9.8 g) and Int. **3C17** (16.5 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 600 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid, filtered, and dried to give Int. **1Z87** 4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-3,5-difluorobenzoic acid (11.5 g). HATU (8.3 g), Int. **1Z87** (5 g), and dimethylamine hydrochloride (1.8 g) were stirred 16h in DMF (30 mL) and DIPEA (13 mL) 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:1) to give Int. **1Z86** *tert*-butyl 4-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)piperidine-1-carboxylate (3.2 g). Int. **1Z86** (3.2 g) was stirred 16h in 2M HCl in dioxane (60 mL) at 0 °C to RT. The mixture was concentrated to give Int. **1Z85** 3,5-difluoro-N,N-dimethyl-4-(piperidin-4-yl)benzamide (2.3 g, HCl salt). Ints. **1J1/1Z85** (0.35 g/0.36 g) and K_2CO_3 (0.93 g) were stirred 16h in ACN (10 mL) at 0 °C to RT. The mixture was filtered, concentrated, and purified by FC (PE/EtOAc 1:4) to give Int. **1Z84** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluoro-N,N-dimethyl-benzamide (0.40 g).



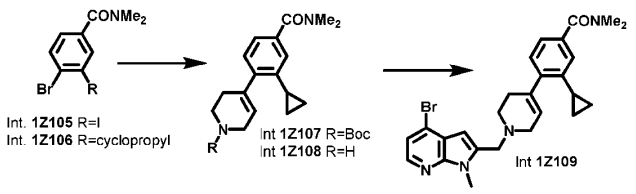
Int. **1Z66** (5 g), bis(methyl-d_3)amine hydrochloride (1.5 g), and HATU (8.4 g) were stirred 16h in DMF (40 mL) and DIPEA (13 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:1) to give Int. **1Z94** *tert*-butyl 4-(4-(bis(methyl-d_3)carbamoyl)-2,6-difluoro-phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (3.5 g). Int. **1Z94** (3.6 g) was stirred 16h in 2M HCl in dioxane (60 mL) at 0 °C to RT. The mixture was concentrated to give Int. **1Z93** 3,5-difluoro-N,N-bis-(methyl-d_3)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (2.7 g, HCl salt). Ints. **1J1/1Z93** (0.40 g/0.57 g), KI (77 mg), and K_2CO_3 (0.64 g) were stirred 16h in ACN (20 mL) at 0 °C to RT. The OL (water / EtOAc) was dried, concentrated and, purified by FC (PE/EtOAc 3:7) to give Int. **1Z92** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluoro-N,N-bis(methyl-d_3)benzamide (0.41 g).



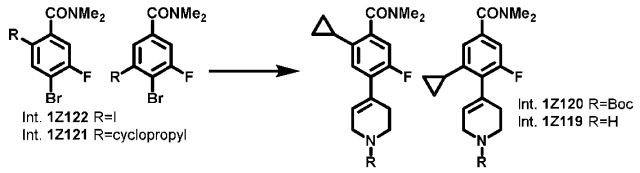
PdDPPFCl$_2$-DCM (0.2 g), methyl 5-bromo-4,6-dimethylpicolinate (1.1 g), K_2CO_3 (2 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.5 g) were stirred 12h in dioxane (8:1, 45 mL) at 80 °C under an inert atmosphere. The mixture was filtered and concentrated to give Int. **1Z99** 1'-(*tert*-butoxycarbonyl)-2,4-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxylic acid (1.4 g). LiOH·H_2O (0.3 g) and Int. **1Z99** (1.4 g) were stirred 12h in MeOH/H_2O (1:1, 60 mL). The mixture was concentrated to give Int. **1Z98** 1'-(*tert*-butoxycarbonyl)-2,4-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxylic acid (1.3 g, Li salt). Int. **1Z98** (1.4 g), dimethylamine hydrochloride (0.4 g) and HATU (1.7 g) were stirred 12h in DMF (50 mL) and Et_3N (2.8 mL). The mixture was concentrated. The OL (water/EtOAc) was concentrated to give Int. **1Z97** *tert*-butyl 6-(dimethylcarbamoyl)-2,4-dimethyl-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (0.95 g). Int. **1Z97** (0.95 g) was stirred ON in MeOH/2.8M HCl in dioxane (1:1, 40 mL). The mixture was concentrated to give Int. **1Z96** N,N,2,4-tetramethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxamide (0.7 g, HCl salt). Int. **1AF89** (0.3 g) was stirred 0.5h in toluene (20 mL) and $SOCl_2$ (0.61 mL) at 80 °C. The mixture was concentrated. The residue, Int. **1Z96** (0.5 g), and Cs_2CO_3 (0.3 g) were stirred 12h in DMF (10 mL). The OL (water/EtOAc) was concentrated and HPLC-purified to give Int. **1Z95** 1'-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-N,N,2,4-tetramethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxamide (0.5 g).



Int. **1Z87** (2 g), bis(methyl-d_3)amine hydrochloride (0.62 g), and HATU (3.3 g) were stirred 16h in DMF (30 mL) and DIPEA (5.1 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:1) to give Int. **1Z103** *tert*-butyl 4-(4-(bis(methyl-d_3)carbamoyl)-2,6-difluorophenyl)-piperidine-1-carboxylate (1.4 g). Int. **1Z103** (1.4 g) was stirred 16h in 2.2M HCl in dioxane (18 mL) at 0 °C to RT. The mixture was concentrated to give Int. **1Z102** 3,5-difluoro-N,N-bis(methyl-d_3)-4-(piperidin-4-yl)benzamide (1.1 g, HCl salt). Ints. **1J1/1Z102** (0.50 g/0.60 g), KI (0.16 g), and K_2CO_3 (1.3 g) were stirred 16h in ACN (20 mL) at 0 °C to RT. The OL (water/EtOAc) was concentrated and purified by FC (hexane/EtOAc 1:4) to give Int. **1Z101** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluoro-N,N-bis(methyl-d_3)benzamide (0.45 g).

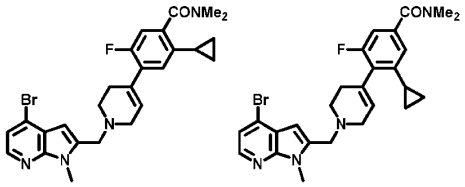


$NaIO_4$ (2.6 g) was added portion-wise to a mixture of I_2 (8.9 g) in sulfuric acid (100 mL). The mixture was stirred 0.5h before 4-bromo-N,N-dimethylbenzamide (17 g) was added and stirring continued for 18h. The mixture was diluted with water to precipitate a solid that was dried and crystallized from CCl_4 to give Int. **1Z105** 4-bromo-3-iodo-N,N-dimethylbenzamide (17 g). PdDPPFCl$_2$-DCM (2.0 g), Int. **1Z105** (17 g), cyclopropylboronic acid (5.0 g), and K_2CO_3 (20 g) were refluxed ON in dioxane/H_2O (3:1, 200 mL) under an inert atmosphere. The mixture was concentrated and purified by FC ($CHCl_3$ to $CHCl_3$/ACN 1:1) to give Int. **1Z106** 4-bromo-3-cyclopropyl-N,N-dimethylbenzamide (12 g). PdDPPFCl$_2$-DCM (1.9 g), Int. **1Z106** (12 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (21 g), and K_2CO_3 (19 g) were refluxed ON in dioxane/H_2O (6:1, 140 mL) under an inert atmosphere. The mixture was concentrated and purified by FC ($CHCl_3$ to $CHCl_3$/ACN 1:1) to give Int. **1Z107** *tert*-butyl 4-(2-cyclopropyl-4-(dimethylcarbamoyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (4.1 g). Int. **1Z107** (4.1 g) was stirred in ON 4M HCl in dioxane (50 mL). The mixture was concentrated and triturated in EtOAc to give Int. **1Z108** 3-cyclopropyl-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.10 g, HCl salt). STAB (0.30 g) and Ints. **1AB8/1Z108** (0.1 g/0.1 g) were stirred ON in DCE/Et_3N (73:1, 10.1 mL) at 0 °C to RT. The mixture was concentrated, dissolved in THF, filtered through silica, and concentrated to give Int. **1Z109** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-cyclopropyl-N,N-dimethylbenzamide (0.19 g).

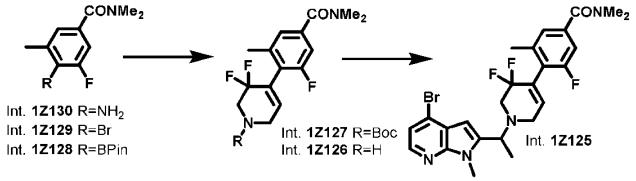


$NaIO_4$ (2.3 g) was added to a mixture of I_2 (8.0 g) in sulfuric acid (100 mL) portion-wise and stirred 0.5h. 4-Bromo-3-fluoro-N,N-dimethylbenzamide (17 g) was added and stirring continued 18h. The reaction mixture was diluted with water to precipitate a solid that was dried and precipitated from CCl_4 to give Int. **1Z122**, a mixture of 4-bromo-5-fluoro-2-iodo-N,N-dimethylbenzamide and 4-bromo-3-fluoro-5-iodo-N,N-dimethylbenzamide mixture (13 g). PdDPPFCl$_2$-DCM (1.4 g), Int. **1Z122** (13 g), cyclopropylboronic acid (3.6 g), and K_2CO_3 (14 g) were refluxed ON in dioxane/H_2O (3:1, 200 mL) under an inert atmosphere. The mixture was concentrated and purified by FC ($CHCl_3$ to $CHCl_3$/ACN 1:1) to give Int. **1Z121**, a mixture of 4-bromo-2-cyclopropyl-5-fluoro-N,N-dimethylbenzamide and 4-bromo-3-cyclopropyl-5-fluoro-N,N-dimethylbenzamide mixture (7 g). PdDPPFCl$_2$-DCM (1.0 g), Int. **1Z121** (7 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (11 g), and K_2CO_3 (10 g) were refluxed ON in dioxane/H_2O (6:1, 140 mL) under an inert atmosphere. The mixture was concentrated and purified by FC ($CHCl_3$ to $CHCl_3$/ACN 1:1) to give Int. **1Z120**, a mixture of *tert*-butyl 4-(5-cyclopropyl-4-

(dimethylcarbamoyl)-2-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate and *tert*-butyl 4-(2-cyclopropyl-4-(dimethylcarbamoyl)-6-fluoro-phenyl)-3,6-dihydropyridine-1(2H)-carboxylate mixture (2.6 g). Int. **1Z120** (2.6 g) was stirred in ON 4M HCl in dioxane (50 mL). The mixture was concentrated and triturated in EtOAc to give Int. **1Z119** 2-cyclopropyl-5-fluoro-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide and 3-cyclopropyl-5-fluoro-N,N-dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide mixture (2.0 g, HCl salt).

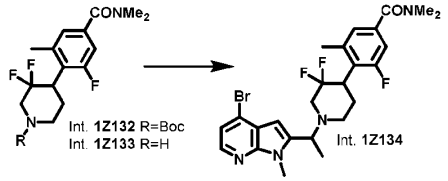


STAB (0.30 g) and Ints. **1AB8/1Z119** (0.1 g/0.1 g) were stirred ON in DCE/Et_3N (73:1, 10.1 mL) at 0 °C to RT. The residue after concentration dissolved in THF, filtered through silica, and concentrated to give a mixture of Ints. **1Z123/1Z124** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-cyclopropyl-5-fluoro-N,N-dimethylbenzamide and 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-cyclopropyl-5-fluoro-N,N-dimethylbenzamide (0.17 g).

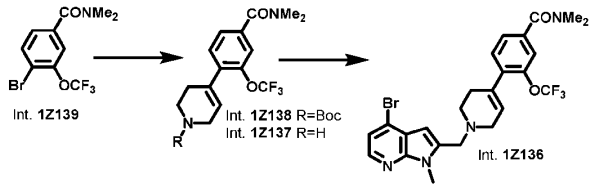


N-Iodosuccinimide (196 g) and 2-fluoro-6-methylaniline (100 g) were stirred 2h in ACN (2.0 L) at 0 °C to RT. The OL (aq. $Na_2S_2O_3$/EtOAc) was dried, and concentrated to give Int. **1Z131** 2-fluoro-4-iodo-6-methylaniline (180 g). Int. **1Z131** (30 g), dimethylamine hydrochloride (24 g), and PdDPPFCl$_2$-DCM (4.9 g) were stirred 16h in dioxane/Et_3N (14:3, 364 mL) at 85 °C under 200 psi of CO. The mixture was filtered and concentrated. The OL (1M HCl/EtOAc) was neutralized to pH ~8 with Na_2CO_3. The OL (water/EtOAc) was dried, and concentrated to give Int. **1Z130** 4-amino-3-fluoro-N,N,5-trimethylbenzamide (17 g). $CuBr_2$ (85 g) and **1Z130** (15 g) were stirred 16h in ACN (300 mL) and ^{t}BuONO (14 mL) at 0-85 °C. The OL (aq. NH_3/PE) was dried, filtered and concentrated to give Int. **1Z129** 4-bromo-3-fluoro-N,N,5-trimethylbenzamide (14 g). Int. **1Z129** (1 g), PdDPPFCl$_2$-DCM (0.31 g), bis(pinacolato)diboron (2.0 g), and KOAc (1.1 g) were stirred 1h in dioxane (10 mL) at 110 °C under MW conditions. The mixture was filtered through celite, concentrated, and washed with pentane to give Int. **1Z128** 3-fluoro-N,N,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.80 g). PdDPPFCl$_2$-DCM (0.11 g), Ints. **3E284/1Z128** (0.50 g/0.77 g), and Na_2CO_3 (0.43 g) were stirred 1.5h in dioxane/H_2O (4:1, 10 mL) at 110 ° C under MW conditions. The mixture was filtered. The OL (water/EtOAc) was concentrated and purified by FC (hexane/EtOAc 3:7) to give

Int. **1Z127** *tert*-butyl 4-(4-(dimethylcarbamoyl)-2-fluoro-6-methylphenyl)-3,3-difluoro-3,6-dihydro-pyridine-1(2H)-carboxylate (65 mg). Int. **1Z127** (0.50 g) was stirred 16h in DCM/4M HCl in dioxane (2:1, 6 mL) at 0 °C to RT. The mixture was concentrated to give Int. **1Z126** 4-(3,3-difluoro-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (0.40 g, HCl salt). Ints. **1AF88/1Z126** (0.40 g/0.59 g), KI (0.17 g), and Cs_2CO_3 (3.3 g) were stirred 12h in ACN (10 mL) at 0 °C to RT. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 4:1) to give Int. **1Z125** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]-pyridin-2-yl)ethyl)-3,3-difluoro-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (0.13 g).

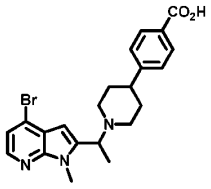


Int. **1Z127** (0.40 g) and PtO_2 (0.80 g) were hydrogenated 75h at 70 psi in THF/EtOH/AcOH (8:8:1, 17 mL). The mixture was filtered and concentrated to give Int. **1Z132** *tert*-butyl 4-(4-(dimethyl-carbamoyl)-2-fluoro-6-methylphenyl)-3,3-difluoropiperidine-1-carboxylate (0.40 g). Int. **1Z133** 4-(3,3-difluoropiperidin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (0.20 g, HCl salt) was prepared similarly to Int. **1Z126** from Int. **1Z132** (0.25 g). Ints. **1AF88/1Z133** (0.15 g/0.18 g), KI (64 mg), and Cs_2CO_3 (0.12 g) were stirred 16h in ACN (10 mL) at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:1 to 1:2) to give Int. **1Z134** 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-3,3-difluoropiperidin-4-yl)-3-fluoro-N,N,5-trimethyl-benzamide (0.13 g).

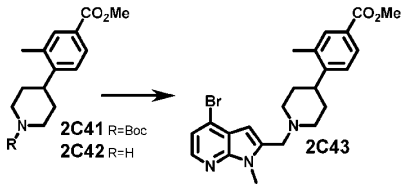


Di(1H-imidazol-1-yl)methanone (1.0 g) and 4-bromo-3-(trifluoromethoxy)benzoic acid (1.8 g) were refluxed 0.3h in dioxane (50 mL). Dimethylamine hydrochloride (0.51 g) and Et_3N (5.2 mL) was added and stirring continued 10h. The mixture was concentrated. The OL (aq. $NaHSO_4$/$CHCl_3$) was concentrated to give Int. **1Z139** 4-bromo-N,N-dimethyl-3-(trifluoro(oxo)-λ6-methyl)benzamide (1.5 g). Int. **1Z139** (1.5 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.6 g), K_2CO_3 (2.0 g), and PdDPPFCl$_2$-DCM (0.20 g) were stirred ON in dioxane/H_2O (4:1, 20 mL) at 100 °C under an inert atmosphere. The mixture was concentrated and purified by FC to give Int. **1Z138** *tert*-butyl 4-(4-(dimethylcarbamoyl)-2-(trifluoromethoxy)phenyl)-3,6-dihydro-pyridine-1(2H)-carboxylate (0.78 g). Int. **1Z138** (0.78 g) was stirred ON in 2.8M HCl in dioxane (10 mL). The mixture was concentrated to give Int. **1Z137** N,N-

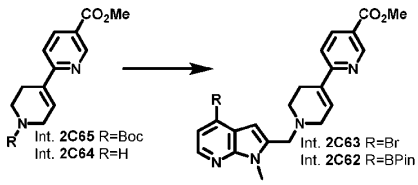
dimethyl-4-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethoxy)benzamide (0.43 g, HCl salt). Ints. **1J1/1Z137** (0.36 g/0.43 g) and K_2CO_3 (0.57 g) were stirred 11h in DMF (10 mL). The mixture was diluted with water to precipitate Int. **1Z136** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,N-dimethyl-3-(trifluoromethoxy)benzamide (0.14 g).



Int. **C3**. 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (0.11 g) was prepared similarly to Int. **2C9** from Int. **3E37** (0.12 g).

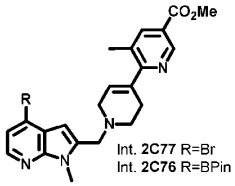


Methyl 4-bromo-3-methylbenzoate (2.5 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (4.0 g), $NaHCO_3$ (2.8 g), and $PdDPPFCl_2$-DCM (0.45 g) were degassed in dioxane/water (10:1, 30 mL) and stirred ON at 100 °C. The mixture was diluted with EtOAc (100 mL), filtered, concentrated, and purified by FC (hexane/EtOAc 9:1 to 85:15) to give Int. **2C41** *tert*-butyl 4-(4-methoxy-carbonyl-2-methyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.2 g). Int. **2C41** (0.25 g) was stirred ON in DCM/4M HCl in dioxane (4:1, 10 mL) and concentrated. The residue was triturated in pentane to give Int. **2C42** methyl 3-methyl-4-(1,2,3,6-tetra-hydropyridin-4-yl)benzoate (0.19 g, HCl salt). Ints. **1AB8/2C42** (1.2 g/1.2 g, HCl salt) were stirred 4h in DCE/DIPEA (2:2:1, 7.3 mL) at 0 °C to RT. STAB (1.9 g) was added and stirring continued ON. The OL (EtOAc / water) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **2C43** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-methyl-benzoate (1.0 g).

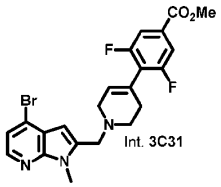


Methyl 6-bromonicotinate (5.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7.8 g), K_2CO_3 (3.0 g) and $PdDPPFCl_2$-DCM (1.9 g) were stirred in dioxane/H_2O (4:1, 100 mL) ON at 100 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated and purified by FC (hexane/MTBE 1:0 to 0:1) to give Int.

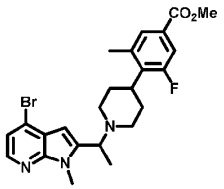
2C65 1'-(*tert*-butyl) 5-methyl 3',6'-dihydro-[2,4'-bipyridine]-1',5(2'H)-dicarboxylate (5.9 g). Int. **2C65** (2.0 g) was stirred 16h in 2M HCl in dioxane (40 mL), concentrated, and washed with Et_2O to give Int. **2C64** methyl 1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxylate (1.8 g, HCl salt). Ints. **1AB8/2C64** (616 mg/750 mg) and 4Å MS were stirred ON in DCE/Et_3N (9:1, 11.1 mL). $(AcO)_3BHNa$ (1.6 g) was added and stirring continued for 3h before it was concentrated and HPLC-purified to give Int. **2C63** methyl 1'-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxylate (0.57 g). Int. **2C63** (0.29 g), bis(pinacolato)diboron (0.18 g), KOAc (0.19 g), and $PdDPPFCl_2$-DCM (53 mg) were stirred ON in dioxane (10 mL) at 80 °C under an inert atmosphere. The residue after concentration was dissolved in THF, filtered through silica, and concentrated to give Int. **2C62** methyl 1'-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-methyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxylate (0.30 g).



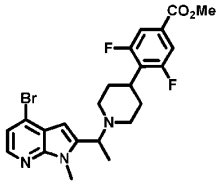
Ints. **1AB8/2C78** (0.50 g/1.0 g) and 4Å MS were stirred ON in DCE/Et_3N (15:1, 15.9 mL). $(AcO)_3BHNa$ (1.0 g) was added and stirring continued 3h. The mixture was concentrated and HPLC-purified to give Int. **2C77** methyl 1'-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-3-methyl-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxylate (0.61 g). Int. **2C77** (0.30 g), bis(pinacolato)diboron (0.30 mg), KOAc (0.30 mg) and $PdDPPFCl_2$-DCM (30 mg) were stirred ON in dioxane (3 mL) at 80 °C under an inert atmosphere. The residue after concentration was dissolved in THF, filtered through silica and concentrated to give Int. **2C76** methyl 3-methyl-1'-((1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxylate (0.30 g).



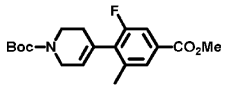
Ints. **1AB8/3C25** (8.0 g/12.6 g) were stirred 16h in DCE (80 mL) and DIPEA (35 mL) at 0 °C to RT under an inert atmosphere. STAB (28 g) was added in portions at 0 °C and stirring was continued for 12h. The OL (water/DCM) was dried, filtered, concentrated, and purified by FC (PE/EtOAc 3:2) to give Int. **3C31** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoate (7.3 g).



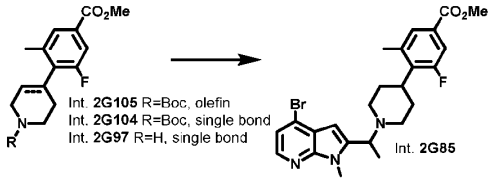
Ints. **1AF88/2G97** (2.0 g/2.3 g), KI (0.85 g) and Cs_2CO_3 (9.5 g) were mixed in ACN (20 mL) at 0 °C and stirred for 16h at RT filtered and concentrated. The residue was purified by FC (hexane/EtOAc 4:1) to give Int. **2G85** methyl 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-3-fluoro-5-methylbenzoate (2.0 g).



Int. **1AF89** (1.5 g) was stirred 0.3h in toluene/$SOCl_2$ (7:3, 14.3 mL) at 90 °C. The residue after concentration, Cs_2CO_3 (7.7 g), KI (0.49 g), and Int. **3C16** (2.1 g) were stirred 16h in ACN (10 mL) at 0 °C to RT under an inert atmosphere. The reaction mixture was concentrated and triturated in water to precipitate a solid that was washed with water, dried, and purified by FC (PE/EtOAc 9:1 to 17:3) to give Int. **2G96** methyl 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-3,5-difluorobenzoate (1.5 g).

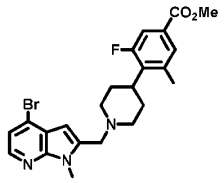


Int. **1AF90** (15 g), Boc_2O (17 g) and DMAP (0.64 g) were mixed in DCM/Et_3N (4:1, 187 mL) at 0 °C and stirred 16h and filtered. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 2:1) to give Int. **2G105** *tert*-butyl 4-(2-fluoro-4-(methoxycarbonyl)-6-methylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (14 g).

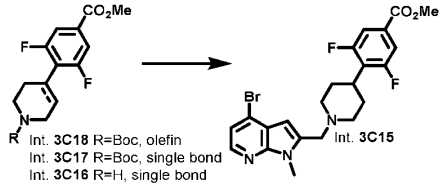


Int. **2G105** (14 g) and Pd/C (7 g) was hydrogenated 16h in MeOH (140 mL), filtered, concentrated to give Int. **2G104** *tert*-butyl 4-(2-fluoro-4-(methoxycarbonyl)-6-methylphenyl)piperidine-1-carboxylate (13.2 g). Int. **2G104** (13.2 g) was stirred 16h in DCM/4M HCl in dioxane (2:5, 105 mL) at 0 °C to RT. The mixture was concentrated and washed with pentane to give Int. **2G97** methyl 3-fluoro-5-methyl-4-(piperidin-4-yl)benzoate (9.0 g, HCl salt). Ints. **1AF88/2G97** (2.0 g/2.3 g), KI (0.85 g), and Cs_2CO_3 (9.5 g) were stirred 16h in ACN (20 mL) at 0 °C

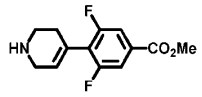
to RT. The mixture was filtered and concentrated. The residue was purified by FC (hexane/EtOAc 4:1) to give Int. **2G85** methyl 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-3-fluoro-5-methylbenzoate (2.0 g).



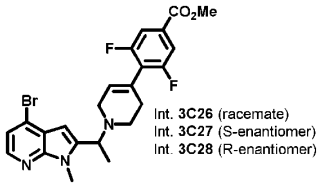
DIPEA (15 mL) was added to a solution of Ints. **1AB8/2G97** (8.0 g/12.5 g) in DCE/DMSO (5:1, 600 mL) at 0 °C and stirred for 16h at RT. STAB (28 g) was added and stirring continued for 16h. The OL (water/DCM/MeOH) was dried, filtered, concentrated and purified by FC (hexane/MeOH 4:1 to 2:1) to give Int. **2G115** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3-fluoro-5-methylbenzoate (8.0 g).



Methyl 4-bromo-3,5-difluorobenzoate (100 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (160 g), $PdDPPFCl_2$-DCM (16 g), and $NaHCO_3$ (100 g) were stirred 16h in dioxane/H_2O (10:3, 1.3 L) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (brine/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:0 to 9:1) to give Int. **3C18** *tert*-butyl 4-(2,6-difluoro-4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (45 g). Int. **3C18** (100 g) and 5% wet Pd/C(20 g) were stirred 16h in MeOH (0.7 L) under an atmosphere of hydrogen. The mixture was filtered and concentrated to give Int. **3C17** *tert*-butyl 4-(2,6-difluoro-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (90 g). Int. **3C17** (20 g) was stirred 16H in DCM/4M HCl in dioxane (2:1, 600 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3C16** methyl 3,5-difluoro-4-(piperidin-4-yl)benzoate (12 g, HCl salt). Ints. **1AB8 / 3C16** (3.5 g/3.6 g) were stirred 16h in DCE/DMSO/DIPEA (7:3:1, 112 mL). STAB (12 g) was added at 0 °C and the mixture was stirred 16h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 9:1) to give Int. **3C15** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoate (4.0 g).

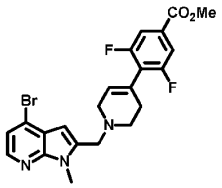


Int. **3C25**. methyl 3,5-difluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)benzoate (16 g, HCl salt) was prepared similarly to Int. **3C16** from Int. **3C18** (20 g).

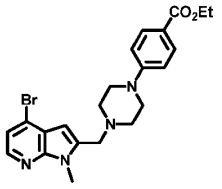


Int. **3C26** (racemate)
Int. **3C27** (S-enantiomer)
Int. **3C28** (R-enantiomer)

Int. **1AF89** (9.0 g) was stirred 0.5h in toluene/$SOCl_2$ (6:1, 174 mL) at 90 °C. The residue after concentration, Cs_2CO_3 (43 g), KI (2.7 g), and Int. **3C25** (10 g) were stirred 16h in ACN (250 mL) at 0 °C to RT under an inert atmosphere. The mixture was concentrated. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 4:1) to give Int. **3C26** methyl 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoate (7.1 g). Int. **3C26** (0.85 g) was resolved by SFC on a SFC-150-008 instrument fitted with a Chiralpak-AD-H 150x25 mm 5µm column operated at 30 °C and an eluent of 65% CO_2 and 35% MeOH (80 g/min) and a back pressure of 100 bar to give Int. **3C27** (0.30 g, first peak) and Int. **3C28** (0.30 g, second peak) methyl (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoate and methyl (R)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoate. The absolute configurations of these compounds were not determined.

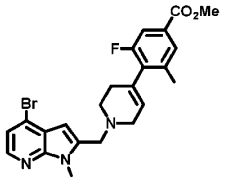


Ints. **1AB8/3C25** (8.0 g/12.6 g) were stirred 16h in DCE (80 mL) and DIPEA (35 mL) at 0 °C to RT under an inert atmosphere. STAB (28 g) was added in portions at 0 °C and stirring was continued for 12h. The OL (water/DCM) was dried, concentrated, and purified by FC (PE/EtOAc 3:2) to give Int. **3C31** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorobenzoate (7.3 g).

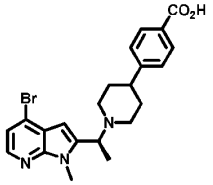


$ZnCl_2$ (1M in Et_2O, 31 mL) was added to a solution of Int. **1AB8** (2.7 g) and ethyl 4-(piperazin-1-yl)-benzoate (2.4 g) in THF (30 mL) at 0 °C and stirred 16h at RT. $NaCNBH_3$ (3.4 g) was added and stirring continued for 16h. The OL (water/EtOAc) was dried, concentrated, and

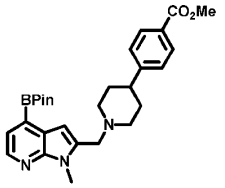
purified by FC (PE/EtOAc 1:1) to give Int. **3C59** ethyl 4-(4-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperazin-1-yl)benzoate (2.2 g).



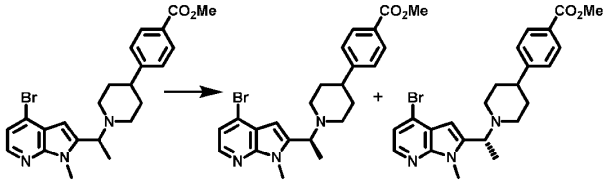
DIPEA (7.3 mL) was added to a solution of Ints. **1AB8/1AF90** (2.0 g/2.9 g) at 0 °C and stirred in DCE (10 mL) for 16h at RT under an inert atmosphere. STAB (5.2 g) was added at 0 °C and stirring continued for 2h. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 3:2) to give Int. **3C73** methyl 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoate (1.3 g).



Int. **3E35** (1.7 g) and LiOH-H_2O (1.1 g) were stirred 3h in THF/MeOH/H_2O (4:2:1, 25 mL) at 0 °C to RT and concentrated. The AL (water/Et_2O) was acidified with $KHSO_4$ to precipitate Int. **2C36** (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (1.5 g). The absolute configuration was determined for derivatives **1AF76** and **1AF76'**.

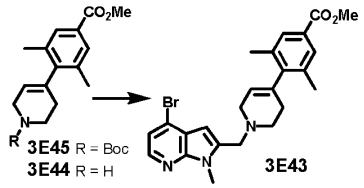


Int. **1AC5** (3.0 g), B_2Pin_2 (1.1 g), KOAc (2.0 g), and PdDPPFCl$_2$-DCM (50 mg) were degassed in dioxane (30 mL) and stirred ON at 90 °C. The filtrate after filtration was concentrated and purified by FC (pentane/EtOAc 1:4) to give Int. **2H14** methyl 4-[1-[[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]benzoate (1.7 g).

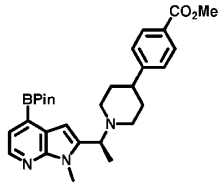


3E37 **3E35** and **3E36**

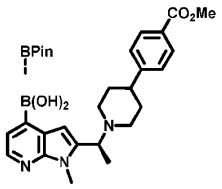
Int. **1AF21** (1.0 g) was stirred 0.3h in toluene/$SOCl_2$ (7.1:1, 22.8 mL) at 85-90 °C. The residue after concentration, Cs_2CO_3 (3.8 g), KI (0.33 g), and methyl 4-(piperidin-4-yl)-benzoate (1.3 g, HCl salt) were stirred ON in ACN (25 mL) at 0 °C to RT. The mixture was concentrated to half volume and diluted with water to precipitate Int. **3E37** methyl 4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-piperidin-4-yl)benzoate (1.4 g). Int. **3E37** (7.4 g) was resolved by SFC using a Chiralpak IA 250X25 5µm column operated at 30 °C using an eluent of 60% CO_2 and 40% MeOH at a flow rate of 90 g/min and a back pressure of 100 bar to give Int. **3E35** methyl (S)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (3.0 g, first eluting isomer) and Int. **3E36** methyl (R)-4-(1-(1-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (3.0 g, second eluting isomer). The absolute configuration was determined for derivatives **1AF76** and **1AF76'**.



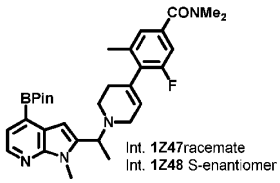
Methyl 4-bromo-3,5-dimethyl-benzoate (0.50 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.70 g), Na_2CO_3 (0.26 g), and $PdDPPFCl_2$-DCM (84 mg) were degassed in dioxane/water (9:1; 8 mL) and stirred ON at 90 °C. The OL (water/EtOAc) was concentrated and purified by FC (hexane/EtOAc 7:3) to give Int. **3E45** *tert*-butyl 4-(4-methoxycarbonyl-2,6-dimethyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (0.55 g). This material was stirred 3h in DCM/4M HCl in dioxane (5:4; 9 mL) at 0 °C to RT and concentrated to give Int. **3E44** methyl 3,5-dimethyl-4-(1,2,3,6-tetrahydro-pyridin-4-yl)benzoate (0.44 g, HCl salt). Ints. **1AB8/3E44** (0.23 g/0.30 g) were stirred 4h in DCE/DIPEA (12.5:1, 5.4 mL). STAB (0.41 g) was added and stirring continued ON. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **3E43** methyl 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-3,5-dimethyl-benzoate (0.33 g).



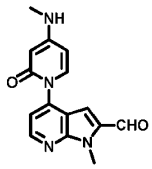
Int. **3E35** (2.0 g), B_2Pin_2 (1.7 g), $PdDPPFCl_2$-DCM (0.18 g), KOAc (0.9 g) were degassed in dioxane (15 mL) and stirred 5h at 95-100 °C, filtered, concentrated, and triturated in Et_2O to give Int. **3E170** methyl 4-[1-[(1S)-1-[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrrolo[2,3-b]pyridin-2-yl]-ethyl]-4-piperidyl]benzoate (2.3 g).



Int. **3E35** (0.50 g), B_2Pin_2 (0.41 g), $PdDPPFCl_2$-DCM (44 mg), KOAc (0.21 g) were degassed in dioxane (10 mL) and stirred 5h at 95-100 °C, filtered, concentrated, and triturated in Et_2O to give a mixture of Int. **3E170** and **3E177** (S)-(2-(1-(4-(4-(methoxycarbonyl)phenyl)piperidin-1-yl)-ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)boronic acid and methyl (S)-4-(1-(1-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (0.50 g).



$PdDPPFCl_2$-DCM (40 mg), Int. **1Z69** (0.24 g), bis(pinacolato)diboron (0.15 g), and KOAc (0.14 g) were stirred ON in dioxane (5 mL) at 100 °C under an inert atmosphere. The mixture was concentrated and purified by FC (THF) to give Int. **1Z47** 3-fluoro-N,N,5-trimethyl-4-(1-(1-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.27 g). Int. **1AF84'** (0.20 g), bis(pinacolato)diboron (0.20 g), $PdDPPFCl_2$-DCM (32 mg), and KOAc (0.12 g) were stirred 6h in dioxane (10 mL) at 90 °C under an inert atmosphere. The mixture was filtered through celite, concentrated, dissolved in Et_2O, filtered, concentrated, washed with pentane, and dried to give Int. **1Z48** (S)-3-fluoro-5-methyl-N,N-bis(methyl-d_3)-4-(1-(1-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.14 g).

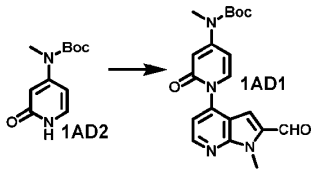


Int. **1AB8** (1.0 g), 4-(methylamino)pyridin-2(1H)-one (0.57 g), K_3PO_4 (1.33 g), CuI (0.40 g), DMDCH (0.60 g) were degassed in dioxane (30 mL) and stirred at 110 °C ON and filtered. The OL (dioxane/water) was washed brine, dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **1M1** 1-Methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (0.34 g).

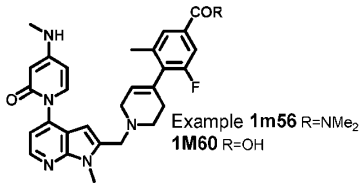


Int. **1AB9**. *tert*-Butyl (*tert*-butoxycarbonyl)(6-oxo-1,6-dihydropyridazin-4-yl)carbamate

5-Aminopyridazin-3(2H)-one (0.3 g), DMAP (0.17 g), and Boc_2O (2.36 g) were stirred ON in ACN/Et_3N (6:1, 11.7 mL) at 0 °C to RT ON and purified by FC (EtOAc/pentane 4:1) to give Int. **1AB9** (80 mg).

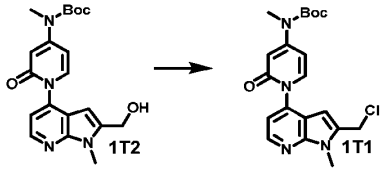


4-(Methylamino)pyridin-2(1H)-one (0.9 g) was dissolved in 0.3M LiHMDS in THF (28 mL) at 0 °C. Boc_2O (2.0 g) was added and stirring continued 2h at 0 °C to 45-50 °C and ON at RT. The OL (aq. NH_4Cl/10% MeOH in DCM) was concentrated and purified by FC (DCM/MeOH 95:5) to give *tert*-butyl methyl(2-oxo-1,2-dihydropyridin-4-yl)carbamate (0.3 g). A larger portion of this material prepared similarly (2.1 g), Int. **1AB8** (2.0 g), CuI (0.8 g), DMDCH (1.2 g), and K_3PO_4 (2.7 g) were degassed in dioxane (50 mL) and stirred at 100 °C ON. This mixture was mixed with another batch prepared similarly on 1.0 g scale and filtered. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (EtOAc/pentane 3:2) to give Int. **1AD1** *tert*-Butyl (1-(2-formyl-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-oxo-1,2-dihydropyridin-4-yl)-(methyl)carbamate (2.5 g).



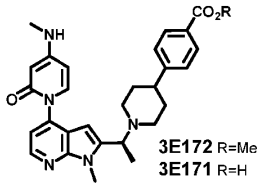
Int. **1M60**. 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid

Example **1m56** (2.4 g) and LiOH-H_2O (1.1 g) were stirred 3h in THF/water (2.5:1, 28 mL) at 0 °C to 60 °C. The residue after concentration was triturated in aq. HCl to give Int. **1M60** (2.4 g).

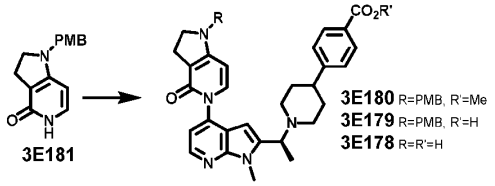


Int. **1AD1** (0.10 g) and $NaBH_4$ (15 mg) were stirred 2h in MeOH (10 mL) at 0 °C to RT and concentrated. The OL (water/EtOAc) was dried, and concentrated to give Int. **1T2** *tert*-butyl (1-(2-(hydroxymethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-oxo-1,2-dihydropyridin-4-

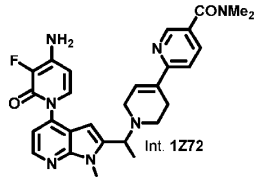
yl)(methyl)carbamate (60 mg). Int. **1T2** (0.10 g) was stirred ON in DCM/Et_3N (45:1, 10.2 mL) and MsCl (60 µL) at 0 °C to RT. The OL (water/DCM) was washed with sat. aq. $NaHCO_3$, dried, and concentrated to give Int. **1T1** *tert*-Butyl *N*-[1-[2-(chloromethyl)-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]-2-oxo-4-pyridyl]-*N*-methyl-carbamate (50 mg).



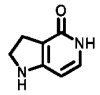
Ints. **3E35/1AD2** (0.40 g/0.29 g), CuI (0.33 g), K_2CO_3 (0.36 g), and DMDCH (0.25 g) were degassed in dioxane (10 mL) and stirred ON at 95-100 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/ MeOH 95:5) to give Int. **3E172** methyl 4-[1-[(1S)-1-[4-[4-[*tert*-butoxycarbonyl(methyl)amino]-2-oxo-1-pyridyl]-1-methyl-pyrrolo[2,3-b]pyridin-2-yl]ethyl]-4-piperidyl]benzoate (0.33 g). A solution of this material (0.22 g) in dioxane/6M aq. HCl (1:1; 8 mL) was stirred ON at 70 °C and concentrated to give Int. **3E171** 4-[1-[(1S)-1-[1-methyl-4-[4-(methylamino)-2-oxo-1-pyridyl]pyrrolo[2,3-b]pyridin-2-yl]ethyl]-4-piperidyl]benzoic acid (0.18 g, HCl salt).



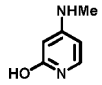
3,5-Dihydro-2H-furo[3,2-c]pyridin-4-one (2.15 g) was stirred 8h in PMB-NH_2 (20 mL) at 180 °C and diluted with Et_2O to precipitate Int. **3E181** 1-[(4-methoxyphenyl)-methyl]-3,5-dihydro-2H-pyrrolo[3,2-c]pyridin-4-one (2.35 g). Ints. **3E53/3E181** (0.30 g/0.2 g), CuI (0.25 g), K_2CO_3 (0.27 g), and DMDCH (0.19 g) were degassed in dioxane (10 mL) and stirred 2h at 120 °C. The OL (water/EtOAc) was dried, concentrated, and triturated in Et_2O to give Int. **3E180** methyl 4-[1-[(1S)-1-[4-[1-[(4-methoxyphenyl)methyl]-4-oxo-2,3-dihydropyrrolo-[3,2-c]pyridin-5-yl]-1-methyl-pyrrolo[2,3-b]pyridin-2-yl]ethyl]-4-piperidyl]benzoate (0.40 g). 0.15 g of this material and LiOH-H_2O (98 mg) were stirred 5h in MeOH/THF/water (2:2:1; 5 mL), concentrated, and triturated in dilute aq. HCl to give Int. **3E179** 4-[1-[(1S)-1-[4-[1-[(4-methoxyphenyl)-methyl]-4-oxo-2,3-dihydropyrrolo[3,2-c]-pyridin-5-yl]-1-methyl-pyrrolo[2,3-b]pyridin-2-yl]ethyl]-4-piperidyl]-benzoic acid (0.13 g). A solution of Int. **3E179** (0.15 g) in TFA/TfOH (10:1: 1.65 mL) was stirred 1h at 80 °C and concentrated to give Int. **3E178** (S)-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (0.15 g, TfOH salt).



CuI (0.24 g), Int. **1Z71** (0.30 g), 4-amino-3-fluoropyridin-2(1H)-one (82 mg), and K_3PO_4 (0.61 g) were stirred 2h in dioxane (5 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine amine (0.20 mL) at 120 °C under an inert atmosphere. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1) and HPLC-purified to give Int. **1Z72** 1'-(1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-N,N-dimethyl-1',2',3',6'-tetrahydro-[2,4'-bipyridine]-5-carboxamide (75 mg).



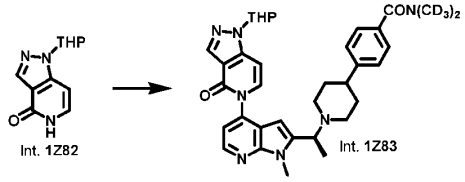
Int. **3E181** (2.3 g) was stirred 6h in TFA (20 mL) at 0-75 °C. The residue after concentration was dissolved in MeOH and concentrated. The residue was dissolved in MeOH and mixed with Amberlyst® A21 ion exchange resin, filtered, and dried to give Int. **1Z74** 1,2,3,5-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (0.90 g).



4-Chloropyridin-2-ol (10 g) was stirred ON in 2M methylamine in MeOH (100 mL) at 100 °C. The mixture was concentrated and purified by FC(ACN/MeOH 1:0 to 3:1) to give Int. **1Z78** 4-(methylamino)pyridin-2-ol (8 g).

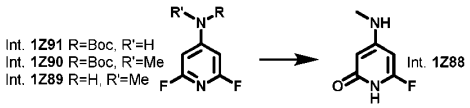


2-Methoxy-3-methylpyridin-4-amine (0.75 g), NaI (0.92 g), and $(CH_3)_3SiCl$ (0.64 mL) were stirred 1h in ACN (2 mL) at 85 °C under MW conditions. The mixture filtered and concentrated. The residue was dissolved in MeOH containing basic Amberlyst ion exchange resin. The mixture was filtered and dried to give Int. **1Z81** 4-amino-3-methylpyridin-2(1H)-one (0.30 g).

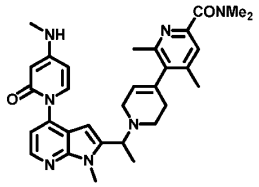


1,5-Dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (2.0 g) and TsOH (1.3 g) were stirred 16h in THF/3,4-dihydro-2H-pyran (22:3, 34 mL) at 0 °C to RT. The OL (aq. $NaHCO_3$/DCM) was dried,

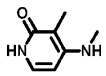
filtered, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **1Z82** 1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (1.3 g). CuI (73 mg), Ints. **1Z82/1AF77** (63 mg/0.10 g), and K_3PO_4 (0.18 g) were stirred 16h in DMF (2 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (60 µL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 49:1) to give Int. **1Z83** N,N-bis(methyl-d_3)-4-(1-((1S)-1-(1-methyl-4-(4-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzamide (40 mg).



Di-*tert*-butyl dicarbonate (22 g) was added portion-wise to a mixture of 2,6-difluoropyridin-4-amine (12 g) and DMAP (1.1 g) in DCM (200 mL). The mixture was stirred 8h and concentrated to give Int. **1Z91** *tert*-butyl (2,6-difluoropyridin-4-yl)carbamate (17 g). Int. **1Z91** (21 g) was added portion-wise to a solution of NaH (2.6 g) in DMF (100 mL) at 0 °C. The mixture was stirred 1h before MeI (6.2 mL) was added drop-wise and stirring continued 12h. The OL (water/MTBE) was concentrated to give Int. **1Z90** *tert*-butyl (2,6-difluoropyridin-4-yl)(methyl)carbamate (22 g). Int. **1Z90** (17 g) was stirred 0.5h in MeOH/2.8M HCl in dioxane (6:1, 350 mL). The mixture was concentrated to give Int. **1Z89** 2,6-di-fluoro-N-methylpyridin-4-amine (10 g). Int. **1Z89** (10 g) was refluxed 15h in 1.7M NaOH (0.2 L). The mixture was diluted with aq. citric acid. The OL (water/EtOAc) was concentrated to give Int. **1Z88** 6-fluoro-4-(methylamino)pyridin-2(1H)-one (1.2 g).

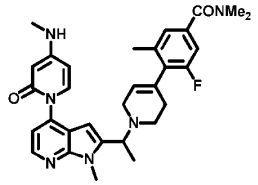


CuI (50 mg), Ints. **1Z78/1Z95** (30 mg/80 mg), and K_2CO_3 (0.1 g) were stirred 12h in DMSO (5 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (83 µL) at 100 °C under an inert atmosphere. The mixture was filtered and HPLC-purified to give Int. **1Z100** N,N,2,4-tetramethyl-1'-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-6-carboxamide (11 mg).

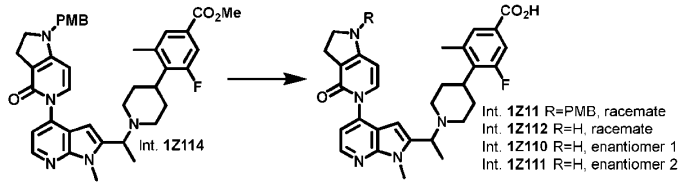


Paraformaldehyde (0.29 g) was added to a solution of Int. **1Z81** (0.40 g) in MeOH (10 mL) under an inert atmosphere. 30% NaOMe in MeOH (3 mL) was added drop-wise and stirring continued 4h at 0-55 °C. $NaBH_4$ (0.38 g) was added portion-wise and stirring continued 4h at 0-55 °C.

The mixture was diluted with aq. citric acid, concentrated, and purified by FC on neutral alumina (DCM/MeOH 9:1) to give Int. **1Z104** 3-methyl-4-(methylamino)pyridin-2(1H)-one (0.30 g).

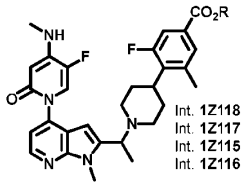


CuI (12 g), Ints. **2G81/1Z69** (8.6 g/32 g), and K_3PO_4 (40 g) were stirred 16h in dioxane (375 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (20 mL) at 107 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, and concentrated. The residue was refluxed 1h in EtOAc/DCM (10:3) and filtered while hot, the filter was washed with EtOAc and Et_2O and the filtrate concentrated to give Int. **1Z105** 3-fluoro-N,N,5-trimethyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide (22 g).



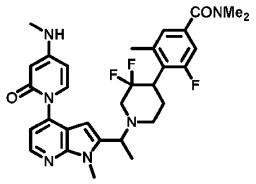
CuI (1.1 g), Ints. **3E181/HH10** (1.6 g/2.8 g), and K_3PO_4 (3.6 g) were stirred 16h in dioxane (15 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (1.8 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **1Z114** methyl 3-fluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoate (1.8 g). $LiOH{\cdot}H_2O$ (1.5 g) and Int. **1Z114** (4.6 g) were stirred 16h in THF/MeOH/H_2O (3:1:2, 90 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **1Z113** 3-fluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoic acid (4.3 g). Int. **1Z113** (0.80 g) was stirred 16h in TFA (7 mL) at 65 °C. The mixture was concentrated and triturated in MTBE to give Int. **1Z112** 3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (0.80 g, TFA salt). Int. **1Z112** (0.80 g) was resolved by SFC on a Sepiatec-200-001 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 65% CO_2 and 35% 30 mM $MeONH_3$ in MeOH at a (90 g/min) and a back pressure of 120 bar to give Int. **1Z110** (0.30 g, first peak) and Int. **1Z111** (0.25 g, second peak) (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid and (R)-3-fluoro-5-

methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.

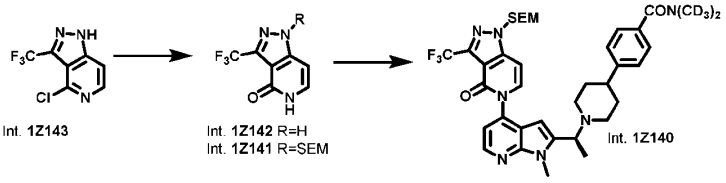


Int. **1Z118** R=Me, racemate
Int. **1Z117** R=H, racemate
Int. **1Z115** R=H, enantiomer 1
Int. **1Z116** R=H, enantiomer 2

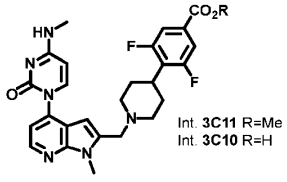
CuI (0.93 g), Ints. **2G68/2G85** (0.42 g/1.2 g), and K_3PO_4 (1.6 g) were stirred 16h in dioxane (5 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.78 mL) at 100 °C under an inert atmosphere. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **1Z118** methyl 3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoate (0.90 g). LiOH·H_2O (0.34 g) and Int. **1Z118** (0.90 g) were stirred 4h in THF/MeOH/H_2O (2:1:1, 10 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **1Z117** 3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoic acid (0.50 g). Int. **1Z117** (0.60 g) was resolved by SFC on a Sepiatec-660 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 55% CO_2 and 45% 30 mM $MeONH_3$ in MeOH at a (100 g/min) and a back pressure of 120 bar to give Int. **1Z115** (0.13 g, first peak) and Int. **1Z116** (0.14 g, second peak) (R)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoic acid and (S)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-5-methylbenzoic acid. The absolute configurations of these compounds were not determined.



CuI (50 mg) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (82 µL) were added to a solution of Ints. **2G81/1Z134** (42 mg/0.14 g) and K_3PO_4 (0.17 g) in dioxane (10 mL) and stirred for 16h at 105 °C under an inert atmosphere and filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered and concentrated to give Int. **1Z135** 4-(3,3-difluoro-1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)-3-fluoro-N,N,5-trimethylbenzamide (95 mg).

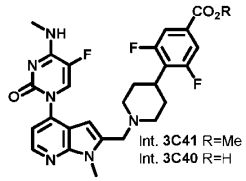


2.5M ^{n}BuLi in hexane (7 mL) was added to a solution of 2,4-dichloropyridine (2.0 g) in THF (135 mL) at -78 °C. The mixture was stirred 0.5h at -78 °C under an inert atmosphere. Ethyl 2,2,2-trifluoro-acetate (3.2 mL) was added drop-wise and stirring continued 0.75h at -78 °C. The OL (water/EtOAc) was dried, filtered and concentrated. The residue was stirred ON in THF (100 mL) and hydrazine hydrate (4.2 mL) at -40 °C to RT. The mixture was stirred ON min at -40 °C to RT. The residue after concentration was precipitated from MTBE to give Int. **1Z143** 4-chloro-3-(trifluoromethyl)-1H-pyrazolo[4,3-c]-pyridine (1.1 g). Int. **1Z143** (1.1 g) was stirred 24h in AcOH/H_2O (75:1, 15.2 mL) at 100 °C. The mixture was concentrated. The OL (water/DCM) was dried, filtered, and concentrated to give Int. **1Z142** 3-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridin-4-ol (0.96 g). SEM-Cl (0.84 mL) was added to a stirred mixture of Cs_2CO_3 (3.1 g) and Int. **1Z142** in DMF (7 mL). Stirring was continued 0.3h. The OL (water/DCM) was dried, filtered, concentrated, and triturated in MTBE to give Int. **1Z141** 3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridin-4-ol (0.33 g). CuI (73 mg), Ints. **1Z141/1AF77** (96 mg/0.10 g), and K_3PO_4 (0.16 g) were stirred 2h in DMF (10 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (56 µL) at 120 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and purified by FC (DCM/MeOH 9:1) to give Int. **1Z140** (S)-N,N-bis(methyl-d_3)-4-(1-(1-(1-methyl-4-(4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzamide (0.10 g).

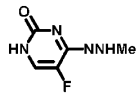


2-Chloro-5-fluoro-*N*-methylpyrimidin-4-amine (5 g) was stirred 16h in water/formic acid (0.61 mL/23 mL) at 90 °C. The mixture was diluted with EtOAc to precipitate Int. **3C12** (3.2 g). CuI (2.4 g), trans-N,N'-dimethylcyclohexane-1,2-diamine (2.0 mL), K_3PO_4 (4.0 g), Int. **3C12** (3 g), and 4-(methylamino)-pyrimidin-2(1H)-one (1.0 g) were stirred 16h in DMF/DMSO (5:1, 30 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MEOH) was filtered, concentrated, and washed with Et_2O to give Int. **3C11** methyl 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (2.6 g). LiOH·H_2O (1.0 g) and Int. **3C11** (2.6 g) were stirred 4h in THF/MeOH/H_2O (15:7:10, 32 mL) and concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate

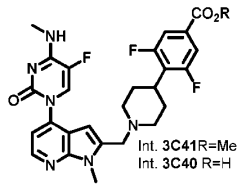
Int. **3C10** 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (2.4 g).



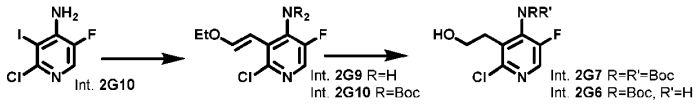
CuI (2.0 g), trans-N,N'-dimethylcyclohexane-1,2-diamine (1.7 mL), K_3PO_4 (3.3 g), and Ints. **3C12/3C15** (0.97 g/2.5 g) were stirred 12h in dioxane (15 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and purified by FC (PE/EtOAc 4:1 to 3:17) to give Int. **3C41** methyl 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (1.6 g). LiOH·H_2O (0.28 g) and Int. **3C41** (1.2 g) were stirred ON in THF/MeOH/H_2O (5:5:2, 24 mL). The residue after concentration was stirred in aq. citric acid to precipitate Int. **3C40** 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (0.90 g).



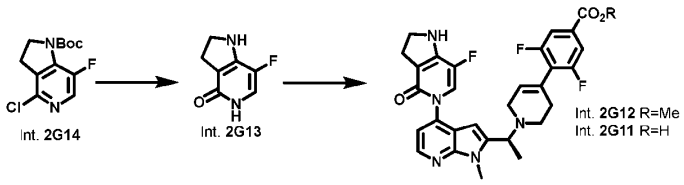
2-Chloro-5-fluoro-*N*-methylpyrimidin-4-amine (5 g) was stirred 16h in water/formic acid (0.61 mL/23 mL) at 90 °C. The mixture was diluted with EtOAc to precipitate Int. **3C12** 5-fluoro-4-(methylamino)-pyrimidin-2(1H)-one (3.2 g).



CuI (2.0 g) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (1.7 mL), K_3PO_4 (3.3 g), and Ints. **3C42/3C15** (0.97 g/2.5 g) were stirred 12h in dioxane (15 mL) at 100 °C under an inert atmosphere. The mixture was filtered and the OL (water/EtOAc) was concentrated and purified by FC (PE/EtOAc 4:1 to 3:17) to give Int. **3C41** methyl 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (1.6 g). LiOH·H_2O (0.28 g) and Int. **3C41** (1.2 g) were stirred ON in THF/MeOH/H_2O (5:5:2, 24 mL). The solid residue after concentration was stirred in water (pH adjusted with aq. citric acid), filtered and dried to give Int. **3C40** 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (0.90 g).

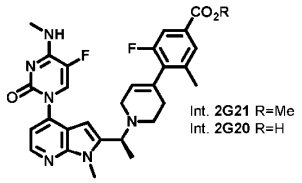


NaOAc (13 g), ICl (20 g), and 2-chloro-5-fluoropyridin-4-amine (12 g) were stirred 48h in AcOH (100 mL). The mixture was concentrated. The OL (sat. aq. $NaHCO_3$/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 4:1) to give Int. **2G10** 2-chloro-5-fluoro-3-iodopyridin-4-amine (12.5 g). Int. **2G10** (11.5 g), K_3PO_4 (18 g), *trans*-2-ethoxyvinylboronic acid pinacol ester (10 g), $Pd(OAc)_2$ (0.28 g), and SPhos (1.3 g) were stirred 16h in ACN/H_2O (3:2, 100 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 3:2) to give Int. **2G9** (*E*)-2-chloro-3-(2-ethoxyvinyl)-5-fluoropyridin-4-amine (6 g). Boc_2O (4.5 g), DMAP (0.17 g), and Int. **2G9** (3 g) were stirred 24h in DCM/Et_3N (5:2, 14 mL). The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 19:1) to give Int. **2G8** *tert*-butyl (*E*)-(*tert*-butoxycarbonyl)(2-chloro-3-(2-ethoxyvinyl)-5-fluoropyridin-4-yl)carbamate (4.5 g). $Hg(OAc)_2$ (5.1 g) in H_2O (100 mL) and Int. **2G8** (4.5 g) were 0.5h in THF (100 mL) at 0 °C. $NaBH_4$ (2.1 g) in aq. K_2CO_3 (50 mL) was added. The mixture was stirred 16h at 0 °C to RT. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 1:0 to 4:1) to give Int. **2G7** *tert*-butyl (*tert*-butoxycarbonyl)(2-chloro-5-fluoro-3-(2-hydroxyethyl)pyridin-4-yl)carbamate (3.2 g). Int. **2G7** (3.2 g) and K_2CO_3 (5.6 g) were stirred 16h in MeOH (50 mL) and concentrated. The OL (sat. aq. $NaHCO_3$/EtOAc/DCM) was concentrated to give Int. **2G6** *tert*-butyl (2-chloro-5-fluoro-3-(2-hydroxyethyl)pyridin-4-yl)carbamate (2 g).

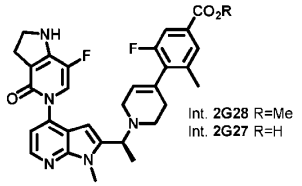


Int. **2G6** (2 g) was stirred 16h in DCM (20 mL) and MsCl (0.80 mL) at 0 °C to RT. Another portion of MsCl (2.7 mL) was added and stirring was continued 5h at 50 °C. The OL (water/DCM) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 4:1) to give Int. **2G14** *tert*-butyl 4-chloro-7-fluoro-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate (1.3 g). Int. **2G14** (1 g), $Pd_2(dba)_3$ (0.17 g), and BippyPhos (0.18 g) were stirred 16h in dioxane (10 mL) and CsOH (50% in water, 5 mL) 105 °C. The mixture was filtered. The residue after concentration was stirred in aq. citric acid to precipitate a solid that was purified by FC (DCM/MeOH 17:3) to give Int. **2G13** 7-fluoro-1,2,3,5-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (0.30 g). CuI (1.6 g), Ints. **2G13/HH5-2** (0.69 g/2.0 g), and Cs_2CO_3 (4.0 g) were stirred 12h in dioxane (30 mL) and 1,2-cyclohexanediamine (1.3 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **2G12** methyl (S)-3,5-

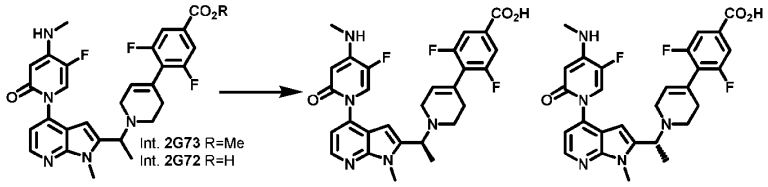
difluoro-4-(1-(1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]-pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (1.4 g). $LiOH{\cdot}H_2O$ (0.43 g) and Int. **2G12** (1.15 g) were stirred 12h in THF/MeOH/H_2O (2:2:1, 20 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **2G11** (S)-3,5-difluoro-4-(1-(1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (0.95 g).



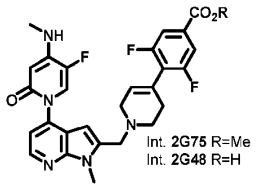
2-Chloro-5-fluoro-*N*-methylpyrimidin-4-amine (5 g) was stirred 16h in water/formic acid (0.61 mL/23 mL) at 90 °C. The mixture was diluted with EtOAc to precipitate Int. **3C12** (3.2 g). CuI (1.6 g), K_3PO_4 (2.6 g), and Ints. **3C12/1AF86** (0.77 g/2 g) were stirred 12h in dioxane (25 mL) and 1,2-cyclohexanediamine (1.3 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated, and purified by FC (PE/EtOAc 1:4 to 3:17) to give Int. **2G21** methyl (S)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (0.95 g). $LiOH{\cdot}H_2O$ (0.16 g) and Int. **2G21** (0.70 g) were stirred 16h in THF/MeOH/H_2O (3:3:1, 23 mL). The residue after concentration was stirred in aq. citric acid to precipitate Int. **2G20** (S)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (0.40 g).



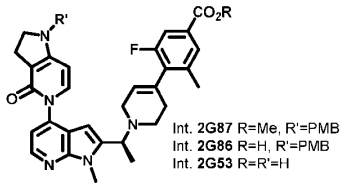
CuI (0.49 g), Cs_2CO_3 (6.7 g), and Ints. **2G13/1AF86** (1.0 g/2.5 g) were stirred 16h in dioxane (25 mL) and 1,2-cyclohexanediamine (0.81 mL) at 90 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/EtOAc) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **2G28** methyl (S)-3-fluoro-4-(1-(1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]-pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoate (1 g). $LiOH{\cdot}H_2O$ (0.24 g) and Int. **2G28** (0.80 g) were stirred 48h in THF/H_2O (1:1, 25 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **2G27** (S)-3-fluoro-4-(1-(1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (0.55 g).



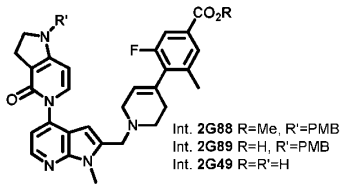
Int. **2G73** methyl 3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (6.3 g) was prepared similarly to Int. **2G67** from Ints. **2G68/3C26** (2.4 g/7.5 g). LiOH (2.3 g) and Int. **2G73** (6.0 g) were stirred 16h in THF/MeOH/water (2:1:2, 80 mL). The residue after concentration was stirred in 10% aq. citric acid to precipitate Int. **2G72** 3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (5.4 g). Int. **2G72** (5.35 g) was resolved by SFC on a SFC-150-009 instrument fitted with a (R,R) Whelk 250x30 mm 25µm column operated at 30 °C and an eluent of 50% CO_2 and 50% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 100 bar to give Int. **2G43** (2.1 g, first peak) and Int. **2G44** (2.5 g, second peak) (R)-3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid and (S)-3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.



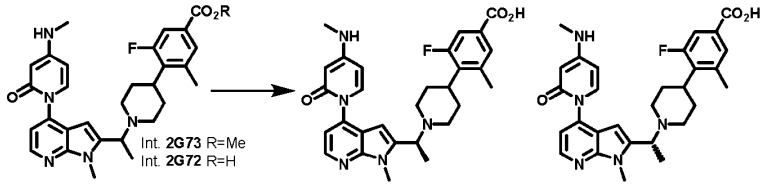
Int. **2G75** methyl 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (4.8 g) was prepared similarly to Int. **2G67** from Ints. **2G68/3C31** (2.9 g/7.5 g). $LiOH{\cdot}H_2O$ (1.8 g) and Int. **GG9** (4.8 g) were stirred 4h in THF/MeOH/H_2O (8:5:3, 80 mL). The mixture was concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **2G48** 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (4.0 g).



CuI (1.6 g), K_3PO_4 (5.2 g), and Ints. **1AF86/3E181** (4.0 g/2.3 g) were stirred 16h in dioxane (60 mL) and 1,2-cyclohexanediamine (2.6 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 19:1 to 9:1) to give Int. **2G87** methyl (S)-3-fluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (4.5 g). LiOH·H_2O (0.46 g) and Int. **2G87** (4.5 g) were stirred 4h in THF / MeOH / H_2O (5:2:1, 42 mL). The residue after concentration was stirred in water at pH 5-7 (adjusted with citric acid), filtered and dried to give Int. **2G86** (S)-3-fluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (4.0 g). Int. **2G86** (4.0 g) was stirred 16h in TFA (40 mL) at 80 °C, concentrated, and washed with Et_2O and hexane to give Int. **2G53** (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (3.4 g, TFA salt).

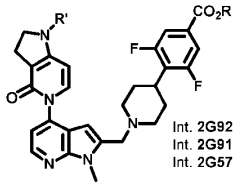


Int. **3E181** methyl 3-fluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (1.2 g) was prepared similarly to Int. **2G67** from Ints. **3E181/3C73** (0.78 g/1.3 g). LiOH·H_2O (0.39 g) and Int. **2G88** (1.2 g) were stirred 5h in THF/MeOH/H_2O (2:1:1, 10 mL) at 0 °C to RT. The residue after concentration was stirred in 10% aq. citric acid to precipitate Int. **2G89** 3-fluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (1.1 g). Int. **2G89** (1.2 g) was stirred 16h in TFA (18 mL) at 70 °C, concentrated, and washed with Et_2O and pentane to give Int. **2G49** 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzoic acid (1.0 g, TFA salt).



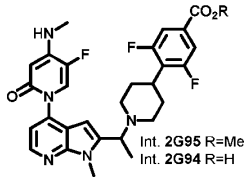
Int. **2G84** methyl 3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (0.80 g) was prepared

similarly to Int. **2G67** from Ints. **2G81/2G85** (0.50 g/1.5 g). $LiOH{\cdot}H_2O$ (0.40 g) and Int. **2G84** (1.0 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 24 mL) at 0 °C to RT. The residue after concentration was stirred in 3% aq. citric acid, filtered, and dried to give Int. **2G83** 3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (0.73 g). Int. **2G83** (0.73 g) was resolved by SFC on a SFC-150-009 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 60% CO_2 and 40% MeOH containing 0.5% $MeONH_3$ at a (90 g/min) and a back pressure of 100 bar to give Int. **2G55** (0.21 g, first peak) and Int. **2G54** (0.22 g, second peak) (R)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid and (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid. The absolute configurations were not determined for these compounds.



Int. **2G92** R=Me, R'=PMB
Int. **2G91** R=H, R'=PMB
Int. **2G57** R=R'=H

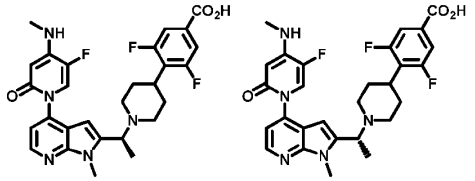
CuI (0.80 g), K_3PO_4 (2.7 g), and Ints. **3E181/3C15** (1.2 g/2.0 g) were stirred 16h in dioxane (20 mL) and 1,2-cyclohexanediamine (1.3 mL) at 90 °C under an inert atmosphere. The OL (aq. NH_3/EtOAc) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **2G92** methyl 3,5-difluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (1.8 g). $LiOH{\cdot}H_2O$ (0.58 g) and Int. **2G92** (1.8 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 40 mL) at 0°C to RT. The residue after concentration was stirred in water and diluted with aq. citric acid to precipitate Int. **2G91** 3,5-difluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (1.5 g). Int. **2G91** (1.5 g) was stirred 16h in TFA (30 mL) at 0 °C to 70 °C, concentrated, and washed with Et_2O to give crude Int. **2G57** 3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (1.1 g, TFA salt).



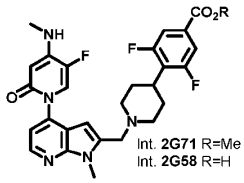
Int. **2G95** R=Me
Int. **2G94** R=H

CuI (6.2 g), K_3PO_4 (10 g), and Ints. **2G68/2G96** (3.0 g/8.0 g) were stirred 16h in dioxane (250 mL) and 1,2-cyclohexanediamine (5 mL) at 110 °C under an inert atmosphere. The mixture was

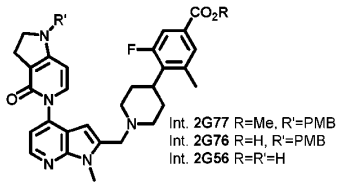
filtered. The OL (aq. NH_3/DCM/MeOH) was dried, concentrated, and washed with Et_2O to give Int. **2G95** methyl 3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (6 g). LiOH·H_2O (1.4 g) and Int. **2G95** (6 g) were stirred 4h in THF/MeOH/H_2O (3:2:1, 120 mL) and concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **2G94** 3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (5.5 g).



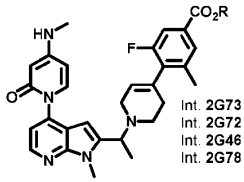
Int. **2G94** (5.5 g) was resolved by SFC on a SFC-150-022 instrument fitted with a (R,R) WHELK-1 250x30 mm 5μm column operated at 30 °C and an eluent of 55% CO_2 and 45% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 100 bar to give Int. **2G93** (2.0 g, first peak) and Int. **2G50** (2.0 g, second peak) (S)-3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid and (R)-3,5-difluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid. The absolute configurations were not determined for these compounds.



Int. **2G71** methyl 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (6.5 g) was prepared similarly to Int. **2G67** from Ints. **2G68/3C15** (3.6 g/10 g). LiOH·H_2O (2.5 g) was added to a solution of Int. **GG4** (6.5 g) in THF/MeOH/H_2O (8:5:3, 80 mL) and stirred for 4h at RT and concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **2G58** 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (6.0 g).



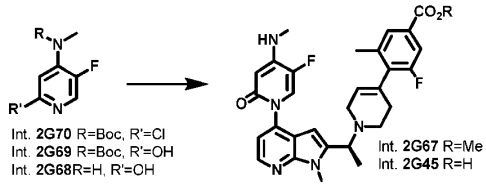
CuI (1.6 g), K_3PO_4 (2.7 g), and Ints. **3E181/HH11** (1.2 g/2.0 g) were stirred 16h in dioxane (20 mL) and 1,2-cyclohexanediamine (1.3 mL) at 120 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **2G77** methyl 3-fluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-5-methylbenzoate (2.4 g). $LiOH·H_2O$ (0.78 g) and Int. **2G77** (2.4 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 40 mL) at 0 °C to RT. The residue after concentration was stirred in water and diluted with aq. citric acid to precipitate Int. **2G76** 3-fluoro-4-(1-((4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-5-methylbenzoic acid (2.1 g). Int. **2G76** (1.2 g) was stirred 16h in TFA (30 mL) at 70 °C, concentrated, and washed with Et_2O and pentane to give Int. **2G56** 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (0.90 g, TFA salt).



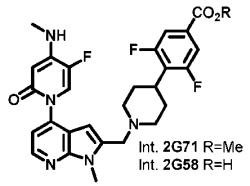
Int. **2G73** R=Me
Int. **2G72** R=H racemate
Int. **2G46** R=H enantiomer 1
Int. **2G78** R=H enantiomer 2

Paraformaldehyde (41 g) and 4-aminopyridin-2(1H)-one (50 g) were stirred 4h in MeOH (200 mL) and NaOMe (30% in MeOH, 0.42 L) at 0 °C to 55 °C. $NaBH_4$ (53 g) was and the mixture stirred 4h at 0 °C to 55 °C. The reaction mixture was diluted with aq. citric acid, concentrated, and washed with DCM/MeOH (3:2). The filtrate was dried, concentrated and purified by FC on neutral alumina (DCM/MeOH 5:1) to give Int. **2G81** 4-(methylamino)pyridin-2(1H)-one (23 g). Int. **2G80** methyl 3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (40.0 g) was prepared similarly to Int. **2G67** from Ints. **2G81/1AF87** (13.8 g/45.0 g). $LiOH·H_2O$ (16 g) and Int. **2G80** (40 g) were stirred 16h in THF/MeOH/H_2O (4:3:3, 150 mL) at 0 °C to RT. The residue after concentration was stirred in water and diluted with aq. citric acid to precipitate Int. **2G79** 3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (38 g). Int. **2G79** (38 g) was resolved by SFC on a SEPIATEC-250 instrument fitted with a (R,R) WHELK PACKED 250x30 mm 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 120 bar to give Int. **2G46** (12 g, first peak) and Int. **2G78** (11 g, second peak) (R)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoic acid and (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

tetrahydropyridin-4-yl)benzoic acid. The absolute configurations were not determined for these compounds.

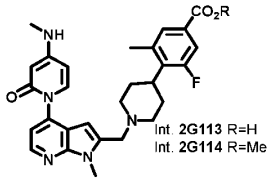


tert-Butyl (2-chloro-5-fluoropyridin-4-yl)carbamate (50.0 g) was added to a solution of NaH (5.8 g) in DMF (500 mL) at 0 °C and stirred for 1h at RT. MeI (25 mL) was added and the mixture stirred for further 4h. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **2G70** *tert*-butyl (2-chloro-5-fluoropyridin-4-yl)(methyl)carbamate (45.0 g). Int. **2G70** (45.0 g), KOH (38.7 g), $Pd_2(dba)_3$ (15.8 g), and *tert*-butyl-Xphos (14.7 g) were stirred 16h in dioxane/H_2O (4:1, 500 mL) at 110 °C under an inert atmosphere. The AL (water/DCM) was diluted with 10% aq. citric acid to precipitate Int. **2G69** *tert*-butyl (5-fluoro-2-oxo-1,2-dihydropyridin-4-yl)-(methyl)carbamate (21.0 g). Int. **2G69** (10.0 g) was stirred 16h in DCM/4M HCl in dioxane (5:6, 110 mL) at 0 °C to RT. The residue after concentrated was washed with Et_2O to give Int. **2G68** 5-fluoro-4-(methylamino)pyridin-2(1H)-one (4.7 g, HCl salt). CuI (2.4 g), K_3PO_4 (8.2 g), and Ints. **2G68/1AF86** (2.8 g/6.2 g) were stirred 16h in dioxane (80 mL) and 1,2-cyclohexanediamine (4.1 mL) at 100 °C under an inert atmosphere of argon. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, concentrated, and triturated in Et_2O/EtOAc (4:1) to give Int. **2G67** methyl (S)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (5.6 g). LiOH (1.7 g) and Int. **2G67** (5.5 g) were stirred 16h in H_2O/MeOH (20 mL/10 mL). The residue after concentration was stirred in 10% aq. citric acid to precipitate Int. **2G45** (S)-3-fluoro-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (5.0 g).

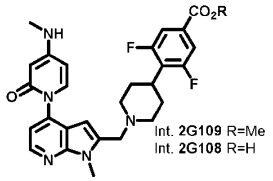


Int. **2G71** methyl 3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (6.5 g) was prepared similarly to Int. **2G67** from Ints. **2G68/3C15** (3.6 g/10 g). LiOH·H_2O (2.5 g) was added to a solution of Int. **GG4** (6.5 g) in THF/MeOH/H_2O (8:5:3, 80 mL) and stirred for 4h at RT and concentrated. The AL (water/Et_2O) was dilute with aq. citric acid to precipitate Int. **2G58** 3,5-difluoro-4-(1-((4-(5-fluoro-4-

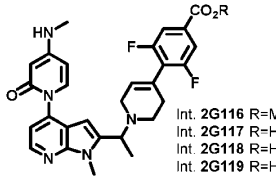
(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (6.0 g).



Int. **2G114** methyl 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (2.0 g) was prepared similarly to Int. **GG1** from Ints. **2G81/2G115** (1.3 g/3.5 g). $LiOH{\cdot}H_2O$ (0.79 g) and Int. **2G114** (2.0 g) were stirred 16h in THF/MeOH/H_2O (3:1:2, 30 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **2G113** 3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (1.7 g).

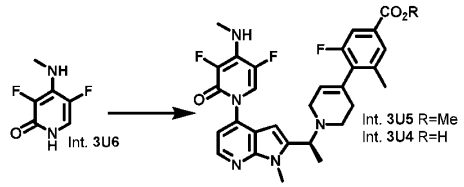


CuI (1.6 g), Ints. **2G81/3C15** (0.62 g/2.0 g), and K_3PO_4 (2.7 g) were stirred 12h in dioxane (70 mL) and 1,2-cyclohexanediamine (1.0 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/DCM/MeOH) was dried, concentrated, and washed with Et_2O to give Int. **2G109** methyl 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (1.5 g). $LiOH{\cdot}H_2O$ (39 mg) and Int. **GG2** (100 mg) were stirred 16h in THF/MeOH/H_2O (2:2:1, 2.5 mL) at 0 °C to RT. The residue after concentration was stirred in aq. HCl to precipitate Int. **2G108** 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (80 mg).

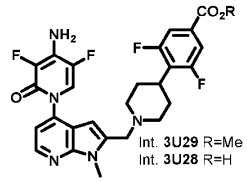


CuI (8.5 g), Ints. **2G81/3C26** (3.3 g/11 g), and K_2CO_3 (14 g) were stirred 12h in dioxane (150 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (7 mL) at 110 °C under an atmosphere of nitrogen. The mixture was filtered. The OL (water/EtOAc) was dried, filtered, concentrated, and reprecipitated from EtOAc/DCM to give Int. **2G116** methyl 3,5-difluoro-4-(1-(1-(1-methyl-4-(4-

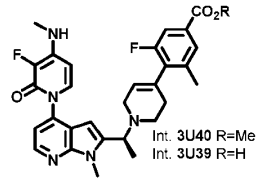
(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (5.5 g). $LiOH{\cdot}H_2O$ (2.2 g) and Int. **2G116** (5.5 g) were stirred 6h in THF/MeOH/H_2O (2:2:1, 100 mL) at 0-60 °C. The residue after concentration was stirred in aq. citric acid to precipitate Int. **2G117** 3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoic acid (4.8 g). Int. **2G117** (4.8 g) was resolved by SFC on a SEPIATEC-200-002 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 120 bar to give Int. **2G118** (1.7 g, first peak) and Int. **2G119** (1.6 g, second peak) (S)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-((methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid and (R)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.



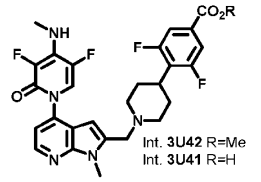
Paraformaldehyde (0.81 g) and 4-amino-3,5-difluoropyridin-2(1H)-one (1.3 g) were stirred 6h in MeOH (30 mL) and NaOMe (30% in MeOH, 4 mL) at 0 °C to 55 °C under an inert atmosphere. $NaBH_4$ (1.0 g) was added portion-wise and stirring was continued 4h at 0 °C to 55 °C. The residue after concentration was diluted with aq. citric acid to precipitate Int. **3U6** 3,5-difluoro-4-(methylamino)-pyridin-2(1H)-one (1 g). CuI (0.78 g), Ints. **3U6/1AF86** (0.43 g/1 g), and K_3PO_4 (1.3 g) were stirred 16h in dioxane (50 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.58 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/EtOAc) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1 to 9:1) to give Int. **3U5** methyl (S)-4-(1-(1-(4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methyl-benzoate (0.20 g). $LiOH{\cdot}H_2O$ (45 mg) and Int. **3U5** (0.20 g) were stirred 16h in THF/MeOH/H_2O (3:2:1, 12 mL) and concentrated. The AL (water/Et_2O) was acidified (pH adjusted to 5 using aq. Citric acid), filtered and dried to give Int. **3U4** (S)-4-(1-(1-(4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoic acid (0.18 g).



CuI (0.80 g), Int. **3C15** (1 g), 4-amino-3,5-difluoropyridin-2(1H)-one (0.40 g), and K_3PO_4 (1.3 g) were stirred 16h in dioxane (10 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.66 mL) at 110 °C under an inert atmosphere. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (PE/EtOAc 1:0 to 0:1) to give Int. **3U29** methyl 4-(1-((4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoate (0.60 g). $LiOH·H_2O$ (0.21 g) and Int. **3U29** (0.55 g) were stirred 4h in THF/MeOH/H_2O (2:1:1, 5.8 mL). The mixture was concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **3U28** 4-(1-((4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoic acid (0.35 g).

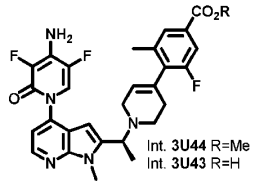


CuI (0.59 g), Ints. **JJ44/1AF86** (0.66 g/1.5 g), and K_3PO_4 (2.0 g) were stirred 12h in dioxane (40 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.97 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and triturated in Et_2O/EtOAc (4:1) to give Int. **3U48** methyl (S)-3-fluoro-4-(1-(1-(4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (1.4 g). $LiOH·H_2O$ (0.52 g) and Int. **3U40** (1.4 g) were stirred 16h in THF/MeOH/H_2O (4:1:2, 20 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U39** (S)-3-fluoro-4-(1-(1-(4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (1.2 g).

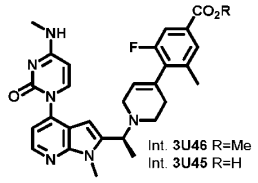


CuI (0.79 g), Ints. **3U6/3C15** (0.44 g/1.0 g), and K_3PO_4 were stirred 12h dioxane (10 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.65 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (DCM / MeOH 1:0 to 9:1) to give Int. **3U42** methyl 4-(1-((4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoate (0.35 g). $LiOH·H_2O$ (0.13 g) and Int. **3U42** (0.35 g) were stirred 2h in THF/MeOH/H_2O (2:1:2, 12.5 mL) at 0-60 °C. The residue after concentration was stirred in aq. HCl

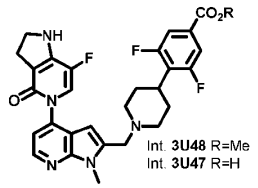
to precipitate Int. **3U41** 4-(1-((4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperidin-4-yl)-3,5-difluorobenzoic acid (0.25 g).



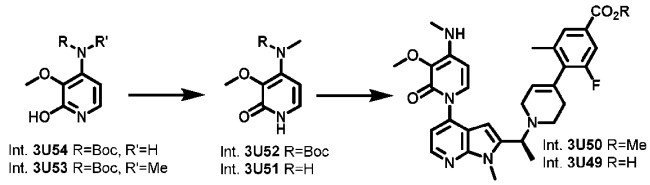
CuI (0.78 g), Int. **1AF86** (1 g), 4-amino-3,5-difluoropyridin-2(1H)-one (0.39 g), and K_3PO_4 (1.3 g) were stirred 16h in dioxane (15 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.58 mL) at 150 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1 to 9:1) to give Int. **3U44** methyl (S)-4-(1-(1-(4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoate (0.48 g). $LiOH{\cdot}H_2O$ (0.15 g) and Int. **3U44** (0.40 g) were stirred 4h in THF/MeOH/H_2O (3:2:1, 24 mL). The mixture was concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **3U43** (S)-4-(1-(1-(4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-5-methylbenzoic acid (0.38 g).



CuI (0.78 g), Int. **HH2** (1 g), 4-(methylamino)pyrimidin-2(1H)-one (0.33 g), and K_3PO_4 (1.3 g) were stirred 16h in DMF/DMSO (10:3, 13 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.65 mL) at 110 °C under an inert atmosphere. The OL (water/EtOAc) was dried, filtered, and concentrated to give Int. **3U46** methyl (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (0.80 g). $LiOH{\cdot}H_2O$ (0.19 g) and Int. **3U46** (0.80 g) were stirred 4h in THF/MeOH/H_2O (2:1:1, 21 mL). The mixture was concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **3U45** (S)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (0.75 g).

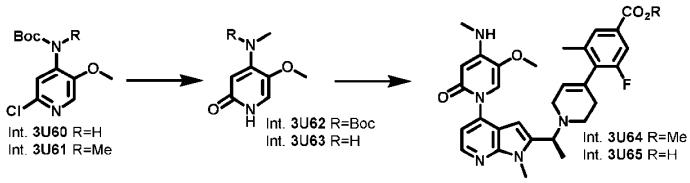


CuI (0.10 g), Ints. **VV14/3C15** (0.24 g/0.50 g), and Cs_2CO_3 (1.0 g) were stirred 16h in dioxane (5 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.16 mL) at 90 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **3U48** methyl 3,5-difluoro-4-(1-((4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo-[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoate (0.35 g). LiOH·H_2O (0.11 g) and Int. **3U48** (0.30 g) were stirred 16h in THF/MeOH/H_2O (2:2:1, 6 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U47** 3,5-difluoro-4-(1-((4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (0.25 g).

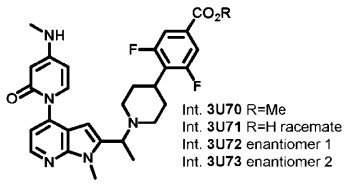


2-Chloro-4-iodo-3-methoxypyridine (3 g), *tert*-butyl carbamate (2.6 g), $Pd_2(dba)_3$ (0.31 g), XantPhos (0.32 g), and Cs_2CO_3 (11 g) were stirred 16h in toluene (10 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, filtered, concentrated, combined with a smaller batch and purified by FC (hexane/EtOAc 2:1) to give Int. **3U54** *tert*-butyl (2-chloro-3-methoxy-pyridin-4-yl)carbamate (3.5 g). Int. **3U54** (3.5 g) was added to a solution of NaH (0.65 g) in DMF (50 mL) and stirred for 0.5h at RT. MeI (1.7 mL) was added at 0 °C and stirring continued for 1h. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **3U53** *tert*-butyl (2-chloro-3-methoxypyridin-4-yl)(methyl)carbamate (3.1 g). Int. **3U53** (1.5 g), $Pd_2(dba)_3$ (0.25 g), and 5-(di-*tert*-butylphosphino)-1', 3', 5'-triphenyl-1'H-[1,4']bipyrazole (0.28 g) were stirred 16h in dioxane (25 mL) and 50% aq. CsOH (5 mL) at 110 °C under an inert atmosphere. The AL (water/EtOAc) was diluted with aq. citric acid and sat. aq. NaCl and extracted with DCM/MeOH. The OL was dried, filtered, and concentrated to give Int. **3U52** *tert*-butyl (3-methoxy-2-oxo-1,2-dihydropyridin-4-yl)(methyl)carbamate (1.0 g). Int. **3U52** (1 g) was stirred 16h in DCM/4M HCl in dioxane (2:1, 15 mL) at 0 °C to RT under an inert atmosphere. The mixture was concentrated and washed with pentane to give Int. **3U51** 3-methoxy-4-(methylamino)-pyridin-2(1H)-one (0.6. g, HCl salt). CuI (0.32 g), Ints. **3U51/1AF86** (0.33 g/0.80 g), and K_3PO_4 (1.0 g) were stirred 16h in dioxane (15 mL) and *trans*-1,2-diaminocyclohexane (0.42 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, filtered, concentrated, and triturated with DCM/MeOH (9:1) to give Int. **3U50** methyl (S)-3-fluoro-4-(1-(1-(4-(3-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (0.56 g). LiOH·H_2O (0.15 g) and Int. **3U50** (0.40 g) were stirred 16h in THF/H_2O (3:2, 25 mL). The residue after concentration was stirred in aq. citric

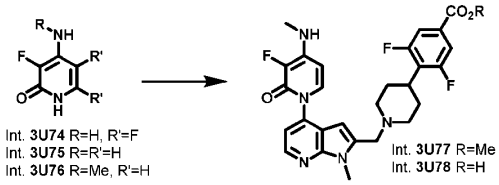
acid to precipitate Int. **3U49** (S)-3-fluoro-4-(1-(1-(4-(3-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (0.35 g).



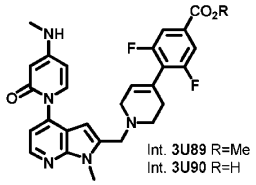
$Pd_2(dba)_3$ (4.3 g), XantPhos (4.5 g), 2-chloro-4-iodo-5-methoxypyridine (42 g), *tert*-butyl carbamate (27 g), and Cs_2CO_3 (152 g) were stirred 16h in toluene (500 mL) at 110 °C under an inert atmosphere. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 4:1 to 2:1) to give Int. **3U60** *tert*-butyl (2-chloro-5-methoxypyridin-4-yl)carbamate (30 g). NaH (1.7 g) and Int. **3U60** (10 g) were stirred 0.5h in DMF (100 mL) at 0 °C to RT. MeI (4.8 mL) was added and stirring continued 4h at 0 °C to RT. The mixture diluted with water to precipitate a solid that was triturated in pentane/EtOAc (1:1) to give Int. **3U61** *tert*-butyl (2-chloro-5-methoxypyridin-4-yl)(methyl)-carbamate (9 g). $Pd_2(dba)_3$ (0.34 g), 5-(di-*tert*-butylphosphino)-1', 3', 5'-triphenyl-1'H-[1,4']bipyrazole (0.37 g), and Int. **3U61** (2 g) were stirred 16h in dioxane (25mL) and CsOH (50% in aq., 20 mL) at 115 °C under an inert atmosphere. The AL (water/DCM) was adjusted to pH 4-5 with aq. citric acid. The OL (water pH 4-5/DCM/MeOH) was dried, filtered, and concentrated to give Int. **3U62** *tert*-butyl (5-methoxy-2-oxo-1,2-dihydropyridin-4-yl)(methyl)-carbamate (1 g). Int. **3U62** (0.55 g) was stirred 16h in DCM/4M HCl under an inert atmosphere. The mixture was concentrated and washed with pentane and Et_2O to give Int. **3U63** 5-methoxy-4-(methylamino)pyridin-2(1H)-one (0.33 g, HCl salt). CuI (0.78 g), Ints. **3U63/1AF86** (0.41 g/1.0 g), and K_3PO_4 (1.3 g) were stirred 20h in dioxane (20 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.6 mL) at 80 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, concentrated, and washed with pentane and Et_2O to give Int. **3U64** methyl (S)-3-fluoro-4-(1-(1-(4-(5-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoate (1.0 g). $LiOH{\cdot}H_2O$ (0.17 g) and Int. **3U64** (0.57 g) in were stirred 16h in THF / MeOH / H_2O (10:8:5, 23 mL). The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U65** (S)-3-fluoro-4-(1-(1-(4-(5-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoic acid (0.50 g).



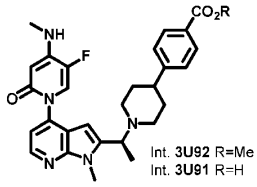
CuI (3.0 g), Ints. **2G81/2G96** (1.3 g/4.0 g), and K_3PO_4 (5.0 g) were stirred 16h in dioxane (100 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (2 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, concentrated, and washed with Et_2O to give Int. **3U70** methyl 3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (3.8 g). $LiOH·H_2O$ (1.1 g) and Int. **3U70** (4 g) were stirred 16h in THF/MeOH/H_2O (2:3:1, 20 mL) at 0 °C to RT. The mixture was concentrated. The AL (water/Et_2O) was diluted with aq. citric acid to precipitate Int. **3U71** 3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (3.8 g). Int. **3U71** (3.8 g) was resolved by SFC on a SEPIATEC-250 instrument fitted with a (R,R) WHELK PACKED 250x30 mm 5µm column operated at 30 °C and an eluent of 70% CO_2 and 30% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 100 bar to give Int. **3U72** (1.3 g, first peak) and Int. **3U73** (1.3 g, second peak) (S)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid and (R)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.



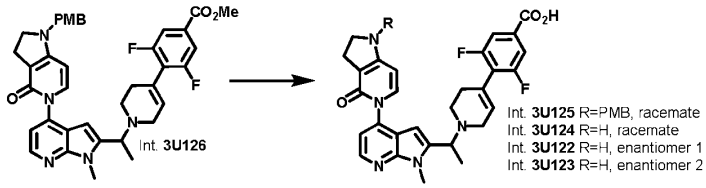
2,3,5,6-tetrafluoropyridin-4-amine (30 g) was stirred 16h in 1M aq. NaOH (400 mL) 100 °C. pH was adjusted to 4 with conc. aq. HCl. The OL (water/EtOAc) was dried, filtered, concentrated, and triturated in Et_2O to give Int. **3U74** 4-amino-3,5,6-trifluoropyridin-2(1H)-one (24 g). Int. **3U74** (5.0 g) was stirred 16h in EtOH (120 mL) and $N_2H_4·H_2O$ (20 mL) at 100 °C. The mixture was concentrated, purified by FC (DCM/MeOH 3:1), and triturated in DCM/DMSO (19:1) to give Int. **3U75** 4-amino-3-fluoropyridin-2(1H)-one (1.5 g). Paraformaldehyde (3.5 g) and Int. **3U75** (1.5 g) were stirred 4h in MeOH (20 mL) and NaOMe (30% in MeOH, 10 mL) at 0 °C to 55 °C. $NaBH_4$ (1.4 g) was added and stirring continued 4h at 0 °C to 55 °C. The mixture diluted with aq. citric acid, concentrated, washed with DCM/MeOH (3:2), dried, and purified by FC on neutral alumina (DCM/MeOH 17:3) to give Int. **3U76** 3-fluoro-4-(methylamino)pyridin-2(1H)-one (0.60 g). Int. **3U77** methyl 3,5-difluoro-4-(1-((4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperidin-4-yl)benzoate (1.2 g) was prepared similarly to Int. **3U70** from Ints. **3U76/3C15** (0.58 g/1.5 g). $LiOH·H_2O$ (0.46 g) and Int. **II22** (1.2 g) were stirred 16h in THF/MeOH/H_2O (6:2:3, 22 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U78** 3,5-difluoro-4-(1-((4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoic acid (1.0 g).



CuI (4.8 g), Ints. **2G81/3C31** (2.0 g/6.0 g), and K_3PO_4 (8.0 g) were stirred 3h in dioxane (70 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (4 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:4) to give Int. **3U89** methyl 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (3.1 g). $LiOH·H_2O$ (1.0 g) and Int. **3U89** (2.5 g) were stirred 3h in THF/MeOH/H_2O (5:1:1, 35 mL) at 0 °C to RT. The residue after concentration was stirred in aq. HCl to precipitate Int. **3U90** 3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (2.0 g).

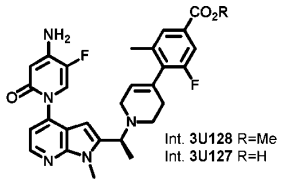


CuI (5.0 g), Ints. **2G68/3E35** (2.4 g/6.0 g), and K_3PO_4 (8.4 g) were stirred 16h in dioxane (30 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (4 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (aq. NH_3/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **3U92** methyl (S)-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (4.0 g). LiOH (0.97 g) and Int. **3U92** (4.0 g) were stirred 16h in THF/MeOH/H_2O (3:2:1, 35 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U91** (S)-4-(1-(1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (4.8 g).

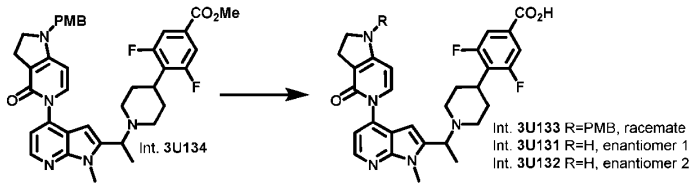


Int. **3U126** methyl 3,5-difluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (2.1 g) was prepared similarly to Int. **3U89** from Ints. **3C26/3E181** (3.3 g/1.9 g) and purified by FC (DCM/MeOH 1:0 to 9:1). $LiOH·H_2O$ (0.66 g) and Int. **3U126** (2.1 g)

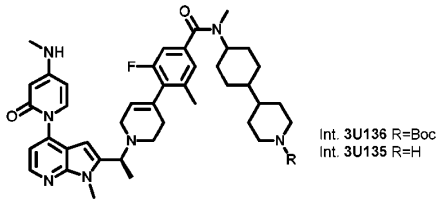
were stirred 6h in THF/MeOH/H_2O (2:2:1, 24 mL) at 0-60 °C. The residue after concentration was stirred in aq. HCl to precipitate Int. **3U125** 3,5-difluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (1.7 g). Int. **3U125** (1.7 g) was stirred 12h in TFA (6 mL) at 65 °C under an inert atmosphere. The residue after concentration washed with Et_2O to give Int. **3U124** 3,5-difluoro-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (1.4 g, TFA salt). Int. **3U124** (1.7 g) was resolved by SFC on a SFC-150-008 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 60% CO_2 and 40% MeOH containing 0.5% $MeONH_3$ at a (100 g/min) and a back pressure of 120 bar to give Int. **3U122** (0.20 g, first peak) and Int. **3U123** (0.16 g, second peak) (R)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid and (S)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.



CuI (78 mg), 4-amino-5-fluoropyridin-2(1H)-one (53 mg), Int. **1AF86** (0.10 g), and K_3PO_4 (0.13 g) were stirred 16h in dioxane (5 mL) and *trans*-N,N'-Dimethylcyclohexane-1,2-diamine (65 µL) at 100 °C under an inert atmosphere. The mixture was combined with two other batches prepared similarly and filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 1:1 to DCM/MeOH 9:1) to give Int. **3U128** methyl (S)-4-(1-(1-(4-(4-amino-5-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methyl-benzoate (0.16 g). LiOH·H_2O (63 mg) and Int. **3U128** (0.16 g) were stirred 2h in THF/MeOH/H_2O (1:1:1, 3 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U127** (S)-4-(1-(1-(4-(4-amino-5-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]-pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoic acid (0.11 g).

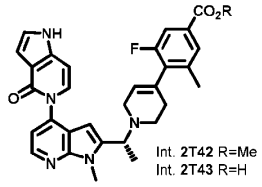


CuI (1.1 g), Ints. **3E181/2G96** (0.87 g/1.4 g), and K_3PO_4 (1.8 g) were stirred 16h in dioxane (8 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.9 mL) at 120 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 19:1 to 9:1) to give Int. **3U134** methyl 3,5-difluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (1.1 g). $LiOH·H_2O$ (0.35 g) and Int. **3U134** (1.1 g) were stirred 16h in THF/MeOH/H_2O (2:2:1, 20 mL). The residue after concentration was stirred in aq. citric acid to precipitate Int. **3U133** 3,5-difluoro-4-(1-(1-(4-(1-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (0.77 g). Int. **3U133** (0.98 g) was stirred 2h in TFA (6 mL) and resolved by SFC on a (R,R) SEPIATEC-200-001 instrument fitted with a (R,R) Whelk-01 250x30 mm 5µm column operated at 30 °C and an eluent of 65% CO_2 and 35% 30mM $MeONH_3$ in MeOH at a (90 g/min) and a back pressure of 130 bar to give Int. **3U131** (0.12 g, first peak) and Int. **3U132** (0.13 g, second peak) (S)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid and (R)-3,5-difluoro-4-(1-(1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid. The absolute configurations of these compounds were not determined.

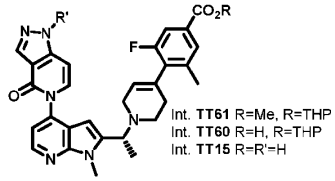


Int. **3U136** R=Boc
Int. **3U135** R=H

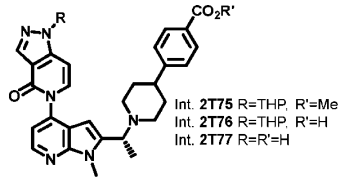
HATU (0.73 g), *tert*-butyl 4-[4-(methylamino)cyclohexyl]piperidine-1-carboxylate (0.38 g), and Int. **2G46** (0.73 g) were stirred ON in DIPEA (0.4 mL) and DMF (4 mL). The OL (EtOAc/brine) was dried and concentrated to give Int. **3u136** *tert*-butyl 4-[4-[[3-fluoro-5-methyl-4-[1-[(1S)-1-[1-methyl-4-[4-(methylamino)-2-oxo-1-pyridyl]pyrrolo[2,3-b]pyridin-2-yl]ethyl]-3,6-dihydro-2H-pyridin-4-yl]-benzoyl]-methyl-amino]cyclohexyl]piperidine-1-carboxylate (0.70 g). This material was stirred 1h in HFIP (10 mL) and 37% aq. HCl (1 mL). The residue after concentration was HPLC-purified to give Int. **3U135** 3-fluoro-N,5-dimethyl-4-[1-[(1S)-1-[1-methyl-4-[4-(methylamino)-2-oxo-1-pyridyl]-pyrrolo-[2,3-b]pyridin-2-yl]ethyl]-3,6-dihydro-2H-pyridin-4-yl]-N-[4-(4-piperidyl)cyclohexyl]benzamide (0.15 g, HCl salt).



Int. **2T42** methyl (R)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,4-dihydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (1.4 g) was prepared similarly to Int. **2G21** from 1,5-dihydro-4H-pyrrolo[3,2-c]pyridin-4-one (1.7 g) and Int. **1AF86'** (2 g). Int. **2T43** (R)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,4-dihydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (20 mg) was prepared similarly to Int. **2G41** from Int. **2T42** (50 g).

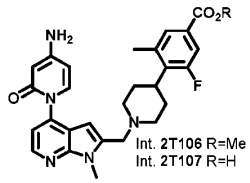


Int. **2T44** methyl 3-fluoro-5-methyl-4-(1-((1R)-1-(1-methyl-4-(4-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoate (1 g) was prepared similarly to Int. **2G21** from Ints. **1Z82/1AF86'** (0.97 g/1 g). Int. **2T45** 3-fluoro-5-methyl-4-(1-((1R)-1-(1-methyl-4-(4-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (0.75 g) was prepared similarly to Int. **VV3** from Int. **2T44** (0.80 g). Int. **2T45** (0.70 g) was stirred in DCM/TFA (1:1, 20 mL) for 16h. The mixture was concentrated, triturated in Et_2O to give Int. **2T46** (R)-3-fluoro-5-methyl-4-(1-(1-(1-methyl-4-(4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid (0.61 g).

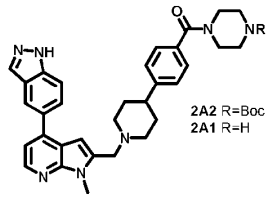


Int. **2T75** methyl 4-(1-((1R)-1-(1-methyl-4-(4-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoate (0.90 g)

was prepared similarly to Int. **3U5** from Ints. **1Z82/3E36** (0.59 g/1.1 g). Int. **2T76** 4-(1-((1R)-1-(1-methyl-4-(4-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]-pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid was prepared similarly to Int. **3U4** from Int. **2T75** (0.40 g). Int. **2T76** (50 mg) was stirred in DCM/TFA (1:1, 1 mL) for 16h. The mixture was concentrated, triturated in Et_2O to give Int. **2T77** (R)-4-(1-(1-(1-methyl-4-(4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]-pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoic acid (40 mg, TFA salt).



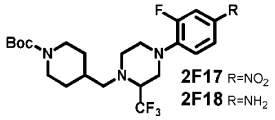
Int. **2G115** (0.50 g), 4-amino-1H-pyridin-2-one (0.15 g), CuI (0.02 g), *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.30 g), and K_3PO_4 (0.89 g) were stirred 2h in dioxane (10 mL) at 130 °C under MW conditions. The mixture was filtered. The OL (EtOAc/aq. NH_3) was dried and concentrated to give Int. **2T106** methyl 4-[1-[[4-(4-amino-2-oxo-1-pyridyl)-1-methyl-pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]-3-fluoro-5-methyl-benzoate (0.45 g). Int. **2T106** (0.90 g) and LiOH-H_2O (0.37 g) were stirred 12h in THF/MeOH/water (2:2:1; 15 mL) at 0 °C to RT. The residue after concentration was stirred in aq. citric acid to precipitate Int. **2T107** 4-[1-[[4-(4-amino-2-oxo-1-pyridyl)-1-methyl-pyrrolo[2,3-b]-pyridin-2-yl]methyl]-4-piperidyl]-3-fluoro-5-methyl-benzoic acid (0.78 g).



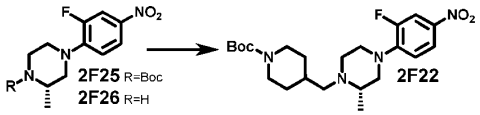
Int. **3A2** (0.20 g, HCl salt), *tert*-butyl piperazine-1-carboxylate (64 mg), and HATU (0.16 g) were stirred 2h in DMF/DIPEA (5.7:1, 4 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and HPLC-purified to give Int. **2A2** *tert*-butyl 4-[4-[1-[[1-methyl-4-(1-tetrahydro-pyran-2-ylindazol-5-yl)pyrrolo[2,3-b]-pyridin-2-yl]methyl]-4-piperidyl]benzoyl]-piperazine-1-carboxylate (0.21 g). This material was stirred 1h in DCM/TFA (2:1, 6 mL). The mixture purified by SCX to give Int. **2A1**(4-(1-((4-(1H-indazol-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)phenyl)(piperazin-1-yl)methanone (0.15 g).



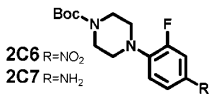
Int. **2B2** *tert*-butyl 4-((4-(4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.45 g) was prepared from 1-fluoro-4-nitrobenzene similarly to Int. **2I4**.



Int. **3E139** (0.36 g), 1,2-difluoro-4-nitrobenzene (162 mg), and K_2CO_3 (0.42 g) were stirred 48h at 80 °C in ACN (5 mL). The OL (EtOAc/water) was concentrated and purified by FC (hexane/EtOAc 7:3) to give Int. **2F17** *tert*-butyl 4-((4-(2-fluoro-4-nitrophenyl)-2-(trifluoro-methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.30 g). Int. **2F17** (0.1 g) was hydrogenated ON using 10% Pd/C (20 mg) in THF/dioxane (3:1, 8 mL), filtered, and concentrated to give Int. **2F18** *tert*-butyl 4-((4-(4-amino-2-fluorophenyl)-2-(trifluoromethyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (50 mg).

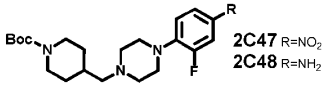


K_2CO_3 (1.36 g), 1,2-difluoro-4-nitro-benzene (0.52 g), and *tert*-butyl (S)-2-methyl-piperazine-1-carboxylate (0.65 g) were stirred ON in DMF (3 mL) at 70 °C. The OL (EtOAc/water) was washed with 3M aq. $CaCl_2$ and brine, concentrated, and purified by FC (heptane/EtOAc 1:0 to 3:1) to give Int. **2F25** *tert*-butyl (S)-4-(2-fluoro-4-nitro-phenyl)-2-methylpiperazine-1-carboxylate (0.95 g). This material was stirred 1.5h in 2.7M HCl in dioxane (15 mL) and concentrated to give Int. **2F26** (S)-1-(2-fluoro-4-nitro-phenyl)-3-methylpiperazine (0.77 g, HCl salt). Int. **2F26** (0.68 g) *tert*-butyl 4-formyl-piperidine-1-carboxylate (0.96 g) were stirred 0.25h in DMF/DIPEA (5.3:1, 12 mL). STAB (2.4 g) was added and stirring continued ON. The OL (EtOAc/water) was washed with 3M aq. $CaCl_2$ and brine, concentrated, and purified by FC (heptane/EtOAc 1:0 to 3:2) to give Int. **2F22** *tert*-butyl (S)-4-((4-(2-fluoro-4-nitrophenyl)-2-methylpiperazin-1-yl)methyl)-piperidine-1-carboxylate (0.74 g).

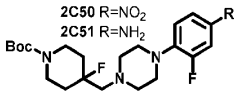


1,2-Difluoro-4-nitrobenzene (0.50 g), *tert*-butyl piperazine-1-carboxylate (0.70 g), and K_2CO_3 (0.65 g) were stirred ON in DMF (5 mL) at 80 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (EtOAc/pentane 0:1 to 1:4) to give Int. **2C6** *tert*-butyl 4-(2-fluoro-4-nitro-phenyl)piperazine-1-carboxylate (0.53 mg). Int. **2C6** (0.5 g), iron powder (0.43 g), and NH_4Cl (0.41

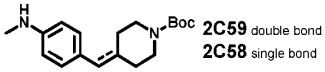
g) were stirred 2h at 80 °C in THF / EtOH / water (4:4:3, 11 mL). The filtrate after filtration was concentrated and purified by FC (hexane/EtOAc 4:1 to 1:1) to give Int. **2C7** *tert*-butyl 4-(4-amino-2-fluorophenyl)-piperazine-1-carboxylate (0.40 g).



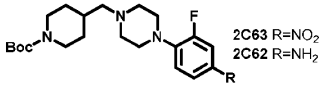
Int. **3E5** (1.07 g), 3,4-difluoronitrobenzene (0.50 g), and K_2CO_3 (0.65 g) were stirred ON in DMF (5 mL) at 80 °C. The OL (EtOAc/water) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 1:4) to give Int. **2C47** *tert*-butyl 4-[[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.47 g). Int. **2C47** (0.44 g), NH_4Cl (0.28 g), and iron powder (0.29 g) were stirred 2h in THF/EtOH/water (4:4:3, 11 mL) at 80 °C, filtered, concentrated, and purified by FC (hexane / EtOAc 1:0 to 1:1) to give Int. **2C48** *tert*-butyl 4-[[4-[4-[(2,6-dioxo-3-piperidyl)-amino]-2-fluoro-phenyl]-piperazin-1-yl]-methyl]piperidine-1-carboxylate (0.30 g).



Int. **2C50** (0.63 g) was prepared from 1,2-difluoro-4-nitrobenzene and Int. **3E143** similarly to Int. **2I4**. Int. **2C49** 3-((3-fluoro-4-(4-((4-fluoropiperidin-4-yl)methyl)-piperazin-1-yl)phenyl)amino)-piperidine-2,6-dione (0.17 g) was prepared from Int. **2C50** similarly to Int. **2N5**. Int. **2C51** was prepared from 1,2-difluoro-4-nitrobenzene and Int. **3E143** similarly to Int. **2C48**.

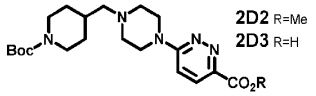


$PdDPPFCl_2$-DCM (0.22 g), *tert*-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (0.87 g), and 4-bromo-N-methylaniline (0.50 g) were degassed in dioxane/10% aq. Na_2CO_3 (1:1.2, 12.4 mL) and stirred 2h at 100 °C. The OL (EtOAc/brine) was dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 0:1) to give Int. **2C59** *tert*-butyl 4-(4-(methylamino)-benzylidene)piperidine-1-carboxylate (0.65 g). Int. **2C59** (0.53 g) was hydrogenated 2h using 10% Pd/C (0.1 g) in MeOH (8.7 mL), filtered, concentrated, and purified by FC (heptane/EtOAc 1:0 to 0:1) to give Int. **2C58** *tert*-butyl 4-(4-(methylamino)benzyl)piperidine-1-carboxylate (1.0 g).

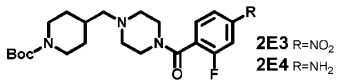


3,4-Difluoro-nitrobenzene (4.0 g), Int. **3E5** (8.6 g), and K_2CO_3 (5.2 g) were stirred ON in DMF (5 mL) at 80 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 1:0 to 4:1) to give Ind **2C63** *tert*-butyl 4-((4-(2-fluoro-4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (6.4 g). Int. **2C63** (8.0 g), iron powder (5.3 g), and NH_4Cl (5.1 g) were stirred 2h in THF/EtOH/water (1.6:1.6:1, 104 mL) at 80 °C. The

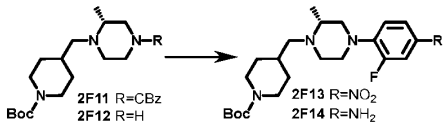
mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 4:1 to 1:1) to give Int. **2C62** *tert*-butyl 4-[[4-(4-amino-2-fluoro-phenyl)-piperazin-1-yl]methyl]piperidine-1-carboxylate (6.0 g).



Methyl 6-chloropyridazine-3-carboxylate (0.5 g) was stirred 0.25h in DMSO/DIPEA (2:1, 4.5 mL). Int. **3E5** (821 g) was added and stirring continued ON at 120 °C. The OL (EtOAc/water) was concentrated and purified by FC (pentane/EtOAc 4:1) to give Int. **2D2** methyl 6-(4-((1-(*tert*-butoxy-carbonyl)piperidin-4-yl)-methyl)-piperazin-1-yl)pyridazine-3-carboxylate (0.7 g). Int. **2D2** (0.8 g) and LiOH-H_2O (0.4 g) were stirred 6h in THF/MeOH/water (2:2:1, 8 mL) and concentrated. The OL (DCM/MeOH (9:1)/water) was concentrated and purified by FC (hexane / EtOAc 1:1) to give Int. **2D3** 6-(4-((1-(*tert*-butoxycarbonyl)-piperidin-4-yl)-methyl)-piperazin-1-yl)-pyridazine-3-carboxylic acid (0.65 g).

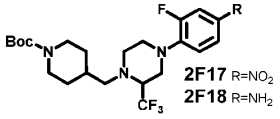


2-Fluoro-4-nitro-benzoic acid (0.16 g), Int. **3E5** (0.20 g), and HATU (322 mg) were stirred ON in DMF/DIPEA (6:1, 3.6 mL). The OL (EtOAc/water) was concentrated. The residue was purified by FC (EtOAc/MeOH 1:0 to 95:5) to give Int. **2E3** *tert*-butyl 4-((4-(2-fluoro-4-nitrobenzoyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.19 g). This material and iron powder (0.2 g) were stirred 0.75h in EtOH/water (1:1, 3 mL) and AcOH (0.05 mL) at 80 °C and filtered and concentrated. The OL (DCM/water) was washed with sat. aq. $NaHCO_3$ and brine, concentrated, and purified by SCX give Int. **2E4** *tert*-butyl 4-((4-(4-amino-2-fluorobenzoyl)-piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.18 g).

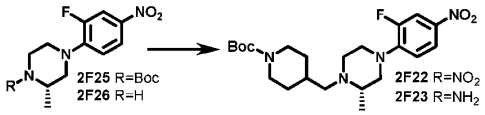


Benzyl (R)-3-methylpiperazine-1-carboxylate (12 g, HCl salt) and *tert*-butyl 4-formyl-piperidine-1-carbo-xylate (11 g) were stirred 2h in DCE/DIPEA (5:1, 240 mL) at 0 °C to RT. STAB (19 g) was added and stirring continued ON before concentration. The OL (water/DCM) was concentrated and purified by FC (hexane / EtOAc 4:1 to 3:2) to give Int. **2F11** benzyl (R)-4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-3-methyl-piperazine-1-carboxylate (12 g). Int. **2F11** (5 g) and 10% Pd/C (1.5 g) were stirred ON in EtOAc/THF (2:1, 75 mL) under a H_2 atmosphere (70 psi). The filtrate after concentration was dried to give Int. **2F12** *tert*-butyl (R)-4-((2-methylpiperazin-1-yl)-methyl)-piperidine-1-carboxylate (3.1 g). Int. **2F12** (9.0 g), K_2CO_3 (12 g) and 1,2-difluoro-4-nitrobenzene (6 g) were stirred 4h in DMF (50 mL) at 0-80 °C and filtered. The OL (EtOAc / water) was concentrated and purified by FC (pentane/EtOAc 7:3 to 3:2) to give Int. **2F13** *tert*-butyl (R)-4-

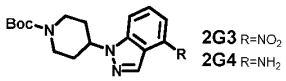
((4-(2-fluoro-4-nitrophenyl)-2-methyl-piperazin-1-yl)methyl)-piperidine-1-carboxylate (4.5 g). Int. **2F13** (4.2 g), NH_4Cl (2.5 g), and iron powder (2.7 g) were stirred 6h in THF/EtOH/water (2:2:1, 62 mL) at 80 °C and concentrated. The OL (water/DCM) was concentrated and purified by FC (hexane/EtOAc 3:1 to 3:2) to give Int. **2F14** *tert*-butyl (R)-4-((4-(4-amino-2-fluoro-phenyl)-2-methylpiperazin-1-yl)methyl)-piperidine-1-carboxylate (3.8 g).



Int. **3E139** (0.36 g), 1,2-difluoro-4-nitrobenzene (162 mg), and K_2CO_3 (0.42 g) were stirred 48h at 80 °C in ACN (5 mL). The OL (EtOAc/water) was concentrated and purified by FC (hexane/EtOAc 7:3) to give Int. **2F17** *tert*-butyl 4-((4-(2-fluoro-4-nitrophenyl)-2-(trifluoro-methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.30 g). Int. **2F17** (0.1 g) was hydrogenated ON using 10% Pd/C (20 mg) in THF/dioxane (3:1, 8 mL), filtered, and concentrated to give Int. **2F18** *tert*-butyl 4-((4-(4-amino-2-fluorophenyl)-2-(trifluoromethyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (50 mg).

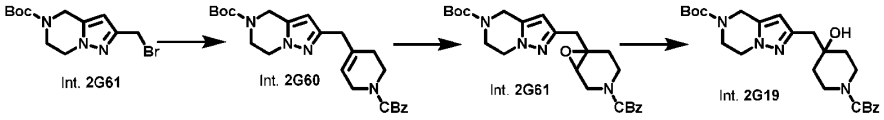


K_2CO_3 (1.36 g), 1,2-difluoro-4-nitro-benzene (0.52 g), and *tert*-butyl (S)-2-methyl-piperazine-1-carboxylate (0.65 g) were stirred ON in DMF (3 mL) at 70 °C. The OL (EtOAc/water) was washed with 3M aq. $CaCl_2$ and brine, concentrated, and purified by FC (heptane/EtOAc 1:0 to 3:1) to give Int. **2F25** *tert*-butyl (S)-4-(2-fluoro-4-nitro-phenyl)-2-methylpiperazine-1-carboxylate (0.95 g). This material was stirred 1.5h in 2.7M HCl in dioxane (15 mL) and concentrated to give Int. **2F26** (S)-1-(2-fluoro-4-nitro-phenyl)-3-methylpiperazine (0.77 g, HCl salt). Int. **2F26** (0.68 g) *tert*-butyl 4-formylpiperidine-1-carboxylate (0.96 g) were stirred 0.25h in DMF/DIPEA (5.3:1, 12 mL). STAB (2.4 g) was added and stirring continued ON. The OL (EtOAc/water) was washed with 3M aq. $CaCl_2$ and brine, concentrated, and purified by FC (heptane/EtOAc 1:0 to 3:2) to give Int. **2F22** *tert*-butyl (S)-4-((4-(2-fluoro-4-nitrophenyl)-2-methyl-piperazin-1-yl)methyl)-piperidine-1-carboxylate (0.74 g).

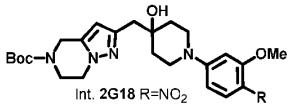


tert-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (0.38 g) was added over 5h to a mixture of 4-nitro-1H-indazole (0.20 g) and K_2CO_3 (0.34 g) in DMF (6 mL) at 100 °C and stirring was continued ON. The OL (EtOAc / water) was concentrated and purified by FC (heptane/EtOAc 1:0 to 0:1) to give Int. **2G3** *tert*-butyl 4-(4-nitro-indazol-1-yl)-piperidine-1-carboxylate (0.42 g). Int. **2G3** (0.42 g) was hydrogenated 4h using 10% Pd/C (50 mg) in EtOH (4 mL), filtered, concentrated,

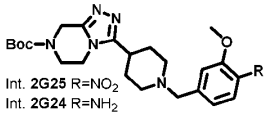
and HPLC-purified to give Int. **2G4** *tert*-butyl 4-(4-aminoindazol-1-yl)-piperidine-1-carboxylat (63 mg).



CBr_4 (15.7 g), PPh_3 (15.5 g), and *tert*-butyl 2-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (10.0 g) were stirred 16h in DCM (80 mL). The OL (water/DCM) was dried, filtered, concentrated and purified by FC (hexane/EtOAc 2:1) to give Int. **2G61** *tert*-butyl 2-(bromomethyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (10.0 g). Int. **2G61** (10.0 g), 1-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)-2l2-ethan-1-one (10.9 g), K_2CO_3 (13.1 g) and $PdDPPFCl_2$-DCM (2.6 g) were stirred 16h in dioxane/H_2O (7:3, 100 mL) under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (hexane/EtOAc 2:1) to give Int. **2G60** *tert*-butyl 2-((1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (7.0 g). m-CPBA (23 g) and Int. **2G60** (30 g) were stirred 4h in DCM (200 mL) at 0 °C to RT. The OL (aq. $NaHCO_3$/DCM) was dried, filtered and concentrated to give Int. **2G59** benzyl 6-((5-(*tert*-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (28 g). Int. **2G59** (17 g) and Pd/C 10% wt. (7 g) were hydrogenated at 60 psi in dioxane (170 mL), filtered, concentrated and HPLC-purified to give Int. **2G19** *tert*-butyl 2-((4-hydroxypiperidin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (11 g).

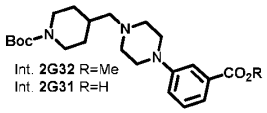


K_2CO_3 (7.3 g), Int. **2G19** (6.5 g), and 4-fluoro-2-methoxy-1-nitrobenzene (3 g) were stirred 15h in DMF (30 mL) at 70 °C. The OL (water/DCM/MeOH) was dried, filtered, concentrated, and purified by FC (EtOAc) to give Int. **2G18** *tert*-butyl 2-((4-hydroxy-1-(3-methoxy-4-nitrophenyl)piperidin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (3.1 g). Int. **2G18** (2.5 g) was hydrogenated for 16h using 10% Pd/C (1.2 g) in MeOH (30 mL), filtered, and concentrated to give Int. **2G17** *tert*-butyl 2-((1-(4-amino-3-methoxyphenyl)-4-hydroxy-piperidin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]-pyrazine-5(4H)-carboxylate (1.7 g).

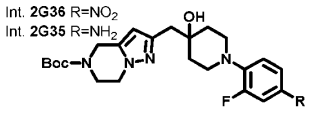


3-Methoxy-4-nitrobenzaldehyde (0.32 g), *tert*-butyl 3-(piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.50 g), and $NaCNBH_3$ (0.31 g) were stirred ON in

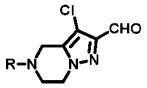
DCE/Et_3N (15:1, 10.7 mL). The mixture was filtered, concentrated, and purified by FC (MTBE/MeOH) to give Int. **2G25** *tert*-butyl 3-(1-(3-methoxy-4-nitrobenzyl)piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.30 g). Int. **2G25** (0.30 g) was hydrogenated ON using Pt/C 10% wt. (50 mg) in MeOH (10 mL), filtered, and concentrated to give Int. **2G24** *tert*-butyl 3-(1-(4-amino-3-methoxybenzyl)-piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.15 g).



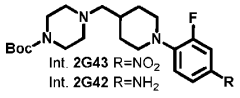
Methyl 3-bromobenzoate (3 g), Cs_2CO_3 (9.1 g), BINAP (1.7 g), $Pd(OAc)_2$ (0.31 g), and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate were stirred 16h in dioxane (20 mL) at 100 °C under an inert atmosphere. The mixture was filtered, concentrated, and purified by FC (hexane/EtOAc 3:2) to give Int. **2G32** *tert*-butyl 4-((4-(3-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (3.3 g). LiOH·H_2O (2.4 g) and Int. **2G32** (4 g) were stirred 16h in THF/MeOH/H_2O (2:1:1, 40 mL) at 0 °C to RT. The mixture was concentrated. The OL (aq. 10% citric acid/EtOAc) was concentrated to give Int. **2G31** 3-(4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)-methyl)-piperazin-1-yl)benzoic acid (3.3 g).



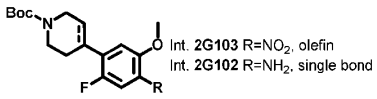
K_2CO_3 (0.22 g), Int. **2G19** (0.20 g), and 1,2-difluoro-4-nitrobenzene (91 mg) were stirred ON in ACN (2 mL) at 80 °C. The mixture was filtered, concentrated, and HPLC-purified to give Int. **2G36** *tert*-butyl 2-((1-(2-fluoro-4-nitrophenyl)-4-hydroxypiperidin-4-yl)methyl)-6,7-dihydropyrazolo-[1,5-a]pyrazine-5(4H)-carboxylate (69 mg). Int. **2G36** (69 mg) and Pd/C (50 mg) were hydrogenated ON in MeOH (5 mL), filtered, and concentrated to give Int. **2G35** *tert*-butyl 2-((1-(4-amino-2-fluoro-phenyl)-4-hydroxypiperidin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (65 mg).



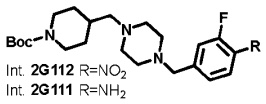
NCS (0.53 g) and *tert*-butyl 2-formyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.50 g) were stirred 16h in DMF (10 mL). The OL (brine/EtOAc) was dried, filtered and concentrated to give Int. **2G39** *tert*-butyl 3-chloro-2-formyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.54 g).



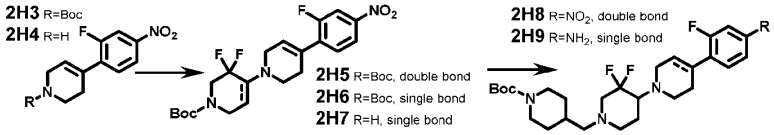
1,2-Difluoro-4-nitrobenzene (1.1 g), *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (2.0 g), and K_2CO_3 (2.9 g) were stirred ON in DMF (50 mL) at 100 °C under an inert atmosphere. The OL (water/EtOAc) dried, filtered, and concentrated to give Int. **2G43** *tert*-butyl 4-((1-(2-fluoro-4-nitro-phenyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (2.2 g). Int. **2G43** (2.2 g) was hydrogenated ON using Pd/C (55 mg) in MeOH (50 mL), filtered, and concentrated to give Int. **2G42** *tert*-butyl 4-((1-(4-amino-2-fluorophenyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (1.5 g).



1-Bromo-2-fluoro-5-methoxy-4-nitrobenzene (5 g), N-Boc-DHP-4-boronic acid pinacol ester (6.5 g) and K_2CO_3 (9 g) were mixed in dioxane/H_2O (40:1, 10 mL). $PdDPPFCl_2$-DCM (1.5 g) was added and the mixture stirred for 12h at 80 °C under an atmosphere of argon. The mixture was filtered and concentrated to give crude Int. **2G103** *tert*-butyl 4-(2-fluoro-5-methoxy-4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (7.4 g). Int. **2G103** (7.2 g) was hydrogenated for 12h using Pd/C (0.5 g) in MeOH (100 mL), filtered, and concentrated to give Int. **2G102** *tert*-butyl 4-(4-amino-2-fluoro-5-methoxyphenyl)piperidine-1-carboxylate (6.0 g).

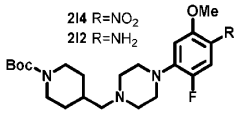


STAB (10 g), 3-fluoro-4-nitrobenzaldehyde (2 g), and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (3.3 g) were stirred 12h in DCE (60 mL). The OL (water/DCE) was concentrated to give Int. **2G112** *tert*-butyl 4-((4-(3-fluoro-4-nitrobenzyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (1.9 g). Int. **2G112** (1.9 g) and Pd/C (0.30 g) were hydrogenated in MeOH (30 mL), filtered, and concentrated to give Int. **2G111** *tert*-butyl 4-((4-(4-amino-3-fluorobenzyl)-piperazin-1-yl)methyl)-piperidine-1-carboxylate (1.5 g).

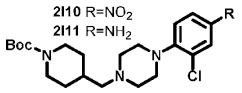


1-Bromo-2-fluoro-4-nitrobenzene (6 g), $PdCl_2(PPh_3)_2$ (1.0 g), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (10 g) were degassed in dioxane/water (12:1, 65 mL) and stirred ON at 90 °C. The OL (EtOAc/water) was concentrated and purified by FC (pentane/EtOAc 7:3 to 65:35) to give Int. **2H3** *tert*-butyl 4-(2-fluoro-4-nitrophenyl)-3,6-dihydro-pyridine-1(2H)-carboxylate (8 g). This material was stirred 2h in 2M HCl in 1,4-dioxane (160 mL) at 0 °C to RT, concentrated, and triturated in pentane to give Int. **2H4** 4-(2-fluoro-4-nitro-phenyl)-1,2,3,6-tetrahydropyridine (5 g, HCl salt). Int. **2H4** (6.0 g) and NaOAc (4.8 g) were stirred

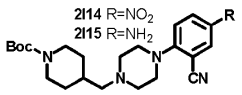
0.5h in ACN/toluene (1:2, 150 mL). *tert*-Butyl 3,3-difluoro-4-oxo-piperidine-1-carboxylate (8.7 g) and AcOH (5 mL) were added and stirring continued ON at 100 °C. The filtrate after filtration was concentrated to give Int. **2H5** *tert*-butyl 3',3'-difluoro-4-(2-fluoro-4-nitro-phenyl)-3,3',6,6'-tetrahydro-2H-[1,4'-bipyridine]-1'(2'H)-carboxylate (7 g). This material and $NaCNBH_3$ (5.0 g) were stirred ON in MeOH/DCE/AcOH (6.7:6.7:1, 43 mL). The residue after concentration was diluted with EtOAc and filtered. The residue after concentration of the filtrate was purified by FC (pentane/EtOAc 1:0 to 7:3) to give Int. **2H6** *tert*-butyl 3,3-difluoro-4-(4-(2-fluoro-4-nitro-phenyl)-3,6-dihydropyridin-1(2H)-yl)piperidine-1-carboxylate (3 g). Int. **2H6** (1.5 g) was stirred 2h in 2M HCl in dioxane (20 mL) at 0 °C to RT. The mixture was concentrated to give Int. **2H7** 1-(3,3-difluoro-piperidin-4-yl)-4-(2-fluoro-4-nitrophenyl)-1,2,3,6-tetrahydropyridine (1.2 g, HCl salt). This material and *tert*-butyl 4-formyl-piperidine-1-carboxylate (0.81 g) were stirred 4h in DCE/DIPEA (10:1, 17 mL). STAB (1.4 g) was added and stirring was continued ON at 0 °C to RT. The OL (water/DCM) was concentrated and purified by FC (pentane / EtOAc 1:1 to 2:3) to give Int. **2H8** *tert*-butyl 4-((3,3-difluoro-4-(4-(2-fluoro-4-nitro-phenyl)-3,6-dihydropyridin-1(2H)-yl)piperidin-1-yl)methyl)-piperidine-1-carboxylate (1.1 g). This material was hydrogenated ON using 50% Pd/C (0.5 g) in EtOAc (6 mL), filtered, and concentrated to give Int. **2H9** *tert*-butyl 4-((4-(4-amino-2-fluoro-phenyl)-3',3'-difluoro-[1,4'-bipiperidin]-1'-yl)-methyl)piperidine-1-carboxylate (1.0 g).



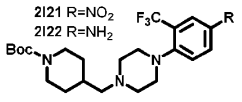
1,2-Difluoro-4-methoxy-5-nitro-benzene (2.7 g), *tert*-butyl 4-(piperazin-1-ylmethyl)-piperidine-1-carboxylate (4.9 g), and K_2CO_3 (2.9 g) were stirred ON in DMF (10 mL) at 80 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 4:1 to 7:3) to give Int. **2I4** *tert*-butyl 4-((4-(2-fluoro-5-methoxy-4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (4 g).



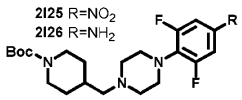
Int. **2I10** *tert*-butyl 4-((4-(2-fluoro-5-methoxy-4-nitrophenyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (1.2 g) prepared similarly to Int. **2I4** from 2-chloro-1-fluoro-4-nitrobenzene (1.8 g).



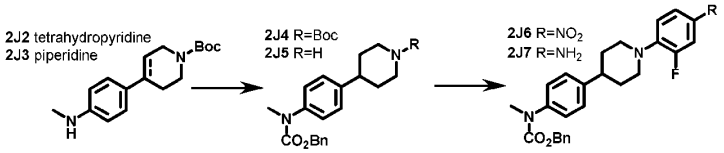
Int. **2I14** *tert*-butyl 4-((4-(2-fluoro-5-methoxy-4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (2 g) prepared similarly to Int. **2I4** from 2-fluoro-5-nitrobenzonitrile (1.0 g).



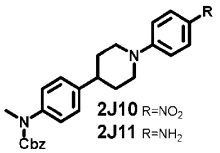
Int. **2I21** *tert*-butyl 4-((4-(4-nitro-2-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (4 g) was prepared from 1-fluoro-4-nitro-2-(trifluoromethyl)-benzene (2.5 g) similarly to Int. **2I4**.



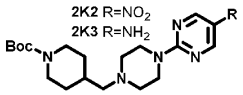
Int. **2I25** *tert*-butyl 4-((4-(2,6-difluoro-4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.45 g) prepared similarly to Int. **2I4** from 1,2,3-trifluoro-5-nitro-benzene.



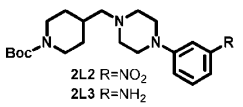
4-Bromo-N-methylaniline (2.4 g), Cs_2CO_3 (13 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (4.8 g), and $PdDPPFCl_2$-DCM (0.5 g) were degassed in dioxane/water (10:1, 44 mL) and stirred ON at 110 °C, filtered, concentration, and purified by FC (heptane / EtOAc 1:0 to 4:1) to give Int. **2J2** *tert*-butyl 4-(4-(methylamino)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.7 g). This material was hydrogenated ON using 10% Pd/C (0.5 g) in MeOH (37 mL), filtered, and concentrated to give Int. **2J3** *tert*-butyl 4-(4-(methyl-amino)phenyl)-piperidine-1-carboxylate (2.6 g). Int. **2J3** (0.83 g) was stirred in DCM/DIPEA (4:1, 7.5 mL) at 0 °C. CBz-Cl (0.55 g) was added and stirring was continued ON at 0 °C to RT. The OL (DCM/water) was washed with brine, concentrated, and purified by FC (hexane/EtOAc 1:0 to 3:2) to give Int. **2J4** *tert*-butyl 4-(4-(((benzyloxy)-carbonyl)(methyl)-amino)phenyl)-piperidine-1-carboxylate (1.1 g). This material was stirred 1h in 2.7M HCl in dioxane (15 mL) and concentrated to give Int. **2J5** benzyl methyl(4-(piperidin-4-yl)phenyl)-carbamate (0.79 g, HCl salt). Int. **2J5** (0.25 g), K_2CO_3 (0.29 g), and 1,2-difluoro-4-nitrobenzene (0.11 g) were stirred ON at 70 °C and 48h at RT. The OL (EtOAc/water) was washed with brine, concentrated, and HPLC-purified to give Int. **2J6** benzyl (4-(1-(2-fluoro-4-nitrophenyl)-piperidin-4-yl)phenyl)(methyl)-carbamate (0.27 g). This material and iron powder (0.33 g) were stirred ON in THF / AcOH (2:1, 9 mL). Iron powder (0.33 g) was added and stirring continued 4h. The filtrate was SCX-purified to give Int. **2J7** benzyl (4-(1-(4-amino-2-fluoro-phenyl)-piperidin-4-yl)phenyl)-(methyl)-carbamate (0.25 g).



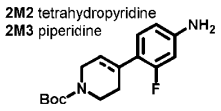
Int. **2J11** was prepared similarly to Int. **2J7** from 1-fluoro-4-nitrobenzene.



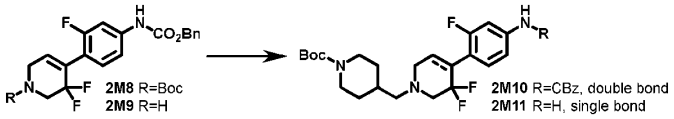
Int. **2K2** *tert*-butyl 4-((4-(5-nitropyrimidin-2-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.2 g) was prepared from 2-chloro-5-nitropyrimidine (0.10 g) similarly to Int. **2I4**.



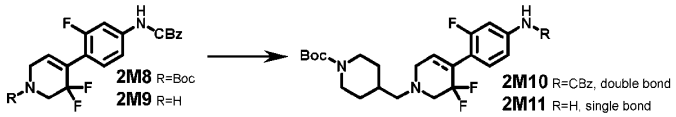
1-Bromo-3-nitrobenzene (0.30 g), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (0.51 g), NaOtBu (214 mg), XantPhos (86 mg), and Pd_2dba_3 (136 mg) were degassed in toluene (12 mL) and stirred 48h at 130 °C. Filtration, concentration, and HPLC-purification gave Int. **2L2** *tert*-butyl 4-((4-(3-nitro-phenyl)-piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.24 g). This material was hydrogenated ON using 10% Pd/C (0.1 g) in EtOH (10 mL), filtered, and concentrated to give Int. **2L3** *tert*-butyl 4-((4-(3-amino-phenyl)-piperazin-1-yl)methyl)-piperidine-1-carboxylate (0.20 g).



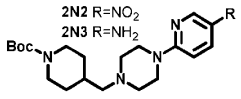
4-Bromo-3-fluoro-aniline (0.22 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (0.43 g), K_2CO_3 (0.48 g), and PdPDDFCl$_2$-DCM (42 mg) were degassed in dioxane / water (6:1, 7 mL) and stirred ON at 90 °C, filtered, concentrated and purified by FC (heptane/EtOAc 1:0 to 65:35) to give Int. **2M2** *tert*-butyl 4-(4-amino-2-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (0.28 g). This material was hydrogenated ON using 10% Pd/C (50 mg) in EtOAc (6 mL), filtered, and concentrated to give Int. **2M3** *tert*-butyl 4-(4-amino-2-fluorophenyl)-piperidine-1-carboxylate (0.27 g).



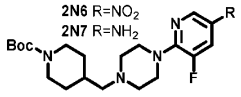
Na_2CO_3 (0.96 g), benzyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (1.4 g), Int. **3E284** (1.7 g), and PdPDDFCl$_2$-DCM (0.28 g) were degassed in dioxane/water (5:1, 24 mL) and stirred ON at 60 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (hexane / EtOAc 4:1 to 7:3) to give Int. **2M8** *tert*-butyl 4-(4-(((benzyloxy)carbonyl)amino)-2-fluorophenyl)-3,3-difluoro-3,6-dihydro-pyridine-1(2H)-carboxylate (1.5 g). This material (1.1 g) was stirred ON in DCM/4M HCl in dioxane (1:1, 22 mL) at 0 °C to RT, concentrated, and triturated in Et_2O/pentane to give Int. **2M9** benzyl (4-(3,3-difluoro-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-phenyl)-carbamate (0.76 g, HCl salt).



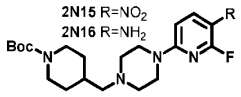
Na_2CO_3 (0.96 g), benzyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)carbamate (1.4 g), Int. **3E284** (1.7 g), and PdPDDFCl$_2$-DCM (0.28 g) were degassed in dioxane/water (5:1, 24 mL) and stirred ON at 60 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 4:1 to 7:3) to give Int. **2M8** *tert*-butyl 4-(4-(((benzyloxy)carbonyl)amino)-2-fluorophenyl)-3,3-difluoro-3,6-dihydro-pyridine-1(2H)-carboxylate (1.5 g). This material (1.1 g) was stirred ON in DCM/4M HCl in dioxane (1:1, 22 mL) at 0 °C to RT, concentrated, and triturated in Et$_2$O/pentane to give Int. **2M9** benzyl (4-(3,3-difluoro-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl)-carbamate (0.76 g, HCl salt). This material (0.73 g) and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.39 g) were stirred 3h in DCE/DIPEA (10:1, 19.6 mL) at 0 °C to RT. STAB (0.78 g) was added and stirring continued ON before concentration. The OL (water/MeOH/DCM (1:9)) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 3:2 to 1:1) to give Int. **2M10** *tert*-butyl 4-((4-(4-(((benzyloxy)-carbonyl)amino)-2-fluorophenyl)-3,3-difluoro-3,6-dihydropyridin-1(2H)-yl)methyl)-piperidine-1-carboxylate (0.70 g). This material was hydrogenated 48h using 10% Pd/C (0.25 g) in EtOAc (15 mL), filtered, concentrated, and purified by FC (hexane/EtAOC 1:4 to 0:1) to give Int. **2M11** *tert*-butyl 4-((4-(4-amino-2-fluorophenyl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate (0.21 g).



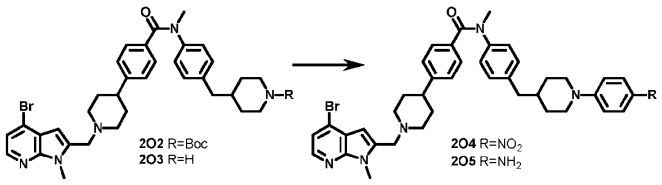
Int. **2N2** *tert*-butyl 4-((4-(5-nitropyridin-2-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.76 g) was prepared from 2-chloro-5-nitropyridine (0.90 g) similarly to Int. **2I4**.



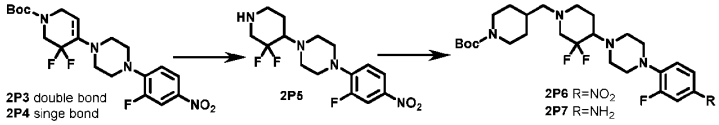
Int. **2N6** *tert*-butyl 4-((4-(3-fluoro-5-nitropyridin-2-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (4.5 g) was prepared from 2-chloro-3-fluoro-5-nitropyridine (2.5 g) similarly to Int. **2I4**.



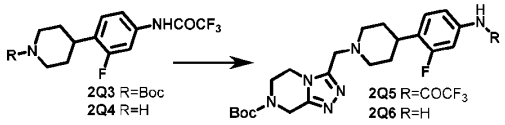
Int. **2N15** *tert*-butyl 4-((4-(6-fluoro-5-nitropyridin-2-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.0 g) was prepared from 2,6-difluoro-3-nitropyridine similarly to Int. **2I4** using DIPEA instead of K_2CO_3.



Int. **2O2** *tert*-butyl 4-(4-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperidin-4-yl)-N-methylbenzamido)benzyl)piperidine-1-carboxylate (357 mg) was prepared similarly to Int. **2C18** from Ints. **1AC4/2C58** (0.21 g/0.18 g). This material was stirred 0.5h in DCM/TFA (4:1, 2.5 mL), concentrated, and purified by SCX to give Int. **2O3** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-methyl)piperidin-4-yl)-N-methyl-N-(4-(piperidin-4-ylmethyl)phenyl)-benzamide (0.20 g). This material (0.10 g), K_2CO_3 (90 mg), and 1-fluoro-4-nitrobenzene (22 mg) were stirred ON in DMF (2 mL) at 100 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:1 to 0:1) to give Int. **2O4** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperidin-4-yl)-N-methyl-N-(4-((1-(4-nitrophenyl)-piperidin-4-yl)methyl)phenyl)benzamide (98 mg).

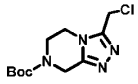


NaOAc (2.7 g) and 1-(2-fluoro-4-nitrophenyl)piperazine (3.5 g, HCl salt) were stirred 0.5h in toluene / CAN / AcOH (8.8:3.8:1, 54 mL). *tert*-Butyl 3,3-difluoro-4-oxopiperidine-1-carboxylate (4.4 g) was added and stirring continued ON at 100 °C. The filtrate after filtration was concentrated to give Int. **2P3** *tert*-butyl 3,3-difluoro-4-(4-(2-fluoro-4-nitro-phenyl)piperazin-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7 g).

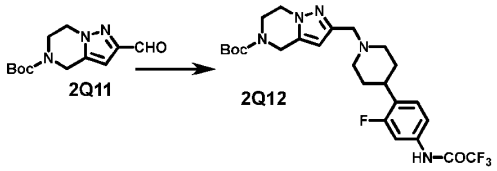


TFAA (2.5 mL) was added to a solution of *tert*-butyl 4-(4-amino-2-fluorophenyl)-piperidine-1-carboxylate (3.5 g) in toluene/Et_3N (6:1, 35 mL) at 0 °C before stirring ON at 0 °C to RT. The OL (EtOAc/water) was dried and concentrated to give Int. **2Q3** *tert*-butyl 4-(2-fluoro-4-(2,2,2-trifluoro-acetamido)phenyl)piperidine-1-carboxylate (4.5 g). This material was stirred 2h in 2.4M HCl in dioxane (50 mL) at 0 °C to RT and concentrated to give Int. **2Q4** 2,2,2-trifluoro-N-(3-fluoro-4-(piperidin-4-yl)-phenyl)-acetamide (3.3 g, HCl salt). Ints. **2Q4/2Q8** (0.65 g, HCl salt/0.79 g) were stirred ON in DMF/DIPEA (3:1, 8 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **2Q5** *tert*-butyl 3-((4-(2-fluoro-4-(2,2,2-trifluoro-acetamido)phenyl)piperidin-1-yl)methyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.45 g). This material and K_2CO_3 (1.2 g) were stirred ON in

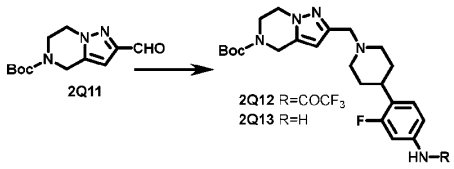
MeOH/water (1:1, 8 mL). The OL (EtOAc/water) was washed with brine, dried, and concentrated to give Int. **2Q6** *tert*-butyl 3-((4-(4-amino-2-fluoro-phenyl)piperidin-1-yl)-methyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.29 g).



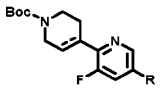
tert-Butyl 3-(hydroxymethyl)-5,6-dihydro-[1,2,4]-triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.70 g) was stirred ON in DCM (10 mL), MsCl (0.4 mL), and Et_3N (1.5 mL) at 0 °C to RT. The OL (DCM/water) was dried and concentrated to give Int. **2Q8** *tert*-butyl 3-(chloromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.81 g).



DMP (1.5 g) and *tert*-butyl 2-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.45 g) were stirred 3h in DCM (4 mL) at 0 °C to RT. The OL (DCM/aq. $NaHCO_3$) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 3:2 to 1:1) to give Int. **2Q11** *tert*-butyl 2-formyl-6,7-dihydro-pyrazolo-[1,5-a]pyrazine-5(4H)-carboxylate (0.22 g). Ints. **2Q11/2Q4** (0.2 g/0.26 g, HCl salt) were stirred 4h in DCE/DIPEA (10:1, 2.2 mL). STAB (0.34 g) was added before stirring ON at 0 °C to RT. The OL (DCM/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 98:2 to 95:5) to give Int. **2Q12** *tert*-butyl 2-((4-(2-fluoro-4-(2,2,2-trifluoro-acetamido)phenyl)-piperidin-1-yl)methyl)-6,7-dihydro-pyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.17 g).

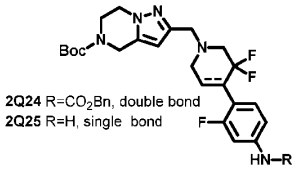


DMP (1.5 g) and *tert*-butyl 2-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.45 g) were stirred 3h in DCM (4 mL) at 0 °C to RT. The OL (DCM/aq. $NaHCO_3$) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 3:2 to 1:1) to give Int. **2Q11** *tert*-butyl 2-formyl-6,7-dihydro-pyrazolo-[1,5-a]pyrazine-5(4H)-carboxylate (0.22 g). Ints. **2Q11/2Q4** (0.2 g/0.26 g, HCl salt) were stirred 4h in DCE/DIPEA (10:1, 2.2 mL). STAB (0.34 g) was added before stirring ON at 0 °C to RT. The OL (DCM/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 98:2 to 95:5) to give Int. **2Q12** *tert*-butyl 2-((4-(2-fluoro-4-(2,2,2-trifluoro-acetamido)phenyl)-piperidin-1-yl)methyl)-6,7-dihydro-pyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.17 g).



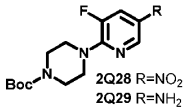
2Q17 R=NO_2, double bond
2Q18 R=NH_2, single bond

$NaHCO_3$ (1.4 g), 2-chloro-3-fluoro-5-nitro-pyridine (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.93 g), and $PdDPPFCl_2$-DCM (0.37 g) were degassed in dioxane / water (5:1, 12 mL) before stirring ON at 100 °C and filtered. The OL (EtOAc/water) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 7:3) to give Int. **2Q17** *tert*-butyl 3-fluoro-5-nitro-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (0.6 g). Int. **2Q17** (7.0 g) and 10% Pd/C (2 g) were stirred 8h in THF/EtOAc (1:1, 80 mL) under a H_2 atmosphere (60 psi), filtered, and concentrated to give Int. **2Q18** *tert*-butyl 4-(5-amino-3-fluoropyridin-2-yl)piperidine-1-carboxylate (6 g).



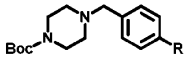
2Q24 R=CO_2Bn, double bond
2Q25 R=H, single bond

Ints. **2Q11/2M9** (1.2 g/2.0 g) were stirred 3h in DCE/DIPEA (5:1, 24 mL) at 0 °C to RT. STAB (3.1 g) was added at 0 °C before stirring ON at 0 °C to RT. The OL (DCM/MeOH (9:1)/water) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 9:1 to 2:3) to give Int. **2Q24** *tert*-butyl 2-((4-(4-(((benzyloxy)carbo-nyl)amino)-2-fluorophenyl)-3,3-difluoro-3,6-dihydro-pyridin-1(2H)-yl)methyl)-6,7-dihydropyrazolo[1,5-a]-pyrazine-5(4H)-carboxylate (1.5 g).



2Q28 R=NO_2
2Q29 R=NH_2

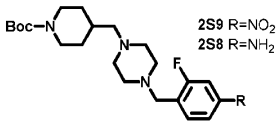
2-Chloro-3-fluoro-5-nitropyridine (4.0 g), *tert*-butyl piperazine-1-carboxylate (4.2 g), and K_2CO_3 (9.4 g) were stirred ON in DMF (7 mL) at 85 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and triturated in pentane and dried to give Int. **2Q28** *tert*-butyl 4-(3-fluoro-5-nitropyridin-2-yl)-piperazine-1-carboxylate (7 g). Int. **2Q28** (1.7 g) was hydrogenated ON using 10% Pd/C (0.5 g) in dioxane/THF (8 mL), filtered, concentrated, and triturated in pentane to give Int. **2Q29** *tert*-butyl 4-(5-amino-3-fluoropyridin-2-yl)piperazine-1-carboxylate (1.4 g).



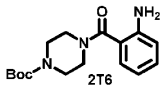
2S2 R=NO_2
2S3 R=NH_2

1-(Chloromethyl)-4-nitrobenzene (0.56 g), *tert*-butyl piperazine-1-carboxylate (0.50 g), and K_2CO_3 (0.75 g) were stirred 2h in DMF (5 mL) at 70 °C. The OL (EtOAc/water) was washed with brine, dried, and concentrated. The residue was purified by FC (heptane/EtOAc 9:1 to 0:1) to give Int. **2S2** *tert*-butyl 4-(4-nitro-benzyl)piperazine-1-carboxylate (0.83 g). Int. **2S2** (0.2 g), zinc powder (0.19 g), and NH_4Cl (0.15 g) were stirred 1h in THF/water (1:1, 12 mL) and filtered. The OL

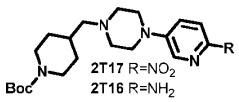
(EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 4:1 to 0:1) to give Int. **2S3** *tert*-butyl 4-(4-aminobenzyl)-piperazine-1-carboxylate (70 mg).



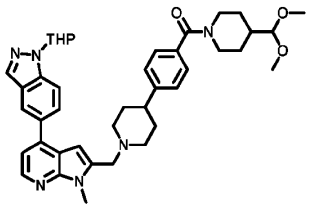
2-Fluoro-4-nitrobenzaldehyde (0.10 g), Int. **3E5** (0.25 g), and STAB (0.38 g) were stirred ON in DCE/DIPEA (19:1, 4.2 mL). STAB (0.10 g) and Int. **3E5** (40 mg) were added and stirring continued 2h. The mixture was concentrated and purified by FC (heptane/EtOAc 1:1 to 0:1) to give Int. **2S9** *tert*-butyl 4-[[4-[(2-fluoro-4-nitro-phenyl)methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.18 g). This material, NH_4Cl (45 mg), and iron powder (0.16 g) were stirred 1.5h in EtOH/water (4:1, 10 mL) at 80 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC to give Int. **2S8** *tert*-butyl 4-[[4-[(4-amino-2-fluoro-phenyl)methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.15 g).



2H-Benzo[d][1,3]oxazine-2,4(1H)-dione (1.0 g) and *tert*-butyl piperazine-1-carboxylate (1.1 g) were stirred 2h in dioxane (9 mL) at 90 °C. The OL (EtOAc/water) was washed with sat. aq. NH_4Cl and brine, dried, and concentrated, and purified by FC to give Int. **2T6** *tert*-butyl 4-(2-amino-benzoyl)-piperazine-1-carboxylate (1.8 g).

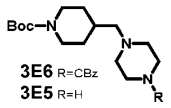


5-Fluoro-2-nitropyridine (0.13 g), Int. **3E5** (0.27 g), K_2CO_3 (0.30 g) were stirred ON in DMF (4 mL) at 60 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane to EtOAc) to give Int. **2T17** *tert*-butyl 4-((4-(6-nitropyridin-3-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.26 g). Int. **2T17** (0.25 g) was hydrogenated ON using 10% Pd/C (80 mg) in MeOH/EtOAc (2:1, 15 mL), filtered, concentrated, and purified by FC (heptane/EtOAc/DCM/MeOH 1:0:0:0 to 0:9:0.5:0.5) to give Int. **2T16** *tert*-butyl 4-((4-(6-aminopyridin-3-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.22 g).

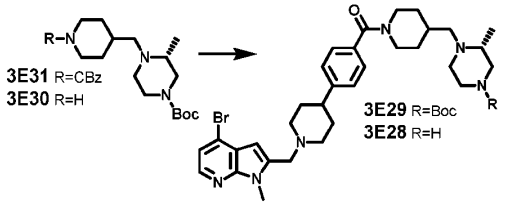


Int. **3A2** (0.50 g, HCl salt) and HATU (0.49 g) were stirred 0.3h in DMF/DIPEA (20:1, 10.5 mL). 4-(Dimethoxy-methyl)piperidine (0.16 g) was added and stirring continued ON. The OL

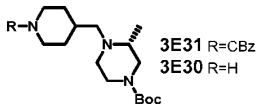
(water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 95:5) to give Int. **3D4** (4-(dimethoxy-methyl)-piperidin-1-yl)(4-(1-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)phenyl)methanone (0.20 g).



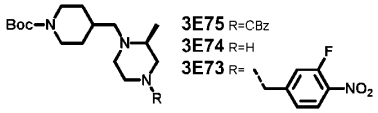
tert-Butyl 4-formylpiperidine-1-carboxylate (25 g) and benzyl piperazine-1-carboxylate (28.4 g) were stirred 4h in DCE/DIPEA (4.1:1, 311 mL). STAB (49.5 g) was added and stirring continued ON at 0 °C to RT ON. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1) to give Int. **3E6** benzyl piperazine-1-carboxylate (70 g). This material was hydrogenated ON using 10% Pd/C (13 g) in EtOH (1 L), filtered, and concentrated to give Int. **3E5** *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (40 g).



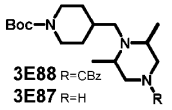
Benzyl 4-formylpiperidine-1-carboxylate (0.50 g) and *tert*-butyl (R)-3-methylpiperazine-1-carboxylate (0.40 g) were stirred 3h in DCE/DIPEA (7:1, 5.7 mL). STAB (0.85 g) was added and stirring continued 3h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **3E31** *tert*-butyl (R)-4-[(1-benzyloxycarbonyl-4-piperidyl)-methyl]-3-methyl-piperazine-1-carboxylate (0.65 g). This material was hydrogenated 8h using and 5% Pd/C (0.1 g) in MeOH (5 mL). Filtration and concentration gave Int. **3E30** *tert*-butyl (3R)-3-methyl-4-(4-piperidylmethyl)-piperazine-1-carboxylate (0.35 g). Ints. **3E30/1AC4** (58 mg/70 mg) and HATU (87 mg) were stirred 3h in DMF/DIPEA (28.1:1, 1.66 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and HPLC-purified to give Int. **3E29** *tert*-butyl (R)-4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazine-1-carboxylate (60 mg). This material was stirred 0.5h in DCM/TFA (2:1; 3 mL). The residue after concentration was SCX-purified to give Int. **3E28** (R)-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)phenyl)(4-((2-methyl-piperazin-1-yl)methyl)-piperidin-1-yl)methanone (40 mg).



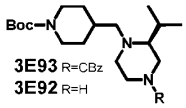
Benzyl 4-formylpiperidine-1-carboxylate (0.50 g) and *tert*-butyl (R)-3-methylpiperazine-1-carboxylate (0.40 g) were stirred 3h in DCE/DIPEA (7:1, 5.7 mL). STAB (0.85 g) was added and stirring continued 3h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **3E31** *tert*-butyl (R)-4-[(1-benzyloxycarbonyl-4-piperidyl)-methyl]-3-methyl-piperazine-1-carboxylate (0.65 g). This material was hydrogenated 8h using and 5% Pd/C (0.1 g) in MeOH (5 mL). Filtration and concentration gave Int. **3E30** *tert*-butyl (3R)-3-methyl-4-(4-piperidylmethyl)-piperazine-1-carboxylate (0.35 g).



Benzyl (S)-3-methylpiperazine-1-carboxylate (2.0 g) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.8 g) were stirred 3h in DCE (30 mL). STAB (3.6 g) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 4:1) to give Int. **3E75** benzyl (3S)-4-[(1-*tert*-butoxy-carbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate (3.0 g). This material was hydrogenated ON using 10% Pd/C (0.45 g) in MeOH (40 mL), filtered, and concentrated to give Int. **3E74** *tert*-butyl 4-[[(2S)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate (1.9 g). Int. **3E74** (5.0 g) and 3-fluoro-4-nitrobenzaldehyde (3.0 g) were stirred 3h in DCE/DIPEA (5.8:1, 59 mL). STAB (7.1 g) was added at 0 °C and stirring continued ON at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 3:2) to give Int. **3E73** *tert*-butyl (S)-4-((4-(3-fluoro-4-nitrobenzyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (1.8 g).

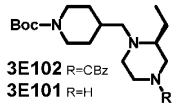


Benzyl 3,5-*cis*-dimethylpiperazine-1-carboxylate (1.5 g) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.7 g) were stirred ON in DCE/DIPEA (8.6:1, 6.7 mL) at 0 °C to RT. STAB (4.5 g) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was washed with brine, dried and, concentrated. The residue was purified by FC (pentane/EtOAc 7:3 to 2:3) to give Int. **3E88** benzyl 4-((1-(*tert*-butoxycarbonyl)-piperidin-4-yl)-methyl)-3,5-*cis*-dimethylpiperazine-1-carboxylate (1.75 g). 1.7 g of this material was hydrogenated ON using 10% Pd/C (0.5 g) in EtOAc (10 mL), filtered, and concentrated to give Int. **3E87** *tert*-butyl 4-[[2,6-*cis*-dimethyl-piperazin-1-yl]methyl]-piperidine-1-carboxylate (1.1 g).



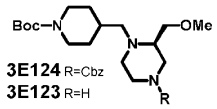
Benzyl (S)-3-*iso*-propylpiperazine-1-carboxylate (2.0 g, HCl salt) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.6 g) were stirred 4h in DCE/DIPEA (4.5:1, 24.4 mL). STAB (2.8

g) was added and stirring continued 4h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 4:1) to give Int. **3E93** benzyl (3S)-4-[(1-*tert*-butoxycarbonyl-4-piperidyl)methyl]-3-*iso*-propyl-piperazine-1-carboxylate (1.9 g). 1.0 g of this material was hydrogenated ON using 10% Pd/C (0.2 g) in THF/EtOAc (1:1; 20 mL), filtered, and concentrated to give Int. **3E92** *tert*-butyl 4-[[(2S)-2-*iso*-propylpiperazin-1-yl]methyl]piperidine-1-carboxylate (0.6 g).



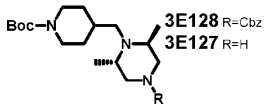
3E102 R=CBz
3E101 R=H

Benzyl (3S)-3-ethylpiperazine-1-carboxylate (2.66 g) and Int. and *tert*-butyl 4-formylpiperidine-1-carboxylate (2.51 g) were stirred 4h in DCE/DIPEA (2.2:1, 29.3 mL). STAB (4.5 g) was added and stirring continued ON. The OL (water/DCM) was washed with brine, dried and, concentrated to give Int. **3E102** benzyl (3S)-4-[(1-*tert*-butoxy-carbonyl-4-piperidyl)methyl]-3-ethyl-piperazine-1-carboxylate (3.4 g). 0.73 g of this material and 10% Pd/C (0.18 g) were hydrogenated 4h in THF/EtOAc (1:2.3, 20 mL), filtered, and concentrated to give Int. **3E101** *tert*-butyl 4-[[(2S)-2-ethylpiperazin-1-yl]methyl]piperidine-1-carboxylate (0.5 g).



3E124 R=Cbz
3E123 R=H

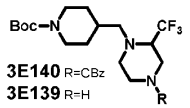
Benzyl (3R)-3-(methoxymethyl)piperazine-1-carboxylate (90 mg, HCl salt) and *tert*-butyl 4-formyl-piperidine-1-carboxylate (70 mg) were stirred 4h in DCE/DIPEA (11.5:1, 3.3 mL). STAB (127 mg) was added and stirring continued ON. The OL (water/DCM) was washed with brine, dried and, concentrated. The residue was purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E124** benzyl (3R)-4-[(1-*tert*-butoxy-carbonyl-4-piperidyl)-methyl]-3-(methoxymethyl)piperazine-1-carboxylate (50 mg). Int. **3E124** (0.6 g) was hydrogenated 4h using 10% Pd/C (0.35 g) in THF/EtOAc (1:1; 40 mL), filtered, concentrated, and triturated in pentane to give Int. **3E123** *tert*-butyl 4-[[(2R)-2-(methoxymethyl)piperazin-1-yl]methyl]piperidine-1-carboxylate (0.5 g).



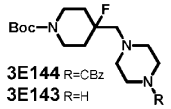
3E128 R=Cbz
3E127 R=H

Benzyl (3S,5S)-3,5-dimethylpiperazine-1-carboxylate (1.2 g, HCl salt) and *tert*-butyl 4-formyl-piperidine-1-carboxylate (1.1 g) were stirred 4h in DCE/DIPEA (1:1.9, 5.7 mL). STAB (1.8 g) was added at 0 °C and stirring continued ON at 0 °C to RT. The OL (water/DCM) was washed with brine, dried and, concentrated. The residue was purified by FC (pentane/EtOAc 7:3) to give Int. **3E128** benzyl (3S,5S)-4-[(1-*tert*-butoxy-carbonyl-4-piperidyl)-methyl]-3,5-dimethyl-piperazine-1-carboxylate (1.1 g). This material was hydrogenated 4h using 10% Pd/C (0.3 g) in MeOH (35 mL),

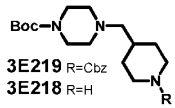
filtered, concentrated, and triturated in MeOH to give Int. **3E127** *tert*-butyl 4-[[(2S,6S)-2,6-dimethylpiperazin-1-yl]-methyl]piperidine-1-carboxylate (0.51 g).



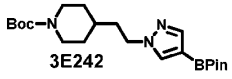
Benzyl 3-(trifluoromethyl)piperazine-1-carboxylate hydrochloride (2.4 g) and *tert*-butyl 4-formyl-piperidine-1-carboxylate (1.4 g) were stirred 4h in DCE/DIPEA (6.4:1, 29 mL). STAB (3.1 g) was added at 0 °C and stirring continued ON at 0 °C to RT. The OL (water/DCM) was washed with brine, dried and, concentrated to give Int. **3E140** benzyl 4-((1-(*tert*-butoxycarbonyl)-piperidin-4-yl)methyl)-3-(trifluoro-methyl)piperazine-1-carboxylate (1.6 g). This material was hydrogenated ON using 10% Pd/C (0.3 g) in EtOAc/water (7:3; 10 mL), filtered, and concentrated to give Int. **3E139** *tert*-butyl 4-((2-(trifluoromethyl)-piperazin-1-yl)methyl)-piperidine-1-carboxylate (1.1 g).



Benzyl piperazine-1-carboxylate (4.3 g) and *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (3.5 g) were stirred 3h in DCE/DIPEA (3.6:1, 51 mL)). STAB (6.4 g) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 4:1) to give Int. **3E144** benzyl 4-((1-(*tert*-butoxy-carbonyl)-4-fluoropiperidin-4-yl)methyl)piperazine-1-carboxylate (4.0 g). This material was hydrogenated ON using 10% Pd/C (1.5 g) in THF/EtOAc (1:1; 30 mL), filtered, a concentrated to give Int. **3E143** *tert*-butyl 4-fluoro-4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (2.3 g).

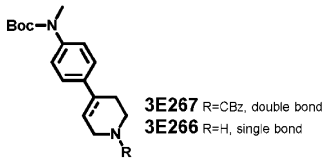


Benzyl 4-formylpiperidine-1-carboxylate (0.10 g) and *tert*-butyl piperazine-1-carboxylate (90 mg) were stirred 3h in DCE/DIPEA (17.9:1, 5.3 mL) at 0 °C to RT. STAB (0.17 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was dried and concentrated to give Int. **3E219** *tert*-butyl 4-[(1-benzyloxycarbonyl-4-piperidyl)-methyl]piperazine-1-carboxylate (0.10 g). Int. **3E219** (5.4 g) was hydrogenated ON using 10% Pd/C in EtOH (60 mL), filtered, and concentrated to give Int. **3E218** *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (3.4 g).

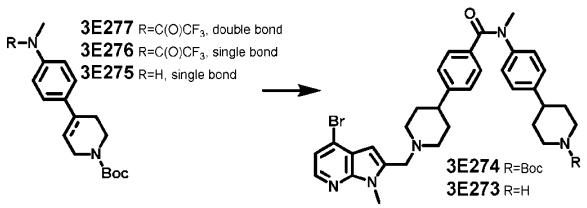


tert-Butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (0.26 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.20 g), and Ph_3P (0.3 g) were dissolved in THF (5 mL) at 0 °C. DIAD (0.22 mL) was added at 3-6 °C and stirring was continued 2h at RT. The residue after concentration was purified by FC (heptane/EtOAc 1:1 and DCM / EtAOAc 0:1 to 2:3) to give Int.

3E242 *tert*-butyl 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)piperidine-1-carboxylate (0.11 g).

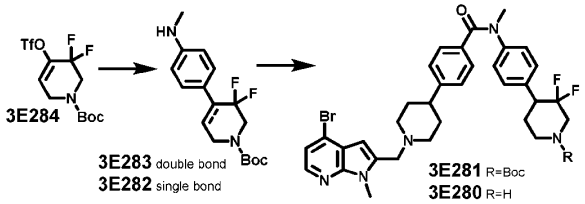


Benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7.1 g), *tert*-butyl (4-bromophenyl)(methyl)carbamate (5.0 g), $NaHCO_3$ (4.3 g), and $PdDPPFCl_2$-DCM (0.7 g) were degassed in dioxane/water (9:1; 50 mL) and stirred ON at 100 °C and filtered. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 9:1 to 88:12) to give Int. **3E267** benzyl 4-(4-((*tert*-butoxy-carbonyl)(methyl)amino)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (4.5 g). 1.0 g of this material was hydrogenated ON using 10% Pd/C (0.5 g) in MeOH (12 mL), filtered, and concentrated to give Int. **3E266** *tert*-butyl methyl(4-(piperidin-4-yl)phenyl)carbamate (0.6 g).

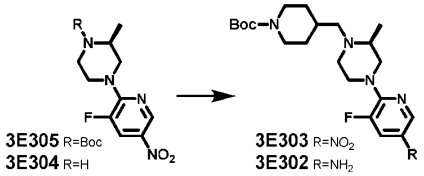


N-(4-bromophenyl)-2,2,2-trifluoro-*N*-methylacetamide (3.5 g), $PdDPPFCl_2$-DCM (0.44 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.3 g), and $NaHCO_3$ (1.8 g) were degassed in dioxane/water (10:1, 34 mL) and stirred ON at 100 °C and filtered. The OL (EtOAc/water) was washed with brine, dried, and concentrated. The residue was mixed with two additional batches prepared similarly and purified by FC (pentane/EtOAc 9:1 to 85:15) to give Int. **3E277** *tert*-butyl 4-(4-(2,2,2-trifluoro-*N*-methylacetamido)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (8.3 g). 3.0 g of this material was hydrogenated ON using 10% Pd/C in MeOH (30 mL), filtered, concentrated, and purified by FC (pentane/EtOAc 9:1 to 85:15) to give Int. **3E276** *tert*-butyl 4-(4-(2,2,2-trifluoro-*N*-methylacetamido)phenyl)piperidine-1-carbo-xylate (2.5 g). 0.8 g of this material and K_2CO_3 (0.7 g) were stirred 3h in MeOH (7 mL) and concentrated. The OL (water/DCM) was dried and concentrated to give Int. **3E275** *tert*-butyl 4-(4-(methylamino)phenyl)-piperidine-1-carboxylate (0.5 g). Ints. **1AC4 / 3E275** (0.5 g/0.58 g) and HATU (0.67 g) were stirred ON in DMF/DIPEA (24.5:1, 15.6 mL) and diluted with water to precipitate Int. **3E274** *tert*-butyl 4-(4-(4-(1-((4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*-methyl-benzamido)-phenyl)piperidine-1-carboxylate (0.6 g). 0.18 g of this material was stirred 0.5h in DCM/TFA (2:1; 1.5 mL), concentrated, and SCX-purified to give Int. **3E273** 4-[1-[(4-bromo-

1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*-methyl-*N*-[4-(4-piperidyl)phenyl]-benzamide (0.15 g).

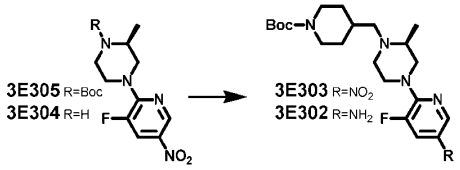


Tf_2O (1.6 g) was added to solution of *tert*-butyl 3,3-difluoro-4-oxopiperidine-1-carboxylate (0.88 g) in DCM/Et_3N (5:1, 9.6 mL) at 0 °C. The mixture was stirred 0.5h at 0 °C, quenched with water, dried, and concentrated. The residue was combined with another batch prepared similarly on 4 g scale and purified by FC (pentane/EtOAc 9:1 to 4:1) to give Int. **3E284** *tert*-butyl 3,3-difluoro-4-(trifluoromethyl-sulfonyloxy)-2,6-dihydro-pyridine-1-carbo-xylate (1.5 g). 0.74 g of this material, *N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.59 g), Na_2CO_3 (0.64 g), and PdDPPFCl$_2$-DCM (0.19 g) were degassed in dioxane / water (4:1, 15 mL) and stirred ON at 55 °C and filtered. The OL (EtOAc/water) dried and concentrated. The residue was purified by FC (pentane/EtOAc 7:3 to 3:2) and by HPLC to give Int. **3E283** *tert*-butyl 3,3-difluoro-4-[4-(methylamino)phenyl]-2,6-dihydro-pyridine-1-carboxylate (0.4 g). This material was hydrogenated ON using 10% Pd/C (0.15 g) in EtOAc/THF (1:1, 6 mL), filtered, and concentrated to give Int. **3E282** *tert*-butyl 3,3-difluoro-4-[4-(methylamino)-phenyl]-piperidine-1-carboxylate (0.34 g). Ints. **1AC4/3E282** (87 mg/60 mg) and HATU (84 mg) were stirred ON in DMF/DIPEA (6.3:1, 2.3 mL). HATU (70 mg) and DIPEA (0.16 mL) added and stirring continued ON at 50 °C. HATU (70 mg) and DIPEA (0.16 mL) were added and stirring continued ON at 50 °C. The OL (EtOAc/water) was concentrated and purified by FC (heptane/EtOAc 1:0 to 0:1) and by HPLC to give Int. **3E281** *tert*-butyl 4-[4-[[4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]benzoyl]-methyl-amino]phenyl]-3,3-difluoro-piperidine-1-carboxylate (82 mg). A solution of this material in DCM/TFA (1:1; 2 mL) was stirred 0.5h, concentrated and SCX-purified to give Int. **3E280** 4-[1-[(4-bromo-1-methyl-pyrrolo-[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*-[4-(3,3-difluoro-4-piperidyl)phenyl]-*N*-methyl-benzamide (52 mg).

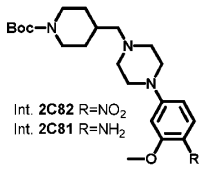


2-Chloro-3-fluoro-5-nitro-pyridine (0.50 g), *tert*-butyl (R)-2-methylpiperazine-1-carboxylate (0.62 g), and K_2CO_3 (1.6 g) were stirred ON in ACN (20 mL) at 85 °C, concentrated, and triturated in water to give Int. **3E305** *tert*-butyl (2R)-4-(3-fluoro-5-nitro-2-pyridyl)-2-methyl-piperazine-1-

carboxylate (0.84 g). This material was stirred 6h in DCM/4M HCl in dioxane (1:2; 15 mL) at 0 °C and concentrated. The residue was triturated in Et_2O/pentane to give Int. **3E304** (3R)-1-(3-fluoro-5-nitro-2-pyridyl)-3-methyl-piperazine (0.65 g, HCl salt). This material and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.42 g) were stirred ON in DCE/DIPEA (6.5:1, 17.3 mL). STAB (1.9 g) was added and stirring was continued 6h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and triturated with Et_2O and dried to give Int. **3E303** *tert*-butyl 4-[[(2R)-4-(3-fluoro-5-nitro-2-pyridyl)-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.85 g). This material was hydrogenated ON using 10% Pd/C (0.4 g) in THF/ EtOAc (1:2; 15 mL), filtered, and concentrated to give Int. **3E302** *tert*-butyl 4-[[(2R)-4-(5-amino-3-fluoro-2-pyridyl)-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.65 g).

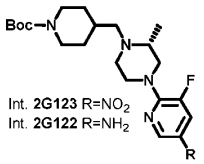


2-Chloro-3-fluoro-5-nitro-pyridine (0.50 g), *tert*-butyl (R)-2-methylpiperazine-1-carboxylate (0.62 g), and K_2CO_3 (1.6 g) were stirred ON in ACN (20 mL) at 85 °C, concentrated, and triturated in water to give Int. **3E305** *tert*-butyl (2R)-4-(3-fluoro-5-nitro-2-pyridyl)-2-methyl-piperazine-1-carboxylate (0.84 g). This material was stirred 6h in DCM/4M HCl in dioxane (1:2; 15 mL) at 0 °C and concentrated. The residue was triturated in Et_2O/pentane to give Int. **3E304** (3R)-1-(3-fluoro-5-nitro-2-pyridyl)-3-methyl-piperazine (0.65 g, HCl salt). This material and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.42 g) were stirred ON in DCE / DIPEA (6.5:1, 17.3 mL). STAB (1.9 g) was added and stirring was continued 6h at 0 °C to RT. The OL (water / DCM) was dried, concentrated, and triturated with Et_2O and dried to give Int. **3E303** *tert*-butyl 4-[[(2R)-4-(3-fluoro-5-nitro-2-pyridyl)-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.85 g). This material was hydrogenated ON using 10% Pd/C (0.4 g) in THF/ EtOAc (1:2; 15 mL), filtered, and concentrated to give Int. **3E302** *tert*-butyl 4-[[(2R)-4-(5-amino-3-fluoro-2-pyridyl)-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.65 g).

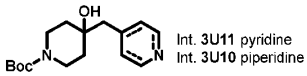


4-Fluoro-2-methoxy-1-nitro-benzene (12.5 g), K_2CO_3 (24 g), and *tert*-butyl 4-(piperazin-1-ylmethyl)-piperidine-1-carboxylate (10 g) were stirred 12h in DMF (100 mL) at 80 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **2C82** *tert*-butyl 4-((4-(3-methoxy-4-nitrophenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (20 g). Int. **2C82** (20 g) and 10% Pd/C (5 g) were stirred ON in MeOH (200 mL) at 70 °C under an

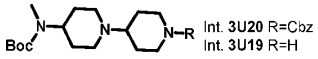
atmosphere of hydrogen. The mixture was filtered and concentrated to give crude Int. **2C81** *tert*-butyl 4-((4-(4-amino-3-methoxyphenyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (15 g).



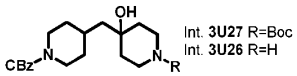
Int. **2F12** (18 g), 2-chloro-3-fluoro-5-nitropyridine (8 g), and K_2CO_3 (13 g) were stirred 16h in ACN (60 mL) at 100 °C under MW conditions. The mixture was concentrated. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:1) to give Int. **2G123** *tert*-butyl (R)-4-((4-(3-fluoro-5-nitro-pyridin-2-yl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (16 g). Int. **2G123** (16 g) and Pd/C 10% (5 g) were hydrogenated 16h at 60 psi in MeOH (250 mL). The mixture was filtered and concentrated to give Int. **2G122** *tert*-butyl (R)-4-((4-(5-amino-3-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (13 g).



1.6M *n*-BuLi in hexane (200 mL) was added to a solution of 4-methylpyridine (26 mL) in THF (200 mL) at -78 °C and the mixture stirred for 30 min. *tert*-Butyl 4-oxopiperidine-1-carboxylate (59 g) in THF (100 mL) was added dropwise and stirring continued 0.5h at -78 °C to RT. The OL (aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:4 to 1:9) to give Int. **3U11** *tert*-butyl 4-hydroxy-4-(pyridin-4-ylmethyl)piperidine-1-carboxylate (30 g). Int. **3U11** (12 g) and PtO_2 (5.6 g) were hydrogenated at 100 psi for 16h at 60 °C in EtOH (200 mL). The mixture was filtered and concentrated. The residue was stirred in aq. Na_2CO_3 and freeze-dried. The residue was dissolved in DCM, filtered, and concentrated to give Int. **3U10** *tert*-butyl 4-hydroxy-4-(piperidin-4-ylmethyl)-piperidine-1-carboxylate (10 g).

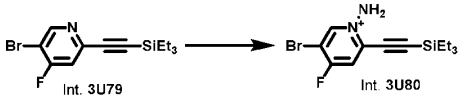


$NaCNBH_3$ (0.75 g), benzyl 4-oxopiperidine-1-carboxylate (2.2 g), and *tert*-butyl methyl(piperidin-4-yl)carbamate (2.0 g) were stirred 18h in MeOH (30 mL). The mixture was concentrated. The OL (sat. aq. $NaHCO_3$/DCM) was dried, and concentrated to give Int. **3U20** benzyl 4-((*tert*-butoxy-carbonyl)(methyl)-amino)-[1,4'-bipiperidine]-1'-carboxylate (2.5 g). Int. **3U20** (2.5 g) and Pd/C (0.25 g) were hydrogenated 72h at 735 psi in MeOH (30 mL) at 50 °C. The mixture was filtered and concentrated to give Int. **3U19** *tert*-butyl [1,4'-bipiperidin]-4-yl(methyl)carbamate (1.8 g).

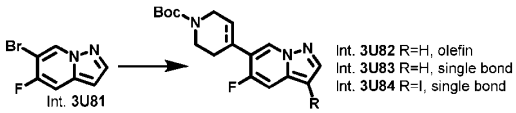


$NaHCO_3$ (19 g) and Int. **3U10** (10 g) were stirred 16h in Et_2O/H_2O (1:1, 100 mL) and 50% benzyl chloro-formate in toluene (11 mL, added drop-wise) at 0 °C to RT. The OL (water/EtOAc)

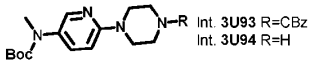
was dried, concentrated, and purified by FC (PE/EtOAc 4:1 to 1:1) to give Int. **3U27** *tert*-butyl 4-((1-((benzyloxy)-carbonyl)piperidin-4-yl)methyl)-4-hydroxypiperidine-1-carboxylate (8 g). Int. **3U27** (1 g) in HFP (15 mL) was heated under MW conditions for 16h at 140 °C. The mixture was combined with two other batches prepared similarly and concentrated to give Int. **3U26** benzyl 4-((4-hydroxypiperidin-4-yl)-methyl)piperidine-1-carboxylate (2.1 g).



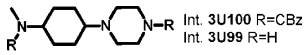
5-bromo-4-fluoro-2-((triethylsilyl)ethynyl)pyridine (11.6 g), $Pd(PPh_3)_2Cl_2$ (1.35 g), and CuI (0.1 g) were stirred ON in Et_3N(ACN (2.1/70 mL) triethyl(ethynyl)silane (7.4 mL) at 0 °C to RT under an inert atmosphere. The mixture was concentrated. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/DCM 1:0 to 0:1) to give Int. **3U79** 5-bromo-4-fluoro-2-((triethylsilyl)-ethynyl)-pyridine (5.0 g). *tert*-butyl ((mesitylsulfonyl)oxy)carbamate (10.0 g) was added in portions to TFA (18 mL) at 0 °C and stirred for 1.5h. The mixture was poured onto ice to precipitate a solid which was dissolved in DCM (80 mL). The OL (water/DCM) was dried and filtered and added slowly to a solution of Int. **3U79** (5.0 g) in DCM (80 mL) at 0 °C and stirred ON at RT and concentrated to give Int. **3U80** 1-amino-5-bromo-4-fluoro-2-((triethylsilyl)ethynyl)pyridin-1-ium (8.0 g, 2,4,6-trimethylbenzenesulfonate salt).



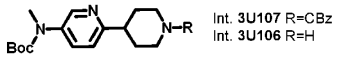
Ag_2CO_3 (5.0 g) and Int. **3U80** (8.0 g) were stirred 12h in DMF (20 mL) at 0 °C to RT. The mixture was filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/MTBE 1:0 to 0:1) to give Int. **3U81** 6-bromo-5-fluoropyrazolo[1,5-a]pyridine (0.33 g). Int. **3U81** (0.33 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.57 g), Cs_2CO_3 (0.64 g), and PdDPPFCl$_2$-DCM (50 mg) were stirred ON in dioxane/H_2O (4:1, 5 mL) at 90 °C under an inert atmosphere. The mixture was concentrated. The OL (water/EtOAc) was dried, concentrated, and HPLC-purified to give Int. **3U82** *tert*-butyl 4-(5-fluoropyrazolo[1,5-a]pyridin-6-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (0.31 g). Int. **3U82** (0.31 g) and Pd/C 5% wt. (0.1 g) were hydrogenated ON in MeOH (5 mL). The mixture was filtered and concentrated to give Int. **3U83** *tert*-butyl 4-(5-fluoropyrazolo[1,5-a]pyridin-6-yl)piperidine-1-carboxylate (0.27 g). NIS (0.19 g) and Int. **3U83** (0.27 g) were stirred 12h in ACN (3 mL) at 0 °C to RT. The mixture was HPLC-purified to give Int. **3U84** *tert*-butyl 4-(5-fluoro-3-iodopyrazolo[1,5-a]pyridin-6-yl)piperidine-1-carboxylate (125 mg).



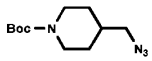
$Pd_2(dba)_3$ (2.3 g), Xantphos (2.8 g), Int. **1Y4** (23 g), benzyl piperazine-1-carboxylate (23 g), and NaO^{t}Bu (12 g) were stirred 16h in toluene (200 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:1 to 2:5) to give Int. **3U93** benzyl 4-(5-((*tert*-butoxycarbonyl)(methyl)amino)pyridin-2-yl)piperazine-1-carboxylate. Int. **3U93** (13 g) and Pd/C 10% wet (4 g) were hydrogenated 5h at 60 psi in MeOH (150 mL). The mixture was filtered and concentrated to give Int. **3U94** *tert*-butyl methyl(6-(piperazin-1-yl)pyridin-3-yl)carbamate (8 g).



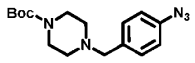
$NaCNBH_3$ (1.8 g), *tert*-butyl methyl(4-oxocyclohexyl)carbamate (5.0 g), benzyl piperazine-1-carboxylate (4.9 g) were stirred 18h in MeOH (50 mL). The mixture was concentrated. The OL (sat. aq. $NaHCO_3$/DCM) was dried, and concentrated to give Int. **3U100** benzyl 4-(4-((*tert*-butoxy-carbonyl)(methyl)amino)cyclohexyl)-piperazine-1-carboxylate (6.1 g). Int. **3U100** (6.1 g) an Pd/C (0.61 g) were hydrogenated 72h at 735 psi at 50 °C in MeOH (75 mL). The mixture was filtered and concentrated to give Int. **3U99** *tert*-butyl methyl(4-(piperazin-1-yl)cyclohexyl)carbamate (1.8 g).



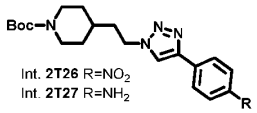
Int. **1Y4** (8.0 g), benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14 g), $PdDPPFCl_2$-DCM (1.1 g), and $NaHCO_3$ (7.0 g) were stirred 16h in THF/H_2O (8:1, 90 mL) at 100 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 4:1) to give Int. **3U107** benzyl 5-((*tert*-butoxy-carbonyl)(methyl)amino)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (8.5). Int. **3U107** (2.5 g) and Pd/C 10% (0.10 g) were hydrogenated 16h at 60 psi in MeOH (30 mL). The mixture was filtered and concentrated to give Int. **3U106** *tert*-butyl methyl(6-(piperidin-4-yl)pyridin-3-yl)-carbamate (2.0 g).



NaN_3 (0.11 g) and *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate (0.40 g) were stirred ON in DMF (5 mL). The OL (water/ EtOAc) was washed with brine, dried, and concentrated to give Int. **3T8** *tert*-butyl 4-(azidomethyl)piperidine-1-carboxylate (0.32 g).

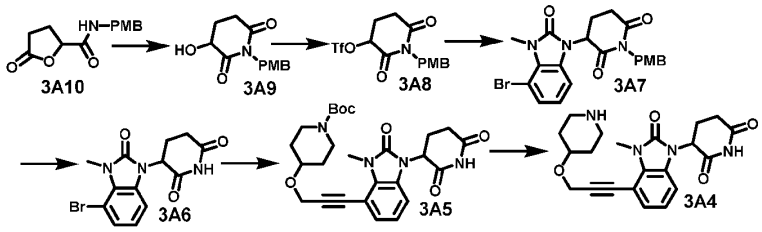


tert-Butyl 4-(4-bromobenzyl)piperazine-1-carboxylate (0.42 g), sodium azide (0.38 g), sodium ascorbate (40 mg), CuI (80 mg) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.12 mL) in EtOH/H_2O (7:3, 12 mL) were refluxed for 6h under an inert atmosphere and concentrated. The OL (water/DCM) was concentrated and purified by FC (heptane/EtOAc 1:0 to 1:1) to give Int. **TT23** *tert*-butyl 4-(4-azidobenzyl)piperazine-1-carboxylate (0.28 g).



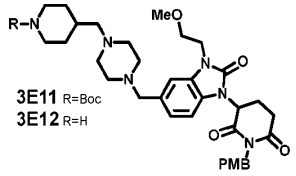
Int. **2T26** R=NO_2
Int. **2T27** R=NH_2

Sodium ascorbate (12 g) was added to a mixture of 1-ethynyl-4-nitrobenzene (3.0 g), tert-butyl 4-(2-azidoethyl)piperidine-1-carboxylate (5.2 g) and $CuSO_4$·H2O (6.5 g) in ^{t}BuOH/H_2O (1:1, 100 mL), stirred for 16h, filtered and concentrated to give Int. **2T26** *tert*-butyl 4-(2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)-ethyl)piperidine-1-carboxylate (4.5 g). Fe powder (2.7 g) and NH_4Cl (5.3 g) were added to a solution of Int. **2T26** (4.0 g) in EtOH/H_2O (5:1. 60 mL) and stirred for 3h at 90 °C and filtered. The OL (brine/EtOAc) was dried, filtered and concentrated to give Int. **2T27** *tert*-butyl 4-(2-(4-(4-aminophenyl)-1H-1,2,3-triazol-1-yl)-ethyl)piperidine-1-carboxylate (3.2 g).

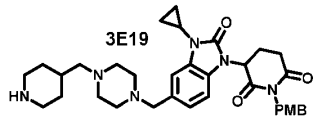


5-Oxotetrahydrofuran-2-carboxylic acid (62 g) was stirred 4h in $SOCl_2$ (90 mL) at 0 °C to 80 °C and concentrated. The residue and (4-methoxy-phenyl)-methanamine (52 g) were stirred 4h in DCM/Et_3N (1.4:1, 340 mL) at 0 °C to RT. The OL (0.5M aq. HCl/DCM) was dried, concentrated, and purified by FC (pentane / EtOAc 1:4) to give Int. **3A10** *N*-(4-methoxybenzyl)-5-oxotetrahydrofuran-2-carboxamide (12 g). Int. **3A10** (20 g) and KOtBu (18 g) was stirred 2h in THF (260 mL) at -78 °C to -40 °C. The OL (sat. aq. NH_4Cl/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane / EtOAc 1:4) to give Int. **3A9** 3-hydroxy-1-[(4-methoxyphenyl)-methyl]piperidine-2,6-dione (5.0 g). Tf_2O (7.1 mL) was added to a solution of Int. **3A9** (7.0 g) in DCM/pyridine (11.7:1, 76 mL) at 0 °C followed by stirring 1h at 0 °C. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3) to give Int. **3A8** 1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl trifluoro-methane-sulfonate (10.1 g). 7-Bromo-1-methyl-1,3-di-hydro-2H-benzo[d]imidazol-2-one (3.0 g) and KOtBu (2.1 g) were stirred 0.5h in THF (30 mL) at 0 °C. Int. **3A8** (9.1 g) was added and stirring continued 2h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 7:3 to 1:1) and by trituration in MeOH/DCM/Et_2O to give Int. **3A7** 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (2.5 g). Int. **3A7** (3.0 g) was stirred 2.5h in TFA/TfOH (10:1, 33 mL) at RT to 80 °C, concentrated, and triturated in pentane/Et_2O to give Int. **3A6** 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (2.0 g). Int. **3A6** (1.5 g), *tert*-butyl 4-(prop-2-yn-1-yloxy)piperidine-1-carboxylate (1.6 g), $Pd(PPh_3)_2Cl_2$ (0.31 g), CuI (0.25 g), Cs_2CO_3 (3.6 g), and 4Å

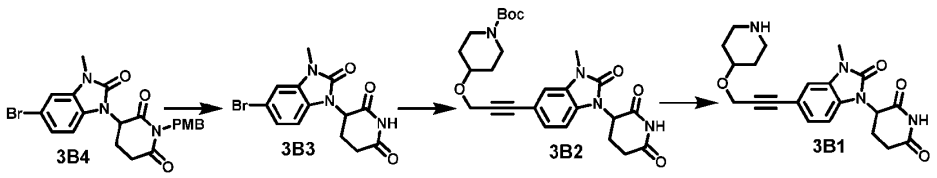
MS were degassed in DMF (3 mL) and stirred 4h at 80 °C. The OL (water/EtOAc) was washed with brine, dried, and concentrated. The residue was combined with another batch prepared similarly on 0.1 g scale and purified by FC (pentane/EtOAc 7:3 to 1:1) to give Int. **3A5** *tert*-butyl 4-((3-(1-(2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)prop-2-yn-1-yl)oxy)piperidine-1-carboxylate (0.60 g). Int. **3A5** (0.5 g) was stirred 3h in DCM/TFA (4:1; 25 mL), concentrated, and triturated in Et_2O to give Int. **3A4** 3-(3-methyl-2-oxo-4-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.50 g).



Ints. **3E13/3E5** (0.12 g/0.11 g) were stirred 0.5h in DCE/DIPEA (87:1, 4.05 mL) at 70 °C. STAB (0.28 g) was added and stirring continued 4h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E11** *tert*-butyl 4-((4-((1-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-piperazin-1-yl)methyl)-piperidine-1-carbo-xylate (0.14 g). This material was stirred 1h in DCM/TFA (3:2; 5 mL) and concentrated to give Int. **3E12** 1-(4-methoxybenzyl)-3-(3-(2-methoxyethyl)-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.12 g, TFA salt).

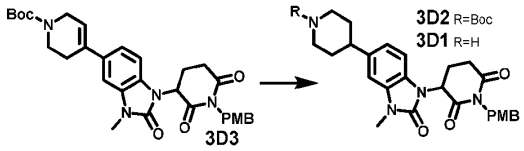


Int. **3E19** 3-(3-*cyclo*-propyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-1-(4-methoxy-benzyl)piperidine-2,6-dione (72 mg) was prepared similarly to Int. **3E1** from Ints. **3E20/3E5** (70 mg/69 mg).

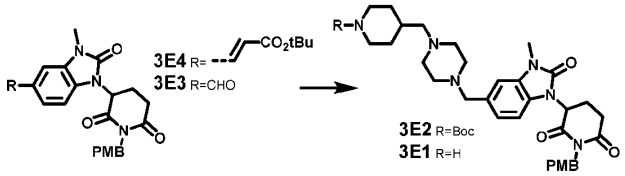


6-Bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (3.5 g) and KOtBu (1.9 g) were stirred 0.5h in THF (35 mL) at 0 °C. Int. **3A8** (7.1 g) was added and stirring continued 2h. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **3B4** 3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (6.0 g). This material was stirred 2.5h in TFA/TfOH (1:3.3, 26 mL) at 0 °C to 80 °C, concentrated, and triturated in Et_2O to give Int. **3B3** 3-(5-bromo-3-methyl-2-

oxo-benzimidazol-1-yl)piperidine-2,6-dione (5.0 g). Int. **3B3** (0.5 g), *tert*-butyl 4-(prop-2-yn-1-yloxy)-piperidine-1-carboxylate (0.5 g), $PdDPPFCl_2$-DCM (109 mg), CuI (56 mg), Cs_2CO_3 (1.9 g), and 4Å MS were degas-sed in DMF (5 mL) and stirred 2h at 80 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 3:7 to 2:3) to give Int. **3B2** *tert*-butyl 4-((3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)prop-2-yn-1-yl)oxy)piperidine-1-carboxylate (0.10 g). 85 mg of this material was stirred 1h in DCM/TFA (4:1; 2.5 mL) at 0 °C, concentrated, and HPLC-purified to give Int. **3B1** 3-(3-methyl-2-oxo-5-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (20 mg).

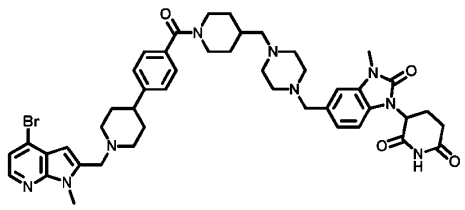


Int. **3B4** (0.15 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carbo-xylate (0.12 g), $PdDPPFCl_2$-DCM (12 mg), and K_3PO_4 (0.21 g) were degassed in dioxane/water (6.6:1, 3.8 mL) and stirred 5h at 90 °C. $PdDPPFCl_2$-DCM (12 mg), and K_2CO_3 (0.1 g) were added and stirring continued 2h at 90 °C. The OL (brine/EtOAc) was dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 1:9) to give Int. **3D3** *tert*-butyl 4-[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.12 g). Int. **3D3** (0.14 g) was hydrogenated ON using 10% Pd/C (14 mg) in EtOAc (1.7 mL), filtered, and concentrated to give Int. **3D2** *tert*-butyl 4-[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-1-carboxylate (0.14 g). This material was stirred 1h in 2.7M HCl in dioxane (1:2; 3 mL), concentrated, and HPLC-purified to give Int. **3D1** 1-(4-methoxybenzyl)-3-(3-methyl-2-oxo-5-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (64 mg).

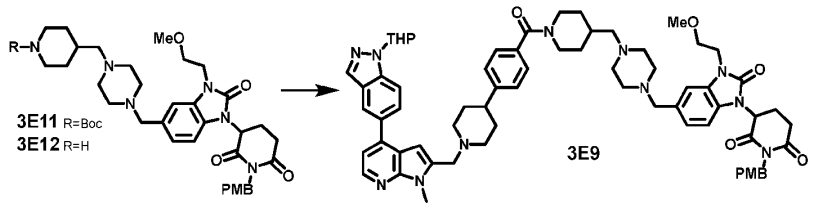


Int. **3B4** (2.5 g), *tert*-butyl acrylate (2.0 g), P(*o*-tol)$_3$ (0.33 g), and $Pd(OAc)_2$ (0.29 g) were degassed in DMF (15 mL) and Et_3N (4.1 mL) and stirred 110 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and triturated in pentane to give Int. **3E4** *tert*-butyl (*E*)-3-(1-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)acrylate (2.4 g). Int. **3E4** (2.5 g), $NaIO_4$ (2.6 g), and OsO_4 (0.25 g) were stirred ON in THF/water (25:8; 33 mL). The OL (sat. aq. $NaHCO_3$ / EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 2:3 to 3:7) to give Int. **3E3** 1-(1-(4-methoxybenzyl)-2,6-

dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazole-5-carbaldehyde (1.0 g). Ints. **3E3/3E5** (50 mg/42 mg) were stirred 0.25h in DCE (2 mL). STAB (36 mg) was added and stirring continued 0.5h. AcOH (1 equiv) was added and stirring continued 144h. DIPEA (2 equiv) and STAB (83 mg) were added and stirring continued 2h at 70 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E2** *tert*-butyl 4-[[1-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]methyl]-4-piperidyl]methyl]-piperazine-1-carboxylate (62 mg). This material was stirred 1h at RT to 100 °C in TFA/TfOH (6:1; 3.5 mL) and concentrated to give Int. **3E1** 3-[3-methyl-2-oxo-5-[[4-(4-piperidylmethyl)-piperazin-1-yl]methyl]-benzimidazol-1-yl]piperidine-2,6-dione (45 mg, TfOH salt).

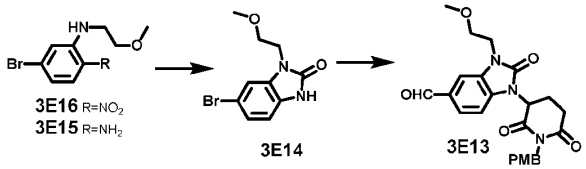


Ints. **1AC4/3E1** (0.10 g/(0.16 g) and HATU (133 mg) were stirred ON in DMF (4 mL) and DIPEA (83 microL). The OL (2MeTHF/aq. $NaHCO_3$) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:1 to 4:1) to give Int. **3E7** 3-(5-((4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (154 mg).

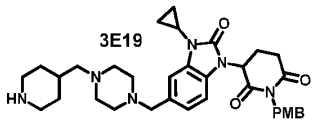


Ints. **3E13/3E5** (0.12 g/0.11 g) were stirred 0.5h in DCE/DIPEA (87:1, 4.05 mL) at 70 °C. STAB (0.28 g) was added and stirring continued 4h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E11** *tert*-butyl 4-((4-((1-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-piperazin-1-yl)methyl)-piperidine-1-carbo-xylate (0.14 g). This material was stirred 1h in DCM/TFA (3:2; 5 mL) and concentrated to give Int. **3E12** 1-(4-methoxybenzyl)-3-(3-(2-methoxyethyl)-2-oxo-5-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.12 g, TFA salt). 30 mg of this material, Int. **3A2** (34 mg), and HATU (24 mg) were stirred 2h in DMF/DIPEA (23.8:1, 2.1 mL), filtered, and HPLC-purified to give Int. **3E9** 1-(4-methoxy-benzyl)-3-(3-(2-methoxyethyl)-5-((4-((1-(4-(1-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-

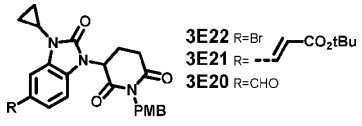
yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (51 mg).



4-Bromo-2-fluoro-1-nitrobenzene (5.0 g) and 2-methoxyethan-1-amine (2.6 g) were stirred in THF (50 mL) at 0 °C to RT ON. The OL (sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and triturated in pentane to give Int. **3E16** 5-bromo-*N*-(2-methoxyethyl)-2-nitro-aniline (5.0 g). Int. **3E16** (9.0 g), iron powder (10.7 g), and NH_4Cl (17.5 g) were stirred 3h in EtOH/AcOH (2:1; 90 mL) at 70-80 °C to RT. The OL (EtOAc/sat. aq. $NaHCO_3$) from the filtrate was dried, concentrated, and triturated in pentane to give Int. **3E15** 5-bromo-*N1*-(2-methoxyethyl)benzene-1,2-diamine (6.8 g). 3.3 g of this material and CDI (5.5 g) were stirred ON in ACN (35 mL) at 80 °C, diluted with ACN (30 mL), filtered, and concentrated. The residue was purified by FC (hexane/EtOAc 1:1 to 2:3) to give Int. **3E14** 6-bromo-1-(2-methoxyethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (1.2 g). This material was converted to Int. **3E13** 1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde similarly to Int. **3E3**.

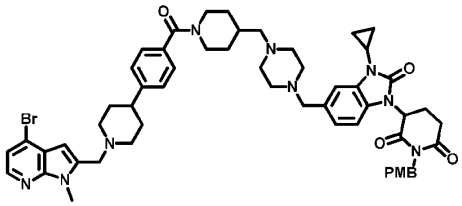


Int. **3E19**. 3-(3-*cyclo*-propyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-1-(4-methoxy-benzyl)piperidine-2,6-dione (72 mg) was prepared similarly to Int. **3E1** from Ints. **3E20/3E5** (70 mg/69 mg).

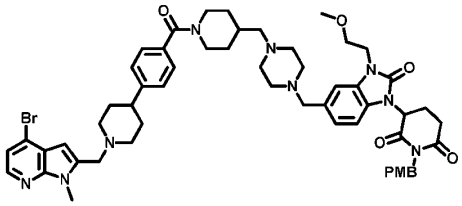


5-Bromo-3-*cyclo*-propyl-1H-benzimidazol-2-one (1.5 g) and KOtBu (1.9 g) were stirred 0.5h in THF (25 mL) before Int. **3A8** (4.6 g) and THF (10 mL) were added and stirring continued 3h at 0 °C. The mixture was combined with another batch prepared similarly and purified by FC (hexane/EtOAc 1:1 to 2:3) and by trituration in pentane to give Int. **3E22** 3-(5-bromo-3-*cyclo*-propyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxy-benzyl)piperidine-2,6-dione (1.15 g). 0.4 g of this material was converted to Int. **3E21** (*E*)-3-(3-*cyclo*-propyl-5-(4,4-dimethyl-3-oxopent-1-en-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)-piperidine-2,6-dione (0.41 g) similarly as Int. **3E4**. Int. **3E20** 3-*cyclo*-Propyl-1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-

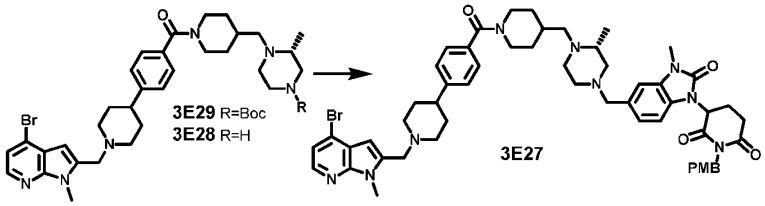
3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde was prepared similarly to Int. **3E3** from Int. **3E21**.



Ints. **1AC4/3E19** (33 mg/36 mg) and HATU (30 mg) were stirred 2h in DMF/DIPEA (201:, 2.1 mL). The filtrate after filtration was HPLC-purified to give Int. **3E25** 3-(5-((4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-cyclopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (33 mg).

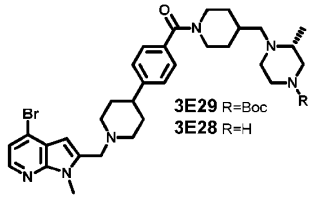


Ints. **3E12/1AC4** (80 mg/72 mg) and HATU (64 mg) were stirred 2h in DMF (4 mL) and DIPEA (0.23 mL). The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) and by HPLC to give Int. **3E26** 3-(5-((4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (40 mg).

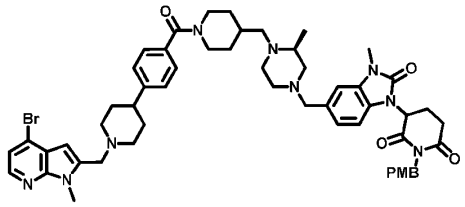


Ints. **3E30/1AC4** (58 mg/70 mg) and HATU (87 mg) were stirred 3h in DMF/DIPEA (28.1:1, 1.66 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and HPLC-purified to give Int. **3E29** *tert*-butyl (R)-4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazine-1-carboxylate (60 mg). This material was stirred 0.5h in DCM/TFA (2:1; 3 mL). The residue after concentration was SCX-purified to give Int. **3E28** (R)-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)phenyl)(4-((2-methyl-piperazin-1-yl)methyl)-piperidin-1-yl)methanone (40 mg). Ints. **3E28/3E3** (39 mg/22 mg), and STAB (57 mg) were stirred 1h in DCE/DIPEA (111:1, 2.02

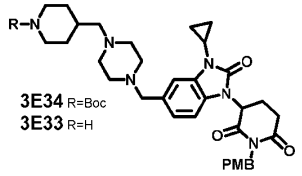
mL) at 70 °C. STAB (57 mg) was added and stirring continued ON. STAB (57 mg) was added and stirring continued ON. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH/Et_3N 94.5:5:0.5) to give Int. **3E27** 3-(5-(((R)-4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (42 mg).



Ints. **3E30/1AC4** (58 mg/70 mg) and HATU (87 mg) were stirred 3h in DMF/DIPEA (28.1:1, 1.66 mL). The OL (EtOAc/water) was washed with brine, dried, concentrated, and HPLC-purified to give Int. **3E29** *tert*-butyl (R)-4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazine-1-carboxylate (60 mg). This material was stirred 0.5h in DCM/TFA (2:1; 3 mL). The residue after concentration was SCX-purified to give Int. **3E28** (R)-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)phenyl)(4-((2-methyl-piperazin-1-yl)methyl)-piperidin-1-yl)methanone (40 mg).

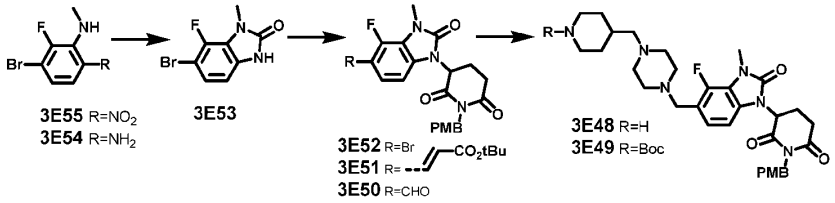


Int. **3E32**. 3-(5-(((S)-4-((1-(4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione was prepared in a similarly to Int. **3E27** from *tert*-butyl (S)-3-methyl-piperazine-1-carboxylate.



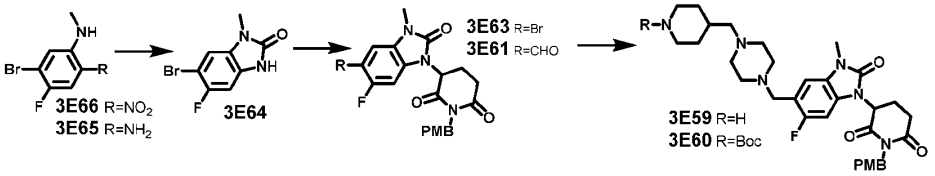
Ints. **3E20/3E5** (0.70 g/0.60 g) were stirred 6h in DCE/DIPEA (10.9:1, 27.3 mL) at 0 °C to RT. STAB (1.4 g) was added and stirring continued ON. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 97:3 to 96:4) to give Int. **3E34** *tert*-butyl

4-((4-((3-*cyclo*-propyl-1-(1-(4-methoxy-benzyl)-2,6-dioxo-piperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperazin-1-yl)-methyl)-piperidine-1-carboxylate (0.6 g). This material was stirred 48h in DCE/TFA/TfOH (33:1:10. 26.6 mL) at 60 °C, concentrated, and triturated in Et_2O/pentane to give Int. **3E33** 3-(3-*cyclo*-propyl-2-oxo-5-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.4 g).

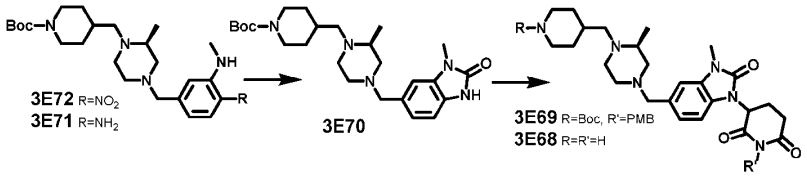


1-Bromo-2,3-difluoro-4-nitrobenzene (3.0 g) was stirred 2h in 0.6M in THF (43 mL) at 0 °C. The OL (sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, and concentrated to give Int. **3E55** 3-bromo-2-fluoro-*N*-methyl-6-nitro-aniline (2.7 g). Int. **3E55** (3.0 g), NH_4Cl (6.4 g), and iron powder (3.4 g) were stirred 8h in EtOH/water (1.7:1, 8 mL), filtered, and concentrated. The OL (sat. aq. $NaHCO_3$/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 3:1) to give Int. **3E54** 4-bromo-3-fluoro-*N2*-methyl-benzene-1,2-diamine (1.9 g). 1.0 g of this material and CDI (1.1 g) were stirred ON in ACN (5 mL) at 90 °C, diluted with water to precipitate Int. **3E53** 5-bromo-4-fluoro-3-methyl-1H-benzimidazol-2-one (0.41 g). Int. **3E53** (0.60 g) and KOtBu (0.36 g) were stirred 0.5h in THF (10 mL) at 0 °C. Int. **3A8** (2.46 g) was added and stirring continued 4h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 1:1) to give Int. **3E52** 3-(5-bromo-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (0.27 g). This material, *tert*-butyl acrylate (0.2 mL), $Pd(OAc)_2$ (12 mg), and P(*o*-tol)$_3$ (33 mg) were degassed in DMF/Et_3N (17.4:1, 4.2 mL) and stirred ON at 120 °C. *tert*-Butyl acrylate (0.1 mL), $Pd(OAc)_2$ (6 mg), and P(*o*-tol)$_3$ (15 mg) were added and stirring continued 4h at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane / EtOAc 1:0 to 0:1) and further by HPLC to give Int. **3E51** *tert*-butyl (*E*)-3-(4-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acrylate (99 mg). Int. **3E51** (95 mg) and $NaIO_4$ (97 mg) were stirred ON in THF/water (2:1; 6 mL) and 2.5% OsO_4 in tBuOH (23 microL). The OL (2MeTHF/water) was washed with 5% aq. $Na_2S_2O_3$ and brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 0:1) and further by HPLC to give Int. **3E50** 4-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (68 mg). This material, Int. **3E5** (54 mg), and 4Å MS were stirred 0.25h in DCE (5 mL) at RT and 0.25h at 40 °C. STAB (169 mg) was added and stirring continued 4h at 40 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3E49** *tert*-butyl 4-((4-((4-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-

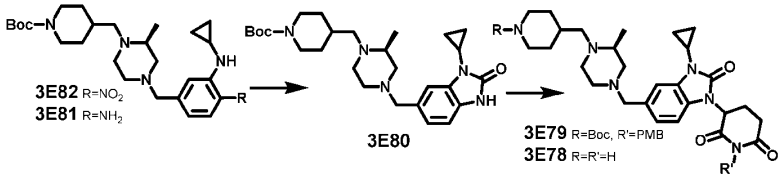
benzo[d]imidazol-5-yl)methyl)-piperazin-1-yl)methyl)-piperidine-1-carboxylate (86 mg). 80 mg of this material was stirred 1h in DCM/TFA (2:1; 3 mL) and concentrated to give Int. **3E48** 3-(4-fluoro-3-methyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (0.10 g, TFA salt).



1-Bromo-2,5-difluoro-4-nitrobenzene (3.0 g) was stirred 2h 0.9M H_2NCH_3 in THF (27.6 mL) at 0 °C and concentrated. The OL (water/EtOAc) was dried and concentrated to give Int. **3E66** 5-bromo-4-fluoro-*N*-methyl-2-nitro-aniline (2.8 g). This material, NH_4Cl (5.8 g), and Iron powder (3.0 g) were stirred 3h in EtOH/water at 80 °C and filtered. The OL (water/EtOAc) was washed with sat. aq. $NaHCO_3$, dried, and concentrated to give Int. **3E65** 4-bromo-5-fluoro-*N2*-methyl-benzene-1,2-diamine (2.1 g). 1.5 g of this material and CDI (2.8 g) were stirred ON in ACN (20 mL) at 80 °C, concentrated, and triturated in water (10 mL) to give Int. **3E64** 5-bromo-6-fluoro-3-methyl-1H-benzimidazol-2-one (1.0 g). Int. **3E64** (1.0 g) and KOtBu (0.64 g) were stirred 0.5h in THF (10 mL) at 0 °C. Int. **3A8** (2.6 g) was added and stirring continued 3h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 2:3) to give Int. **3E63** 3-(5-bromo-6-fluoro-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]-piperidine-2,6-dione (0.29 g). 280 mg of this material, *tert*-butyl acrylate (0.22 mL), $Pd(OAc)_2$ (13 mg), and P(*o*-tol)$_3$ (36 mg) were degassed in DMF/Et_3N (16.7:1, 4.24 mL) and stirred ON at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 1:4) to give Int. **3E62** *tert*-butyl (*E*)-3-(6-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acrylate (48 mg). This material and $NaIO_4$ (59 mg) were stirred ON in THF/water (2:1; 3 mL) and 2.5% OsO_4 in tBuOH (23 microL). The OL (2MeTHF/water) was washed with 5% aq. $Na_2S_2O_3$ and brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 0:1) to give Int. **3E61** 6-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazole-5-carbaldehyde (28 mg). This material and Int. **3E5** (28 mg) were stirred 0.3h in DCE (2 mL) at RT and 0.3h at 40 °C. STAB (70 mg) was added and stirring continued 3h at 40 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and HPLC-purified to Int. **3E60** *tert*-butyl 4-((4-((6-fluoro-1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (41 mg).

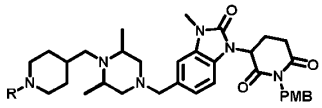


Int. **3E73** (1.8 g) was stirred 6h in 1M H_2NCH_3 in THF (20 mL) at 0 °C to RT and concentrated to give Int. **3E72** *tert*-butyl 4-[[(2S)-2-methyl-4-[[3-(methylamino)-4-nitrophenyl]-methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (1.5 g). Int. **3E72** (2.3 g) was hydrogenated ON using 10% Pd/C (0.5 g) THF/EtOAc (1:1 mL. 20 mL). Filtration, concentration, and purification by FC (pentane/EtOAc 1:0 to 1:9) to give Int. **3E71** *tert*-butyl 4-[[(2S)-4-[[4-amino-3-(methylamino)phenyl]methyl]-2-methyl-piperazin-1-yl]-methyl]-piperidine-1-carboxylate (1.8 g). This material and CDI (1.0 g) were stirred ON in ACN (20 mL) at 80 °C. The mixture was concentrated. The OL (water/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 1:9) to give Int. **3E70** *tert*-butyl 4-[[(2S)-2-methyl-4-[(3-methyl-2-oxo-1H-benzimidazol-5-yl)methyl]-piperazin-1-yl]methyl]-piperidine-1-carboxylate (1.2 g). 0.55 g of this material and KOtBu (189 mg) were stirred 0.5h in THF (3 mL) at 0 °C. Int. **3A8** (0.8 g) was added and stirring continued 4h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 95:5) to give Int. **3E69** *tert*-butyl 4-[[(2S)-4-[[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benz-imidazol-5-yl]methyl]-2-methyl-piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.50 g). This material was stirred 2h in TFA /TfOH (5:1; 1.2 mL) at 80 °C, concentrated, and triturated in water/Et_2O to give Int. **3E68** 3-[3-methyl-5-[[(3S)-3-methyl-4-(4-piperidyl-methyl)piperazin-1-yl]methyl]-2-oxo-benzimidazol-1-yl]-piperidine-2,6-dione (0.35 g).



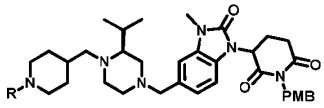
Int. **3E73** (5.0 g) and *cyclo*-propyl amine (3.2 g) were stirred ON in THF (50 mL) at 0 °C to RT. The residue after concentration was purified by FC (pentane/EtOAc 7:3) to give Int. **3E82** *tert*-butyl 4-[[(2S)-4-[[3-(*cyclo*-propyl-amino)-4-nitro-phenyl]methyl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (4.5 g). This material was hydrogenated 4h using 10% Pd/C (2.0 g) in MeOH (50 mL), filtered, and concentrated to give Int. **3E81** *tert*-butyl 4-[[(2S)-4-[[4-amino-3-(cyclopropylamino)phenyl]methyl]-2-methyl-piperazin-1-yl]-methyl]-piperidine-1-carboxylate (3.0 g). This material and CDI (1.5 g) were stirred ON in ACN (30 mL) at 80 °C and concentrated. The OL (water / EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:4 to 1:9) to give Int. **3E80** *tert*-butyl 4-[[(2S)-4-[(3-*cyclo*-propyl-2-oxo-1H-benzimidazol-5-yl)methyl]-2-methyl-piperazin-1-yl]methyl]-piperidine-1-carboxylate (1.65 g). 1.0 g of this material and KOtBu (0.35 g)

were stirred 0.5h in THF (15 mL) at 0 °C. Int. **3A8** (1.6 g) was added and stirring continued 4h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E79** *tert*-butyl 4-[[(2S)-4-[[3-*cyclo*-propyl-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]methyl]-2-methyl-piperazin-1-yl]-methyl]-piperidine-1-carboxylate (0.7 g). A solution of 0.12 g of this material in DCE/TFA/TfOH (40:10:1; 5.3 mL) was stirred ON at 60 °C and concentrated to give Int. **3E78** 3-(3-*cyclo*-propyl-5-(((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.11 g).



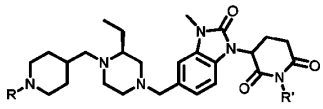
3E86 R=Boc
3E85 R=H

Ints. **3E87/3E3** (0.15 g/0.20 g) were stirred 3h in DCE/DIPEA (10:2, 2.75 mL). STAB (0.78 g) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E86** *tert*-butyl 4-[[4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]methyl]-2,6-*cis*-dimethyl-piperazin-1-yl]-methyl]piperidine-1-carboxylate (0.15 g). This material (0.15 g) was stirred 2h in DCM/4M HCl in dioxane (2:1; 3 mL), concentrated, and triturated in DCM to give Int. **3E85** 3-[5-[[3,5-*cis*-dimethyl-4-(4-piperidyl-methyl)-piperazin-1-yl]methyl]-3-methyl-2-oxo-benzimidazol-1-yl]-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione (0.1 g, HCl salt).



3E91 R=Boc
3E90 R=H

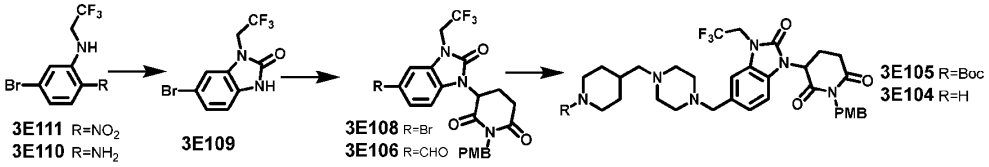
Ints. **3E92/3E3** (0.23 g/0.32 g) were stirred 6h in DCE/DIPEA (28:1, 10.4 mL). STAB (1.13 g) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E91** *tert*-butyl 4-[[(2S)-2-*iso*-propyl-4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.2 g). This material was stirred 2h in DCM/4M HCl in dioxane (5:4; 9 mL) and concentrated to give Int. **3E90** 3-[5-[[(3S)-3-*iso*-propyl-4-(4-piperidylmethyl)piperazin-1-yl]-methyl]-3-methyl-2-oxo-benzimidazol-1-yl]-1-[(4-methoxyphenyl)methyl]-piperidine-2,6-dione (0.16 g, HCl salt).



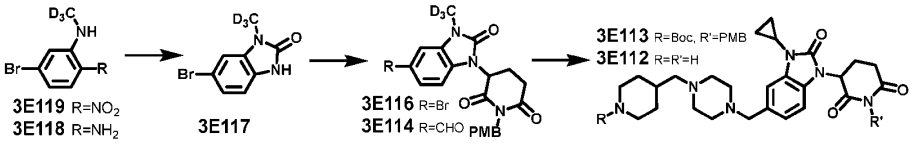
3E100 R=Boc, R'=PMB
3E99 R=R'=H

Ints. **3E3/3E101** (0.27 g/0.25 g) were stirred 6h in DCE/DIPEA (8.6:1, 5.4 mL). STAB (0.35 g) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **3E100** *tert*-butyl 4-[[(2S)-2-ethyl-4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benz-imidazol-5-yl]-

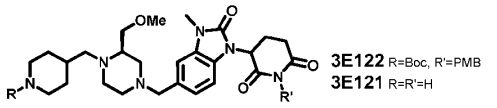
methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.20 g). This material was stirred ON in TFA/TfOH (10:1; 2 mL) at 0-80 °C and concentrated to give Int. **3E99** 3-(5-(((S)-3-ethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.10 g, TfOH salt).



4-Bromo-2-fluoro-1-nitrobenzene (5.0 g) and 2,2,2-trifluoroethanamine (6.2 g, HCl salt) were stirred ON in THF/DIPEA (1.3:1, 36 mL) at 80 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 4:1 to 1:1) to give Int. **3E111** 5-bromo-2-nitro-*N*-(2,2,2-trifluoroethyl)aniline (6.4 g). 5.0 g of this material, NH_4Cl (8.9 g), and iron powder (4.6 g) were stirred ON in EtOH/water (2:1; 30 mL) at 70 °C and filtered. The OL (water/EtOAc) was dried and concentrated to give Int. **3E110** 4-bromo-*N2*-(2,2,2-trifluoroethyl)benzene-1,2-diamine (2.3 g). This material and CDI (1.62 g) were stirred ON in ACN (5 mL) at 0 °C to 80 °C, concentrated and triturated in water to give Int. **3E109** 5-bromo-3-(2,2,2-trifluoro-ethyl)-1H-benzimida-zol-2-one (1.2 g). 1.0 g of this material and KOtBu (0.57 g) were stirred 0.5h in THF (10 mL) at 0 °C. Int. **3E3** (2.2 g) was added and stirring continued 4h at 0 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 7:3 to 1:1) to give Int. **3E108** 3-[5-bromo-2-oxo-3-(2,2,2-trifluoro-ethyl)benzimidazol-1-yl]-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione (1.0 g). 0.3 g of this material, *tert*-butyl acrylate, $Pd(OAc)_2$ (29 mg), and $P(o\text{-tol})_3$ (33 mg) were degassed in DMF/Et_3N (27.3:1, 6.2 mL) and stirred ON at 110 °C. The OL (water/ EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1 to 85:15) to give Int. **3E107** *tert*-butyl (*E*)-3-[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(2,2,2-trifluoroethyl)-benzimidazol-5-yl]prop-2-enoate (0.26 g). This material, $NaIO_4$ (0.14 g), and OsO_4 (14 mg) were stirred ON in THF/water (3:1; 20 mL). The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, and concentrated to give Int. **3E106** 1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(2,2,2-trifluoro-ethyl)benzimidazole-5-carb-aldehyde (0.24 g). Ints. **3E5/3E106** (76 mg/0.24 g) were stirred 6h in DCE/DIPEA (86:1, 12.1 mL). STAB (0.23 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 97:3 to 95:5) to give Int. **3E105** *tert*-butyl 4-[[4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(2,2,2-trifluoroethyl)benzimidazol-5-yl]methyl]-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.19 g), which was stirred 4h in DCM/4M HCl in dioxane (5:2; 7 mL) and concentrated to give Int. **3E104** 1-[(4-methoxyphenyl)methyl]-3-[2-oxo-5-[[4-(4-piperidyl-methyl)piperazin-1-yl]methyl]-3-(2,2,2-trifluoroethyl)benzimidazol-1-yl]piperidine-2,6-dione (0.16 g, HCl salt).

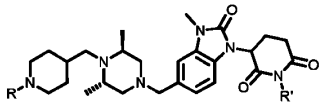


4-Bromo-2-fluoro-1-nitrobenzene (5.0 g), K_2CO_3 (9.4 g), and H_2NCD_3 (8.0 g, HCl salt) were stirred ON in MeOH, and diluted with water to precipitate Int. **3E119** 5-bromo-2-nitro-*N*-(trideuteriomethyl)aniline (5.0 g). This material, NH_4Cl (10.9 g), and iron powder (5.7 g) were stirred 3h in EtOH/water (2:1; 60 mL) and filtered. The OL (water/EtOAc) was dried and concentrated to give Int. **3E118** 4-bromo-*N2*-(trideuterio-methyl)-benzene-1,2-diamine (4.0 g). 2.0 g of this material and CDI (1.1 g) were stirred ON in ACN (20 mL) at 0 °C to 80 °C, concentrated, and triturated in Et_2O to give Int. **3E117** 5-bromo-3-(trideuteriomethyl)-1H-benzimidazol-2-one (1.7 g). 1.0 g of this material and KOtBu (0.69 g) were stirred 0.5h in THF (20 mL) at 0 °C. Int. **3E3** (3.3 g) was added and stirring continued 4h at 0 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E116** 3-[5-bromo-2-oxo-3-(trideuterio-methyl)-benzimidazol-1-yl]-1-[(4-methoxyphenyl)-methyl]piperidine-2,6-dione (1.3 g). 0.3 g of this material, *tert*-butyl acrylate (0.27 mL), $Pd(OAc)_2$ (35 mg), and P(*o*-tol)$_3$ (40 mg) were degassed in DMF/Et_3N (18.5:1, 5.3 mL) and stirred ON at 110 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and triturated in pentane to give Int. **3E115** *tert*-butyl (*E*)-3-[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(trideuteriomethyl)-benzimidazol-5-yl]prop-2-enoate (0.3 g). This material, $NaIO_4$ (0.31 g), and OsO_4 (15 mg) were stirred ON in THF/water (3:1; 16 mL). The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 2:3 to 3:7) to give Int. **3E114** 1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(trideuteriomethyl)-benzimidazole-5-carbaldehyde (0.16 g). Ints. **3E5/3E114** (0.17 g/0.12 g) were stirred ON in DCE/DIPEA (26.7:1, 4.2 mL) at 0 °C to RT. STAB (0.25 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give Int. **3E113** *tert*-butyl 4-[[4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-3-(trideuteriomethyl)-benzimidazol-5-yl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.15 g). Int. **3E113** (0.18 g) was stirred 1h in TFA/TfOH (1.6:2; 3.6 mL) at 80 °C, concentrated, and triturated in Et_2O to give Int. **3E112** 3-(3-(methyl-d_3)-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.14 g).

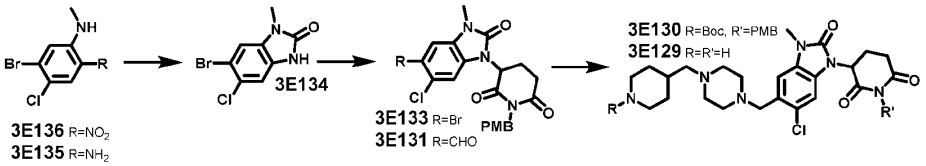


Ints. **3E3/3E123** (31 mg/50 mg) were stirred 6h in DCE/DIPEA (12.5:1, 1.1 mL). STAB (64 mg) was added and stirring continued ON. The OL (water/DCM) was dried and concentrated. The residue was combined with another batch prepared similarly and purified by FC (hexane/EtOAc 1:4)

to give Int. **3E122** *tert*-butyl 4-[[(2R)-2-(methoxy-methyl)-4-[[1-[1-[(4-methoxy-phenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benz-imidazol-5-yl]methyl]piperazin-1-yl]methyl]-piperidine-1-carboxylate (30 mg). This material (20 mg) was stirred 1h in TFA/TfOH (10:1; 0.22 mL) at 80 °C and concentrated to give Int. **3E121** 3-(5-(((R)-3-(methoxymethyl)-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (15 mg, TfOH salt).

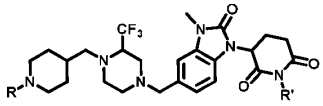


Ints. **3E3/3E127** (0.13 g/0.1 g) were stirred ON in DCE/DIPEA (14.7:1, 5.3 mL). STAB (0.27 g) was added and stirring continued ON. The OL (water/DCM/MeOH (9:1)) was washed with brine, dried, and concentrated to give Int. **3E126** *tert*-butyl 4-[[(2S,6S)-4-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]-methyl]-2,6-dimethyl-piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.15 g). This material was stirred 4h in TFA/TfOH (5:2; 1.2 mL) at 80 °C, concentrated, and triturated in Et_2O to give Int. **3E125** 3-(5-(((3S,5S)-3,5-dimethyl-4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione (0.1 g, TfOH salt).



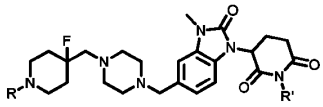
1-Bromo-2-chloro-5-fluoro-4-nitro-benzene (5.0 g) was stirred 4h in 2M H_2NMe in THF (19.6 mL) at 0 °C to RT, concentrated, and triturated in pentane to give Int. **3E136** 5-bromo-4-chloro-*N*-methyl-2-nitro-aniline (4.5 g). This material, NH_4Cl (9.1 g), and Iron powder (5.5 g) were stirred 3h in EtOH/water (3.5:1, 45 mL) at 70-80 °C and filtered. The OL (water/EtOAc) was dried and concentrated to afford Int. **3E135** 4-bromo-5-chloro-*N*2-methyl-benzene-1,2-diamine (4.0 g). 1.5 g of this material and CDI (2.1 g) were stirred ON in ACN (15 mL) at 80 °C. The mixture was diluted with water to precipitate Int. **3E134** 5-bromo-6-chloro-3-methyl-1H-benzimidazol-2-one (1.4 g). This material and KOtBu (1.2 g) were stirred 1h in THF (30 mL) at 0 °C. Int. **3E3** (3.1 g) was added and stirring continued 6h at 0 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E133** 3-(5-bromo-6-chloro-3-methyl-2-oxo-benz-imidazol-1-yl)-1-[(4-methoxyphenyl)methyl]-piperidine-2,6-dione (1.3 g). Int. **3E133** (2.0 g), *tert*-butyl acrylate (1.6 g), $Pd(OAc)_2$ (0.22 g), and $P(o\text{-tol})_3$ (0.25 g) were degassed in DMF/Et_3N (11.8:1, 22 mL) and stirred ON at 110 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 7:3) to give Int. **3E132** *tert*-butyl (*E*)-3-(6-chloro-1-(1-(4-methoxy-benzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acrylate (1.6 g).

This material, $NaIO_4$ (1.9 g), and OsO_4 (0.15 g) were stirred ON in THF/water (1:1; 20 mL). The OL (sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 3:7) to give Int. **3E131** 6-chloro-1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (1.1 g). Ints. **3E5/3E131** (0.1 g/0.1 g) were stirred ON in DCE/ DIPEA (16.7:1, 2.1 mL). STAB (0.1 g) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **3E130** *tert*-butyl 4-[[4-[[6-chloro-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]-methyl]piperazin-1-yl]-methyl]piperidine-1-carboxylate (trideuterio-methyl)-benzimidazol-5-yl]methyl]piperazin-1-yl]-methyl]piperidine-1-carboxylate (0.1 g). Int. **3E130** (0.26 g) was stirred in TFA/TfOH (1:0.13; 2.26 mL) at 80 °C and concentrated to give Int. **3E129** 3-(6-chloro-3-methyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)-methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.3 g, TfOH salt).



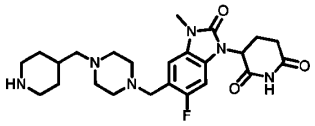
3E138 R=Boc, R'=PMB
3E137 R=R'=H

Ints. **3E3/3E139** (0.30 g/0.28 g) were stirred ON in MeOH (5 mL) and 1M $ZnCl_2$ in THF (1.5 mL). STAB was added and stirring continued ON. The OL (DCM/MeOH (9:1)/water) was dried, concentrated, and purified by FC (DCM/ MeOH 9:1 to give Int. **3E138** *tert*-butyl 4-[[4-[[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benz-imidazol-5-yl]methyl]-2-(trifluoromethyl)piperazin-1-yl]methyl]piperidine-1-carboxylate (0.3 g). A solution of this material (0.2 g) in TFA/TfOH (10:1; 3.3 mL) was stirred 5h at 80 °C and concentrated to give Int. **3E137** 3-(3-methyl-2-oxo-5-((4-(piperidin-4-yl-methyl)-3-(trifluoromethyl)-piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.1 g, TfOH salt).

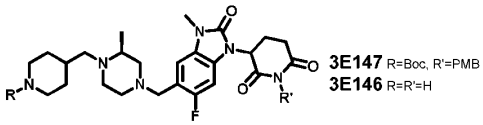


3E142 R=Boc, R'=PMB
3E141 R=R'=H

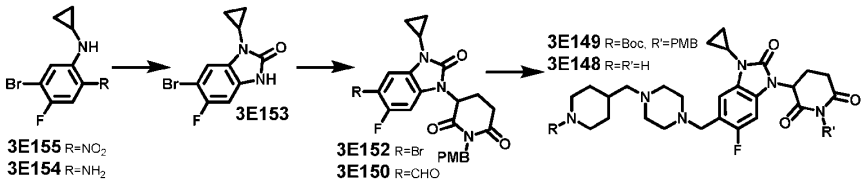
Ints. **3E3/3E143** (1.0 g/0.96 g) were stirred 6h in DCE/DIPEA (8.8:1, 16.7 mL). STAB (1.0 g) was added and stirring continued ON at 0 °C to RT. The OL (DCM/water) was dried and concentrated. The residue was combined with another batch prepared similarly and purified by FC (pentane/EtOAc 1:4 to 1:9) to give Int. **3E142** *tert*-butyl 4-fluoro-4-[[4-[[1-[1-[(4-methoxy-phenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]methyl]piperazin-1-yl]methyl]-piperidine-1-carboxylate (1.12 g). 0.3 g of this material was stirred 4h in TFA/TfOH (10:1; 5.5 mL) at 60 °C and concentrated to give Int. **3E141** 3-(5-((4-((4-fluoro-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione (0.20 g, TfOH salt).



Int. **3E60** (0.25 g) was stirred 3h in TFA/TfOH (4:0.3; 4.3 mL) at 80 °C and concentrated to give Int. **3E145** 3-(6-fluoro-3-methyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.20 g, TfOH salt).

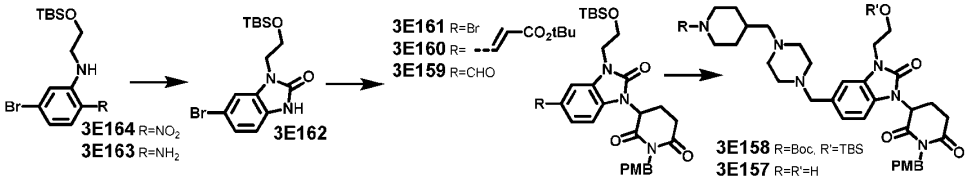


Ints. **3E61/3E74** (0.70 g/0.73 g) were stirred in DCE/DMSO/DIPEA (5:1:0.75; 13.5 mL). STAB (0.7 g) was added and stirring continued 48h at 0 °C to RT. The OL (water/DCM) was dried, concentrated, and purified by FC (DCM/ MeOH 1:0 to 95:5) to give Int. **3E147** *tert*-butyl 4-(((2S)-4-((6-fluoro-1-(1-(4-methoxy-benzyl)-2,6-dioxo-piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-2-methyl-piperazin-1-yl)methyl)piperidine-1-carboxylate (0.75 g). This material was stirred 3h in TFA/TfOH (10:1; 11 mL) at 80 °C and concentrated to give Int. **3E146** 3-(6-fluoro-3-methyl-5-(((S)-3-methyl-4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.7 g, TfOH salt).



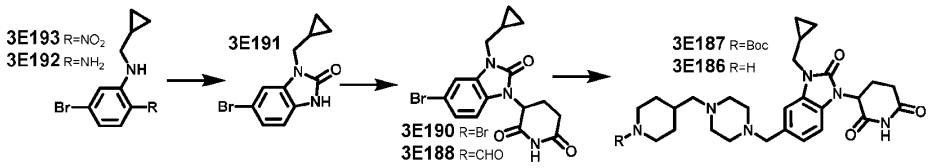
1-Bromo-2,5-difluoro-4-nitrobenzene (7.0 g) and *cyclo*-propyl amine (3.4 g) were stirred ON in THF (70 mL). The OL (water/EtOAc) was dried and concentrated to give Int. **3E155** 5-bromo-*N*-*cyclo*-propyl-4-fluoro-2-nitro-aniline (8.0 g). This material, NH_4Cl (13.5 g), and Iron powder (7.1 g) were stirred 3h in EtOH/water (1:1; 70 mL) at 70-80 °C and filtered. The OL (water/EtOAc) was dried and concentrated to give Int. **3E154** 4-bromo-*N2*-*cyclo*-propyl-5-fluoro-benzene-1,2-diamine (5.0 g). Int. **3E154** (6.0 g) and CDI (6.0 g) were stirred ON in ACN (60 mL) at 80 °C, and diluted with water to precipitate Int. **3E153** 5-bromo-3-*cyclo*-propyl-6-fluoro-1H-benzimidazol-2-one (4.2 g). This material and KOtBu (2.8 g) were stirred 0.5h in THF (42 mL) at 0 °C. Int. **3E3** (9.5 g in 10 mL THF) was added and stirring continued 3h at 0 °C. The OL (EtOAc/water) was washed with brine, dried, and concentrated to give Int. **3E152** 3-(5-bromo-3-*cyclo*-propyl-6-fluoro-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]-piperidine-2,6-dione (4.2 g). This material, *tert*-butyl acrylate (3.1 mL), $Pd(OAc)_2$ (0.45 g), and P(*o*-tol)$_3$ (0.51 g) were degassed in DMF/Et_3N (5.9:1, 23.4 mL) and stirred ON at 110 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified

by FC (hexane/EtOAc 3:2) to give Int. **3E151** *tert*-butyl (*E*)-3-[3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]prop-2-enoate (4.3 g). This material, $NaIO_4$ (4.2 g), and OsO_4 (0.4 g) were stirred ON in THF/water (3:1; 44 mL). The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ / EtOAc) was washed with brine, dried, and concentrated to give Int. **3E150** 3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazole-5-carbaldehyde (2.4 g). Ints. **3E5 / 3E150** (0.59 g/0.47 g) were stirred ON in DCE/DIPEA (9.3:1, 5.5 mL). STAB (0.44 g) was added and stirring continued ON at 0 °C to RT. The OL (10% aq. NH_4Cl/DCM/MeOH (9:1) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 1:4) to give Int. **3E149** *tert*-butyl 4-[[4-[[3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]methyl]-piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.23 g). 0.18 g of this material was stirred 1h in TFA/TfOH (10:1; 3.3 mL) at 0 °C and 1h at 70 °C and concentrated to give Int. **3E148** 3-(3-*cyclo*-propyl-6-fluoro-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.27 g, TfOH salt).



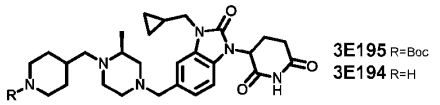
1-Bromo-3-fluoro-4-nitrobenzene (1.0 g), 2-[*tert*-butyl(dimethyl)silyl]oxyethanamine (0.96 g), and K_2CO_3 (1.3 g) were stirred ON in THF (5 mL) at 80 °C. The OL (EtOAc / water) was dried and concentrated and combined with another batch prepared similarly from 1-bromo-3-fluoro-4-nitrobenzene (4.8 g) to give Int. **3E164** 5-bromo-*N*-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-2-nitro-aniline (8.0 g). This material, NH_4Cl (11.3 g), and iron powder (5.8 g) were stirred ON in EtOH/water (1:1; 60 mL) at 70 °C and filtered. The OL (water / EtOAc) was dried and concentrated to give Int. **3E163** 4-bromo-*N*2-[2-[*tert*-butyl(dimethyl)silyl]-oxyethyl]-benzene-1,2-diamine (6.0 g). Int. **3E163** (5.5 g) and CDI (5.2 g) were stirred ON in ACN (30 mL) at 80 °C, concentrated, and triturated in water to give Int. **3E162** 5-bromo-3-[2-[*tert*-butyl-(dimethyl)-silyl]-oxyethyl]-1H-benz-imidazol-2-one (5.0 g). Int. **3E162** (4.1 g) and KOtBu (1.9 g) were stirred 0.5h in THF (10 mL) at 0 °C. Int. **3E3** (8.4 g) was added and stirring continued 4h at 0 °C. The OL (water/EtOAc) was washed with brine, dried, and concentrated to give Int. **3E161** 3-[5-bromo-3-[2-[*tert*-butyl-(dimethyl)silyl]oxy-ethyl]-2-oxo-benzimidazol-1-yl]-1-[(4-methoxyphenyl)-methyl]piperidine-2,6-dione (2.0 g). This material, *tert*-butyl acrylate (1.7 g), $Pd(OAc)_2$ (0.23 g), and P(*o*-tol)$_3$ (0.21 g) were degassed in DMF/Et_3N (5.9:1, 5.4 mL) and stirred ON at 110 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 7:3 to 3:2) to give Int. **3E160** *tert*-butyl (*E*)-3-[3-[2-[*tert*-butyl(dimethyl)silyl]-oxyethyl]-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]prop-2-enoate (1.5 g). This material, $NaIO_4$ (1.5 g), and OsO_4 (6 mg) were stirred

ON in THF/water (2:1; 15 mL) at 0 °C to RT. The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 3:7 to 1:4) to give Int. **3E159** 3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-1-[1-[(4-methoxy-phenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazole-5-carbaldehyde (0.8 g). Ints. **3E5/3E159** (0.53 g/0.8 g) were stirred ON in DCE/DIPEA (19:1, 26 mL). STAB (0.77 g) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was concentrated and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E158** *tert*-butyl 4-[[4-[[3-[2-[*tert*-butyl-(dimethyl)silyl]oxyethyl]-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]methyl]piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.24 g). This material (0.16 g) was stirred 4h in 1.8M HCl in dioxane (9 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **3E157** 3-[3-(2-hydroxyethyl)-2-oxo-5-[[4-(4-piperidylmethyl)-piperazin-1-yl]methyl]benzimidazol-1-yl]-1-[(4-methoxy-phenyl)methyl]-piperidine-2,6-dione (0.13 g, HCl salt).

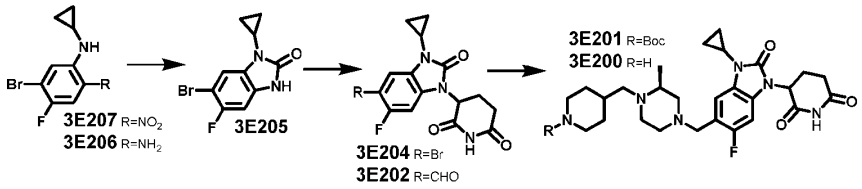


cyclo-Propylmethanamine (4.5 g) and 4-bromo-2-fluoro-1-nitrobenzene (7.0 g) were stirred in THF (50 mL) at 0 °C. The OL (water/EtOAc) was washed with brine, dried, and concentrated to give Int. **3E193** 5-bromo-*N*-(*cyclo*-propylmethyl)-2-nitro-aniline (8.0 g). This material, NH_4Cl (15.0 g), and iron powder (7.8 g) were stirred 3h in EtOH/water (2:1; 60 mL) at 80 °C and filtered. The OL (water/EtOAc) was dried and concentrated to give Int. **3E194** 4-bromo-*N2*-(*cyclo*-propylmethyl)benzene-1,2-diamine (6.5 g). Int. **3E194** (5.0 g) and CDI (4.3 g) were stirred 3h in ACN (30 mL) at 80 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and triturated in Et_2O to give Int. **3E191** 5-bromo-3-(*cyclo*-propylmethyl)-1H-benzimidazol-2-one (4.7 g). Int. **3E191** (2.5 g) and NaH (60% oil disp., 2.6 g) were stirred 0.5h in THF (25 mL). 3-Bromo-piperidine-2,6-dione (6.3 g) was added and stirring continued ON at 65 °C. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 7:3 to 1:1) to Int. **3E190** 3-[5-bromo-3-(*cyclo*-propylmethyl)-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (1.5 g). This material, *tert*-butyl acrylate (2.0 g), $Pd(OAc)_2$ (0.27 g), and P(*o*-tol)$_3$ (0.24 g) were degassed in DMF/Et_3N (4.5:1, 12.2 mL) and stirred ON at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 7:3 to 3:2) to give Int. **3E189** *tert*-butyl (*E*)-3-[3-(*cyclo*-propyl-methyl)-1-(2,6-dioxo-3-piperidyl)-2-oxo-benzimidazol-5-yl]prop-2-enoate (1.0 g). Int. **3E189** (1.4 g), $NaIO_4$ (1.8 g), and OsO_4 (17 mg) were stirred ON in THF/water (5:1; 18 mL) at 0 °C to RT. The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 4:1) to give Int. **3E188** 3-(*cyclo*-propylmethyl)-1-(2,6-dioxo-3-piperidyl)-2-oxo-benzimidazole-5-carbaldehyde (0.7 g). Ints. **3E5/3E188** (0.35 g/0.25 g)

were stirred ON in DCE/DIPEA (10:1, 5.5 mL). STAB (0.23 g) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was concentrated and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E187** *tert*-butyl 4-[[4-[[3-(*cyclo*-propylmethyl)-1-(2,6-dioxo-3-piperidyl)-2-oxo-benzimidazol-5-yl]methyl]piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.14 g). Int. **3E187** (0.13 g) was stirred 5h in DCM/4M HCl in dioxane (5:1.3; 6.3 mL) at 0 °C to RT and concentrated to give Int. **3E186** 3-(3-(*cyclo*-propylmethyl)-2-oxo-5-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.12 g, HCl salt).

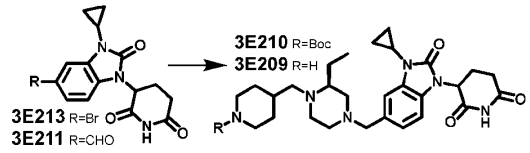


Ints. **3E74/3E188** (0.27 g/0.20 g) were stirred ON in DCE/DIPEA (9.4:1, 2.5 mL). STAB (0.39 g) was added and stirring continued 36h at 0 °C to RT. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 95:5 to 9:1) to give Int. **3E195** *tert*-butyl 4-(((2S)-4-((3-(*cyclo*-propylmethyl)-1-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)-2-methyl-piperazin-1-yl)-methyl)-piperidine-1-carboxylate (0.20 g), which was stirred 3h in 0.5M HCl in dioxane (2.3 mL) at 0 °C to RT and concentrated to give Int. **3E194** 3-(3-(*cyclo*-propylmethyl)-5-(((S)-3-methyl-4-(piperidin-4-yl-methyl)-piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.15 g, HCl salt).

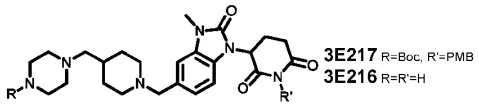


cyclo-Propylmethanamine (3.4 g) and 1-bromo-2,5-difluoro-4-nitrobenzene (7.0 g) were stirred ON in THF (70 mL). The OL (water/EtOAc) was dried and concentrated to give Int. **3E207** 5-bromo-*N*-*cyclo*-propyl-4-fluoro-2-nitro-aniline (8.0 g). 7.0 g of this material, NH_4Cl (13.6 g), and iron powder (7.1 g) were stirred 3h in EtOH/water (1:1; 70 mL) at 70-80 °C and filtered. The OL (water/EtOAc) was dried and concentrated to give Int. **3E206** 4-bromo-*N2*-*cyclo*-propyl-5-fluoro-benzene-1,2-diamine (5.0 g). Int. **3E206** (6.0 g) and CDI (5.9 g) were stirred ON in ACN (60 mL) at 80 °C, concentrated, and triturated in water to give Int. **3E205** 5-bromo-3-*cyclo*-propyl-6-fluoro-1H-benzimidazol-2-one (4.2 g). Int. **3E205** (6.0 g) and KOtBu (4.0 g) were stirred 0.5h in THF (60 mL). Int. **3A8** (13.5 g) was added and stirring continued 3h at 0 °C. The OL (aq. NH_4Cl / DCM / MeOH (9:1)) was washed with brine, dried, and concentrated to give Int. **3E204** 3-(5-bromo-3-*cyclo*-propyl-6-fluoro-2-oxo-benzimidazol-1-yl)-1-[(4-methoxy-phenyl)methyl]-piperidine-2,6-dione (7.1 g). 6.1 g of this material, *tert*-butyl acrylate (5.3 mL), $Pd(OAc)_2$ (0.82 g), and P(*o*-tol)$_3$ (0.74 g) were degassed in DMF/Et_3N (10:1, 55 mL) and stirred ON at 110 °C.. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/ EtOAc 3:2) to give Int. **3E203** *tert*-butyl (*E*)-

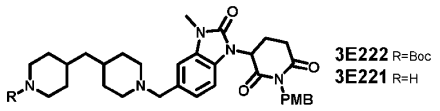
3-[3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazol-5-yl]prop-2-enoate (6.0 g). This material, $NaIO_4$ (5.8 g), and OsO_4 (0.55 mg) were stirred ON in THF/water (3:1; 60 mL). The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 3:2) to give Int. **3E202** 3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benzimidazole-5-carbaldehyde (3.1 g). Ints. **3E5/3E202** (0.99 g/1.5 g) were stirred ON in DCE/DIPEA (5.6:1, 11.8 mL). STAB (1.4 g in DMSO (5 mL)) was added at 0 °C and stirring continued ON at 0 °C to 60 °C. The OL (aq. NH_4Cl/EtOAc) was concentrated and purified by FC (hexane/EtOAc 1:4) to give Int. **3E201** *tert*-butyl 4-[[(2S)-4-[[3-*cyclo*-propyl-6-fluoro-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benz-imidazol-5-yl]methyl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (1.2 g). This material was stirred 2h in TFA/TfOH (9:1; 10 mL) at 70 °C and concentrated to give Int. **3E200** 3-(3-*cyclo*-propyl-6-fluoro-5-(((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (1.5 g, TfOH salt).



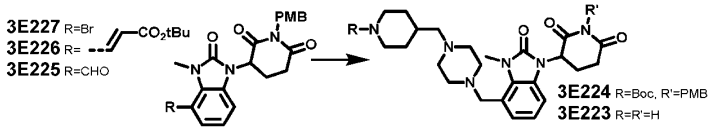
5-Bromo-3-*cyclo*-propyl-1H-benzimidazol-2-one (3.0 g) and NaH (60% oil disp. 7.9 g) were stirred 0.3h in THF (70 mL) at 0 °C. 3-Bromopiperidine-2,6-dione (19.0 g) was added and stirring continued ON at 0-60 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and triturated in hexane to give Int. **3E213** 3-(5-bromo-3-*cyclo*-propyl-2-oxo-benzimidazol-1-yl)piperidine-2,6-dione (5.2 g). Int. **3E213** (6.1 g), *tert*-butyl acrylate (2.6 g), $Pd(OAc)_2$ (0.44 g), and P(*o*-tol)$_3$ (0.50 g) were degassed in DMF/Et_3N (17.6:1, 63.4 mL) and stirred ON at 110 °C and filtered. The OL (water / EtOAc). was washed with brine, dried, concentrated, and triturated in pentane to give Int. **3E212** *tert*-butyl (*E*)-3-[3-*cyclo*-propyl-1-(2,6-dioxo-3-piperidyl)-2-oxo-benz-imidazol-5-yl]prop-2-enoate (2.9 g). 1.4 g of this material, $NaIO_4$ (1.8 g), and OsO_4 (0.43 g) were stirred ON in THF/water (4.7:1, 17 mL). The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E211** 3-*cyclo*-propyl-1-(2,6-dioxo-3-piperidyl)-2-oxo-benzimidazole-5-carbaldehyde (0.80 g). Ints. **3E101/3E211** (1.4 g/0.55 g) and $ZnCl_2$ were stirred ON in DCE (6 mL). $NaCNBH_3$ (0.22 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E210** *tert*-butyl 4-[[(2S)-4-[[3-*cyclo*-propyl-1-(2,6-dioxo-3-piperidyl)-2-oxo-benzimidazol-5-yl]methyl]-2-ethyl-piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.80 g). A solution of 0.75 g of this material in DCM/4M HCl in dioxane (5:1, 6 mL) was stirred ON at 0 °C to RT and concentrated to give Int. **3E209** 3-[3-*cyclo*-propyl-5-[[(3S)-3-ethyl-4-(4-piperidylmethyl)piperazin-1-yl]methyl]-2-oxo-benzimidazol-1-yl]-piperidine-2,6-dione (0.65 g, HCl salt).



Ints. **3E3/3E218** (50 mg/42 mg) were stirred 0.25h in DCE (2 mL) and a few drops of DMF. STAB (36 mg) was added and stirring continued 120h. STAB (77 mg) and DIPEA (86 microL) were added and stirring continued 2h at 70 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E217** *tert*-butyl 4-[[1-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]methyl]-4-piperidyl]-methyl]piperazine-1-carboxylate (33 mg). This material was stirred 4h in TFA/TfOH (2:0.05; 2.05 mL) and ON at 50 °C and concentrated to give Int. **3E216** 3-(3-methyl-2-oxo-5-((4-(piperazin-1-ylmethyl)-piperidin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (22 mg, TfOH salt).

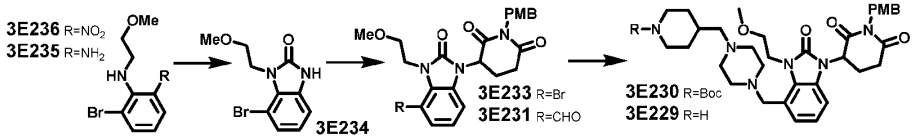


Int. **3E3** (50 mg) *tert*-butyl 4-(piperidin-4-ylmethyl)piperidine-1-carboxylate (47 mg, HCl salt) were stirred 0.3h in DCE/AcOH/DIPEA (28.6:1:6.1, 2.5 mL) at 70 °C. STAB (0.13 g) was added and stirring continued 3h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E222** *tert*-butyl 4-[[1-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benz-imidazol-4-yl]methyl]-4-piperidyl]-methyl]piperazine-1-carboxylate (57 mg). A solution of this material in DCM/TFA (4:1; 2.5 mL) was stirred 0.5h and concentrated to give Int. **3E221** 3-[3-methyl-2-oxo-4-[[4-(4-piperidylmethyl)piperazin-1-yl]-methyl]benzimidazol-1-yl]piperidine-2,6-dione (58 mg, TFA salt).



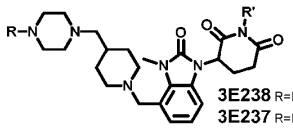
7-Bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (0.25 g) and KOtBu (0.16 g) were stirred 0.25h in THF (3 mL) at 0 °C. Int. **3A8** (0.67 g) was added and stirring continued 1h. The residue after concentration was purified by FC (pentane/EtOAc 1:0 to 7:3) to give Int. **3E227** 3-(4-bromo-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxy-phenyl)methyl]-piperidine-2,6-dione (0.15 g). Int. **3E227** (0.4 g), *tert*-butyl acrylate (0.32 mL), $Pd(OAc)_2$ (20 mg), and $P(o\text{-tol})_3$ (53 mg) were degassed in DMF/Et_3N (16.6:1, 5,4 mL) and stirred ON at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:1 to 0:1) to give Int. **3E226** *tert*-butyl (*E*)-3-[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]prop-2-enoate (0.44 g). This material and NaIO4 (0.47 g) were stirred ON in THF/water (2:1; 3 mL) and 2.5% OsO_4 in tBuOH (0.11 mL). The OL (2MeTHF/sat. aq. $NaHCO_3$)

was washed with 5% aq. $Na_2S_2O_3$ and brine, dried, concentrated, and triturated in DCM/heptane to give Int. **3E225** 1-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbaldehyde (0.34 g). Ints. **3E5/3E225** (42 mg/50 mg) were stirred 0.3h in DCE/AcOH/DIPEA (28.6:1:6.1, 2.1 mL) at 70 °C. STAB (0.13 g) was added and stirring continued 1h at 70 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E224** *tert*-butyl 4-[[1-[[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]-methyl]-4-piperidyl]-methyl]piperazine-1-carboxylate (74 mg). A solution of this material in TFA/TfOH (2:0.1; 2.1 mL) was stirred 4h at 70 °C and ON at 50 °C and concentrated to give Int. **3E223** 3-(3-methyl-2-oxo-4-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (50 mg, TfOH salt).

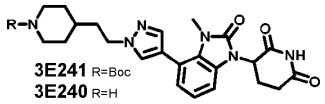


1-Bromo-2-fluoro-3-nitro-benzene (5.0 g) and 2-methoxyethan-1-amine (1.9 g) were stirred ON in MeOH (50 mL) at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, and concentrated to give Int. **3E236** 2-bromo-*N*-(2-methoxyethyl)-6-nitro-aniline (6.0 g). 3.8 g of this material and iron powder (3.9 g) were stirred 2h in AcOH (38 mL) at 40 °C and filtered. The OL (aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 9:1 to 4:1) to give Int. **3E235** 3-bromo-*N2*-(2-methoxyethyl)benzene-1,2-diamine (2.5 g). This material and CDI (2.5 g) were stirred ON in ACN (25 mL) at 80 °C and concentrated. The residue was triturated in water to give Int. **3E234** 4-bromo-3-(2-methoxy-ethyl)-1H-benzimidazol-2-one (2.5 g). 0.7 g of this material and KOtBu (0.32 g) were stirred 0.5h in THF (14 mL) at -10 °C to 0 °C. Int. **3A8** (1.48 g) was added as a solution in THF (20 mL) at -10 °C and stirring was continued 1h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 9:1 to 4:1) to give Int. **3E233** 3-[4-bromo-3-(2-methoxyethyl)-2-oxo-benzimidazol-1-yl]-1-[(4-methoxy-phenyl)-methyl]-piperidine-2,6-dione (0.61 g). 0.4 g of this material, *tert*-butyl acrylate (0.29 mL), $Pd(OAc)_2$ (18 mg), and P(*o*-tol)$_3$ (48 mg) were degassed in DMF/Et_3N (16.7:1, 5.3 mL) and stirred ON at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 1:0 to 0:1) to give Int. **3E232** *tert*-butyl (*E*)-3-(1-(1-(4-methoxybenzyl)-2,6-dioxo-piperidin-3-yl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-acrylate (0.41 g). 0.39 g of this material and $NaIO_4$ (0.38 g), and 2.5% OsO_4 in tBuOH (89 microL) were stirred ON in THF / water (2:1; 9 mL). The OL (sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (EtOAc / heptane 0:1 to 1:0) to give Int. **3E231** 3-(2-methoxy-ethyl)-1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-2-oxo-benz-imidazole-4-carbaldehyde (0.26 g). Ints. **3E5/3E231** (0.11 g/0.12 g)

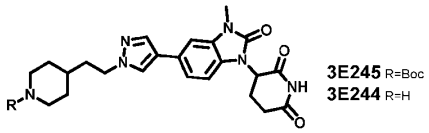
were stirred 0.5h in DCE/DIPEA (87:1, 4.05) at 70 °C. STAB (0.28 g) was added and stirring continued 4h at 70 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E230** *tert*-butyl 4-((4-((1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-(2-methoxyethyl)-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-4-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.15 g), which was stirred 1h in DCM/TFA (3:2; 5 mL) and concentrated to give Int. **3E229** 1-(4-methoxybenzyl)-3-(3-(2-methoxy-ethyl)-2-oxo-4-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-piperidine-2,6-dione (0.11 g, TFA salt).



Ints. **3E225/3E218** (50 mg/42 mg) were stirred 0.3h in DCE/AcOH/DIPEA (28.6:1:6.4, 2.0.5 mL) at 70 °C. STAB (0.13 g) was added and stirring continued 1h at 70 °C. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM / MeOH 1:0 to 4:1) to give Int. **3E238** *tert*-butyl 4-[[1-[[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]methyl]-4-piperidyl]-methyl]piperazine-1-carboxylate (77 mg). This material was stirred 4h in TFA/TfOH (2:0.1; 2.1 mL) at 70 °C and concentrated to give Int. **3E237** 3-[3-methyl-2-oxo-4-[[4-(piperazin-1-ylmethyl)-1-piperidyl]methyl]-benzimidazol-1-yl]piperidine-2,6-dione (52 mg, TfOH salt).

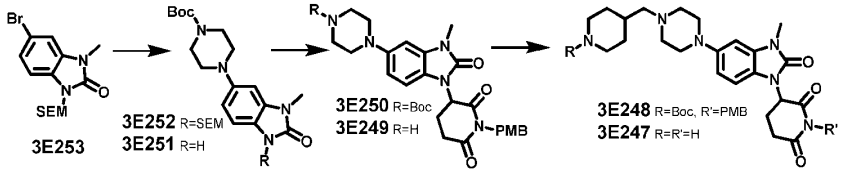


Ints. **3E242/3A6** (55 mg/35 mg), and $PdDPPFCl_2$-DCM (9 mg) were degassed in DMF/10% aq. Na_2CO_3 (5.6:1, 1.5 mL) and stirred 1.25h at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 3:2 to 0:1) to give Int. **3E241** *tert*-butyl 4-(2-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1H-pyrazol-1-yl)-ethyl)-piperidine-1-carboxylate (18 mg). A solution of Int. **3E241** (16 mg) in MeOH/4M HCl in dioxane (1:1; 0.4 mL) was stirred 0.75h and concentrated to give Int. **3E240** 3-(3-methyl-2-oxo-4-(1-(2-(piperidin-4-yl)-ethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione (17 mg, HCl salt).

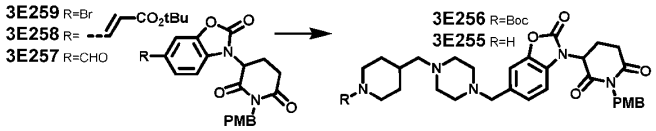


Ints. **3E242/3B3** (55 mg/35 mg), and $PdDPPFCl_2$-DCM (9 mg) were degassed in DMF/10% aq. Na_2CO_3 (5.7:1, 1.5 mL) and stirred 1.25h at 100 °C. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 3:2 to 0:1) to give Int. **3E245** *tert*-butyl

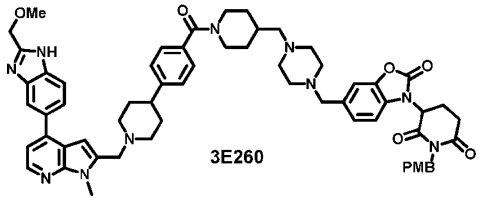
4-(2-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)ethyl)-piperidine-1-carboxylate (27 mg). 25 mg of this material was stirred 0.75h in MeOH/4M HCl in dioxane (1:1; 0.6 mL) and concentrated to give Int. **3E244** 3-[3-methyl-2-oxo-5-[1-[2-(4-piperidyl)ethyl]pyrazol-4-yl]benzimidazol-1-yl]-piperidine-2,6-dione (26 mg, HCl salt).



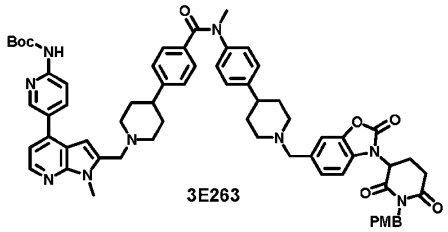
6-Bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (5.0 g) and NaH (1.32 g) were stirred 0.5h in DMF (50 mL) at 0 °C. SEM-Cl (4.0 g) was added and stirring continued ON at 0 °C to RT. The OL (water / EtOAc) was washed with brine, dried, concentrated, and purified by FC (hexane/EtOAc 3:2) to give Int. **3E253** 5-bromo-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (6.5 g). This material, *tert*-butyl piperazine-1-carboxylate (5.1 g), Pd_2dba_3 (1.7 g), RuPhos (0.85 g), and NaOtBu (3.5 g) were degassed in dioxane (65 mL) and stirred ON at 90 °C. Filtration, concentration, and purification by FC (EtOAc/ hexane 1:1) to give Int. **3E252** *tert*-butyl 4-(3-methyl-2-oxo-1-((2-(trimethylsilyl)ethoxy)-methyl)-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)piperazine-1-carboxylate (8.0 g). 2.0 g of this material and TBAF (9.6 g) were stirred ON in THF (20 mL) at 80 °C. The OL (water / EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 3:7) to give Int. **3E251** *tert*-butyl 4-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)piperazine-1-carboxylate (1.1 g). This material and KOtBu (0.48 g) were stirred 0.5h in THF (20 mL) at 0 °C. Int. **3A8** (2.5 g) was added and stirring continued 2h at 0 °C to RT. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 3:7) to give Int. **3E250** *tert*-butyl 4-[1-[1-[(4-methoxy-phenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]piperazine-1-carboxylate (0.9 g). Int. **3E250** (2.7 g)was stirred 2h in 1.5M HCl in dioxane (40 mL) at 0 °C and concentrated to give Int. **3E249** 1-[(4-methoxy-phenyl)-methyl]-3-(3-methyl-2-oxo-5-piperazin-1-yl-benzimidazol-1-yl)-piperidine-2,6-dione (1.8 g, HCl salt). 0.40 g of this material and *tert*-butyl 4-formyl-piperidine-1-carboxylate (0.22 g) were stirred 3h in DMSO/DIPEA (13.3:1, 8.6 mL). STAB (0.55 g) was added at 0 °C and stirring continued 72h at 0 °C to RT. The mixture was combined with another batch prepared from 1.0 g Int. **3E249**. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give on Int. **3E248** *tert*-butyl 4-[[4-[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzi-midazol-5-yl]-piperazin-1-yl]methyl]-piperidine-1-carboxylate (1.1 g). 0.8 g of this material was stirred 2h in TFA/TfOH (2:1, 15 mL) at 0 °C to 80 °C and concentrated. The residue was triturated in Et_2O and HPLC-purified to give Int. **3E247** 3-[3-methyl-2-oxo-5-[4-(4-piperidylmethyl)-piperazin-1-yl]benzimidazol-1-yl]-piperidine-2,6-dione (0.21 g, TfOH salt).



6-Bromo-3H-1,3-benzoxazol-2-one (2.0 g) and KOtBu (1.57 g) were stirred 0.5h in THF (35 mL) at 0 °C. Int. **3A8** (6.7 g) was added and stirring continued 3h at 0 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane / EtOAc 5:1 to 4:1) to give Int. **3E259** 3-(6-bromo-2-oxo-1,3-benzoxazol-3-yl)-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione (4.1 g). 2.0 g of this material, *tert*-butyl acrylate (1.6 mL), $Pd(OAc)_2$ (0.15 g), and $P(o\text{-tol})_3$ (0.27 g) were degassed in DMF/Et_3N (10:1, 21.9 mL) and stirred ON at 110 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane/EtOAc 5:1 to 4:1) to give Int. **3E58** *tert*-butyl (*E*)-3-[3-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-1,3-benzoxazol-6-yl]prop-2-enoate (1.5 g). This material, OsO_4 (0.27 g), and $NaIO_4$ (1.1 g) were stirred ON in THF/water (2:1; 18 mL). The OL (water/EtOAc) was washed with sat. aq. $NaHCO_3$ and brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E257** 3-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-1,3-benzoxazole-6-carbaldehyde (0.6 g). Ints. **3E5/3E257** (0.41 g/0.30 g) were stirred 2h in DCE/DIPEA (40:1, 15.4 mL) at 0 °C. STAB (0.3 g) was added and stirring continued ON at 0 °C to RT. Int. **3E5** (0.41 g) and DIPEA (0.3 mL) were added and stirring continued at 2h. STAB (0.30 g) was added and stirring continued ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1 and 2:3) to give **3E256** *tert*-butyl 4-((4-((3-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-benzo[d]oxazol-6-yl)methyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (0.6 g). A solution of this material in 1.5M HCl in dioxane (16 mL) was stirred 3h at 0 °C to RT and concentrated to give Int. **3E255** 1-(4-methoxybenzyl)-3-(2-oxo-6-((4-(piperidin-4-yl-methyl)-piperazin-1-yl)-methyl)benzo[d]oxazol-3(2H)-yl)-piperidine-2,6-dione (0.48 g, HCl salt).

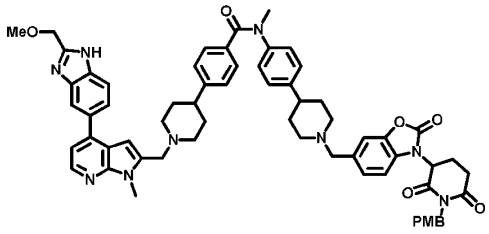


Ints. **3E255/3E261** (40 mg/42 mg) and HATU (31 mg) were stirred ON in DMF/DIPEA (1:0.06, 2.1 mL). The OL (water/EtOAc) was concentrated and purified by FC (DCM/MeOH 1:0 to 3:1) to give Int. **3E260** 1-(4-methoxybenzyl)-3-(6-((4-((1-(4-(1-((4-(2-(methoxymethyl)-1H-benzo[d]imidazol-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)piperidine-2,6-dione (48 mg).

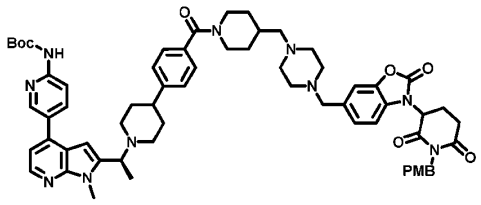


3E263

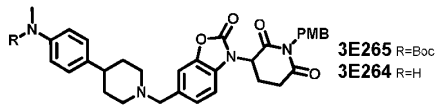
Int. **3E264** (20 mg), HATU (30 mg), and DIPEA (0.12 mL) were added and stirring continued ON. The OL (water/EtOAc) was concentrated and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3E263** *tert*-butyl (5-(2-((4-(4-((4-(1-((3-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)methyl)piperidin-4-yl)phenyl)(methyl)carbamoyl)phenyl)piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)carbamate (28 mg).



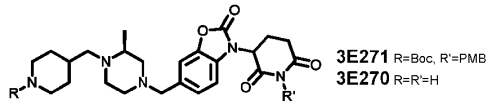
Ints. **3E264/3E261** (40 mg/41 mg) and HATU (31 mg) were stirred 72h in DMF/DIPEA (16.7:1, 2.1 mL). Int. **3E264** (19 mg), HATU (25 mg), and DIPEA (0.12 mL) were added and stirring continued ON. The OL (water/EtOAc) was washed with 3M aq. $CaCl_2$ and brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3E268** 4-[1-[[4-[2-(methoxymethyl)-1H-benzimidazol-5-yl]-1-methyl-pyrrolo[2,3-b]pyridin-2-yl]methyl]-4-piperidyl]-*N*-[4-[1-[[3-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-1,3-benzoxazol-6-yl]methyl]-4-piperidyl]phenyl]-*N*-methyl-benzamide (16 mg).



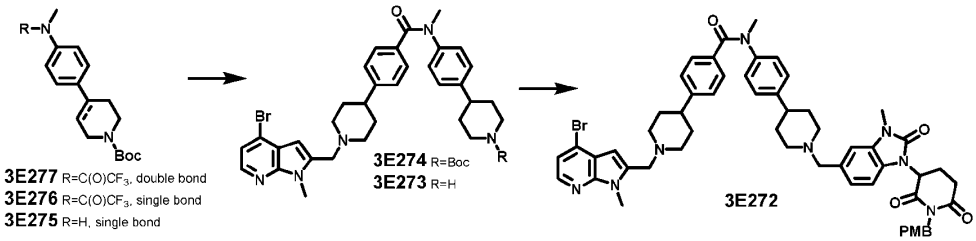
Ints. **3E76/3E255** (50 mg/51 mg) and HATU (39 mg) were stirred ON in DMF/DIPEA (12.51, 2.2 mL). The OL (water/EtOAc) was concentrated and purified by FC (DCM/MeOH/Et_3N 1:0:0 to 80:19.2:0.8) to give Int. **3E269** *tert*-butyl (5-(2-(((1S)-1-(4-(4-(4-((4-((3-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]-oxazol-6-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carbonyl)phenyl)piperidin-1-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)carbamate (59 mg).



Ints. **3E257/3E266** (0.32 g/0.42 g) were stirred 2h in DCE/DIPEA (25:1, 10.4 mL) at 0 °C to RT. STAB (0.33 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:1 to 2:3) to give Int. **3E265** *tert*-butyl *N*-[4-[1-[[3-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-1,3-benzoxazol-6-yl]methyl]-4-piperidyl]-phenyl]-*N*-methyl-carbamate (0.43 g). A solution of 0.13 g of this material in 1.3M HCl in dioxane (4.5 mL) was stirred 3h at 0 °C to RT and concentrated to give Int. **3E264** 1-[(4-methoxy-phenyl)methyl]-3-[6-[[4-[4-(methyl-amino)phenyl]-1-piperidyl]-methyl]-2-oxo-1,3-benzoxazol-3-yl]-piperidine-2,6-dione (80 mg, HCl salt).

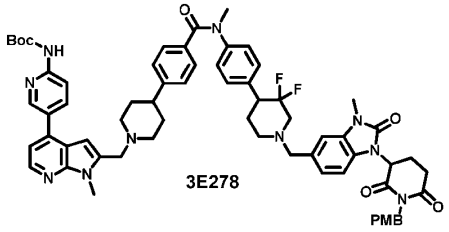


Ints. **3E74/3E257** (0.28 g/0.25 g) were stirred ON in DCE/DIPEA (24:1, 8.3 mL). STAB (0.40 g) was added and stirring continued ON. The OL (water/DCM) was dried, concentrated, and purified by FC (pentane/EtOAc 1:1) to give Int. **3E271** *tert*-butyl 4-[[(2S)-4-[[3-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-2-oxo-1,3-benz-oxazol-6-yl]methyl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.30 g). A solution of this material in TFA/TfOH (10:1; 3.3 mL) was stirred 1h at 80 °C and concentrated to give Int. **3E270** 3-[6-[[(3S)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]methyl]-2-oxo-1,3-benzoxazol-3-yl]piperidine-2,6-dione (0.25 g, TfOH salt).

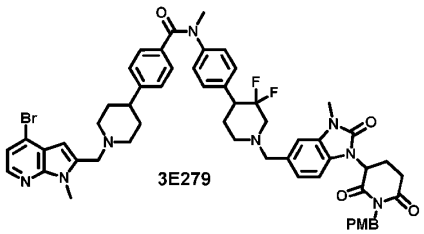


N-(4-bromophenyl)-2,2,2-trifluoro-*N*-methylacetamide (3.5 g), $PdDPPFCl_2$-DCM (0.44 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.3 g), and $NaHCO_3$ (1.8 g) were degassed in dioxane/water (10:1, 34 mL) and stirred ON at 100 °C and filtered. The OL (EtOAc/water) was washed with brine, dried, and concentrated. The residue was mixed with two additional batches prepared similarly and purified by FC (pentane/EtOAc 9:1 to 85:15) to give Int. **3E277** *tert*-butyl 4-(4-(2,2,2-trifluoro-*N*-methyl-acetamido)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (8.3 g). 3.0 g of this material was hydrogenated ON using 10% Pd/C in MeOH (30 mL), filtered, concentrated, and purified by FC (pentane/EtOAc 9:1 to 85:15) to give Int. **3E276** *tert*-butyl 4-(4-(2,2,2-trifluoro-*N*-methyl-acetamido)phenyl)piperidine-1-carbo-xylate

(2.5 g). 0.8 g of this material and K_2CO_3 (0.7 g) were stirred 3h in MeOH (7 mL) and concentrated. The OL (water/DCM) was dried and concentrated to give Int. **3E275** *tert*-butyl 4-(4-(methylamino)phenyl)-piperidine-1-carboxylate (0.5 g). Ints. **1AC4/3E275** (0.5 g/0.58 g) and HATU (0.67 g) were stirred ON in DMF/DIPEA (24.5:1, 15.6 mL) and diluted with water to precipitate Int. **3E274** *tert*-butyl 4-(4-(4-(1-((4-bromo-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*-methyl-benzamido)-phenyl)piperidine-1-carboxylate (0.6 g). 0.18 g of this material was stirred 0.5h in DCM/TFA (2:1; 1.5 mL), concentrated, and SCX-purified to give Int. **3E273** 4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*-methyl-*N*-[4-(4-piperidyl)phenyl]-benzamide (0.15 g). Ints. **3E3/3E273** (0.99 g/0.15 g) and 4Å MS and STAB (0.27 g) were stirred 2h in DCE (4 mL) at 70 °C. The mixture was purified by FC (DCM/MeOH 95:5) to give Int. **3E272** 4-(1-((4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-*N*-(4-(1-((1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-*N*-methylbenzamide (41 mg).

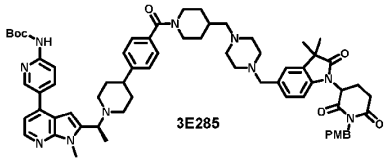


Int. **3E279** (49 mg), *tert*-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (21 mg), and $PdDPPFCl_2$-DCM (5 mg) were degassed in DMF/10% aq. Na_2CO_3 (10:1, 2.2 mL) and stirred 1.5h at 90 °C. The OL (water/EtOAc) was concentrated and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3E278** *tert*-butyl (5-(2-((4-(4-((4-(3,3-difluoro-1-((1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)(methyl)-carbamoyl)phenyl)-piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)carbamate (37 mg).

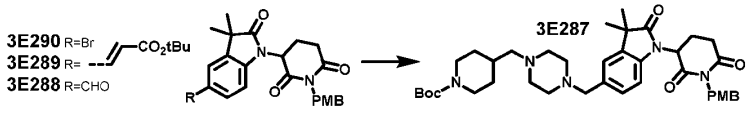


Ints. **3E3/3E280** (30 mg/52 mg) and 4Å MS were stirred 0.5h in DCE/DIPEA (100:1, 1.4 mL) at 70 °C. STAB (78 mg) was added and stirring continued 3h. The OL (water/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3E279** 4-[1-[(4-bromo-1-methyl-pyrrolo-[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]-*N*-[4-[3,3-difluoro-1-[[1-[1-[(4-

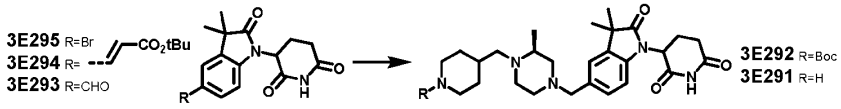
methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]methyl]-4-piperidyl]-phenyl]-*N*-methyl-benzamide (49 mg).



Int. **3E287** (50 mg) was stirred ON in 2.4M HCl in dioxane (5 mL) and concentrated. The residue, Int. **3E76** (55 mg), and HATU (49 mg) were stirred ON in DMF/DIPEA (15:1, 1.6 mL). The OL (EtOAc/water) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 95:5) to give Int. **3E285** *tert*-butyl (5-(2-((1S)-1-(4-(4-(4-((4-((1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carbonyl)phenyl)piperidin-1-yl)ethyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)carbamate (65 mg).

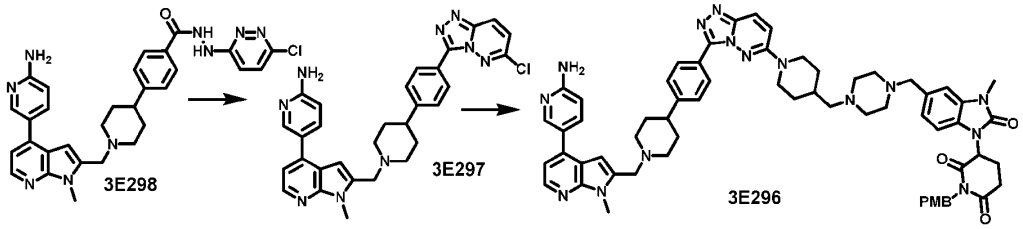


KOtBu (0.68 g) was added to a solution of 5-bromo-3,3-dimethyl-indolin-2-one (1.0 g) in THF (15 mL) at 0 °C. Int. **3A8** (2.3 g) was added and stirring continued 2h at 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (pentane / EtOAc 4:1) to give Int. **3E290** 3-(5-bromo-3,3-dimethyl-2-oxo-indolin-1-yl)-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione (1.0 g). 0.4 g of this material, *tert*-butyl acrylate (0.33 g), $Pd(OAc)_2$ (19 mg), and P(*o*-tol)$_3$ (52 mg) were degassed in DMF/Et_3N (173:1, 50 mL) and stirred ON at 120 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (pentane/EtOAc 1:0 to 3:2) to give Int. **3E289** *tert*-butyl (*E*)-3-[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3,3-dimethyl-2-oxo-indolin-5-yl]prop-2-enoate (0.35 g). 0.3 g of this material, $NaIO_4$ (0.12 g), and OsO_4 (14 mg) were stirred ON in THF/water (2:1; 9 mL). The OL (EtOAc/sat. aq. $Na_2S_2O_3$) was concentrated and purified by FC (pentane/EtOAc 1:0 to 7:3) to give Int. **3E288** 1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3,3-dimethyl-2-oxo-indoline-5-carbaldehyde (70 mg). Ints. **3E5/3E288** (40 mg/50 mg) were stirred 3h in DCE/DIPEA (43:1, 3 mL). STAB (46 mg) was added and stirring continued ON at 0 °C to RT. The OL (water/DCM) was concentrated and purified by FC (DCM/MeOH 92:5 to 9:1) to give **3E287** *tert*-butyl 4-[[4-[[1-[1-[(4-methoxyphenyl)-methyl]-2,6-dioxo-3-piperidyl]-3,3-dimethyl-2-oxo-indolin-5-yl]methyl]-piperazin-1-yl]methyl]piperidine-1-carboxylate (40 mg).

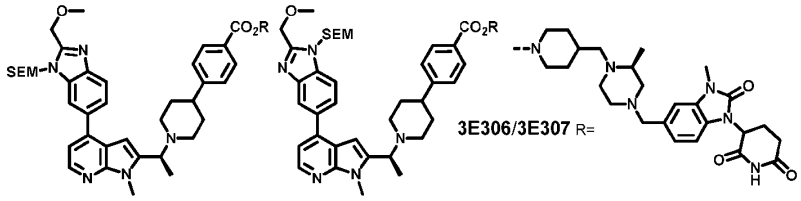


NaH (60% oil dispersion, 1.7 g) was added to a solution of 5-bromo-3,3-dimethyl-indolin-2-one (2.5 g) in THF (10 mL) at 0 °C. 3-Bromopiperidine-2,6-dione (8.0 g) was added and stirring

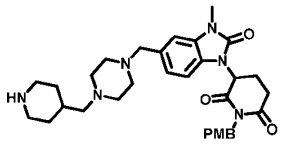
continued ON at 60 °C. The OL (water/ EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 7:3 to 1:1) to give Int. **3E295** 3-(5-bromo-3,3-dimethyl-2-oxo-indolin-1-yl)piperidine-2,6-dione (1.5 g). Int. **3E295** (1.8 g), *tert*-butyl acrylate (3.0 mL), $Pd(OAc)_2$ (92 mg), and P(*o*-tol)$_3$ (0.31 g) were degassed in DMF/Et_3N (4.8:1, 12 mL) and stirred ON at 120 °C. The OL was (water/EtOAc) washed with brine, dried, and concentrated to give Int. **3E294** *tert*-butyl (*E*)-3-[1-(2,6-dioxo-3-piperidyl)-3,3-dimethyl-2-oxo-indolin-5-yl]prop-2-enoate (1.5 g). 0.5 g of this material, $NaIO_4$ (1.1 g), and OsO_4 (0.1 g) were stirred ON in THF/water (3:1; 20 mL). The OL (EtOAc/sat. aq. $Na_2S_2O_3$) was washed with sat. aq. $NaHCO_3$, dried, and concentrated to give Int. **3E293** 1-(2,6-dioxo-3-piperidyl)-3,3-dimethyl-2-oxo-indoline-5-carbaldehyde (0.18 g). Ints. **3E74/3E293** (0.25 g/0.10 g) were stirred 5h in THF/1M $ZnCl_2$ in THF (1:1, 2 mL). $NaCNBH_3$ (41 mg) was added and stirring continued ON. The OL (water / EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 9:1) to give **3E292** *tert*-butyl 4-[[(2S)-4-[[1-(2,6-dioxo-3-piperidyl)-3,3-dimethyl-2-oxo-indolin-5-yl]-methyl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (0.11 g). Int. **3E292** (0.12 g) was stirred 3h in DCM/4M HCl in dioxane (6:1; 6.2 mL) at 0 °C to RT and concentrated to give Int. **3E291** 3-(3,3-dimethyl-5-(((S)-3-methyl-4-(piperidin-4-yl-methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione (0.11 g, HCl salt).



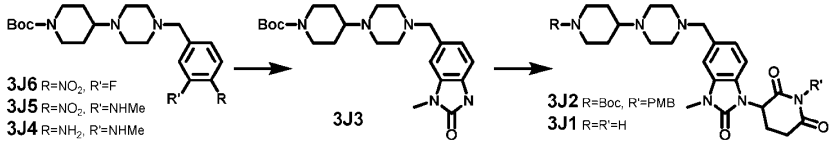
Int. **3E2** (80 mg) was stirred 0.3h in DCM/TFA (4:1, 2.5 mL) and concentrated to give Int. **3E299** 3-[3-methyl-2-oxo-4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-benzimidazol-1-yl]piperidine-2,6-dione (85 mg, TFA salt). Int. **3E23** (0.17 g) and HATU (0.2 g) were stirred 4h in DMF/DIPEA (5.6:1, 1.8 mL). 3-Chloro-6-hydrazineyl-pyridazine (67 mg) was added and stirring continued ON. The OL (2MeTHF/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH/Et_3N 1:0:0 to 90:8.5:0.5) to give Int. **3E298** 4-[1-[[4-(6-amino-3-pyridyl)-1-methyl-pyrrolo[2,3-b]-pyridin-2-yl]methyl]-4-piperidyl]-*N'*-(6-chloropyridazin-3-yl)benzohydrazide (0.12 g). This material was stirred 3h in AcOH (4 mL) at 90 °C, concentrated, and purified by FC (DCM/MeOH/ Et_3N 95:4.5:0.5) to give Int. **3E297** 5-[2-[[4-[4-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)phenyl]-1-piperidyl]-methyl]-1-methyl-pyrrolo[2,3-b]pyridin-4-yl]pyridin-2-amine (77 mg). Ints. **3E299/3E297** (57 mg/38 mg) were stirred 1.5h in NMP/DIPEA (42:1, 2.05 mL) at 90 °C, 48h at 100 °C, and 4h at 120 °C. The OL (2MeTHF/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH/Et_3N 95:4.5:0.5) to give Int. **3E296** (40 mg).



Ints. **3E68/3E308/3E309** (0.11 g/0.12 g) and HATU (91 mg) were stirred ON in DMF/DIPEA (18.4:1. 3.7 mL) and diluted with water to precipitate Int. **3E306/3E307** 3-(5-(((S)-4-((1-(4-(1-((S)-1-(4-(2-(methoxymethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and 3-(5-(((S)-4-((1-(4-(1-((S)-1-(4-(2-(methoxymethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]-imidazol-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.12 g).

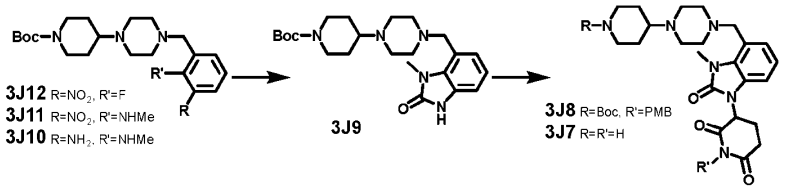


Int. **3E2** (80 mg) was stirred 0.3h in DCM/TFA (4:1, 2.5 mL) and concentrated to give Int. **3E299** 3-[3-methyl-2-oxo-4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-benzimidazol-1-yl]piperidine-2,6-dione (85 mg, TFA salt).



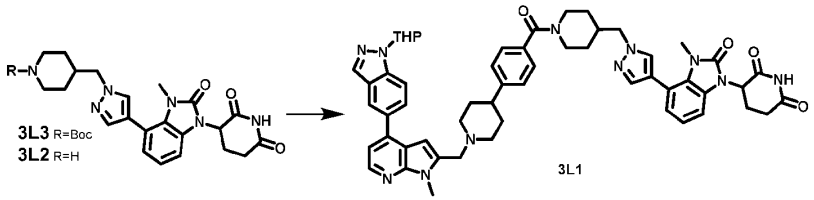
tert-Butyl 4-(piperazin-1-yl)piperidine-1-carboxylate (5.1 g) and 3-fluoro-4-nitro-benzaldehyde (3.0 g) were stirred 6h in DCE/DIPEA (4.2:1, 62 mL). STAB (11 g) was added and stirring continued ON at 0 °C to RT. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **3J6** *tert*-butyl 4-(4-(3-fluoro-4-nitrobenzyl)piperazin-1-yl)piperidine-1-carboxylate (4.0 g). This material was stirred in THF/2M $MeNH_2$ in MeOH (4.2:1, 50 mL) ON at 0 °C to RT, diluted with sat. aq. $NaHCO_3$, and partially concentrated. The product was extracted into EtOAc, dried, concentrated, and triturated in pentane to give Int. **3J5** *tert*-butyl 4-(4-(3-(methylamino)-4-nitrobenzyl)-piperazin-1-yl)-piperidine-1-carboxylate (4.0 g). This material was hydrogenated ON using Raney-nickel (1.3 g) in EtOH (50 mL), filtered, and concentrated to give Int. **3J4** *tert*-butyl 4-(4-(4-amino-3-(methylamino)benzyl)-piperazin-1-yl)piperidine-1-carboxylate (3.2 g). This material and CDI (2.6 g) were stirred in ACN (40 mL) at

80 °C and concentrated. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 95:5) to give Int. **3J3** *tert*-butyl 4-(4-((3-methyl-2-oxo-2,3-dihydro-1λ^2-benzo[d]imidazol-5-yl)-methyl)-piperazin-1-yl)piperidine-1-carboxylate (1.4 g). This material and KOtBu (0.47 g) were stirred 0.5h in THF (20 mL). Int. **3A8** (3.2 g) was added and stirring continued 3h at 0 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 98:2 to 97:3) to give Int. **3J2** *tert*-butyl 4-(4-((1-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)-piperazin-1-yl)piperidine-1-carboxylate (1.2 g). 0.5 g of this material was stirred 1h in TFA/TfOH (1:10, 5.5 mL) at 80 °C, concentrated, and triturated in Et_2O to give Int. **3J1** 3-(3-methyl-2-oxo-5-((4-(piperidin-4-yl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione. This material was combined with another batch prepared similarly and HPLC-purified to give Int. **3J1** (0.24 g).

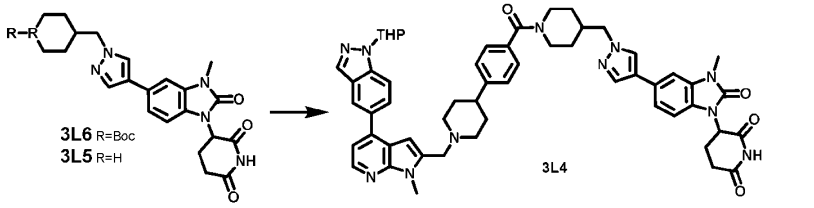


2-Fluoro-3-nitro-benzaldehyde (4.4 g) and *tert*-Butyl 4-(piperazin-1-yl)piperidine-1-carboxylate (8.4 g) were stirred 4h in DCE/DIPEA (5.7:1, 97 mL). STAB (16 g) was added and stirring continued ON at 0 °C to RT and concentrated. The OL (sat. aq. $NaHCO_3$/DCM) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3J12** *tert*-butyl 4-(4-(2-fluoro-3-nitrobenzyl)-piperazin-1-yl)-piperidine-1-carboxylate (2.4 g). This material was stirred in THF/2M $MeNH_2$ in MeOH (4:1, 29 mL) ON and concentrated to give Int. **3J11** *tert*-butyl 4-[4-[[2-(methylamino)-3-nitro-phenyl]methyl]-piperazin-1-yl]piperidine-1-carboxylate (2.3 g). Int. **3J11** (0.30 g) was hydrogenated 2h using 10% $Pd(OH)_2$/C (0.15 g) in MeOH (6 mL), filtered, and concentrated to give Int. **3J10** *tert*-butyl 4-[4-[[3-amino-2-(methylamino)-phenyl]-methyl]-piperazin-1-yl]-piperidine-1-carboxylate (0.25 g). Int **3J10** (2.1 g) and CDI (2.5 g) were stirred ON in ACN (25 mL) at 80 °C and concentrated. The OL (water/DCM/MeOH (9:1)) was washed with water and brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3J9** *tert*-butyl 4-[4-[(3-methyl-2-oxo-1H-benzimidazol-4-yl)methyl]piperazin-1-yl]piperidine-1-carboxylate (1.6 g). Int. **3J9** (1.47 g) and KOtBu (0.42 g) were stirred 0.5h in THF (40 mL) at -10 °C to 0 °C. Int. **3A8** (3.2 g in THF (20 mL)) was added and stirring continued 3h at -10 °C to 0 °C. The OL (sat. aq. NH_4Cl/EtOAc) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3J8** *tert*-butyl 4-[4-[[1-[1-[(4-methoxy-phenyl)-methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]methyl]-piperazin-1-yl]piperidine-1-carboxylate (1.5 g). 0.3 g of this material was stirred 1h in TFA/TfOH (10:1, 3.3 mL) at 80 °C, concentrated, and triturated in Et_2O to give Int. **3J1**. This material was combined with another batch prepared similarly from Int. **3J8** (0.60 g) and HPLC-

purified to give Int. **3J7** 3-(3-methyl-2-oxo-4-((4-(piperidin-4-yl)piperazin-1-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.20 g).

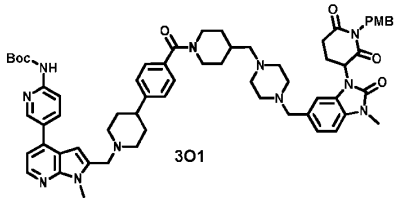


Int. **3A6** (40 mg), PdDPPFCl$_2$-DCM (10 mg), and *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate (60 mg) were degassed in DMF/10% aq. Na_2CO_3 (5.6:1, 1.65 mL) and stirred 0.5h at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (EtOAc) to give Int. **3L3** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate (32 mg). Int. **3L3** (22 mg) was stirred 1h in 2M HCl in dioxane (0.4 mL). The mixture was diluted with MeOH, concentrated, and co-concentrated with DCM to give Int. **3L2** 3-(3-methyl-2-oxo-4-(1-(piperidin-4-ylmethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione. This material, Int. **3A2** (24 mg), and HATU (17 mg) were stirred 1h in DMF/DIPEA (5.4:1, 0.41 mL). The mixture was HPLC-purified to give Int. **3L1** 3-(3-methyl-4-(1-((1-(4-(1-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)-1H-pyrazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione (27 mg).

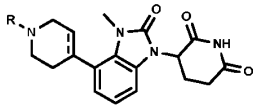


Int. **3B3** (40 mg), PdDPPFCl$_2$-DCM (10 mg), and *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate (60 mg) were degassed in DMF/10% aq. Na_2CO_3 (5.6:1, 1.65 mL) and stirred 0.5h at 100 °C. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (EtOAc) to give Int. **3L6** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate (30 mg). Int. **3L6** (20 mg) was stirred 1h in 2M HCl in dioxane (0.4 mL). The mixture was diluted with MeOH, concentrated, and co-concentrated with DCM to give Int. **3L5** 3-(3-methyl-2-oxo-5-(1-(piperidin-4-ylmethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione. This material, Int. **3A2** (25 mg), and HATU (18 mg) were stirred 1h in DMF/DIPEA (5.4:1, 0.41 mL). The mixture was HPLC-purified to give Int. **3L4** 3-(3-methyl-5-(1-((1-(4-(1-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1H-

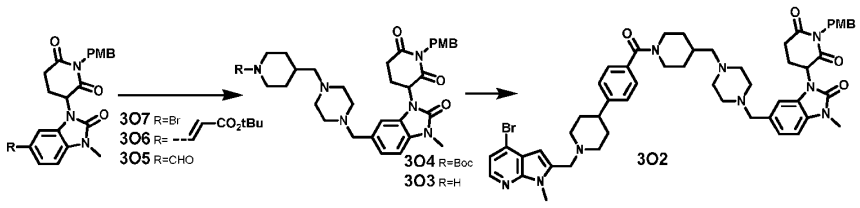
pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-1H-pyrazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (24 mg).



Int. **3O2** (0.99 g), *tert*-butyl *N*-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]carbamate (48 mg), and $PdDPPFCl_2$-DCM (8 mg) were degassed in DMF/10% aq. Na_2CO_3 (5:1, 2.4 mL) and stirred 1.5h at 90 °C. The OL (EtOAc/water) was washed with brine, dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 4:1) to give Int. **3O1** *tert*-butyl (5-(2-((4-(4-(4-((4-((3-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carbonyl)phenyl)piperidin-1-yl)methyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)carbamate (0.11 g).

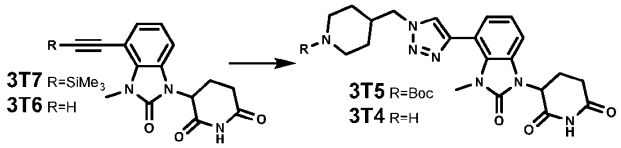


Int. **3A6** (0.10 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.12 g), and $PdDPPFCl_2$-DCM (24 mg) were degassed in DMF/10% aq. Na_2CO_3 (4.8:1, 3.6 mL) and stirred 0.5h at 100 °C. The OL (EtOAc/3M aq. $CaCl_2$) was washed with brine, dried, concentrated, and purified by FC (heptane to EtOAc) to give Int. **3T1** *tert*-butyl 4-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (70 mg). 65 mg of this material was hydrogenated ON using 10% Pd/C (16 mg) and $Pd(OH)_2$ (10 mg) in THF/DMF (2:1, 3 mL), filtered, and purified by FC (heptane to EtOAc) to give Int. **3T2** *tert*-butyl 4-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-4-yl]piperidine-1-carboxylate (22 mg). Int. **3T3** 3-(3-methyl-2-oxo-4-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione was obtained from Int. **3T1** by treatment with HCl.



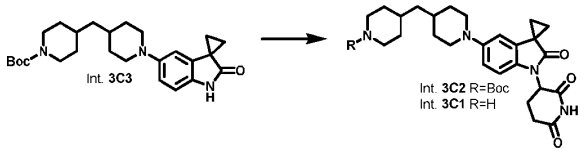
KOtBu (1.3 g) was added to a solution of 6-bromo-3-methyl-1H-benzimidazol-2-one (2.0 g) in THF (10 mL) at 0 °C and the mixture was stirred at RT for 0.5h. Int. **3A8** (5.42 g) was added and stirring continued 3h. The OL (sat. aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 1:0 to 2:3) and by trituration in Et_2O/EtOAc to give Int. **3O7** 3-(6-bromo-3-methyl-2-

oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]-piperidine-2,6-dione (2.24 g). Int. **3O7** (0.5 g), *tert*-butyl acrylate (0.35 g), P(*o*-tol)$_3$ (66 mg), and Pd(OAc)$_2$ (25 mg) were degassed in DMF/Et$_3$N (10:1, 5.5 mL) and stirred 120 °C ON. The OL (water/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane to EtOAc) to give Int. **3O6** *tert*-butyl (E)-3-(3-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acrylate (0.52 g). Int. **3O6** (0.5 g), $NaIO_4$ (0.57 g), and OsO_4 (0.11 g) were stirred ON in THF/water (2:1; 12 mL). The OL (sat. aq. $NaHCO_3$/EtOAc) was washed with brine, dried, concentrated, and purified by FC (heptane to EtOAc) to give Int. **3O5** 3-(1-(4-methoxybenzyl)-2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (0.31 g). Ints. **3O5/3E5** (0.30 g/0.31 g) were stirred 0.5h in DCE/DIPEA (78:1, 10.1 mL) at 70 °C. STAB (0.78 g) was added at RT and stirring continued 3h at 70 °C. The OL (water/DCM) was washed with brine, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3O4** *tert*-butyl 4-((4-((3-(1-(4-methoxy-benzyl)-2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.43 g). Int. **3O4** (0.17 g) was stirred 0.5h in DCM/TFA (2:1, 3 mL) and concentrated to give Int. **3O3** 1-[(4-methoxyphenyl)methyl]-3-[3-methyl-2-oxo-6-[[4-(4-piperidylmethyl)-piperazin-1-yl]methyl]benzimidazol-1-yl]piperidine-2,6-dione (0.14 g, TFA salt). Ints. **1AC4/3O3** (71 mg/79 mg) and HATU (68 mg) were stirred ON in DMF/DIPEA (8.3:1, 2.2 mL). The OL (EtOAc/water) was washed with brine, concentrated, and purified by FC (DCM/MeOH 1:0 to 85:15) to give Int. **3O2** 3-[6-[[4-[[1-[4-[1-[(4-bromo-1-methyl-pyrrolo[2,3-b]pyridin-2-yl)methyl]-4-piperidyl]benzoyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-3-methyl-2-oxo-benzimidazol-1-yl]-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione (0.99 g).

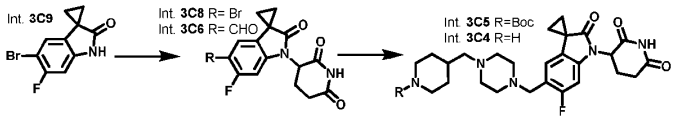


Int. **3A6** (0.25 mg), ethynyltrimethylsilane (0.18 g), CuI (0.15 g), and PdDPPFCl$_2$-DCM (0.11 g) were degassed in DMF/Et$_3$N (5:1, 4.8 mL) and stirred 5h at 70 °C. The OL (water/EtOAc) was washed with brine, dried, and concentrated. The residue was purified by FC (heptane/EtOAc 1:0 to 1:1) and by HPLC to give Int. **3T7** 3-(3-methyl-2-oxo-4-((trimethylsilyl)ethynyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (28 mg). Int. **3T7** (43 mg) was stirred 0.5 h in 0.7M TBAF in THF (3.2 mL). The mixture was HPLC-purified to give Int. **3T6** 3-(4-ethynyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (26 mg). NaN_3 (0.11 g) and *tert*-butyl 4-(bromo-methyl)piperidine-1-carboxylate (0.40 g) were stirred ON in DMF (5 mL). The OL (water/ EtOAc) was washed with brine, dried, and concentrated to give Int. **3T8** *tert*-butyl 4-(azidomethyl)piperidine-1-carboxylate (0.32 g). Ints. **3T8/3T6** (21 mg/22 mg), $CuSO_4$ (2 mg), ascorbic acid (9 mg) were degassed in *tert*-butanol/water (4:1, 1.5 mL) and stirred 2h at 80-90 °C. The mixture was diluted with DMSO/MeOH (2:1, 3 mL) and HPLC-purified to give Int. **3T5** *tert*-butyl 4-

((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (27 mg). Int. **3T5** (23 mg) was stirred 1h on DCM/TFA (2:1, 3 mL). The mixture was concentrated to give Int. **3T4** 3-(3-methyl-2-oxo-4-(1-(piperidin-4-yl-methyl)-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (18 mg, TFA salt).

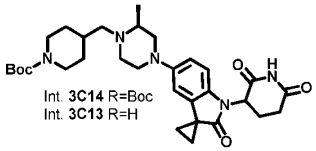


tert-Butyl 4-(piperidin-4-ylmethyl)piperidine-1-carboxylate (1.3 g), 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (1 g) and RuPhos (0.27 g) were mixed in toluene (20 mL) under an inert atmosphere. 1.0 M LiHMDs in THF (17 mL) and RuPhos Pd-G4 (0.36 g) were added and the mixture was stirred 4h at 90 °C. The OL (aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 2:3 to 1:4) to give Int. **3C3** *tert*-butyl 4-((1-(2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidin-4-yl)methyl)piperidine-1-carboxylate (1.4 g). 3-Bromopiperidine-2,6-dione (2.2 g) was added to a solution of Int. **3C3** (1 g) and 1.0 M LiHMDs in THF (11 mL) in THF (15 mL) and stirred 1h at 55 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:4) to give Int. **3C2** *tert*-butyl 4-((1-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-piperidin-4-yl)methyl)piperidine-1-carboxylate (0.8 g). Int. **3C2** (0.90 g) was stirred 16h in DCM/TFA (10:1, 22 mL) at 0 °C to RT, concentrated, and triturated in Et_2O to give Int. **3C1** 3-(2'-oxo-5'-(4-(piperidin-4-ylmethyl)piperidin-1-yl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.90 g, TFA salt).

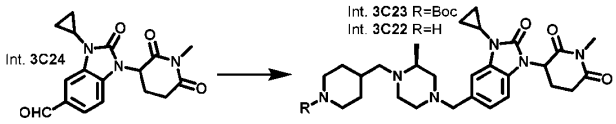


NBS (18.8 g) was added to a solution of 6'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one (17 g) in ACN (340 mL) and stirred for 16h at RT. The OL (water/EtOAc) was dried, concentrated and washed with Et_2O to give Int. **3C9** 5'-bromo-6'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one (15 g). NaH (21 g) was added to a solution of Int. **3C9** (14 g) in THF (0.6 L) at 0 °C. 3-Bromopiperidine-2,6-dione (52.5 g) was added and the mixture was stirred 6h at 60 °C. The OL (water/EtOAc) was concentrated, and triturated in PE/MTBE (1:1) to give Int. **3C8** 3-(5'-bromo-6'-fluoro-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (15 g). $Pd(OAc)_2$ (0.92 g), Int. **LL22** (15 g), P(*o*-tol)$_3$ (3.7 g), and *tert*-butyl acrylate (60 mL) were stirred 16h in DMF (200 mL) and Et_3N (73 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and washed with Et_2O to give Int. **3C7** *tert*-butyl (E)-3-(1'-(2,6-dioxopiperidin-3-yl)-6'-fluoro-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)acrylate (9 g). OsO_4 (0.11 g), $NaIO_4$ (14 g), and

Int. **3C7** (9 g) were stirred 16h in THF/H_2O (1:1, 180 mL). The mixture diluted with sat. aq. $Na_2S_2O_3$ and $NaHCO_3$ to precipitate a solid that was washed with Et_2O to give Int. **3C6** 1'-(2,6-dioxopiperidin-3-yl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indoline]-5'-carbaldehyde (4.5 g). Int. **3C6** (3.5 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (6.9 g) were stirred 24h in DMSO/DIPEA (5:1, 42 mL). STAB (9.4 g) was added at 0 °C and stirring continued for 16h. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **3C5** *tert*-butyl 4-((4-((1'-(2,6-dioxopiperidin-3-yl)-6'-fluoro-2'-oxospiro[cyclo-propane-1,3'-indolin]-5'-yl)methyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (4 g). Int. **3C5** (0.50 g) was stirred 16h in DCM/TFA (5:2, 7 mL), concentrated, and washed with DCM/Et_2O (1:1) to give Int. **3C4** 3-(6'-fluoro-2'-oxo-5'-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dion (0.30 g, TFA salt).

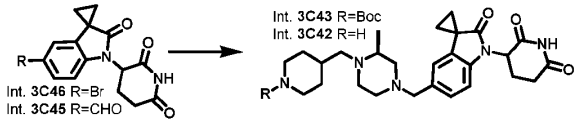


RuPhos (0.98 g) and RuPhos Pd-G4 (0.89 g) were added to a mixture of Int. **3E74** (4.1 g) and 5'-bromo-spiro[cyclopropane-1,3'-indolin]-2'-one (2.5 g) in toluene (30 mL) under an inert atmosphere. 1.0 M LiHMDs in THF (42 mL) was added at 0 °C and the mixture stirred 3h at 110 °C. The OL (aq. NH_4Cl/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:0 to 0:1) to give Int. **3C14** *tert*-butyl 4-(((2S)-4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-2-methylpiperazin-1-yl)methyl)-piperidine-1-carboxylate (2.4 g). Int. **3C14** (1.1 g) was dissolved in DCM/TFA (27:1, 21 mL) at 0 °C and stirred 16h at 0 °C to RT, concentrated, and washed with Et_2O to give Int. **3C13** 3-(5'-((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.78 g, TFA salt).

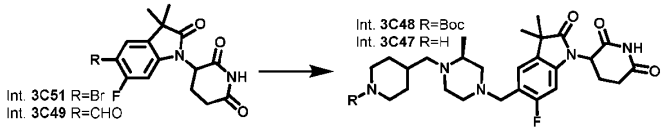


Int. **3E211** (0.50 g) and K_2CO_3 were stirred 16h in ACN (15 mL) and MeI (0.28 mL) at 10 °C to RT under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3C24** 3-cyclopropyl-1-(1-methyl-2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]-imidazole-5-carbaldehyde (0.40 g). Ints. **3E74/3C24** (0.53 g/0.30 g) were stirred 16h in DMSO/DIPEA (13:2, 6.9 mL) under an inert atmosphere. STAB (0.76 g) was added and stirring continued for 8h. The OL (water / EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3C23** *tert*-butyl 4-(((2S)-4-((3-cyclopropyl-1-(1-methyl-2,6-dioxo-piperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)-piperidine-1-carboxylate (0.54 g). Int. **3C23** (0.60 g) was stirred 6h in DCM/4M HCl in

dioxane (5:2, 7 mL) at 0 °C. The residue after concentration was washed with Et_2O to give Int. **3C22** 3-(3-cyclopropyl-5-(((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-methylpiperidine-2,6-dione (0.45 g, HCl salt).

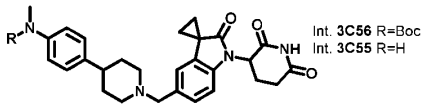


NaH (14.5 g) was added to a solution of 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (9 g) in THF (270 mL) at 0 °C. 3-Bromopiperidine-2,6-dione (36 g) was added and the mixture stirred 6h at 60 °C. The OL (water/EtOAc) was concentrated and triturated in PE/MTBE (1:1) to give Int. **3C46** 3-(5'-bromo-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (8 g). Et_3N (7.5 mL), $Pd(OAc)_2$ (0.48 g) and *tert*-butyl acrylate (32 mL) were added to a solution of Int. **3C46** (7.5 g) and P(*o*-tol)$_3$ (2.0 g) in DMF (70 mL) and stirred 16h at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and washed with PE to give Int. **3C45** *tert*-butyl (E)-3-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)acrylate (5 g). OsO_4 (64 mg), $NaIO_4$ (8.1 g), and Int. **3C45** (5.0 g) were stirred 2h in THF/H_2O (1:1, 100 mL). The mixture was diluted with sat. aq. $Na_2S_2O_3{\cdot}5H_2O$ to precipitate Int. **3C44** 1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indoline]-5'-carbaldehyde (3.0 g). Ints. **3E74/3C44** (1.5 g/2.5 g) were stirred 24h in DMSO/DIPEA (1:1, 10.5 mL). STAB (7.1 g) was added at 0 °C and stirring was continued for 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **3C43** *tert*-butyl 4-(((2S)-4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (0.4 g). Int. **3C43** (1.0 g) was stirred 4h in DCM/4M HCl in dioxane (7:1, 23 mL) at 0 °C to RT, concentrated, and washed with Et_2O to give Int. **3C42** 3-(5'-(((S)-3-methyl-4-(piperidin-4-ylmethyl)-piperazin-1-yl)-methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.80 g, HCl salt).

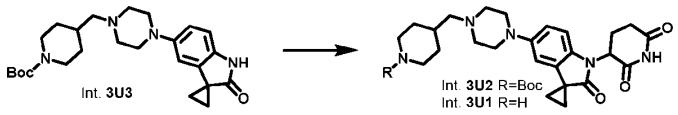


NaH (15.5 g) was added to a solution of 5-bromo-6-fluoro-3,3-dimethylindolin-2-one (10 g) in THF (200 mL) at 0 °C and stirred for 15 min at RT. 3-Bromopiperidine-2,6-dione (37 g) was added and the mixture was stirred 16h at 70 °C. The OL (water/EtOAc) was dried, concentrated, and washed with hexane/EtOAc (2:1) to give Int. **3C51** 3-(5-bromo-6-fluoro-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione (7.5 g). $Pd(OAc)_2$ (0.61 g), P(*o*-tol)$_3$ (2.5 g), and Int. **3C51** (10 g) were stirred 16h in DMF/Et_3N (2:1, 148 mL) and *tert*-butyl acrylate (40 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and washed with Et_2O to give Int. **3C50** *tert*-butyl (E)-3-(1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3,3-dimethyl-2-oxoindolin-5-yl)acrylate

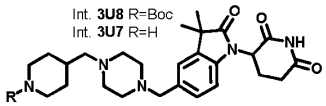
(7 g). OsO_4 (67 mg) and $NaIO_4$ (7.0 g) were added to a solution of Int. **3C50** (5.5 g) in THF/H_2O (1:1, 60 mL) and stirred 12h. The mixture diluted with sat. aq. $Na_2S_2O_3{\cdot}5H_2O$ to precipitate Int. **3C49** 1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3,3-dimethyl-2-oxoindoline-5-carbaldehyde (4.0 g). Ints. **3E74/3C49** (4.5 g/4.0 g) were stirred 24h in DMSO/DIPEA (4:1, 49 mL). STAB (11 g) was added at 0 °C and stirring continued for 16h at RT. The OL (water/EtOAc) was dried, and concentrated to give Int. **3C48** *tert*-butyl 4-(((2S)-4-((1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3,3-dimethyl-2-oxoindolin-5-yl)-methyl)-2-methyl-piperazin-1-yl)methyl)piperidine-1-carboxylate (2.5 g). Int. **3C48** (1.8 g) was mixed in DCM/4M HCl in dioxane (2:1, 15 mL) at 0 °C and was stirred for 5h at RT, concentrated, and washed with Et_2O to give Int. **3C47** 3-(6-fluoro-3,3-dimethyl-5-(((S)-3-methyl-4-(piperidin-4-yl-methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione (1.2 g, HCl salt).



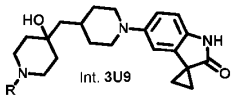
Ints. **3E266/3C44** (2.0 g/1.8 g) were stirred in DMSO/DIPEA (4:1, 19 mL) for 24h at RT. STAB (4.9 g) was added and the mixture was stirred 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 14:1) to give Int. **3C56** *tert*-butyl (4-(1-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)piperidin-4-yl)phenyl)-(methyl)carbamate (1.3 g). Int. **3C56** (1.3 g) was stirred 16h in DCM/TFA (4:1, 25 mL) at 0 °C to RT, concentrated and washed with Et_2O to give Int. **3C55** 3-(5'-((4-(4-(methylamino)phenyl)piperidin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (1.2 g, TFA salt).



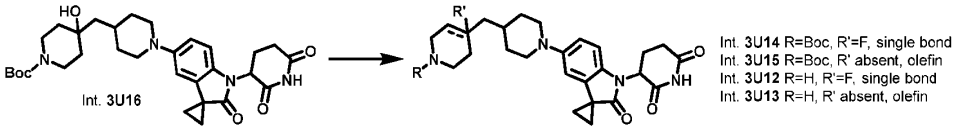
5'-Bromospiro[cyclopropane-1,3'-indolin]-2'-one (3 g), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (7.1 g), RuPhos (1.2 g), and RuPhos Pd-G4 (1.1 g) were stirred 3h in toluene (35 mL) and 1M LiHMDs in THF (63 mL) at 70 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:0 to 1:4) to give Int. **3U3** *tert*-butyl 4-((4-(2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)piperidin-1-yl)methyl)-piperidine-1-carboxylate (2.5 g). NaH (1.4 g) and 3-bromopiperidine-2,6-dione (3.3 g) were added to a mixture of Int. **3U3** (1.5 g) in DMF (15 mL) and stirred for 48h at 60 °C. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **3U2** *tert*-butyl 4-((4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.3 g). Int. **2U2** (1.5 g) was stirred 12h in DCM/TFA (2:1, 22 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U1** 3-(2'-oxo-5'-(4-(piperidin-4-ylmethyl)piperazin-1-yl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (1.3 g, TFA salt).



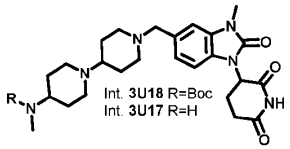
Int. **3E293** (1 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.9 g) were stirred 24h in DMSO/DIPEA (15/2.3 mL). STAB (2.8 g) was added and stirring continued 12h at 0 °C to RT. The OL (water/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **3U8** *tert*-butyl 4-((4-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)-methyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (0.80 g). Int. **3U8** (0.80 g) was stirred 5h in DCM/4M HCl in dioxane (3:2, 10 mL) at 0 °C to RT and concentrated to give Int. **3U7** 3-(3,3-dimethyl-2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)indolin-1-yl)-piperidine-2,6-dione (0.50 g, HCl salt).



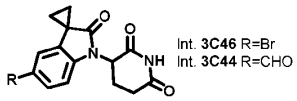
Int. **3U10** (4.5 g), 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (3 g), RuPhos (0.59 g), and RuPhos Pd-G4 (1.1 g) were stirred 2h in toluene/1M LiHMDS in THF (30/63 mL) at 0 °C to 85 °C. The OL (water / EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:1 to 1:4) to give Int. **3U9** *tert*-butyl 4-hydroxy-4-((1-(2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidin-4-yl)-methyl)piperidine-1-carboxylate (1 g).



NaH (1.1 g) and Int. **3U9** (2 g) were stirred 0.5h in THF (50 mL) at 0 °C. 3-Bromopiperidine-2,6-dione (3.0 g) was added portion-wise and stirring continued 5h at 0-75 °C. The OL (water/EtOAc) was dried, concentrated, and washed with pentane/Et_2O (1:1) to give Int. **3U16** *tert*-butyl 4-((1-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-piperidin-4-yl)methyl)-4-hydroxy-piperidine-1-carboxylate (1 g). Int. **3U16** (0.70 g) was stirred 1h in DCM (10 mL) and DAST (0.20 mL) in DCM (5 mL) at -78 °C. The OL (sat. aq. $NaHCO_3$/DCM) was dried and concentrated to give Int. **3U14** and **3U15** *tert*-butyl 4-((1-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)piperidin-4-yl)methyl)-4-fluoro-piperidine-1-carboxylate and *tert*-butyl 4-((1-(1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidin-4-yl)-methyl)-3,6-dihydro-pyridine-1(2H)-carboxylate mixture (0.50 g). Int. **3U14/3U15** mixture (0.60 g) was stirred 3h in DCM/TFA (2:1, 7.5 mL). The mixture was concentrated and washed with Et_2O to give Int. **3U12** and **3U13** 3-(5'-(4-((4-fluoropiperidin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and 3-(2'-oxo-5'-(4-((1,2,3,6-tetrahydropyridin-4-yl)methyl)-piperidin-1-yl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione mixture (0.50 g).

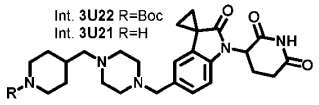


Ints. **3U19/3U67** (0.15 g/0.18 g) and 4Å MS were stirred in DCE (2 mL) ON at RT. $NaCNBH_3$ (41 mg) was added and stirring continued for 3h. The mixture was concentrated and HPLC-purified to give Int. **3U18** *tert*-butyl (1'-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-[1,4'-bipiperidin]-4-yl)(methyl)carbamate (74 mg). Int. **3U18** (74 mg) was stirred 20h in DCM/TFA (10:1, 1.1 mL). The mixture was concentrated to give Int. **3U17** 3-(3-methyl-5-((4-(methylamino)-[1,4'-bipiperidin]-1'-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (70 mg, TFA salt).



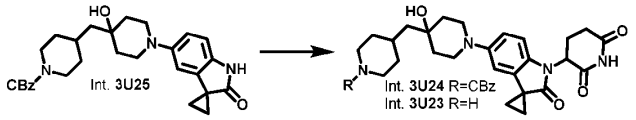
Int. **3C44**. 1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-5'-carbaldehyde

NaH (14.5 g) was added to a solution of 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (9 g) in THF (270 mL) at 0 °C. 3-Bromopiperidine-2,6-dione (36 g) was added and the mixture stirred 6h at 60 °C. The OL (water/EtOAc) was concentrated and triturated in PE/MTBE (1:1) to give Int. **3C46** 3-(5'-bromo-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (8 g). Et_3N (7.5 mL), $Pd(OAc)_2$ (0.48 g) and *tert*-butyl acrylate (32 mL) were added to a solution of Int. **3C46** (7.5 g) and P(*o*-tol)$_3$ (2.0 g) in DMF (70 mL) and stirred 16h at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated and washed with PE to give Int. **3C45** *tert*-butyl (E)-3-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)acrylate (5 g). OsO_4 (64 mg), $NaIO_4$ (8.1 g), and Int. **3C45** (5.0 g) were stirred 2h in THF/H_2O (1:1, 100 mL). The mixture was diluted with sat. aq. $Na_2S_2O_3{\cdot}5H_2O$ to precipitate Int. **3C44** 1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-5'-carbaldehyde (3.0 g).

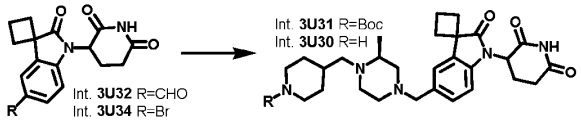


Int. **3C44** (8 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (12 g) were stirred 24h in DMSO (50 mL) and DIPEA (9.8 mL). STAB (15 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **3U22** *tert*-butyl 4-((4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (2.3 g). Int. **3U22** (0.50 g) was stirred 5h in DCM/TFA (5:1, 6 mL) at 0 °C to RT. The mixture was concentrated and triturated in

Et_2O to give Int. **3U21** 3-(2'-oxo-5'-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.30 g, TFA salt).

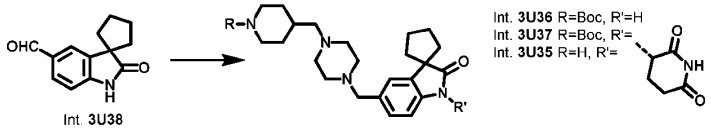


RuPhos (1.8 g), RuPhos Pd-G4 (1.6 g), Int. **3U26** (7.7 g), and 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (4.6 g) were stirred 5h in toluene/THF (1:1, 200 mL) and 1M LiHMDs in THF (97 mL) at 0-80 °C under an inert atmosphere. The OL (water/EtOAc) was dried, and concentrated to give Int. **3U25** benzyl 4-((4-hydroxy-1-(2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidin-4-yl)methyl)piperidine-1-carboxylate (3 g). NaH (1.5 g) was added to a solution of Int. **3U25** (1.5 g) in THF (150 mL) and stirred for 0.5h at 0 °C. 3-Bromopiperidine-2,6-dione (4.1 g) was added and stirring continued for 2h at 75 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and washed with Et_2O/pentane (1:1) to give Int. **3U24** (0.60 g). $AlCl_3$ (68 mg) and Int. **3U24** benzyl 4-((1-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)-4-hydroxypiperidin-4-yl)methyl)piperidine-1-carboxylate (0.10 g) were stirred 16h in HFP (5 mL) under an inert atmosphere. The mixture was concentrated and washed with Et_2O to give Int. **3U23** 3-(5'-(4-hydroxy-4-(piperidin-4-ylmethyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.15 g).

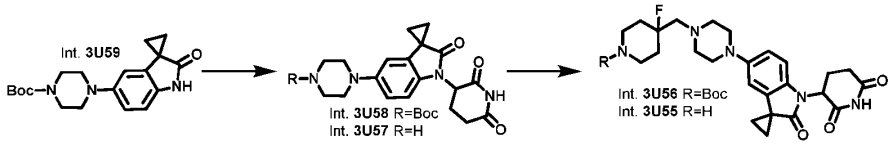


NaH (48 g) was added portion-wise to a solution of 5'-bromospiro[cyclobutane-1,3'-indolin]-2'-one (30 g) in THF (500 mL) at 0 °C and stirred for 30 min. 3-Bromopiperidine-2,6-dione (30 g) was added and stirring continued 16h at 0 °C to 65 °C. The OL (aq. NH_4Cl/EtOAc) was dried, concentrated, and triturated in Et_2O to give Int. **3U34** 3-(5'-bromo-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione (25 g). $Pd(OAc)_2$ (0.82 g), P(*o*-tol)$_3$ (4.4 g), and Int. **3U34** (22 g) were stirred 16h in DMF/Et_3N (25:3, 280 mL) and *tert*-butyl acrylate (27 mL) at 110 °C under an inert atmosphere and filtered. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:1) to give Int. **3U33** *tert*-butyl (E)-3-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclobutane-1,3'-indolin]-5'-yl)acrylate (13 g). $NaIO_4$ (16 g) and OsO_4 (0.74 g) were added to a solution of Int. **3U33** (12 g) in THF/H_2O (4:3, 140 mL). The mixture was stirred 16h. The OL (sat. aq. $Na_2S_2O_3$ / EtOAc) was dried, concentrated, and triturated in Et_2O to give Int. **3U32** 1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclobutane-1,3'-indoline]-5'-carbaldehyde (7.0 g). Ints. **3E74/3U32** (6.9 g/4.0 g) were stirred 16h in DIPEA (14 mL) and DMSO (50 mL). STAB (11 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 24:1) to give Int. **3U31** *tert*-butyl 4-(((2S)-4-((1'-(2,6-dioxopiperidin-3-yl)-2'-

oxospiro[cyclobutane-1,3'-indolin]-5'-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (4.5 g). Int. **3U31** (4.5 g) was stirred 6h in DCM/4M HCl in dioxane (5:2, 70 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U30** 3-(5'-(((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione (3.5 g, HCl salt).

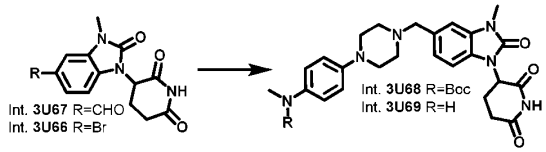


$PdDPPFCl_2$-DCM (1.5 g) and 5'-bromospiro[cyclopentane-1,3'-indolin]-2'-one (5 g) were stirred 16h in DMF/Et_3N (19:2, 55 mL) and Et_3SiH (9 mL) at 130 °C under 440 psi of CO. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/MTBE 3:2 to 1:2) to give Int. **3U38** 2'-oxospiro-[cyclopentane-1,3'-indoline]-5'-carbaldehyde (2.8 g). *tert*-Butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.4 g) and Int. **3U38** (1 g) were stirred 0.3h in DCM/AcOH (56:1, 30.5 mL). STAB (3.0 g) was added and stirring continued for 11h. The OL (sat. aq. $NaHCO_3$/EtOAc) was concentrated and purified by FC (MTBE/MeOH 1:0 to 19:1) to give Int. **3U37** *tert*-butyl 4-((4-((2'-oxospiro-[cyclopentane-1,3'-indolin]-5'-yl)methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (2 g). NaH (1.0 g) was added to a solution of Int. **3U37** (2 g) in THF (50 mL) and stirred for 20 min at RT. 3-Bromopiperidine-2,6-dione (4.0 g) was added and stirring continued for 14h at 60 °C. The OL (aq. NH_4Cl/EtOAc) was concentrated and purified by FC (MTBE/MeOH) to give Int. **3U36** *tert*-butyl 4-((4-((1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro[cyclopentane-1,3'-indolin]-5'-yl)methyl)-piperazin-1-yl)-methyl)piperidine-1-carboxylate (1 g). Int. **3U36** (0.5 g) was stirred 14h in MeOH/4M HCl in dioxane (1:2, 30 mL). The mixture was concentrated to give Int. **3U35** 3-(2'-oxo-5'-((4-(piperidin-4-yl-methyl)-piperazin-1-yl)methyl)spiro[cyclopentane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.6 g, HCl salt).

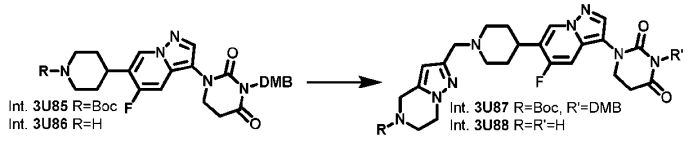


RuPhos (0.59 g), RuPhos Pd-G4 (0.54 g), and *tert*-butyl piperazine-1-carboxylate (1.4 g), 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (1.5 g) were stirred 16h in toluene (20 mL) and 1M LiHMDs in THF (25 mL) at 110 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC (hexane/EtOAc 3:7) to give Int. **3U59** *tert*-butyl 4-(2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)piperazine-1-carboxylate (1.2 g). NaH (1.7 g) and 3-bromo-piperidine-2,6-dione (4.7 g) were added to a mixture of Int. **3U59** (1.2 g) in DMF (20 mL) and stirred for 16h at 70 °C. The OL (water/EtOAc) was dried, concentrated, and triturated in Et_2O to give Int. **3U58** *tert*-butyl 4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-5'-yl)-

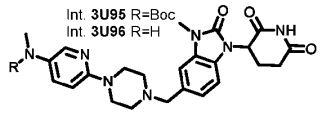
piperazine-1-carboxylate (1 g). Int. **3U58** (1 g) was stirred 16h in DCM/TFA (2:1, 15 mL) at 0 °C to RT. The mixture was concentrated and triturated in Et_2O to give Int. **3U57** 3-(2'-oxo-5'-(piperazin-1-yl)-spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.90 g, TFA salt). Int. **3U57** (1.2 g) and *tert*-butyl 4-fluoro-4-formylpiperidine-1-carboxylate (0.60 g) in were stirred 16h in DMSO (10 mL) and DIPEA (2.2 mL) 0°C to RT. STAB (2.1 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 19:1) to give Int. **3U56** *tert*-butyl 4-((4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-piperazin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate (0.60 g). Int. **3U56** (0.8 g) was stirred 16h in DCM/TFA (20:1, 10.5 mL) at 0 °C to RT. The mixture was concentrated and triturated in Et_2O to give Int. **3U55** 3-(5'-(4-((4-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.75 g, TFA salt).



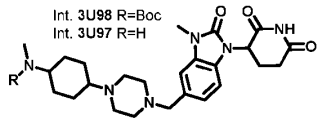
$Pd(OAc)_2$ (1.7 g), Int. **3B3** (25 g), and $P(o\text{-tol})_3$ (4.5 g) were stirred 16h in DMF/Et_3N (7:3, 172 mL) and *tert*-butyl acrylate (54 mL) at 110 °C under an inert atmosphere. The mixture was filtered. The OL (water/EtOAc) was concentrated, and triturated in pentane to give *tert*-butyl (E)-3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acrylate (17 g). $NaIO_4$ (56 g) and OsO_4 (2.2 g) and were added to a solution of Int. *tert*-butyl (E)-3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)acrylate (34 g) in THF/H_2O (1:1, 100 mL) and stirred for 2h at RT. The mixture diluted with sat. aq. $Na_2S_2O_3{\cdot}5H_2O$ and stirred for 1h to precipitate a solid that was washed with Et_2O to give Int. **3U67** 1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (14 g). Ints. **3E266/3U67** (3.4 g/2.0 g) were stirred 24h in DMSO/DIPEA (10:3, 26 mL). STAB (5.9 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 19:1 to 10:1) to give Int. **3U68** *tert*-butyl (4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)(methyl)carbamate (1 g). Int. **3U68** (1.2 g) was stirred 5h in DCM/4M HCl in dioxane (3:2, 25 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U69** 3-(3-methyl-5-((4-(4-(methylamino)phenyl)-piperidin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (1.0 g, HCl salt).



Int. **3U84**, (125 mg), CuI (43 mg), 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (89 mg), and Cs_2CO_3 (274 mg) were stirred ON in dioxane (4 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (71 µL) at 90 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and HPLC-purified to give Int. **3U85** *tert*-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoropyrazolo[1,5-a]pyridin-6-yl)piperidine-1-carboxylate (162 mg). Int. **3U85** (162 mg) was stirred 2h in HFP/HCl 10M (100:1, 3.03 mL). The mixture was concentrated to give Int. **3U86** 3-(2,4-dimethoxybenzyl)-1-(5-fluoro-6-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (150 mg, HCl salt). Ints. **2Q11/3U86** (87 mg/150 mg), Et_3N (81 µL) and crushed 4Å MS were stirred ON in DCE (5 mL). STAB (250 mg) was added and stirring continued for 3h. The mixture was filtered and concentrated. The OL (water/DCM) was dried, and concentrated to give Int. **3U87** *tert*-butyl 2-((4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-5-fluoropyrazolo[1,5-a]pyridin-6-yl)piperidin-1-yl)methyl)-6,7-di-hydro-pyrazolo-[1,5-a]pyrazine-5(4H)-carboxylate (208 mg). Int. **3U87** (208 mg) was stirred 3 days in TFA (5 mL) at 70 °C and concentrated to give Int. **3U88** 1-(5-fluoro-6-(1-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperidin-4-yl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.13g, TFA salt).

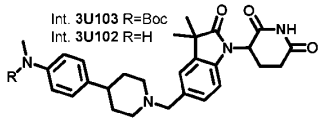


Ints. **3U94/3U67** (4.0 g/3.0 g) were stirred 24h in DMSO/DIPEA (9:1, 56 mL). STAB (8.9 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 19:1 to 9:1) to give Int. **3U95** *tert*-butyl (6-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-methyl)piperazin-1-yl)pyridin-3-yl)(methyl)carbamate (1.5 g). Int. **3U95** (0.50 g) was stirred 5h in DCM/4M HCl in dioxane (1:1, 10 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O/EtOAc to give Int. **3U96** 3-(3-methyl-5-((4-(5-(methylamino)pyridin-2-yl)-piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.43 g, HCl salt).

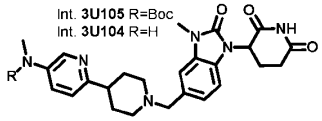


Ints. **3U99/3U67** (0.10 g/0.12 g) and 4Å MS were stirred ON in DCE (2 mL). $NaCNBH_3$ (31 mg) was added and stirring continued 3h. The mixture was filtered, concentrated, and HPLC-purified to give Int. **3U98** *tert*-butyl (4-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)-piperazin-1-yl)cyclohexyl)(methyl)carbamate (22 mg). Int. **3U98** (22 mg) was stirred 20h in DCM/TFA (29:1, 1.03 mL). The mixture was concentrated to give Int. **3U97** 3-

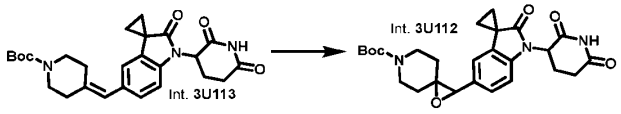
(3-methyl-5-((4-(4-(methylamino)cyclohexyl)-piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (17 mg, TFA salt).



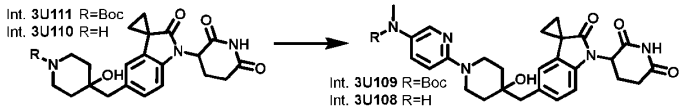
Ints. **3E266/3E293** (2.3 g/2.0 g) were stirred 24h in DMSO/DIPEA (9:1, 44 mL). STAB (5.6 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 14:1) to give Int. **3U103** *tert*-butyl (4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)(methyl)-carbamate (1.8 g). Int. **3U103** (0.90 g) was stirred 16h in DCM/4M HCl in dioxane (2:1, 15 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U102** 3-(3,3-dimethyl-5-((4-(4-(methylamino)-phenyl)piperidin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione (0.75 g, HCl salt).



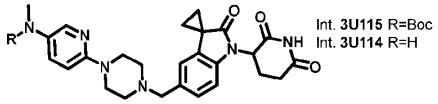
Ints. **3U106/3U67** (1.7 g/1.3 g) were stirred 16h in DMSO/DIPEA (13:3, 12.3 mL) at 0 °C to RT. STAB (1.8 g) and DCE (10 mL) were added and stirring was continued 16h at 0-60 °C under an inert atmosphere. The OL (aq. NH_4Cl/EtOAc) was dried, and concentrated to give Int. **3U105** *tert*-butyl (6-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)-methyl)-piperidin-4-yl)pyridin-3-yl)(methyl)-carbamate (1.2 g). Int. **3U105** (0.20 g) was dissolved in DCM/4M HCl in dioxane (3:2, 5 mL) at 0 °C and stirred for 16h at RT, concentrated and washed with Et_2O to give Int. **3U104** 3-(3-methyl-5-((4-(5-(methyl-amino)pyridin-2-yl)piperidin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.14 g, HCl salt).



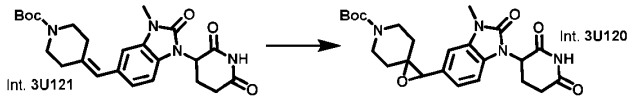
CsF (0.65 g), Int. **3C46** (0.50 g) and *tert*-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-methylene)piperidine-1-carboxylate (0.56 g), and $PdDPPFCl_2$-DCM (0.12 g) were stirred 16h in DMF (5 mL) at 100 °C under an inert atmosphere. The OL (water/EtOAc) was dried, concentrated, and purified by FC (PE/EtOAc 1:4 to 1:9) to give Int. **3U113** *tert*-butyl 4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methylene)piperidine-1-carboxylate (0.18 g). m-CPBA (0.12 g) was added to a solution of Int. **3U113** (0.30 g) in DCM (20 mL) at 0 °C and stirred for 2h at RT. The OL (aq. $NaHCO_3$/DCM) was dried, concentrated and purified by FC (hexane/EtOAc 2:3) to give Int. **3U112** *tert*-butyl 2-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.20 g).



Int. **3U112** (0.20 g) and Pd/C 10% (50 mg) were hydrogenated 16h in MeOH (10 mL). The mixture was filtered and concentrated to give Int. **3U111** *tert*-butyl 4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)-4-hydroxypiperidine-1-carboxylate (0.12 g). Int. **3U111** (0.10 g) was stirred 2h in DCM/TFA (25:1, 10.4 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U110** 3-(5'-((4-hydroxypiperidin-4-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.12 g, TFA salt). Ints. **1Y4/3U110** (40 mg/80 mg), Pd-PEPPSI-IHept-Cl (14 mg), and Cs_2CO_3 (0.18 g) were stirred 1h dioxane (1 mL) at 120 °C under an inert atmosphere. The mixture was concentrated and purified by FC (DCM/MeOH 19:1) to give Int. **3U109** *tert*-butyl (6-(4-((1'-(2,6-dioxo-piperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)(methyl)carbamate (80 mg). Int. **3U109** (70 mg) was stirred 2h in DCM/TFA (10:1, 3.3 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U108** 3-(5'-((4-hydroxy-1-(5-(methyl-amino)pyridin-2-yl)piperidin-4-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (80 mg, TFA salt).

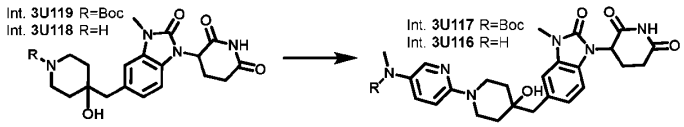


Ints. **3U94/3C44** (3.7 g/2.9 g) were stirred 24h in DMSO/DIPEA (7:1, 40 mL). STAB (8.2 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/DCM/MeOH) was dried, concentrated, and purified by FC (DCM/MeOH 19:1 to 10:1) to give Int. **3U115** *tert*-butyl (6-(4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)piperazin-1-yl)pyridin-3-yl)(methyl)-carbamate (0.60 g). Int. **3U115** (0.30 g) was stirred 2h in DCM/TFA (3:2, 5 mL) at 0 °C to RT. The mixture was concentrated and washed with Et_2O to give Int. **3U114** 3-(5'-((4-(5-(methylamino)-pyridin-2-yl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (1.8 g, TFA salt).

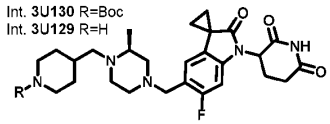


Int. **3U121** *tert*-butyl 4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methylene)piperidine-1-carboxylate (2.8 g) was prepared similarly to Int. **3U113** from of Int. **3B3** (5 g) and *tert*-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (5.7 g) and purified by FC (PE/EtOAc 1:1 to 2:3). m-CPBA (0.31 g) and Int. **3U121** (0.60 g) were stirred 1h in DCM (10 mL) at 0 °C to RT. The OL (aq. $NaHCO_3$/DCM) was dried and concentrated. The residue was combined with a batch prepared

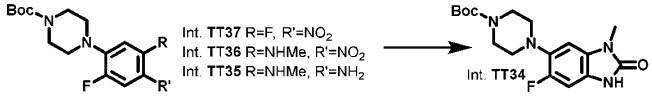
similarly from Int. **3U121** (0.20 g) and purified by FC (PE/EtOAc 1:0 to 0:1) to give Int. **3U120** *tert*-butyl 2-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.50 g).



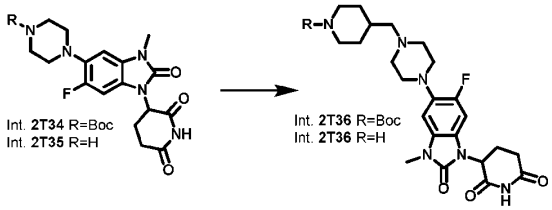
Int. **3U120** (0.50 g) and Pd/C 10% wet (0.12 g) were hydrogenated 20h at 50 psi in EtOAc (10 mL). The mixture was filtered, concentrated, and purified by FC (PE/EtOAc 1:0 to 0:1) to give Int. **3U119** *tert*-butyl 4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-methyl)-4-hydroxy-piperidine-1-carboxylate (0.26 g). Int. **3U119** (0.25 g) was stirred 5h in DCM/4M HCl in dioxane (5:1, 6 mL) at 0 °C to RT. The residue after concentration washed with Et_2O to give Int. **3U118** 3-(5-((4-hydroxy-piperidin-4-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.18 g, HCl salt). Ints. **1Y4/3U118** (0.20 g/0.34 g), Cs_2CO_3 (0.68 g), and Pd-PEPPSI-IHept-Cl (68 mg) were stirred 1h in dioxane (3 mL) at 110 °C under an inert atmosphere of argon. The mixture was filtered. The OL (water / EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 9:1) to give Int. **3U117** *tert*-butyl (6-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-4-hydroxy-piperidin-1-yl)pyridin-3-yl)(methyl)-carbamate (0.27 g). Int. **3U117** (0.30 g) was stirred 5h in DCM/4M HCl in dioxane (5:2, 7 mL) at 0 °C to RT. The residue after concentration was washed with Et_2O to give Int. **3U116** 3-(5-((4-hydroxy-1-(5-(methylamino)pyridin-2-yl)piperidin-4-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (0.24 g, HCl salt).



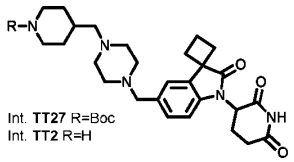
Ints. **3E74/3C6** (1.5 g/4.0 g) were stirred 24h in DMSO/DIPEA (5:2, 28.3 mL). STAB (7.1 g) was added and stirring continued 16h at 0 °C to RT. The OL (water/EtOAc) was dried, concentrated, and purified by FC (DCM/MeOH 1:0 to 19:1) to give Int. **3U130** *tert*-butyl 4-(((2S)-4-((1'-(2,6-dioxopiperidin-3-yl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (0.80 g). Int. **3U130** (1.0 g) was stirred 1h in DCM/4M HCl in dioxane (3:1, 13 mL) at 0 °C to RT. The residue after concentration was washed with Et_2O to give Int. **3U129** 3-(6'-fluoro-5'-(((S)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.80 g, HCl salt).



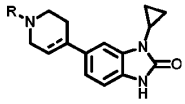
1,2,4-Trifluoro-5-nitrobenzene (19 g) and K_2CO_3 (15 g) was stirred in DMF (100 mL) for 15 min. *tert*-Butyl piperazine-1-carboxylate (20 g) in THF (25 mL) was added at 0 °C and stirred for 4h at RT and concentrated. The OL (water/EtOAc) was dried, filtered, concentrated, and purified by FC (PE/EtOAc 9:1) to give Int. **2T30** *tert*-butyl 4-(2,5-difluoro-4-nitrophenyl)piperazine-1-carboxylate (30 g). 2M Methylamine in THF (219 mL) was added to a mixture of Int. **2T30** (30 g) in THF (300 mL) and stirred for 4h. The OL (water/EtOAc) was dried, filtered, concentrated and purified by FC (PE/EtOAc 9:1) to give Int. **2T31** tert-butyl 4-(2-fluoro-5-(methylamino)-4-nitrophenyl)piperazine-1-carboxylate (26 g). Int. **2T31** (10 g) was hydrogenated for 16h at 100 °C using 10% Pd/C (5 g) in MeOH (150 mL), filtered and concentrated to give Int. **2T32** *tert*-butyl 4-(4-amino-2-fluoro-5-(methylamino)phenyl)piperazine-1-carboxylate (7.0 g). Int. **2T32** (8 g) and CDI (6 g) were stirred in ACN (50 mL) for 12h at 80 °C. The OL (water/EtOAc) was dried, filtered, concentrated and purified by FC (PE/EtOAc 3:17) to give Int. **2T34** *tert*-butyl 4-(6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazine-1-carboxylate (5.0 g).



Int. **2T34** *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazine-1-carboxylate (2.3 g) was prepared similarly to Int. **3U36** from Int. **2T33** (5.0 g) and 3-bromopiperidine-2,6-dione (14 g). Int. **2T35** 3-(6-fluoro-3-methyl-2-oxo-5-(piperazin-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (1.6 g, HCl salt) was prepared similarly to Int. **2T39** from Int. **2T34** (2.0 g). Int. **2T35** (2. 0 g) and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.90 g) were stirred in DCE/DIPEA (7:2, 19.4 mL) for 16h under an inert atmosphere. STAB (3.6 g) was added at 0 °C and stirring continued for 4h. The OL (water/DCM) was dried, filtered, concentrated and purified by FC (PE/EtOAc 3:2) to give Int. **2T36** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.3 g). Int. **2T37** 3-(6-fluoro-3-methyl-2-oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.80 g, HCl salt) was prepared similarly to Int. **2T39** from Int. **2T36** (1.2 g).

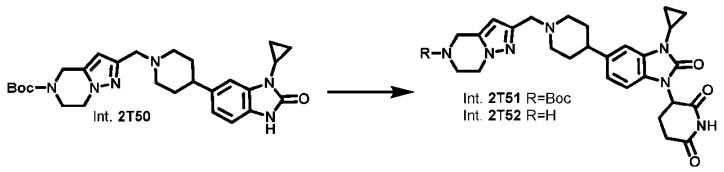


Int. **2T38** *tert*-butyl 4-((4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclobutane-1,3'-indolin]-5'-yl)-methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.12 g) was prepared similarly to Int. **3U31** from Int. **3U32** (0.20 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (0.36 g). Int. **2T38** (0.12 g) was mixed in DCM/4M HCl in dioxane (1:2, 15 mL) at 0 °C and stirred for 6h at RT. The mixture was concentrated and washed with Et_2O to give Int. **2T39** 3-(2'-oxo-5'-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)spiro[cyclobutane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.10 g, HCl salt).



Int. **2T47** R=Boc, double bond
Int. **2T48** R=Boc, single bond
Int. **2T49** R=H, single bond

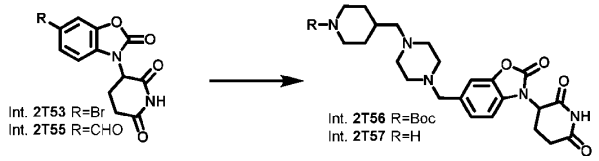
6-Bromo-1-cyclopropyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (7 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (9 g), K_2CO_3 (15 g) and $PdDPPFCl_2$-DCM (2 g) were stirred in dioxane/H_2O (4:1, 200 mL) for 12h at 80 °C under an inert atmosphere. The mixture was filtered and concentrated to give Int. **2T47** *tert*-butyl 4-(3-cyclopropyl-2-oxoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.2 g). Int. **2T47** (1.2 g) was hydrogenated for 12h using Pd/C (0.5 g) in MeOH (50 mL), filtered and concentrated to give Int. **2T48** *tert*-butyl 4-(3-cyclopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-piperidine-1-carboxylate (1.2 g). Int. **2T48** (1.2 g) was stirred ON in MeOH/2.8M HCl in dioxane (5:1, 60 mL) and concentrated to give Int. **2T49** 1-cyclopropyl-6-(piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (0.5 g).



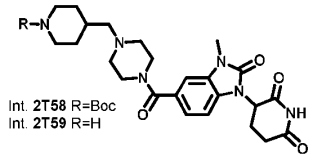
Int. **2T50**

Int. **2T51** R=Boc
Int. **2T52** R=H

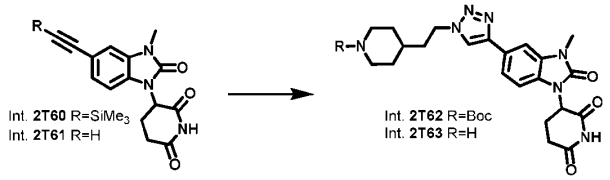
Ints. **2Q11/2T49** (0.4 g/0.5 g) and STAB (0.9 g) were stirred in DCE/DIPEA (74:1, 50.7 mL) for 48h under an inert atmosphere. The OL (water/DCE) was concentrated to give Int. **2T50** *tert*-butyl 2-((4-(3-cyclopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-1-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.4 g). Int. **2T51** *tert*-butyl 2-((4-(3-cyclopropyl-1-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-1-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.21 g) was prepared similarly to Int. **YY45** from Int. **2T50** (0.4 g) and 3-bromopiperidine-2,6-dione (0.5 g). Int. **2T51** (0.21 g) was stirred ON in MeOH/2.8M HCl in dioxane (4:1, 25 mL), concentrated and crystallized from ? to give Int. **2T52** 3-(3-cyclopropyl-2-oxo-5-(1-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.12 g, HCl salt).



Int. **2T53** 3-(6-bromo-2-oxobenzo[d]oxazol-3(2H)-yl)piperidine-2,6-dione (10 g) was prepared similarly to Int. **3U36** from 6-bromobenzo[d]oxazol-2(3H)-one (15 g) and 3-bromopiperidine-2,6-dione (135 g). *tert*-Butyl (E)-3-(3-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)acrylate (7 g) was prepared similarly to Int. **3U33** from Int. **2T53** (10 g) and *tert*-butyl acrylate (22 mL). Int. **2T55** 3-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carbaldehyde (2.5 g) was prepared similarly to Int. **3U32** from Int. **2T54** (7 g). Int. **2T54** *tert*-butyl 4-((4-((3-(2,6-dioxo-piperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)methyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (2 g) was prepared similarly to Int. **3U31** from Int. **2T55** (2.5 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (5.2 g). Int. **2T56** (0.60 g) was stirred in DCM / TFA (5:1, 12 mL) for 16h. The mixture was concentrated, triturated in Et_2O to give Int. **2T57** 3-(2-oxo-6-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)benzo[d]oxazol-3(2H)-yl)piperidine-2,6-dione (0.55 g, TFA salt).

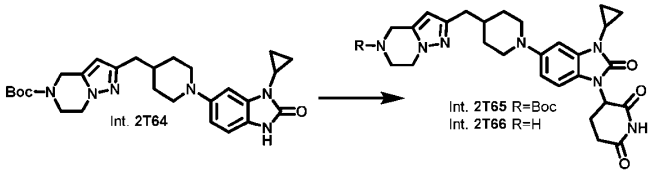


Int. **3B3** (2 g), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (2.5 g) and $PdDPPFCl_2$-DCM (0.48 g) in dioxane/Et_3N (12:1, 32.5 mL) and stirred for 16h at 100 °C under 200 psi of CO. The mixture was filtered, concentrated and purified by FC (DCM/MeOH 9:1) to give Int. **2T58** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbonyl)-piperazin-1-yl)methyl)piperidine-1-carboxylate (0.90 g). Int. **2T59** 3-(3-methyl-2-oxo-5-(4-(piperidin-4-ylmethyl)piperazine-1-carbonyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.35, HCl salt) was prepared similarly to Int. **2T39** from Int. **2T58** (0.50 g).

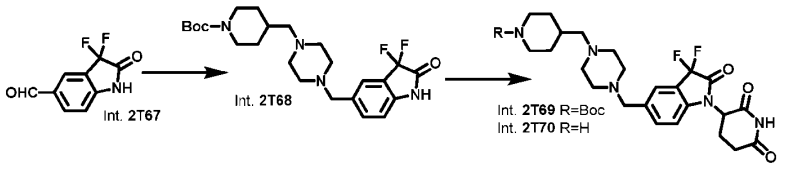


Int. **3B3** (2 g), ethynyltrimethylsilane (1.6 mL), $Pd(PPh_3)_2Cl_2$ (0.41 g), CuI (0.34 g) and Et_3N (2.1 mL) were stirred in DMF (15 mL) for 2h at 80 °C under an inert atmosphere under MW conditions. The OL (water / EtOAc) was dried, filtered, concentrated, and purified by FC (PE/EtOAc

1:0 to 1:1) to give Int. **2T60** 3-(3-methyl-2-oxo-5-((trimethylsilyl)ethynyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.80 g). CsF (0.68 g) was added to a solution of Int. **2T60** (0.80 g) in DMSO (8 mL) at 0 °C and stirred for 6h. The OL (water/EtOAc) was dried, filtered and concentrated to give Int. **2T61** 3-(5-ethynyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.60 g). Sodium ascorbate (1.7 g) was added to a mixture of Int. **2T61** (0.80 g), *tert*-butyl 4-(2-azidoethyl)piperidine-1-carboxylate (0.86 g) and $CuSO_4$·H2O (0.90 g) in ^{t}BuOH/H_2O (5:4, 18 mL), stirred for 4h and filtered. The OL (water/EtOAc) was concentrated to give Int. **2T62** *tert*-butyl 4-(2-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)-1H-1,2,3-triazol-1-yl)ethyl)piperidine-1-carboxylate (0.60 g). Int. **2T63** 3-(3-methyl-2-oxo-5-(1-(2-(piperidin-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.40 g, HCl salt) was prepared similarly to Int. **2T39** from Int. **2T62** (0.60 g).

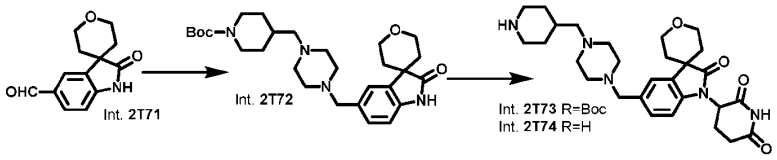


tert-Butyl 2-(piperidin-4-ylmethyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.6 g), 6-bromo-1-cyclopropyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (0.5 g), RuPhos (90 mg) and 1.1M LiHMDS in THF (6 mL) were stirred in toluene (50 mL) at 110 °C under an inert atmosphere. RuPhos Pd-G2 (10 mg) was added and stirring continued for 14h at 100 °C. The mixture was filtered, concentrated and purified by FC ($CHCl_3$/ACN 1:0 to 3:7) to give Int. **2T64** *tert*-butyl 2-((1-(3-cyclopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-piperidin-4-yl)methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.1 g). Int. **2T65** *tert*-butyl 2-((1-(3-cyclopropyl-1-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-4-yl)-methyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.15 g) was prepared similarly to Int. **3U36** from Int. **2T64** (0.1 g) and 3-bromopiperidine-2,6-dione (0.2 g). Int. **2T65** (0.15 g) was stirred in DCM/TFA (165:1, 20.1 mL) for 14h, concentrated and HPLC-purified to give Int. **2T66** 3-(3-cyclopropyl-2-oxo-5-(4-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperidin-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (25 mg, TFA salt).

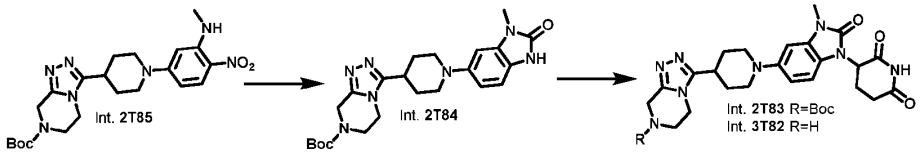


5-bromo-3,3-difluoroindolin-2-one (6 g), Et_3SiH (12 mL) and $PdDPPFCl_2$-DCM (2.0 g) in DMF/Et_3N (16:1, 85 mL) and stirred for 16h at 130 °C under 440 psi of CO. The OL (water/EtOAc) was dried, filtered, concentrated and purified by FC ($CHCl_3$/ACN 1:0 to 6:1) to give Int. **2T67** 3,3-difluoro-2-oxoindoline-5-carbaldehyde (2.2 g). Int. **2T68** *tert*-butyl 4-((4-((3,3-difluoro-2-oxoindolin-

5-yl)-methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.1 g) was prepared similarly to Int. **3U37** from Int. **2T67** (1 g) and tert-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.5 g). Int. **2T69** *tert*-butyl 4-((4-((1-(2,6-dioxo-piperidin-3-yl)-3,3-difluoro-2-oxoindolin-5-yl)methyl)piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.2 g) was prepared similarly to Int. **3U36** from Int. **2T68** (0.7 g) and 3-bromopiperidine-2,6-dione (1 g). Int. **2T69** (0.2 g) was stirred in DCM/4M HCl in dioxane (2:1, 60 mL) for 14h and concentrated to give Int. **2T70** 3-(3,3-difluoro-2-oxo-5-((4-(piperidin-4-ylmethyl)-piperazin-1-yl)methyl)indolin-1-yl)piperidine-2,6-dione (0.28 g, HCl salt).

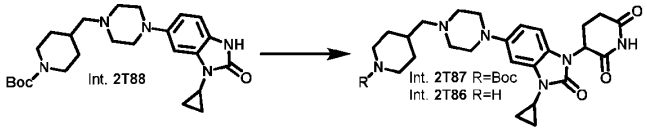


5-Bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (5 g), Et_3SiH (5 mL) and $PdDPPFCl_2$-DCM (1 g) in DMA/Et_3N (10:1, 55 mL) and stirred for 12h at 130 °C under 294 psi of CO. The OL (water/EtOAc) was dried, filtered, concentrated and HPLC-purified to give Int. **2T71** 2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-5-carbaldehyde (2.8 g). Int. **2T71** (2.8 g), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (3.4 g) and STAB (10 g) were stirred in DCE (50 mL) for 48h. The OL (water/DCE) was concentrated to give Int. **2T72** *tert*-butyl 4-((4-((2-oxo-2',3',5',6'-tetrahydro-spiro[indoline-3,4'-pyran]-5-yl)-methyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.6 g). Int. **2T73** *tert*-butyl 4-((4-((1-(2,6-dioxo-piperidin-3-yl)-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-5-yl)methyl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (0.7 g) was prepared similarly to Int. **3U36** from Int. **2T72** (1.6 g) and 3-bromo-piperidine-2,6-dione (2.2 g). Int. **2T73** (0.45 g) was stirred in MeOH/4M HCl in dioxane (4:1, 25 mL) ON, concentrated and precipitated from EtOH to give Int. **2T74** 3-(2-oxo-5-((4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-yl)piperidine-2,6-dione (0.2, HCl salt).

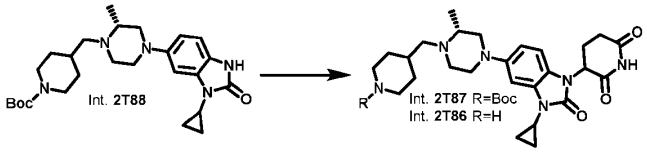


5-Fluoro-N-methyl-2-nitroaniline (0.6 g), *tert*-butyl 3-(piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (1 g), and K_2CO_3 (0.5 g) were stirred 8h in DMSO (50 mL) at 80 °C. The mixture was filtered and concentrated to give Int. **2T85** *tert*-butyl 3-(1-(3-(methylamino)-4-nitro-phenyl)piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.6 g), which was mixed with CDI (2 g) and Pd/C and hydrogenated for 12h in EtOAc (40 mL). The mixture was filtered and concentrated to give Int. **2T84** *tert*-butyl 3-(1-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-

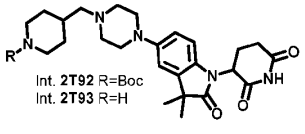
7(8H)-carboxylate (0.2 g). Int. **2T83** *tert*-butyl 3-(1-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]-pyrazine-7(8H)-carboxylate (0.15 g) was prepared similarly to Int. **3U36** from Int. **2T84** (0.2 g) and 3-bromo-piperidine-2,6-dione (0.4 g). Int. **2T83** (0.15 g) was stirred in DCM/TFA (175:1, 20.1 mL) for 14h. The mixture was concentrated and HPLC-purified to give Int. **2T82** 3-(3-methyl-2-oxo-5-(4-(5,6,7,8-tetrahydro-[1,2,4]-triazolo[4,3-a]pyrazin-3-yl)piperidin-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (25 mg).



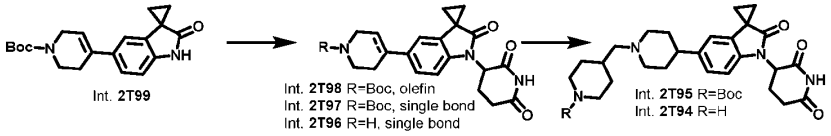
Int. **2T88** *tert*-butyl 4-((4-(3-cyclopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (2 g) was prepared similarly to Int. **3U9** from 6-bromo-1-cyclo-propyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (5.3 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)-piperidine-1-carboxylate (5 g). Int. **2T87** *tert*-butyl 4-((4-(3-cyclopropyl-1-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (2.1 g) was prepared similarly to Int. **3U36** from Int. **2T88** (2 g) and 3-bromopiperidine-2,6-dione (5.9 g). Int. **2T87** (2.1 g) was stirred in ACN/TFA (3:1, 20 mL) for 16h. The mixture was concentrated to give Int. **2T86** 3-(3-cyclopropyl-2-oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione (1.4 g, TFA salt).



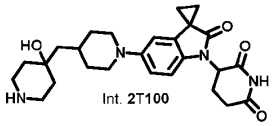
Int. **2T91** *tert*-butyl (R)-4-((2-methyl-4-(2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (2.5 g) was prepared similarly to Int. **3U9** from Int. **2F12** (4.5 g) and 5'-bromospiro-[cyclopropane-1,3'-indolin]-2'-one (3 g). Int. **2T90** *tert*-butyl 4-(((2R)-4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-2-methylpiperazin-1-yl)methyl)-piperidine-1-carboxylate (0.50 g) was prepared similarly to Int. **YY45** from Int. **2T91** (1 g) and 3-bromopiperidine-2,6-dione (3.0 g). Int. **2T90** (0.55 g) was stirred in DCM/TFA (15:2, 17 mL) for 12h. The mixture was concentrated and triturated in Et_2O/EtOAc (1:1) to give Int. **2T89** 3-(5'-((R)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione (0.65 g, TFA salt).



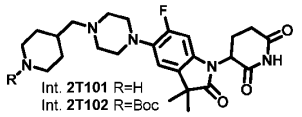
Int. **2T92** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)piperazin-1-yl)methyl)-piperidine-1-carboxylate (0.70 g) was prepared similarly to Int. **3U9** from Int. **3E295** (1.0 g) and tert-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.2 g) by stirring for 2h at 120 °C. Int. **2T92** (0.70 g) was stirred 16h in DCM/4M HCl in dioxane (5:1, 24 mL) at 10 °C to RT. The mixture was concentrated and triturated in ACN and Et_2O to give Int. **2T93** 3-(3,3-dimethyl-2-oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)indolin-1-yl)piperidine-2,6-dione (0.6 g, HCl salt).



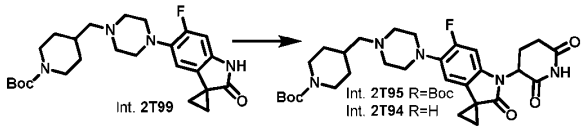
Int. **2T99** *tert*-butyl 4-(2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.75 g) was prepared similarly to Int. **3U37** from Int. 5'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (1.0 g), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (1.7 g) and $NaHCO_3$ (1.1 g). Int. **2T98** *tert*-butyl 4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.3 g) was prepared similarly to Int. **3U36** from Int. **TT100** (2.3 g) and 3-bromopiperidine-2,6-dione (6.5 g). Int. **2T98** (2.3 g) was hydrogenated for 16h using 10% wet Pd/C (1.0 g) in THF/EtOAc (1:1, 20 mL), filtered, concentrated and triturated in Et_2O to give Int. **2T97** *tert*-butyl 4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidine-1-carboxylate (2.0 g). Int. **2T97** (2.0 g) was mixed in DCM/4M HCl in dioxane (15:1, 32 mL) at 0 °C and stirred for 16h at RT. The mixture was concentrated and triturated in ACN and Et_2O to give Int. **2T96** 3-(2'-oxo-5'-(piperidin-4-yl)spiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (2.0 g, TFA salt). Int. **2T95** *tert*-butyl 4-((4-(1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperidin-1-yl)methyl)-piperidine-1-carboxylate (0.90 g) was prepared similarly to Int. **2T36** from Int. **2T96** (2.0 g) and *tert*-butyl 4-formyl-piperidine-1-carboxylate (0.90 g) in DMSO (30 mL). Int. **2T94** 3-(2'-oxo-5'-(1-(piperidin-4-ylmethyl)piperidin-4-yl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.68 g, TFA salt) was prepared similarly to Int. **2T36** from Int. **2T95** (0.90 g).



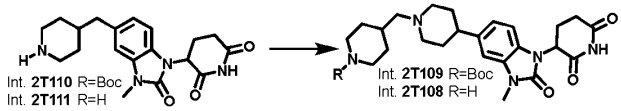
Int. **3U16** (0.50 g) was stirred in DCM/TFA (5:3, 8 mL) for 3h, concentrated and washed with Et_2O to give Int. **2T100** 3-(5'-(4-((4-hydroxypiperidin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione (0,50 g, TFA salt).



Int. **3C51** (0.50 g), tert-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (0.58 g), Cs_2CO_3 (1.3 g) and Pd-PEPPSI-IHept-Cl (66 mg) were stirred in dioxane (10 mL) for 16h at 110 °C under an inert atmosphere and concentrated. The residue was combined with three batches prepared similarly and purified by FC (DCM/MeOH 9:1) and HPLC to give Int. **2T102** *tert*-butyl 4-((4-(1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3,3-dimethyl-2-oxoindolin-5-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (80 mg). Int. **2T102** (80 mg) was stirred 12h in DCM/4M HCl in dioxane (2:5, 7 mL) at 0 °C to RT. The residue after concentration was washed with Et_2O to give Int. **2T101** 3-(6-fluoro-3,3-dimethyl-2-oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)indolin-1-yl)piperidine-2,6-dione (60 mg, HCl salt).

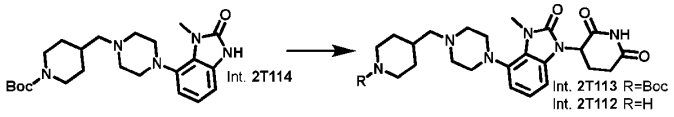


Int. **2T103** *tert*-butyl 4-((4-(6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.60 g) was prepared similarly to Int. **3U9** from Int. **3C9** (1 g) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (2.2 g). Int. **2T104** *tert*-butyl 4-((4-(1'-(2,6-dioxopiperidin-3-yl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)piperazin-1-yl)-methyl)piperidine-1-carboxylate (0.55 g) was prepared similarly to Int. **3U36** from Int. **2T103** (1 g) and 3-bromopiperidine-2,6-dione (2.1 g). Int. **2T104** (0.55 g) was stirred 16h in DCM/TFA (10:1, 11 mL). The residue after concentration washed with Et_2O/PE to give Int. **2T105** 3-(6'-fluoro-2'-oxo-5'-(4-(piperidin-4-ylmethyl)piperazin-1-yl)spiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione (0.50 g, TFA salt).

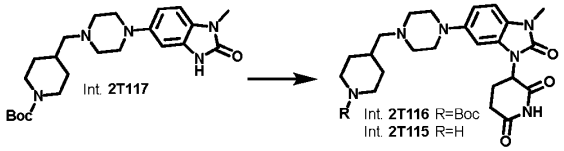


Int. **3U121** (1 g) and 10% Pd/C (0.5 g) was hydrogenated 16h in MeOH (30 mL). The mixture was filtered and concentrated to give Int. **2T110** *tert*-butyl 4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidine-1-carboxylate (0.80 g). Int. **2T110** (1.6 g) was stirred 4h in DCM/4M HCl in dioxane (10:1, 22 mL) at 0 °C to RT. The residue after concentration was triturated in Et_2O to give Int. **2T111** 3-(3-methyl-2-oxo-5-(piperidin-4-ylmethyl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (1.2 g, HCl salt). Int. **2T111** (1.20 g) and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.50 g) were stirred in 16h in DMSO (10 ml) and DIPEA (2.5 mL). STAB (1.98 g) was added and stirring continued 16h at 0 °C to RT. The OL (EtOAc/ice-cold water) was washed with brine, dried, and concentrated. The residue was purified by FC (4%

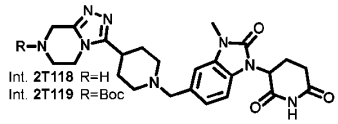
MeOH in DCM) to give Int. **2T109** *tert*-butyl 4-[[4-[[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate (0.45 g). Int. **2T109** (0.45 g) was stirred 4h in DCM (15 mL) and 4M HCl in dioxane (5 mL) at 0 °C to RT. The residue after concentration was triturated with Et_2O to precipitate Int. **2T108** 3-[3-methyl-2-oxo-5-(4-piperidylmethyl)benzimidazol-1-yl]piperidine-2,6-dione;hydrochloride (0.80 g).



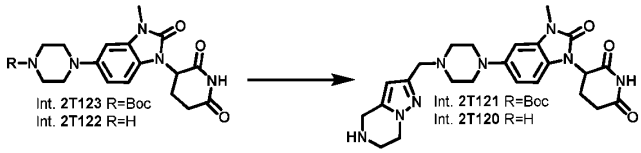
7-Bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (0.10 g), Int. **3E5** (0.16 g), RuPhos Pd G4 (37 mg) and RuPhos (41 mg) were stirred 5h in toluene (10 mL) and 1M LiHMDS in THF (2.2 mL) at 0-80 °C under an inert atmosphere. The OL (EtOAc/water) was dried, concentrated, and purified by FC (50-70% of EtOAc in PE) to give Int. **2T114** *tert*-butyl 4-[[4-(3-methyl-2-oxo-1H-benzimidazol-4-yl)piperazin-1-yl]methyl]piperidine-1-carboxylate (0.48 g). Int. **2T114** (0.45 g) and 60% NaH (60% oil dispersion, 0.21 g) were stirred in THF (15 mL) at 0 °C to RT. 3-bromopiperidine-2,6-dione (1.0 g) was added and stirring continued 12h at 60 °C. The OL (EtOAc/ice-cold water) was concentrated. The residue was triturated with 50% MTBE in PE to precipitate Int. **2T113** *tert*-butyl 4-[[4-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-4-yl]piperazin-1-yl]methyl]-piperidine-1-carboxylate (0.32 g). Int. **2T113** (0.3 g) was stirred 16h in DCM/TFA (5 mL/2 mL) at 0 °C to RT. The residue after concentration was washed with Et_2O. The OL (10% MeOH in DCM/aq. $NaHCO_3$) was concentrated to give Int. **2T112** 3-[3-methyl-2-oxo-4-[4-(4-piperidylmethyl)piperazin-1-yl]benzimidazol-1-yl]piperidine-2,6-dione (0.22 g).



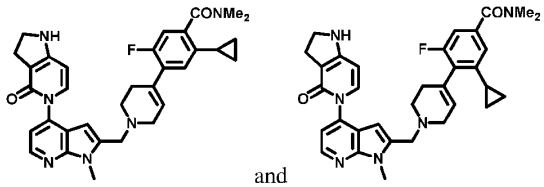
Int. **2T117** *tert*-butyl 4-[[4-(1-methyl-2-oxo-3H-benzimidazol-5-yl)piperazin-1-yl]methyl]piperidine-1-carboxylate (0.45 g) was prepared similarly to Int. **2T114 from** Int. **3E5** (1.62 g) and 5-bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (1.0 g). Int. **2T117** (0.35 g) and NaH (60% oil dispersion, 0.33 g) were stirred 0.5h in THF (150 mL) at 0-10 °C. 3-Bromopiperidine-2,6-dione (0.78 g) was added at 0 °C and stirring was continued 16h at 75-80 °C. The OL (EtOAc/ice-cold water) was washed with brine, dried, and concentrated. The residue was purified washed with Et_2O/PE/DCM (1: 2: 0.5) to precipitate Int. **2T116** *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-2-oxo-benzimidazol-5-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.28 g). Int. **2T116** (0.28 g) was stirred 5h in DCM/TFA (5 mL/3 mL) at 0 °C to RT. The residue after concentration was washed with Et_2O and dried to give Int. **2T115** 3-[3-methyl-2-oxo-6-[4-(4-piperidyl-methyl)piperazin-1-yl]benzimidazol-1-yl]piperidine-2,6-dione (0.25 g, TFA salt).



Int. **3U67** (0.20 g), *tert*-butyl 3-(piperidin-4-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate (0.20 g), and 4Å molecular sieves were stirred ON in DCE. $NaCNBH_3$ (51 mg) was added and stirring continued 3h. The mixture was filtered and concentrated. The residue was HPLC-purified to give Int. **2T119** *tert*-butyl 3-[1-[[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]methyl]-4-piperidyl]-6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylate (52 mg). Int. **2T119** (52 mg) was stirred 1h in HFIP (2 mL) concentrated aq. HCl (0.1 mL). The residue was diluted with TBME to precipitate Int. **2T118** 3-[3-methyl-2-oxo-5-[[4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)-1-piperidyl]methyl]benzimidazol-1-yl]-piperidine-2,6-dione (34 mg, HCl salt).



Int. **3E251** (1.0 g) and NaH (60% oil dispersion, 0.72 g) were stirred 0.3h in THF (50 mL). 3-Bromopiperidine-2,6-dione (2.89 g) was added and stirring continued 14h at 60 °C. The OL (EtOAc/aq. NH_4Cl) was concentrated to give Int. **2T123** *tert*-butyl 4-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-piperazine-1-carboxylate (1.8 g). Int. **2T123** (1.0 g) was stirred 14h in DCM/TFA (20 mL/0.95 mL). The residue after concentration was HPLC-purified to give Int. **2T122** 3-(3-methyl-2-oxo-5-piperazin-1-yl-benzimidazol-1-yl)piperidine-2,6-dione (0.36 g). To solution of Int. **2T122** (0.36 g), *tert*-butyl 2-formyl-6,7-dihydropyrazolo-[1,5-a]pyrazine-5(4H)-carboxylate (0.28 g) were stirred 0.3h in DCM (30 mL). STAB (0.67 g) was added and stirring continued 11h. The OL (DCM/sat. aq. $NaHCO_3$) was concentrated to give Int. **2T121** *tert*-butyl 2-[[4-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperazin-1-yl]methyl]-6,7-dihydro-4H-pyrazolo-[1,5-a]pyrazine-5-carboxylate (0.5 g). Int. **2T121** (0.50 g) was stirred 14h in DCM/TFA (20 mL/0.33 mL). The residue after concentration was HPLC-purified to give Int. **2T120** 3-[3-methyl-2-oxo-5-[4-(4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylmethyl)piperazin-1-yl]benzimidazol-1-yl]piperidine-2,6-dione (0.19 g).

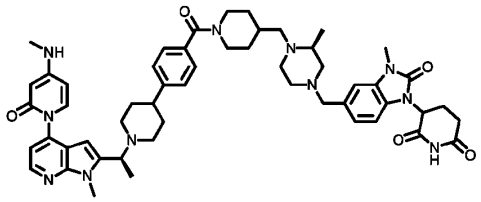


and

Example **1m134**. 2-cyclopropyl-5-fluoro-N,N-dimethyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide and Example **1m135**. 3-cyclopropyl-5-fluoro-N,N-dimethyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

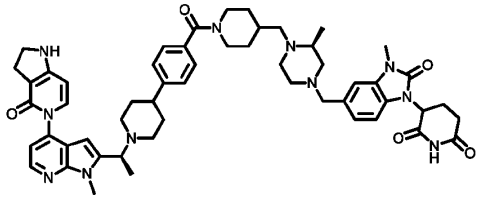
CuI (6 mg), Ints. **1Z74/1Z123+1Z124** (59 mg/0.17 g), and K_2CO_3 (0.14 g) were stirred 16h in DMSO (8 mL) and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (11 μL) at 110 °C under an inert atmosphere. The mixture was HPLC-purified and resolved by HPLC using a Chiralpak IC 250x20 mm 5μm column with an eluent of 50% IPA containing 0.1% Et_2NH and 50% MeOH containing 0.1% Et_2NH (12 mL/min) to give Example **1m134** (9 mg, first peak) and Example **1m135** (3 mg, second peak).

Example 2 – Preparation of Compounds of the Disclosure



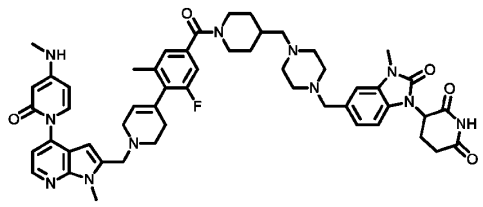
Example **3e39**. 3-(3-methyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Ints. **3E171/3E68** (0.22 g/0.25 g) and PyBrop (0.3 g) were stirred ON in THF/DIPEA (37:1, 15.4 mL) at 0 °C to RT and diluted with water to precipitate a solid that was HPLC-purified to give Example **3e39** (48 mg).



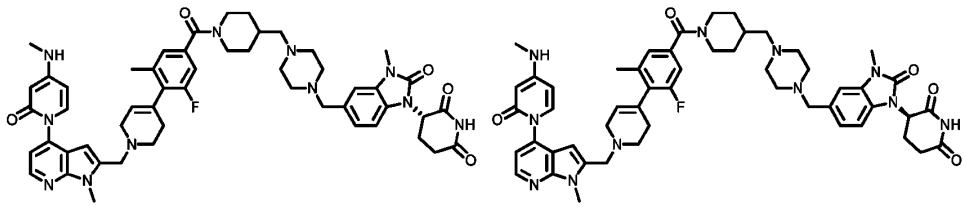
Example **3e44**. 3-(3-methyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Ints. **3E178/3E68** (0.15 g/0.13 g) and HATU (96 mg) were stirred ON in DMF/DIPEA (28:1, 5.2 mL) and diluted with water to precipitate a solid that was HPLC-purified to give Example **3e44** (14 mg).



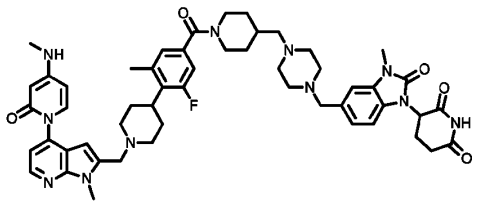
Example **3u163**. 3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Ints. **1M60/3E1** (0.30 g/0.41 g) were mixed in DMF/Et_3N (6:1, 5.8 mL). T3P (50% in EtOAc, 0.53 mL) was added at 0 °C and stirred for 16h at RT. The mixture was diluted with water to precipitate a solid that was HPLC-purified to give Example **3u163** (95 mg).



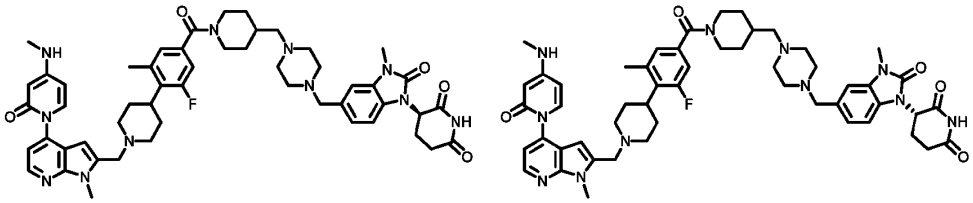
Example **3u161** and **3u162**. (S)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u163** (80 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (42 mL/min) to give Example **3u161** (31 mg, first peak) and Example **3u162** (23 mg, second peak). The absolute configurations for these compounds were not determined.



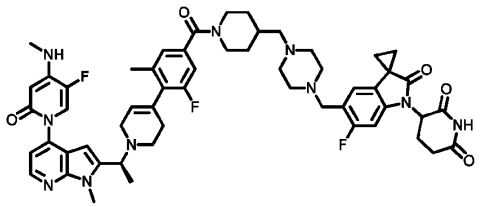
Example **3u158**. 3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u158** (40 mg) was prepared similarly to Example **3u163** from Ints. **2G113/3E1** (0.30 g/0.41 g).



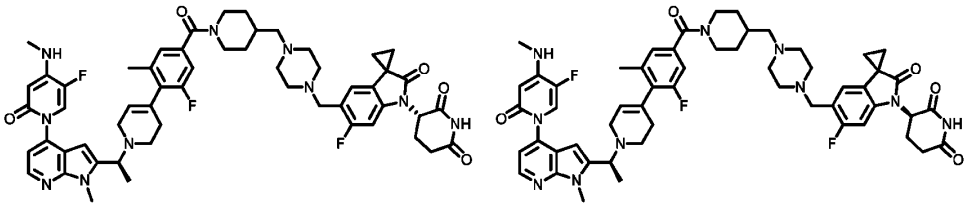
Example **3u159** and **3u160**. (R)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **2u158** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u160** (17 mg, first peak) and Example **3u159** (32 mg, second peak). The absolute configurations for these compounds were not determined.



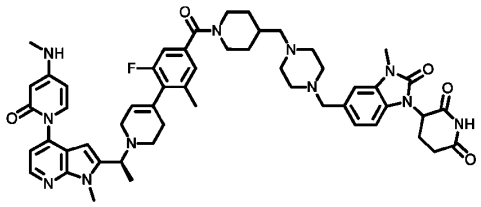
Example **3u152**. 3-(6'-fluoro-5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u152** (0.12 g) was prepared similarly to Example **3u163** from Ints. **2G45/3C4** (0.30 g/0.44 g).



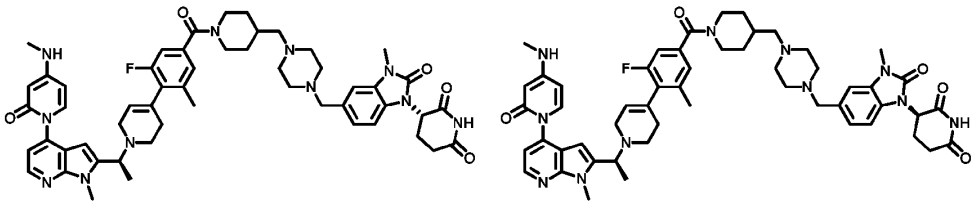
Example **3u154** and **3u153**. (S)-3-(6'-fluoro-5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(6'-fluoro-5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u152** (0.10 g) was resolved by HPLC using a CELLULOSE-SC 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (26 mL/min) to give Example **3u153** (25 mg, first peak) and Example **3u154** (25 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u155**. 3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

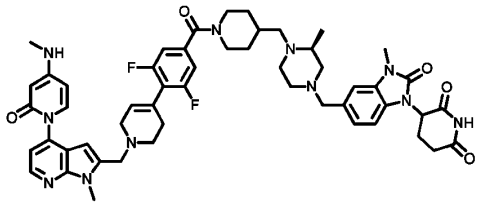
Example **3u155** (0.19 g) was prepared similarly to Example **3u163** from Ints. **2G46/3E1** (0.30 g/0.40 g).



Example **3u156** and **3u157**. (S)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

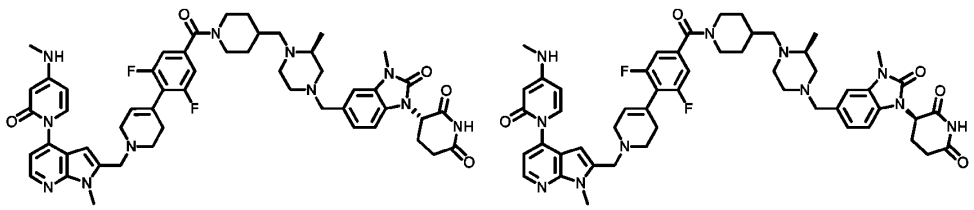
tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

Example **3u155** (0.17 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (38 mL/min) to give Example **3u157** (35 mg, first peak) and Example **3u156** (55 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



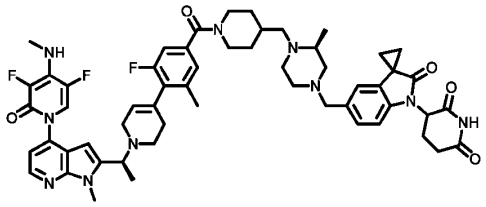
Example **3u1**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u1** (85 mg) was prepared similarly to Example **3u163** from Ints. **3U90 /3E68** (0.30 g/0.36 g).



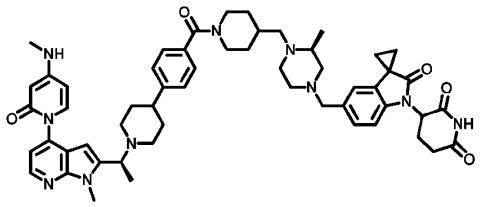
Example **3u2** and **3u3**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u1** (65 mg) was resolved by HPLC using a Chiralpak IK 150x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u2** (17 mg, first peak) and Example **3u3** (15 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



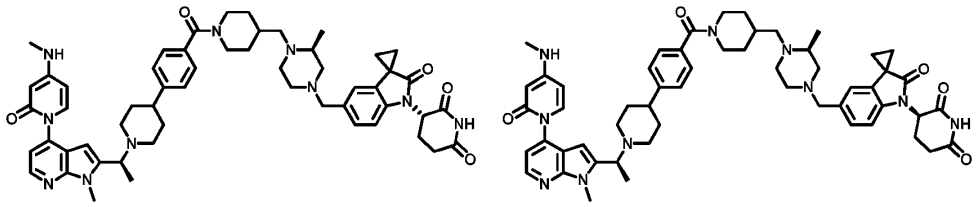
Example **3u4**. 3-(5'-(((S)-4-((1-(4-(1-((S)-1-(4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methyl-benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u4** (21 mg) was prepared similarly to Example **3u163** from Ints. **3U4/3C42** (0.10 g/0.12 g).



Example **3u5**. 3-(5'-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

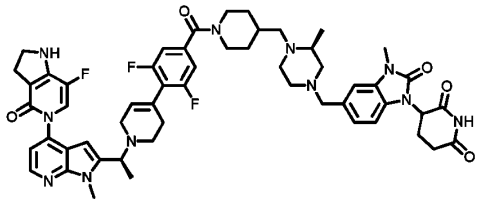
Example **3u5** (0.10 g) was prepared similarly to Example **3u163** from Ints. **3E171/3C42** (0.28 g/0.41 g).



Example **3u6** and **3u7**. (S)-3-(5'-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

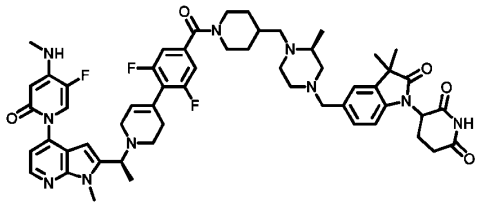
Example **3u5** (0.14 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (37 mL/min) to give Example **3u6** (8 mg, first

peak) and Example **3u7** (10 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



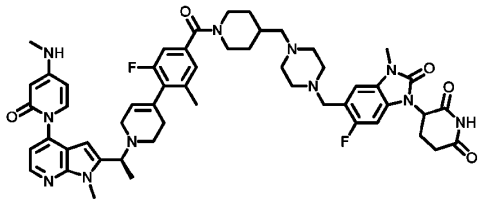
Example **3u8**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u8** (15 mg) was prepared similarly to Example **3u163** from Ints. **2G11/3E68** (0.10 g/0.12 g).



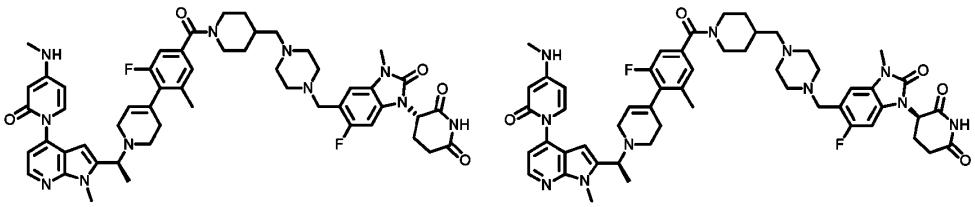
Example **3u9**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u9** (15 mg) was prepared similarly to Example **3u163** from Ints. **2G43/3E291** (0.20 g/0.22 g).



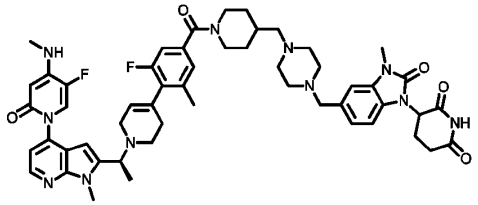
Example **3u10**. 3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u10** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G46/3E145** (0.25 g/0.35 g).



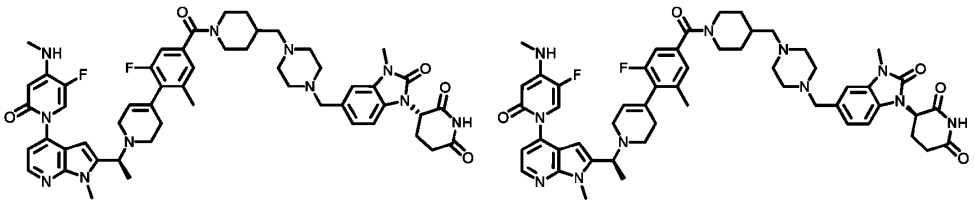
Example **3u11** and **3u12**. (S)-3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione and (R)-3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u10** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (30 mL/min) to give Example **3u11** (42 mg, first peak) and Example **3u12** (31 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u13**. 3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

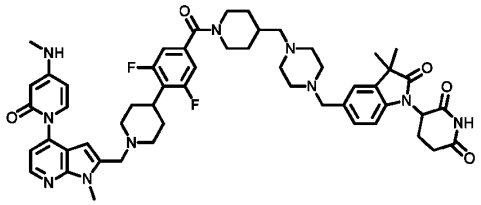
Example **3u13** (0.16 g) was prepared similarly to Example **3u163** from Ints. **2G45/3E1** (0.30 g/0.41 g).



Example **3u14** and **3u15**. (S)-3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3-fluoro-4-(1-

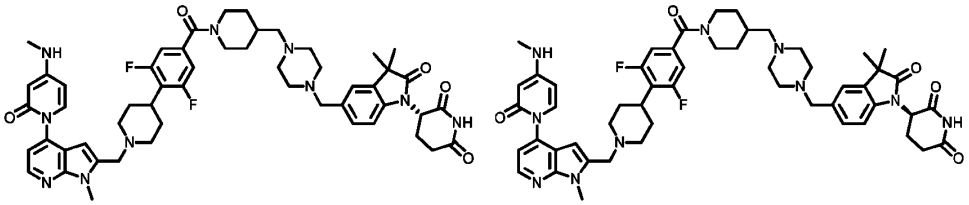
((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u13** (0.13 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u14** (31 mg, first peak) and Example **3u15** (21 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



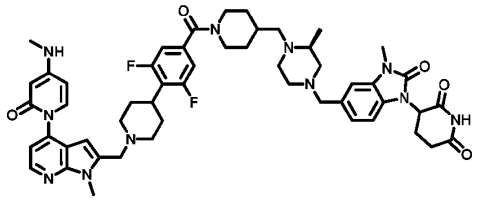
Example **3u16**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u16** (64 mg) was prepared similarly to Example **3u163** from Ints. **2G108/3U7** (0.27 g/0.43 g).



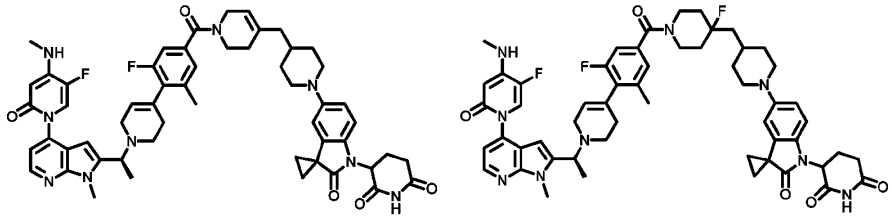
Example **3u17** and **3u18**. (S)-3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u16** (48 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u17** (9 mg, TFA salt, first peak) and Example **3u18** (12 mg, TFA salt, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



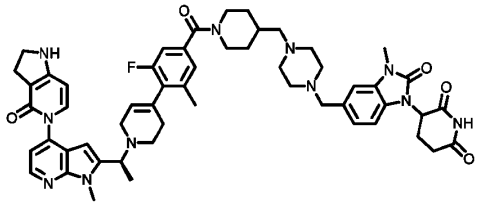
Example **3u19**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u19** (80 mg) was prepared similarly to Example **3u163** from Ints. **2G108/3E68** (0.30 g/0.38 g).



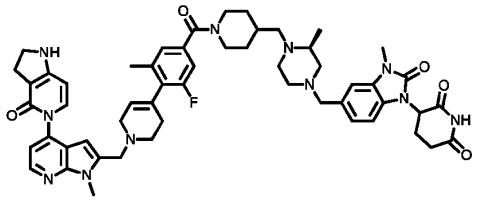
Example **3u20** and **3u21**. 3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoyl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and 3-(5'-(4-((4-fluoro-1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione

Examples **3u20** (63 mg) **3u21** (60 mg) were prepared similarly to Example **3u163** from Ints. **2G45/3U12/3U13** (0.30 g/0.44 g).



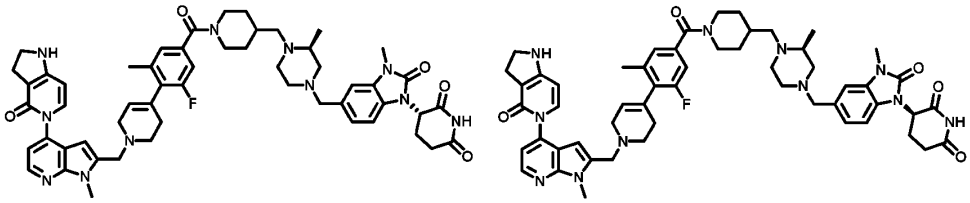
Example **3u22**. 3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

Example **3u22** (30 mg) was prepared similarly to Example **3u163** from Ints. **2G53/3E1** (0.15 g/0.16 g).



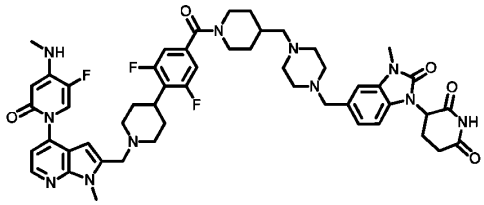
Example **3u23**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u23** (0.10 g) was prepared similarly to Example **3u163** from Ints. **2G49/3E68** (0.30 g/0.29 g).



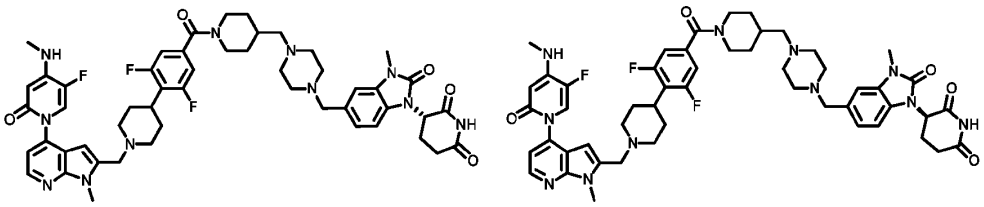
Example **3u24** and **3u25**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u23** (80 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u24** (15 mg, first peak) and Example **3u25** (18 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



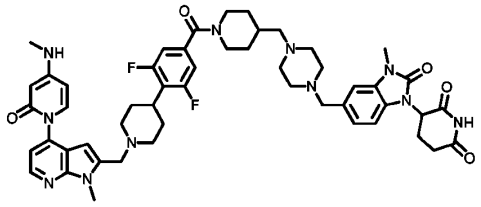
Example **3u26**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u26** (0.11 g) was prepared similarly to Example **3u163** from Ints. **2G58/3E1** (0.25 g/0.30 g).



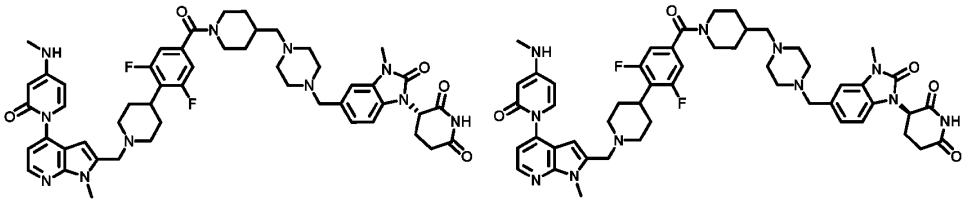
Example **3u27** and **3u28**. (S)-3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u26** (90 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u27** (11 mg, first peak) and Example **3u28** (19 mg, second peak). The absolute configurations for these compounds were not determined.



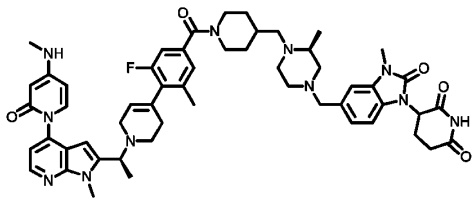
Example **3u29**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u29** (60 mg) was prepared similarly to Example **3u163** from Ints. **2G108/3E1** (0.25 g/0.29 g).



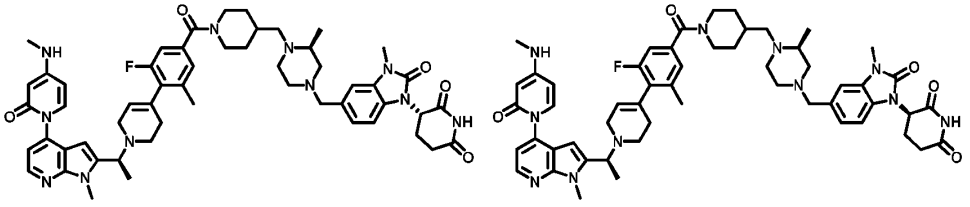
Example **3u30** and **3u31**. (S)-3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dionc

Example **3u29** (95 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (26 mL/min) to give Example **3u30** (25 mg, first peak) and Example **3u31** (25 mg, second peak). The absolute configurations for these compounds were not determined.



Example **3u32**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

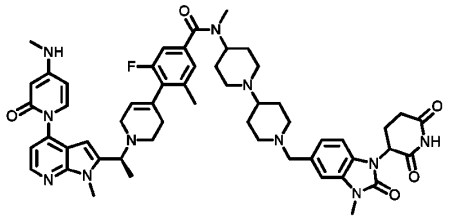
Example **3u32** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G46/3E68** (0.30 g/0.41 g).



Example **3u33** and **3u34**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-

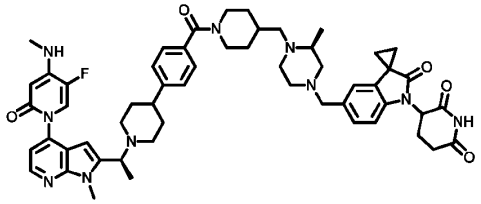
methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u32** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u33** (25 mg, first peak) and Example **3u34** (40 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



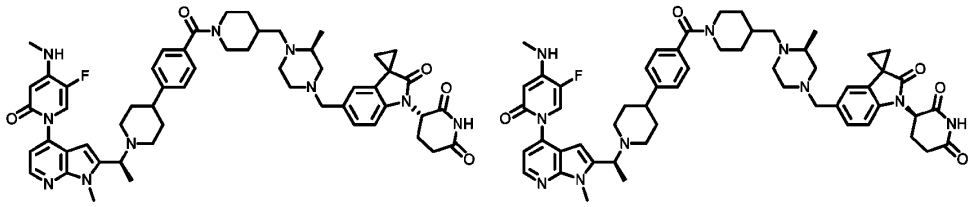
Example **3u35**. N-(1'-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-[1,4'-bipiperidin]-4-yl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u35** (9 mg) was prepared similarly to Example **3u163** from Ints. **2G46/3U17** (48 mg/70 mg) using HATU (50 mg) instead of T3P and DIPEA instead of Et_3N.



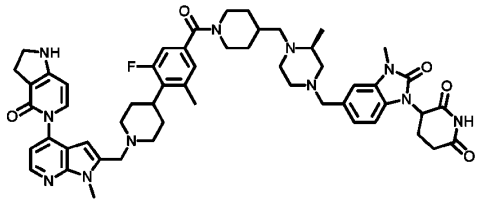
Example **3u36**. 3-(5'-(((S)-4-((1-(4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u36** (80 mg) was prepared similarly to Example **3u163** from Ints. **3U91/3C42** (0.20 g/0.31 g).



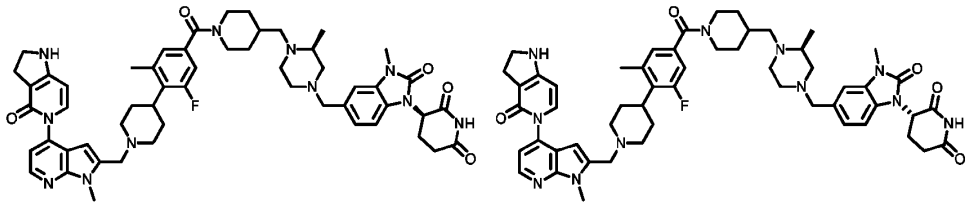
Example **3u37** and **3u38**. (S)-3-(5'-(((S)-4-((1-(4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-4-((1-(4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u36** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u37** (22 mg, first peak) and Example **3u38** (25 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u39**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

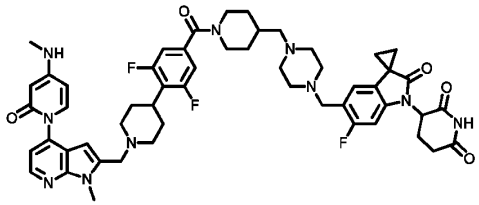
Example **3u39** (0.13 g) was prepared similarly to Example **3u163** from Ints. **2G56/3E68** (0.40 g/0.42 g).



Example **3u40** and **3u41**. (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

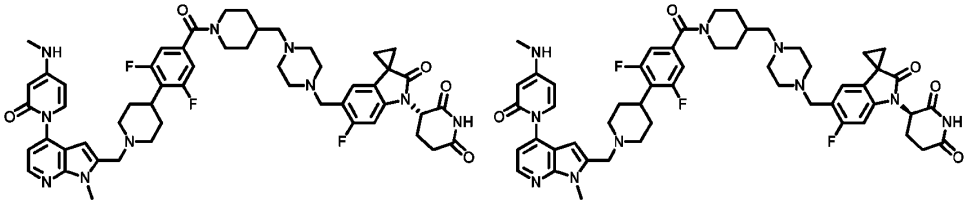
Example **3u39** (0.13 g) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u40** (17

mg, first peak) and Example **3u41** (17 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



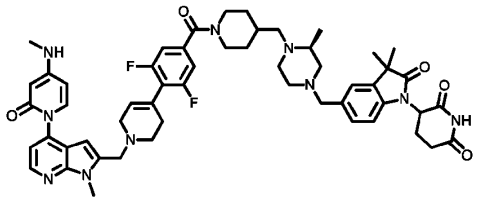
Example **3u42**. 3-(5'-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u42** (80 mg) was prepared similarly to Example **3u163** from Ints. **2G108/3C4** (0.25 g/0.44 g).



Example **3u43** and **3u44**. (S)-3-(5'-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-((4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

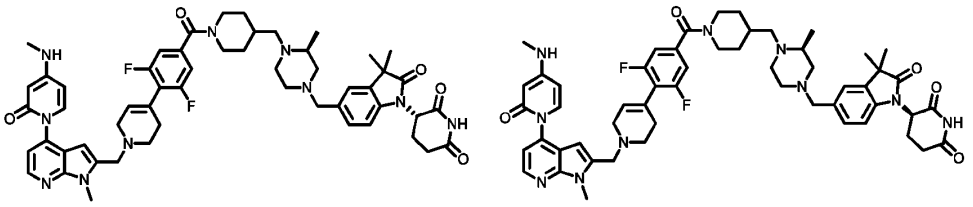
Example **3u42** (80 mg) was resolved by HPLC using a CELLULOSE-SC 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (42 mL/min) to give Example **3u43** (15 mg, first peak) and Example **3u44** (6 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u45**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-

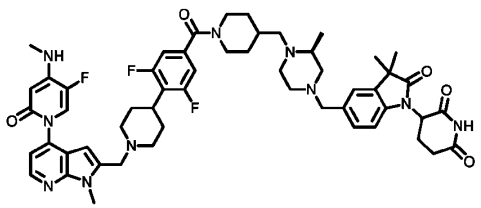
yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u45** (0.16 g) was prepared similarly to Example **3u163** from Ints. **3U90/3E291** (0.30 g/0.34 g).



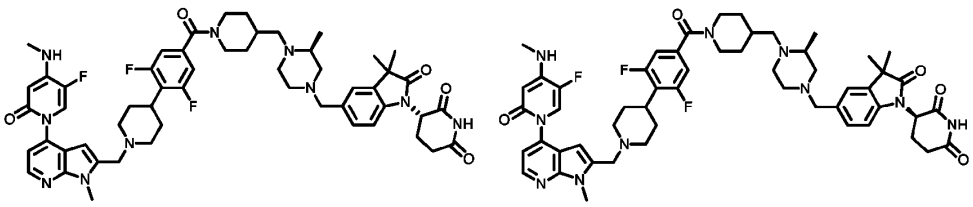
Example **3u46** and **3u47**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u45** (0.14 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (37 mL/min) to give Example **3u46** (37 mg, first peak) and Example **3u47** (39 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



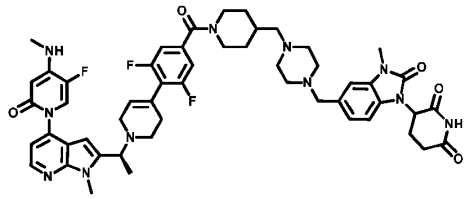
Example **3u48**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u48** (0.10 g) was prepared similarly to Example **3u163** from Ints. **2G58/3E291** (0.30 g/0.34 g).



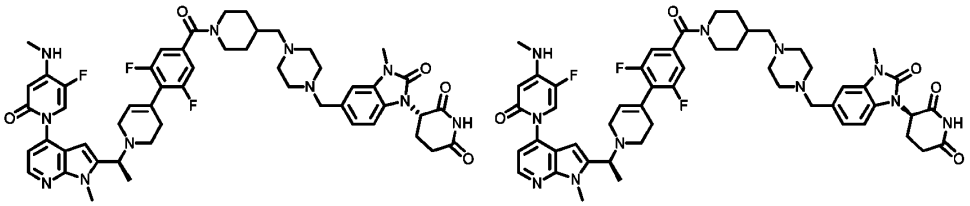
Example **3u49** and **3u50**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u48** (0.10 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (38 mL/min) to give Example **3u49** (10 mg, first peak) and Example **3u50** (8 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u51**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

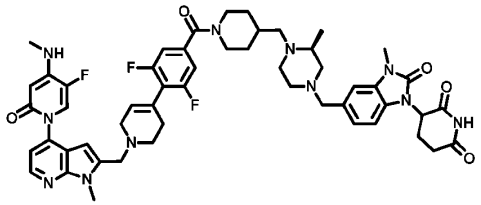
Example **3u51** (85 mg) was prepared similarly to Example **3u163** from Ints. **2G43/3E1** (0.20 g/0.24 g).



Example **3u52** and **3u53**. (S)-3-(5-((4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

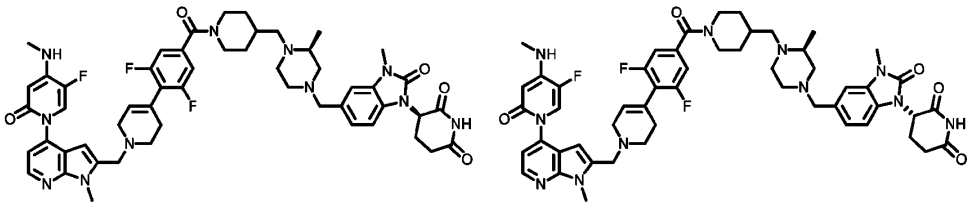
Example **3u51** (75 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u52** (10

mg, first peak) and Example **3u53** (24 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



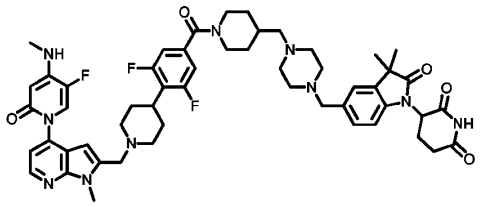
Example **3u54**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u54** (0.18 g) was prepared similarly to Example **3u163** from Ints. **2G48/3E68** (0.25 g/0.36 g).



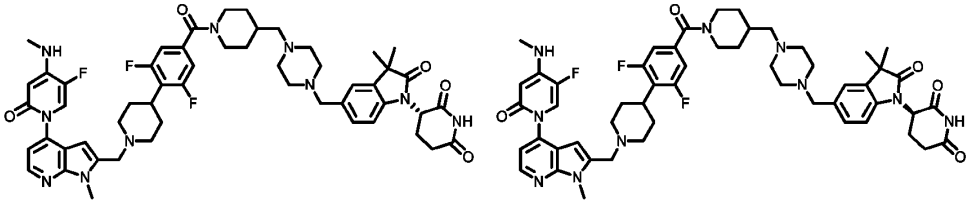
Example **3u55** and **3u56.** (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u54** (0.11 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u55** (46 mg, first peak) and Example **3u56** (14 mg, second peak). The second peak required a subsequent HPLC-purification. The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



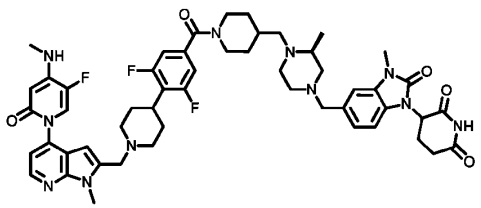
Example **3u57**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u57** (94 mg) was prepared similarly to Example **3u163** from Ints. **2G58/3U7** (0.30 g/0.46 g).



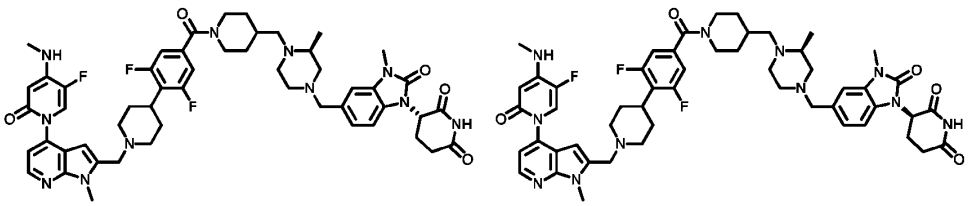
Example **3u58** and **3u59**. (S)-3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u57** (70 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u58** (17 mg, first peak) and Example **3u59** (27 mg, second peak). The absolute configurations for these compounds were not determined.



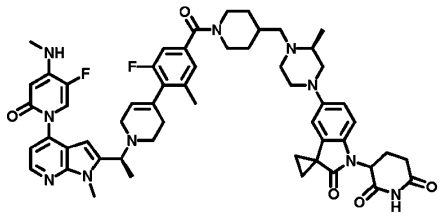
Example **3u60**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u60** (95 mg) was prepared similarly to Example **3u163** from Ints. **2G58/3E68** (0.25 g/0.29 g).



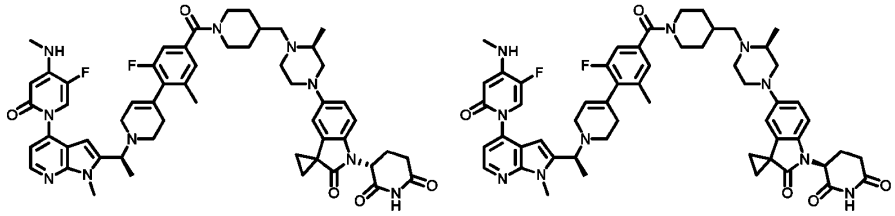
Example **3u61** and **3u62**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u60** (90 mg) was resolved by HPLC using a CELLULOSE-SC 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (42 mL/min) to give Example **3u62** (20 mg, first peak) and Example **3u61** (21 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



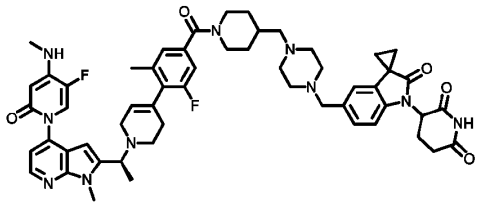
Example **3u63**. 3-(5'-((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione

Example **3u63** (0.12 g) was prepared similarly to Example **3u163** from Ints. **2G45/3C13** (0.30 g/0.55 g).



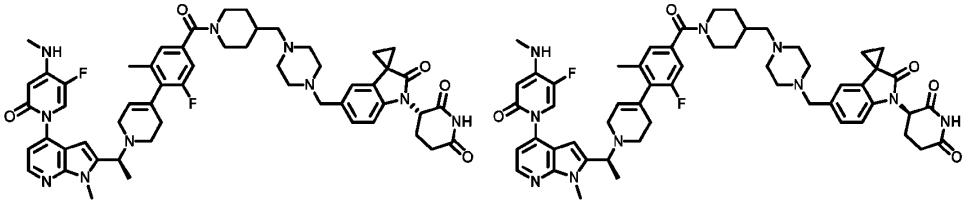
Example **3u64** and **3u65**. (R)-3-(5'-((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (S)-3-(5'-((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u63** (0.10 g) was resolved by HPLC using a CELLULOSE-SZ 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (22 mL/min) to give Example **3u64** (26 mg, first peak) and Example **3u65** (17 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



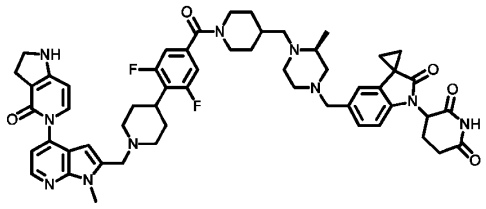
Example **3u66**. 3-(5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u66** (85 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3U21** (0.20 g/0.37 g).



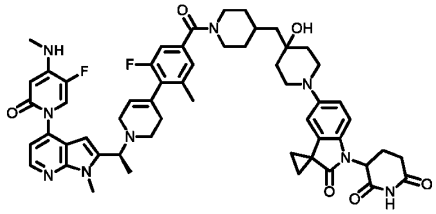
Example **3u67** and **3u68**. (S)-3-(5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u66** (65 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u67** (10 mg, first peak) and Example **3u68** (12 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



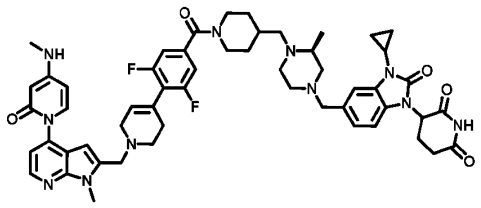
Example **3u69**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u69** (80 mg) was prepared similarly to Example **3u163** from Ints. **2G57/3C42** (0.30 g/0.37 g).



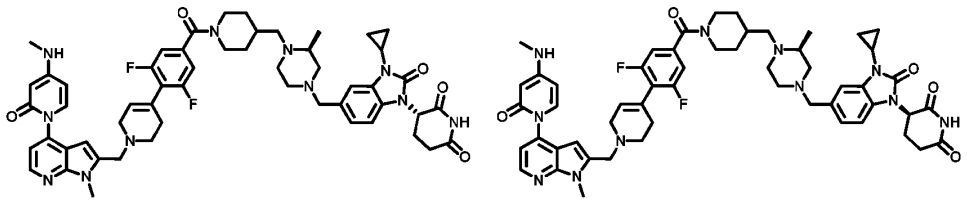
Example **3u70**. 3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)-4-hydroxypiperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)-piperidine-2,6-dione

Example **3u70** (15 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3U23** (45 mg/0.14 g).



Example **3u71**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

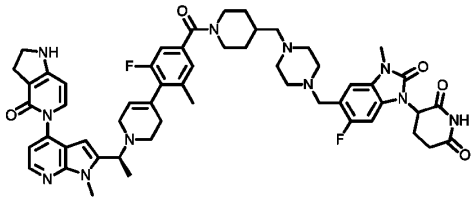
Example **3u71** (0.16 g) was prepared similarly to Example **3u163** from Ints. **3U88/3E78** (0.30 g/0.35 g).



Example **3u72** and **3u73**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-

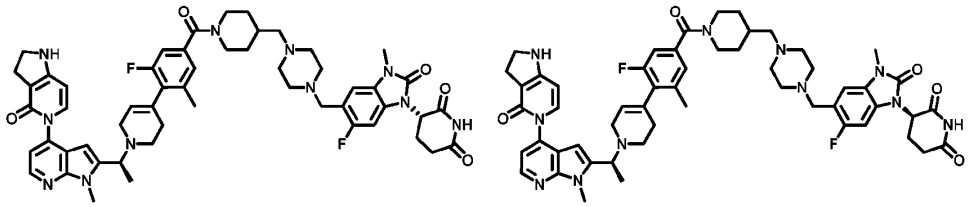
tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u71** (0.14 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u72** (35 mg, first peak) and Example **3u73** (60 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



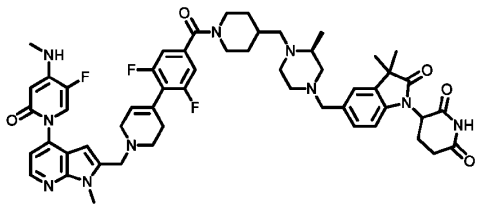
Example **3u74**. 3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u74** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G53/3E145** (0.15 g/0.20 g).



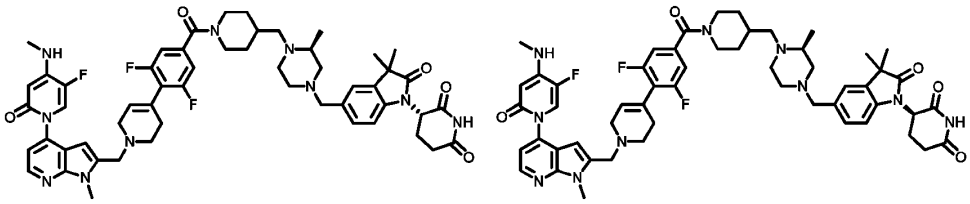
Example **3u75** and **3u76**. (S)-3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u74** (0.10 g) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 40% ACN, 40% IPA and 20% DCM (4 mL/min) to give Example **3u75** (28 mg, first peak) and Example **2u76** (39 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



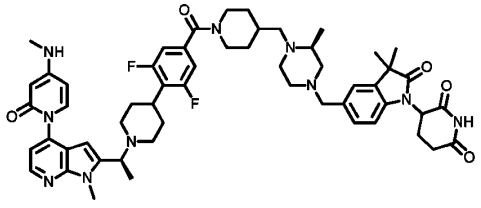
Example **3u77**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u77** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G48/3E291** (0.10 g/0.13 g).



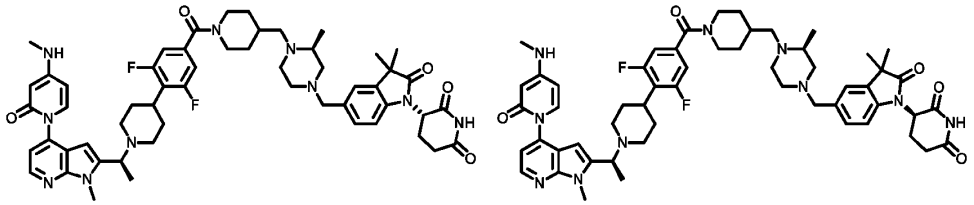
Example **3u78** and **3u79**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u77** (70 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (25 mL/min) to give Example **3u78** (15 mg, first peak) and Example **3u79** (13 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



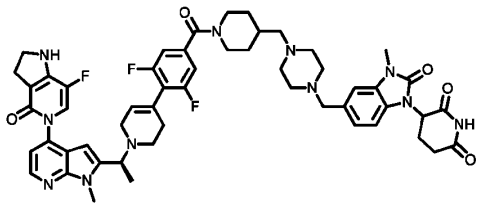
Example **3u80**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u80** (0.11 g) was prepared similarly to Example **3u163** from Ints. **3U72/3E291** (0.25 g/0.32 g).



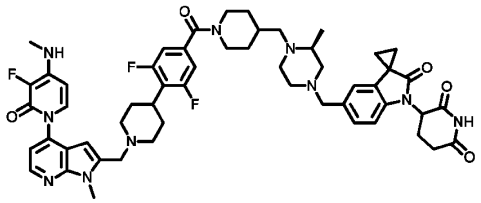
Example **3u81** and **3u82**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u80** (90 mg) was resolved by HPLC using a CELLULOSE-SC 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u81** (10 mg, first peak) and Example **3u82** (12 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u83**. 3-(5-((4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

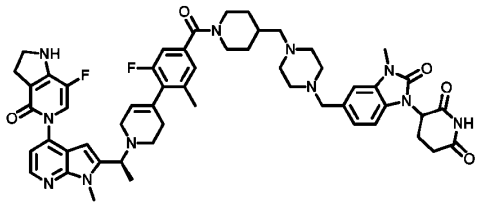
Example **3u82** (28 mg) was prepared similarly to Example **3u163** from Ints. **2G11/3E1** (0.10 g/0.13 g).



Example **3u84**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-

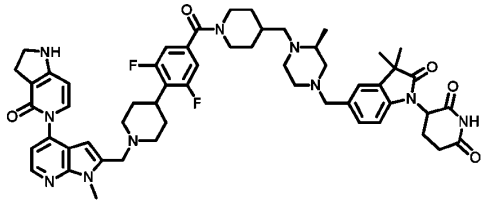
yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u84** (32 mg) was prepared similarly to Example **3u163** from Ints. **3U78/3C42** (0.10 g/0.16 g).



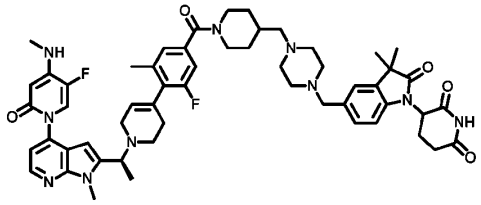
Example **3u85**. 3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u85** (16 mg) was prepared similarly to Example **3u163** from Ints. **2G27/3E1** (0.10 g/0.11 g).



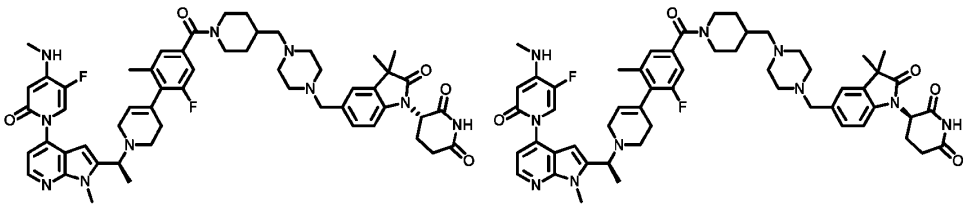
Example **3u86**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u86** (50 mg) was prepared similarly to Example **3u163** from Ints. **2G57/3E291** (0.30 g/0.32 g).



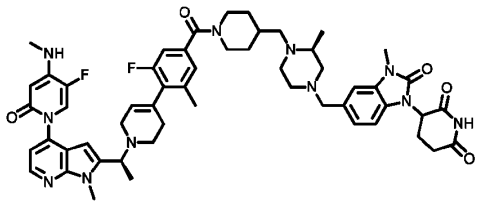
Example **3u87**. 3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u87** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G45/3U7** (0.30 g/0.42 g).



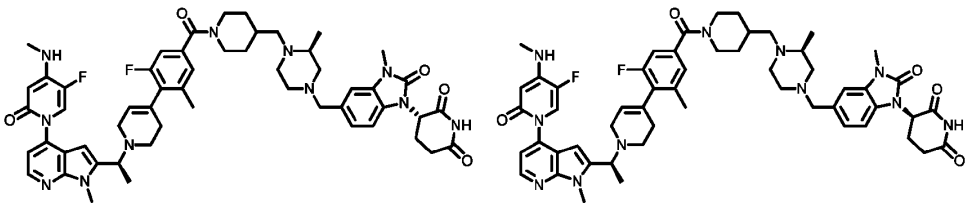
Example **3u88** and **3u89**. (S)-3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u87** (0.10 g) was resolved by HPLC using a Chiralpak IC 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (6 mL/min) to give Example **3u88** (15 mg, first peak) and Example **3u89** (31 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u90**. 3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

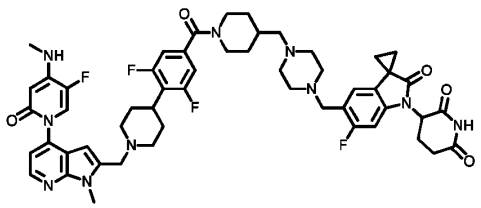
Example **3u90** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3E68** (0.20 g/0.26 g).



Example **3u91** and **3u92**. (S)-3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

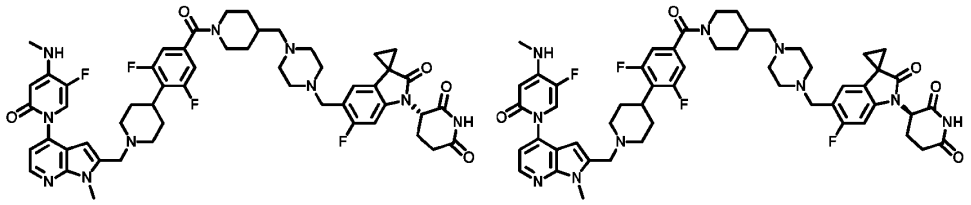
tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u90** (60 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 40% ACN, 40% IPA and 20% DCM (3 mL/min) to give Example **3u91** (19 mg, first peak) and Example **3u92** (20 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u93**. 3-(5'-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

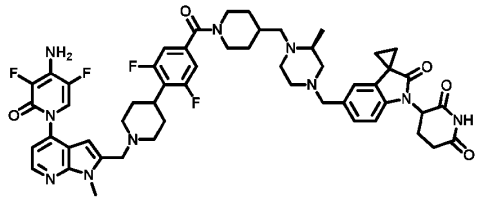
Example **3u93** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G58/3C4** (0.30 g/0.36 g).



Example **3u94** and **3u95**. (S)-3-(5'-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-((4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-6'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

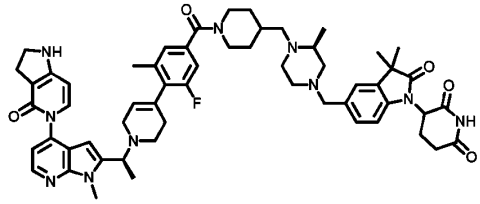
Example **3u93** (84 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 50% IPA and 50% DCM (6 mL/min) to give Example **3u94** (23 mg, first

peak) and Example **3u95** (25 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



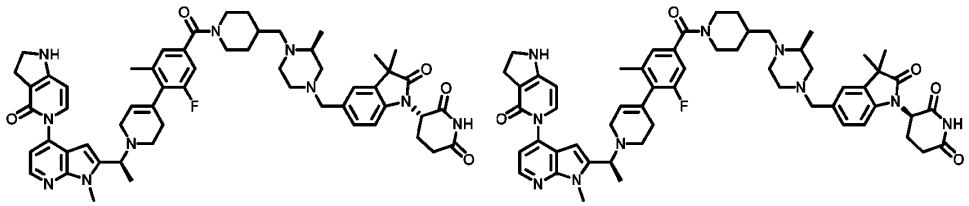
Example **3u96**. 3-(5'-(((S)-4-((1-(4-(1-((4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u96** (10 mg) was prepared similarly to Example **3u163** from Ints. **3U28/3C42** (0.10 g/0.15 g).



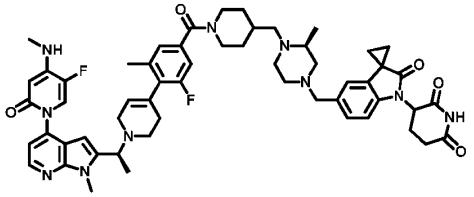
Example **3u165**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u165** (45 mg) was prepared similarly to Example **3u163** from Ints. **2G53/3E291** (0.15 g/0.18 g).



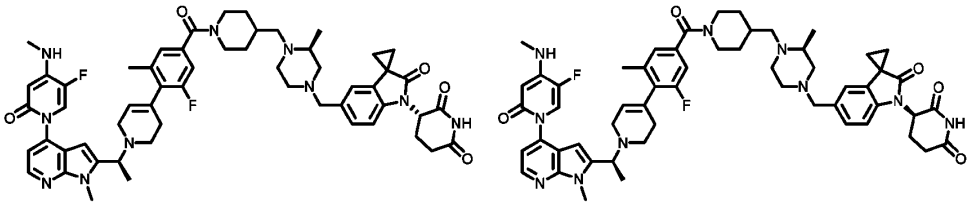
Example **3u97** and **3u98**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u165** (45 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u98** (4 mg, first peak) and Example **3u97** (8 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



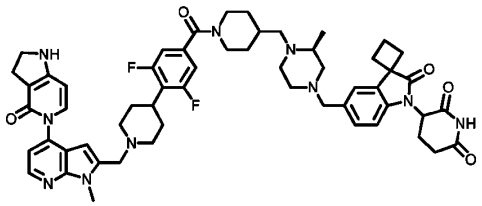
Example **3u164**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u164** (80 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3C42** (0.25 g/0.36 g).



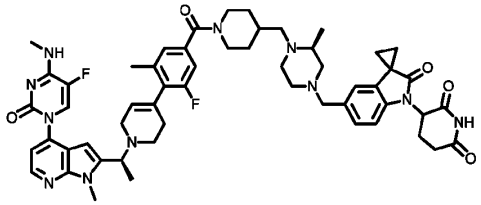
Example **3u99** and **3u100**. (S)-3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u164** (0.10 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (22 mL/min) to give Example **3u99** (27 mg, first peak) and Example **3u100** (22 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



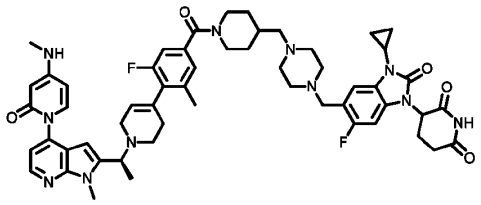
Example **3u101**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u101** (90 mg) was prepared similarly to Example **3u163** from Ints. **2G57/3U30** (0.30 g/0.33 g).



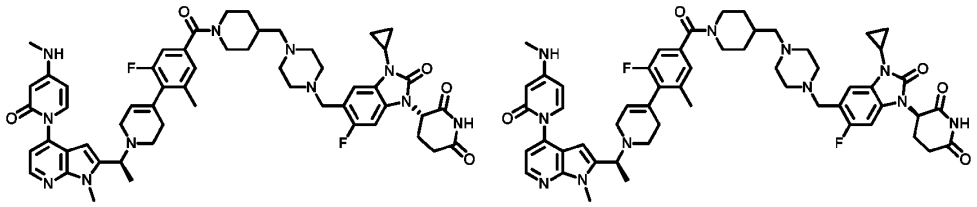
Example **3u102**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u102** (21 mg) was prepared similarly to Example **3u163** from Ints. **2G20/3C42** (0.10 g/0.13 g).



Example **3u103**. 3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

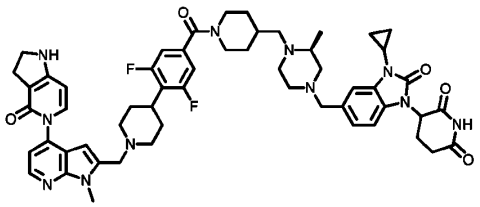
Example **3u103** (60 mg) was prepared similarly to Example **3u163** from Ints. **2G46/3E148** (0.30 g/0.40 g).



Example **3u104** and **3u105**. (S)-3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-

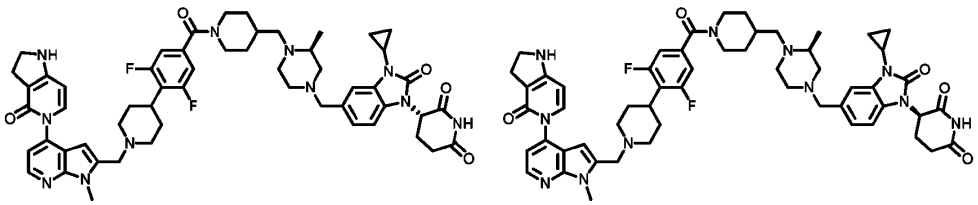
dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u103** (45 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u104** (15 mg, first peak) and Example **3u105** (14 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



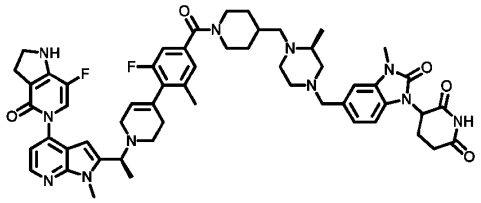
Example **3u106**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u106** (85 mg) was prepared similarly to Example **3u163** from Ints. **2G57/3E78** (0.35 g/0.35 g).



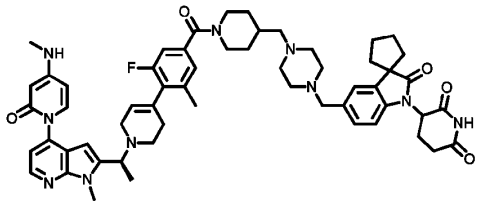
Example **3u107** and **3u108**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u106** (45 mg) was resolved by HPLC using a CELLULOSE SZ 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (6 mL/min) to give Example **3u107** (21 mg, first peak) and Example **3u108** (21 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



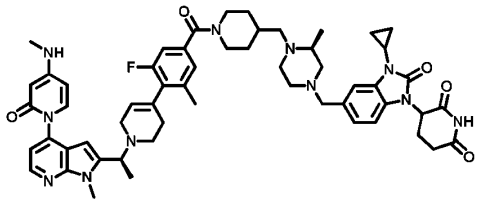
Example **3u109**. 3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u109** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G27/3E78** (0.10 g/0.12 g).



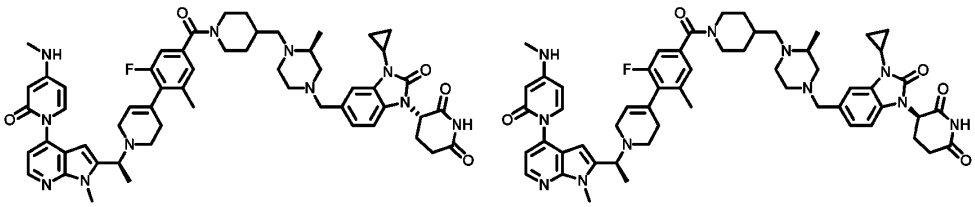
Example **3u110**. 3-(5'-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclopentane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u110** (4 mg) was prepared similarly to Example **3u163** from Ints. **3U35/2G46** (81 mg/62 mg) using HATU (48 mg) instead of T3P.



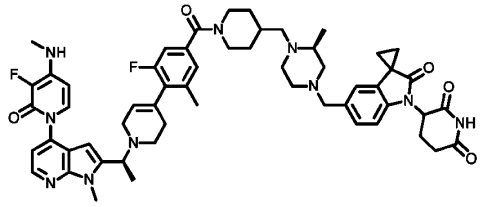
Example **3u111**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u111** (85 mg) was prepared similarly to Example **3u163** from Ints. **2G46/3E78** (0.30 g/0.45 g).



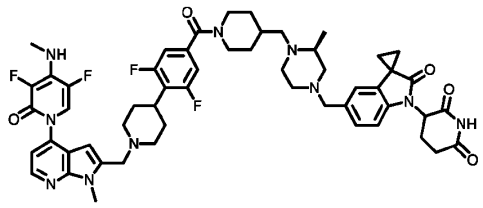
Example **3u112** and **3u113**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u111** (85 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (48 mL/min) to give Example **3u112** (25 mg, first peak) and Example **3u113** (24 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



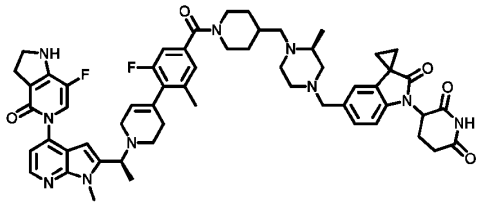
Example **3u114**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u114** (32 mg) was prepared similarly to Example **3u163** from Ints. **3U39/3C42** (0.11 g/0.16 g).



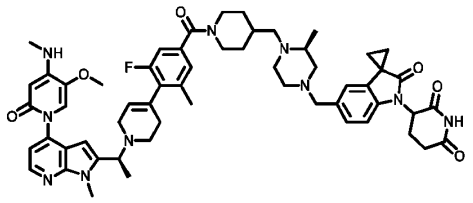
Example **3u115**. 3-(5'-(((S)-4-((1-(4-(1-((4-(3,5-difluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3,5-difluorobenzoyl)piperidin-4-yl)-methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u115** (46 mg) was prepared similarly to Example **3u163** from Ints. **3U41/3C42** (0.10 g/0.21 g).



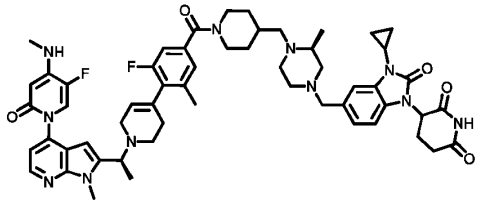
Example **3u116**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u116** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G27/3C42** (0.10 g/0.14 g).



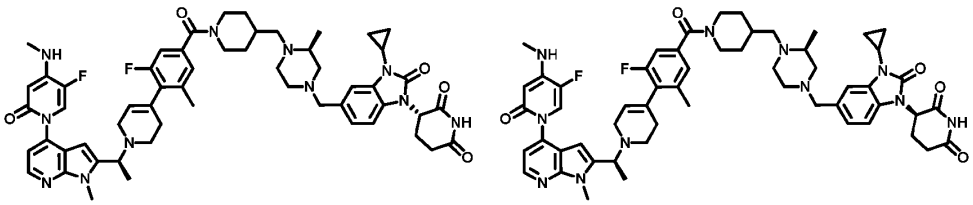
Example **3u117**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u117** (62 mg) was prepared similarly to Example **3u163** from Ints. **3U65/3C42** (0.12 g/0.17 g).



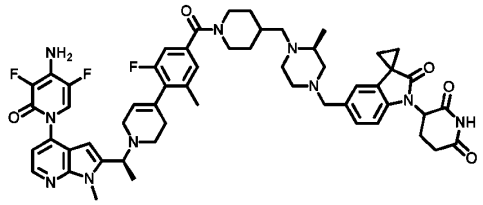
Example **3u118**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u118** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G45/3E78** (0.30 g/0.48 g).



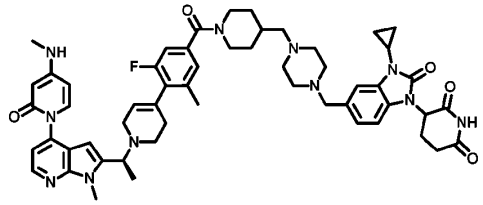
Example **3u119** and **3u120**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo-[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u118** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (6 mL/min) to give Example **3u119** (42 mg, first peak) and Example **3u120** (35 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u121**. 3-(5'-(((S)-4-((1-(4-(1-((S)-1-(4-(4-amino-3,5-difluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

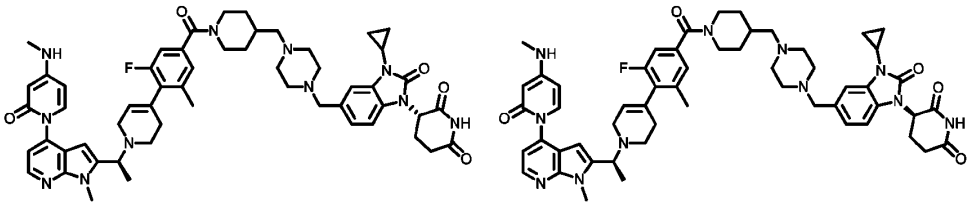
Example **3u121** (20 mg) was prepared similarly to Example **3u163** from Ints. **3U43/3C42** (0.20 g/0.14 g).



Example **3u122.** 3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

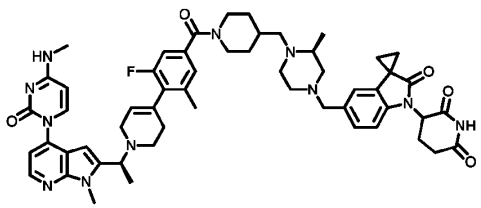
tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u122** (0.15 g) was prepared similarly to Example **3u163** from Ints. **2G46/3E33** (0.30 g/0.36 g).



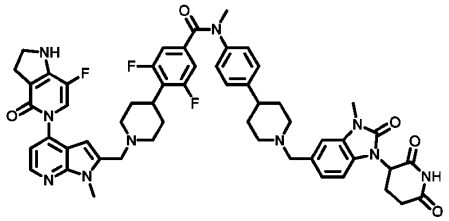
Example **3u123** and **3u124**. (S)-3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u122** (0.12 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (30 mL/min) to give Example **3u123** (25 mg, first peak) and Example **3u124** (26 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



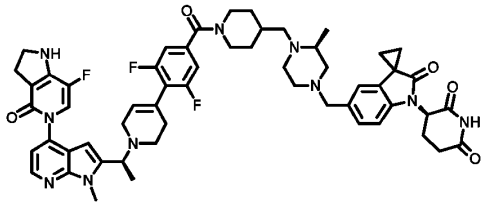
Example **3u125**. 3-(5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u125** (27 mg) was prepared similarly to Example **3u163** from Ints. **3U45/3C42** (0.10 g/0.15 g).



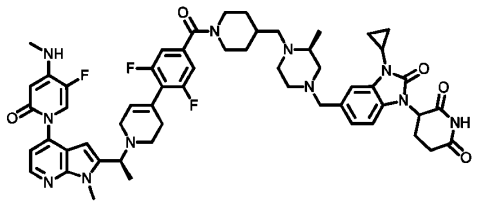
Example **3u126**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3,5-difluoro-4-(1-((4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-N-methylbenzamide

Example **3u126** (0.14 g) was prepared similarly to Example **3u163** from Ints. **3U47/3U69** (0.15 g/0.18 g) using 2-bromo-1-ethyl-pyridinium tetrafluoroborate (1.19 g) instead of T3P.



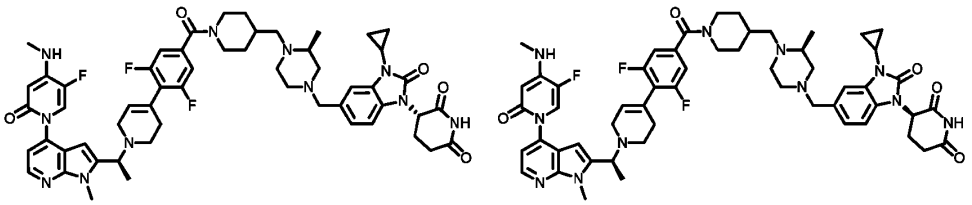
Example **3u127**. (R)-3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u127** (15 mg) was prepared similarly to Example **3u163** from Ints. **2G11/3C42** (90 mg/0.14 g).



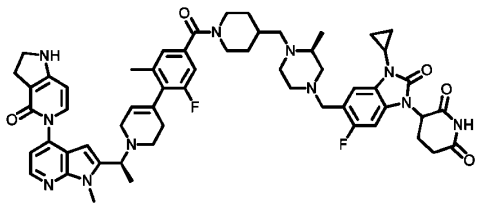
Example **3u128**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u128** (0.14 g) was prepared similarly to Example **3u163** from Ints. **2G43/3E78** (0.30 g/0.39 g).



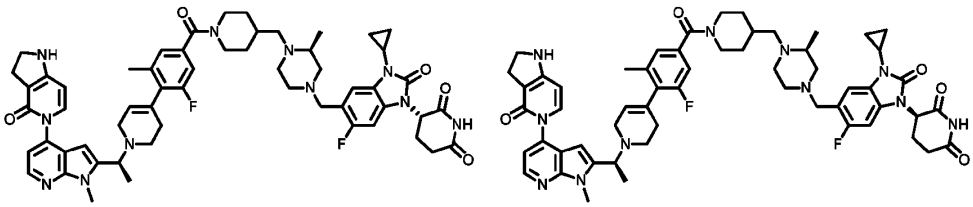
Example **3u129** and **3u130**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetra-hydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u128** (0.14 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u129** (28 mg, first peak) and Example **3u129** (22 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u131**. 3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

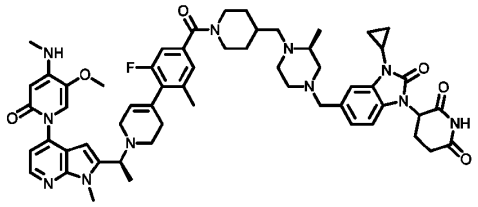
Example **3u131** (0.18 g) was prepared similarly to Example **3u163** from Ints. **2G53/3E200** (0.25 g/0.41g).



Example **3u132** and **3u133**. (S)-3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and

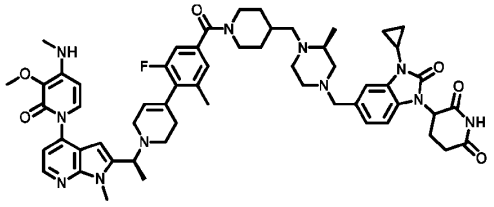
(R)-3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u131** (0.15 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u132** (25 mg, first peak) and Example **3u133** (25 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



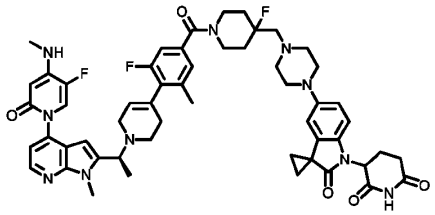
Example **3u134**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u134** (53 mg) was prepared similarly to Example **3u163** from Ints. **3U65/3E78** (0.12 g/0.15 g).



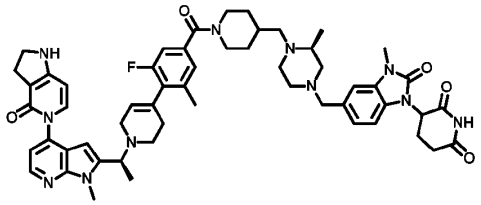
Example **3u135**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(3-methoxy-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u135** (40 mg) was prepared similarly to Example **3u163** from Ints. **3U49/3E78** (70 mg/89 mg).



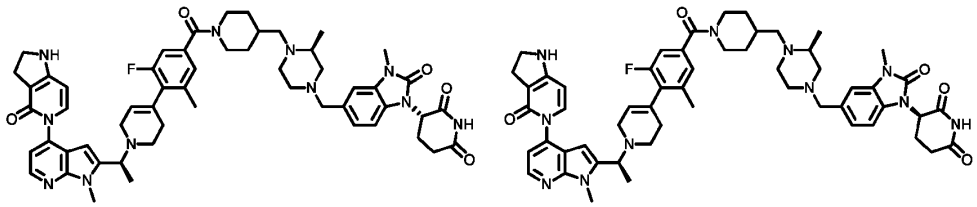
Example **3u136**. 3-(5'-(4-((4-fluoro-1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u136** (40 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3U55** (0.13 g/0.11 g).



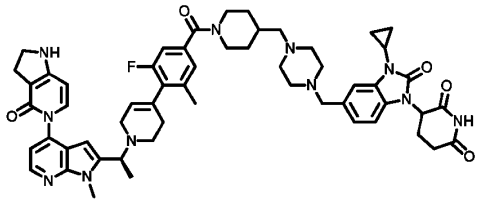
Example **3u137**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u137** (85 mg) was prepared similarly to Example **3u163** from Ints. **2G53/3E68** (0.30 g/0.34 g).



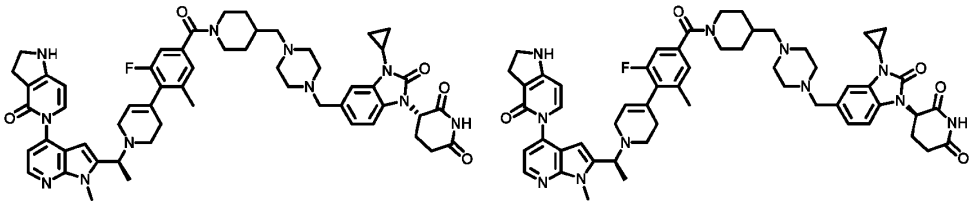
Example **3u138** and **3u139**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u137** (85 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (38 mL/min) to give Example **3u139** (20 mg, first peak) and Example **3u138** (20 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



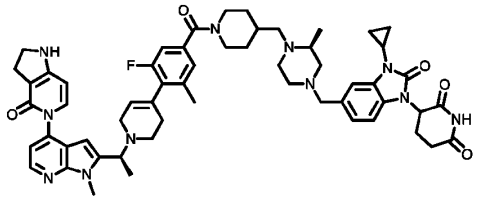
Example **3u140**. 3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u140** (70 mg, TFA) was prepared similarly to Example **3u163** from Ints. **2G53/3E33** (0.25 g/0.32 g).



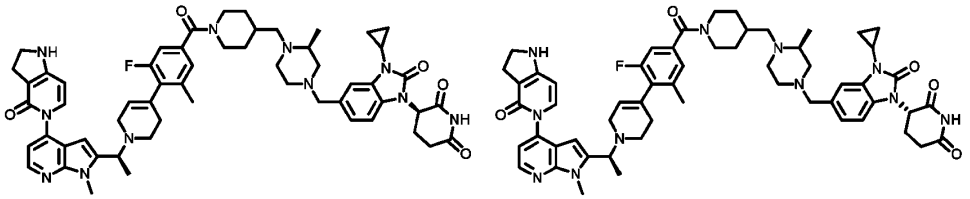
Example **3u141** and **3u142**. (S)-3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]-pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u140** (57 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u141** (6 mg, first peak) and Example **3u142** (13 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



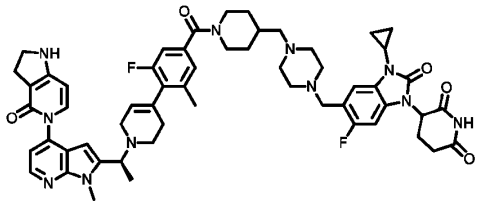
Example **3u143**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u143** (0.12 g, TFA salt) was prepared similarly to Example **3u163** from Ints. **2G53/3E78** (0.20 g/0.30 g).



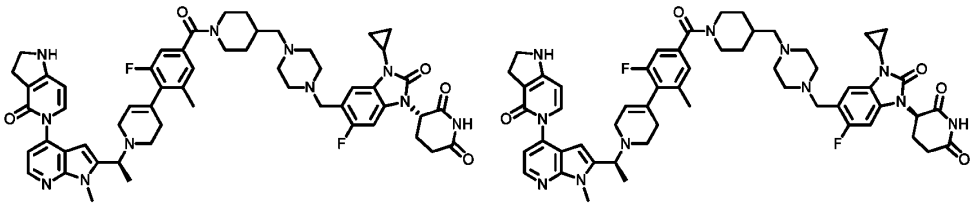
Example **3u144** and **3u145**. (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u143** (95 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (42 mL/min) to give Example **3u144** (32 mg, first peak) and Example **3u145** (18 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



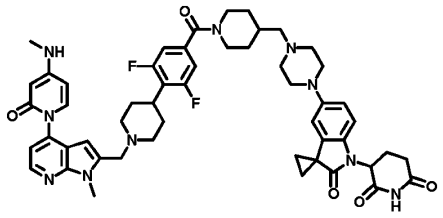
Example **3u146**. 3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u146** (95 mg, TFA) was prepared similarly to Example **3u163** from Ints. **2G53/3E200** (0.20 g/0.23 g).



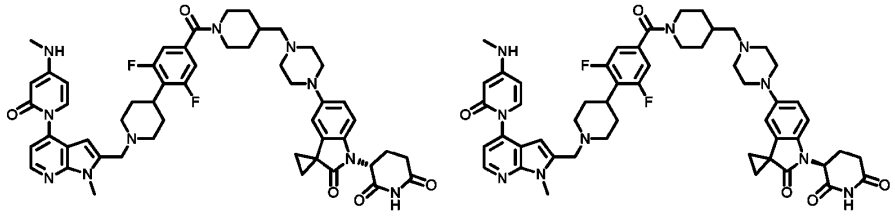
Example **3u147** and **3u148**. (S)-3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-6-fluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u146** (40 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u147** (11 mg, first peak) and Example **3u148** (13 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u149**. 3-(5'-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

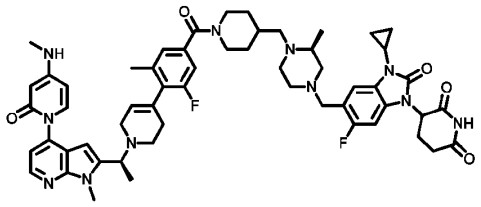
Example **3u149** (0.32 g) was prepared similarly to Example **3u163** from Ints. **2G108/3U1** (0.30 g/0.43 g).



Example **3u150** and **3u151**. (R)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (S)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]-pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

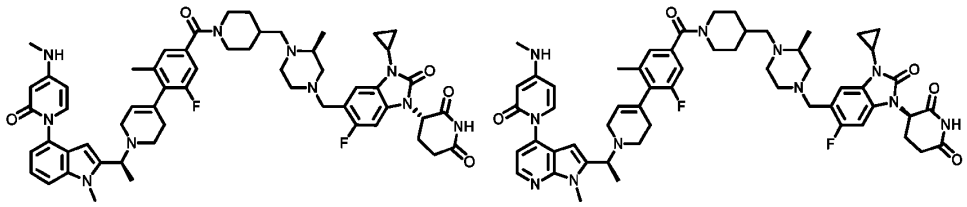
Example **3u149** (0.31 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (26 mL/min) to give Example **3u151**

(57 mg, first peak) and Example **3u150** (6 mg, second peak). The second peak required a second resolution using a Chiralpak IK 250x10 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (6 mL/min). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



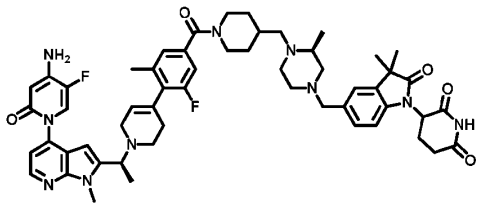
Example **3u166**. 3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Ints. **2G46/3E200** (0.40 g/0.30 g) were stirred 16h in DMF/Et_3N (5:1, 2.4 mL) and T3P (50% in EtOAc, 0.48 mL) at 0 °C to RT. The reaction mixture diluted with water to precipitate a solid that was HPLC-purified to give Example **3u166** (140 mg).



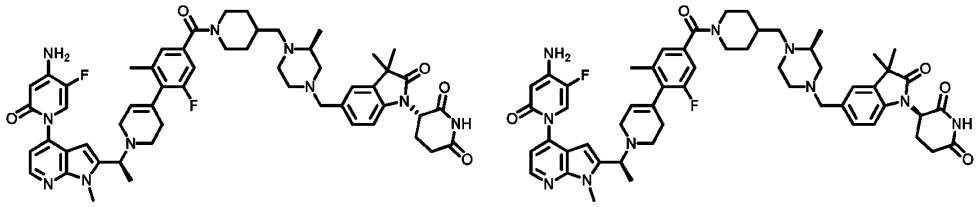
Example **3u167** and **3u168**. (S)-3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-indol-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u166** (140 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (30 mL/min) to give Example **3u167** (55 mg, first peak) and Example **3u168** (50 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



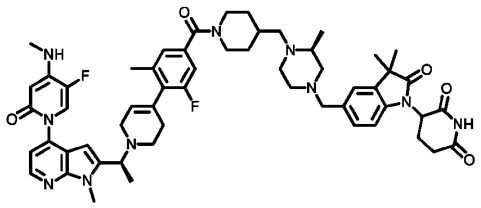
Example **3u169**. 3-(5-(((S)-4-((1-(4-(1-((S)-1-(4-(4-amino-5-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u169** (30 mg) was prepared similarly to Example **3u166** from Ints. **3U127/3E291** (0.15 g/0.21 g).



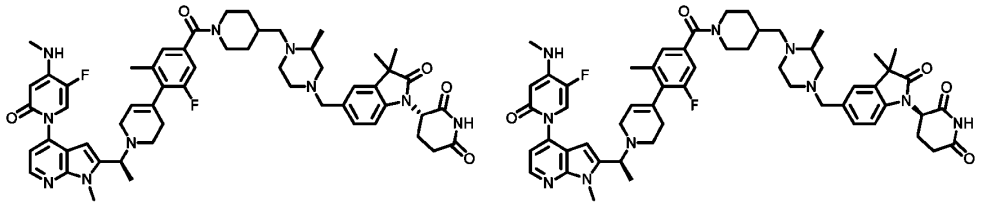
Example **3u170** and **3u171**. (S)-3-(5-(((S)-4-((1-(4-(1-((S)-1-(4-(4-amino-5-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(4-(1-((S)-1-(4-(4-amino-5-fluoro-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-fluoro-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u169** (30 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u170** (7 mg, first peak) and Example **3u171** (8 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



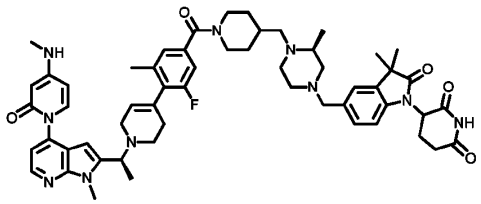
Example **3u172**. 3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u172** (80 mg) was prepared similarly to Example **3u166** from Ints. **2G45/3E291** (0.30 g/0.38 g).



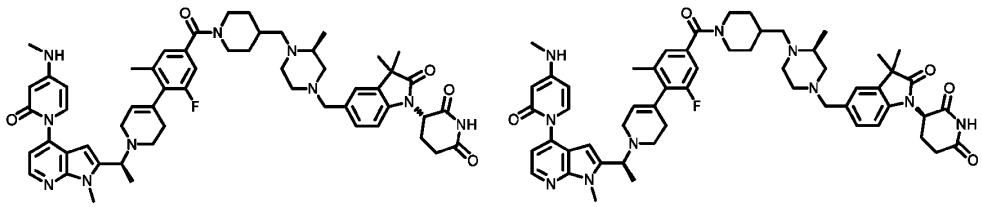
Example **3u173** and **3u174**. (S)-3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u172** (65 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u173** (10 mg, first peak) and Example **3u174** (19 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u175**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

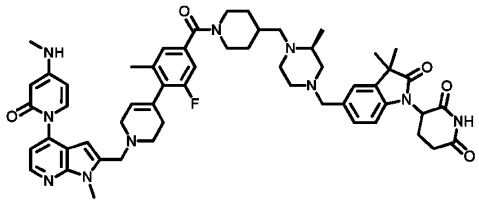
Example **3u175** (0.12 g) was prepared similarly to Example **3u166** from Ints. **2G46/3E291** (0.25 g/0.43 g).



Example **3u176** and **3u177**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

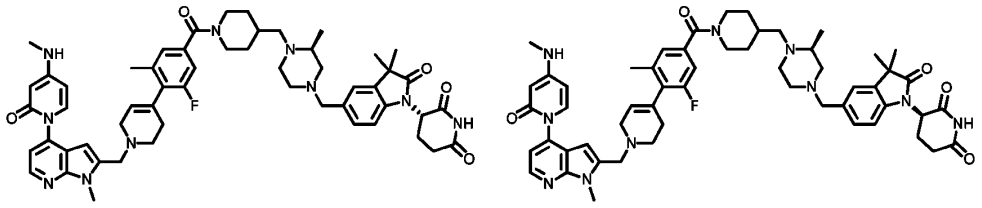
tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)-piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)-piperidine-2,6-dione

Example **3u175** (100 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u176** (15 mg, first peak) and Example **3u177** (18 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



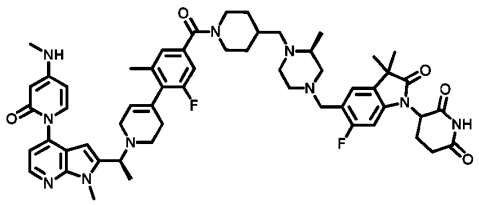
Example **3u178**. 3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u178** (0.14 g) was prepared similarly to Example **3u166** from Ints. **1M60/3E291** (0.30 g/0.50 g).



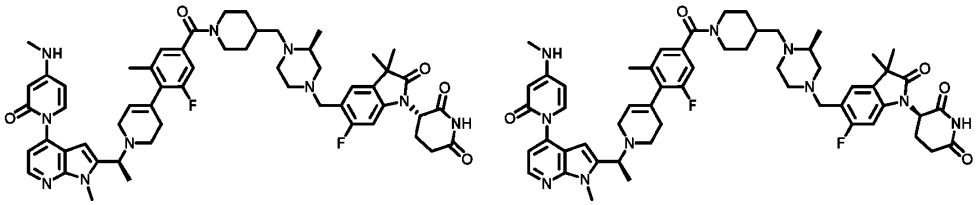
Example **3u179** and **3u180**. (S)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u178** (130 mg) was resolved by HPLC using a CELLULOSE-SC 10x250 mm 5μm column with an eluent of 40% ACN, 40% IPA and 20% DCM (28 mL/min) to give Example **3u179** (42 mg, first peak) and Example **3u180** (55 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



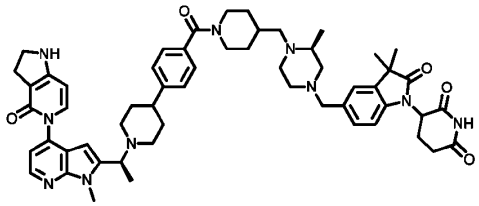
Example **3u181**. 3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)-piperidine-2,6-dione

Example **3u181** (80 mg) was prepared similarly to Example **3u166** from Ints. **2G46/3C47** (0.30 g/0.37 g).



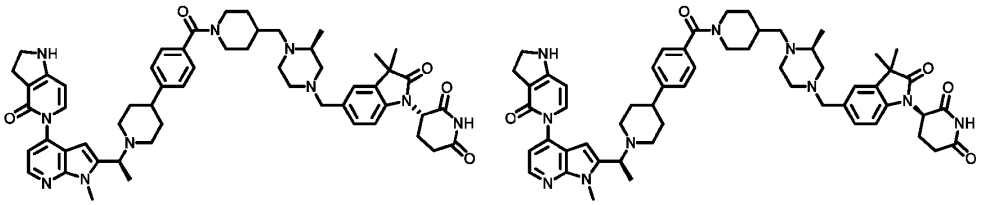
Example **3u182** and **3u183**. (S)-3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u181** (60 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u182** (19 mg, first peak) and Example **3u183** (20 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



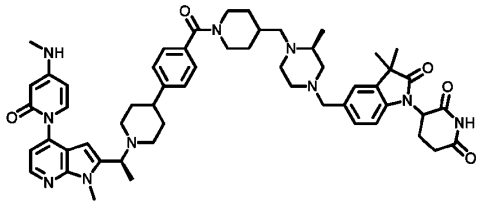
Example **3u184**. 3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u184** (90 mg) was prepared similarly to Example **3u166** from Ints. **3E178/3E291** (0.30 g/0.37 g).



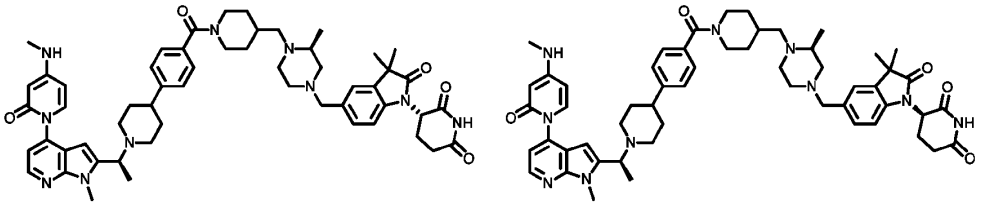
Example **3u185** and **3u186**. (S)-3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u184** (70 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u185** (25 mg, first peak) and Example **3u186** (24 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u187**. 3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione

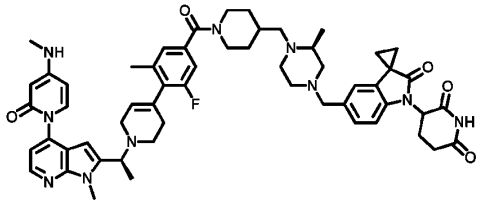
Example **3u184** (90 mg) was prepared similarly to Example **3u166** from Ints. **3E171/3E291** (0.25 g/0.43 g).



Example **3u188** and **3u189**. (S)-3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(3,3-dimethyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-

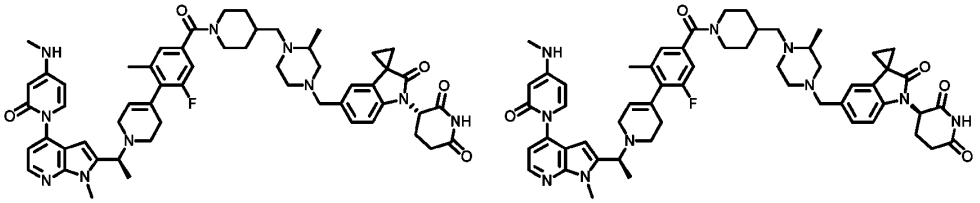
1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u187** (91 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (3 mL/min) to give Example **3u188** (28 mg, first peak) and Example **3u189** (32 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



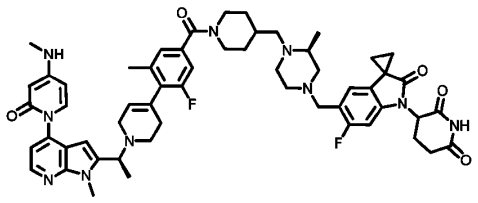
Example **3u190**. 3-(5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u184** (90 mg) was prepared similarly to Example **3u166** from Ints. **2G46/3C42** (0.28 g/0.57 g).



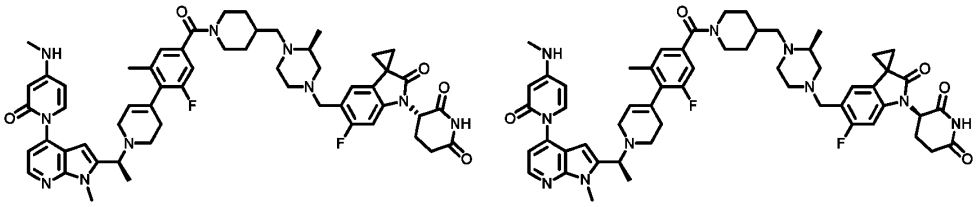
Example **3u191** and **3u192**. (S)-3-(5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro-[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u190** (114 mg) was resolved by HPLC using a Chiralpak IK 30x150 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u191** (35 mg, first peak) and Example **3u192** (35 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



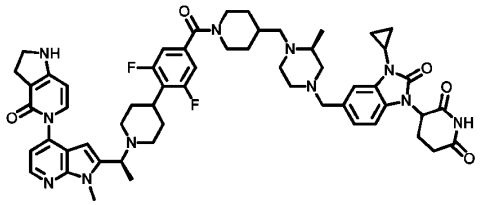
Example **3u193**. 3-(6'-fluoro-5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u193** (155 mg) was prepared similarly to Example **3u190** from Ints. **2G46/3U129** (0.28 g/0.41 g).



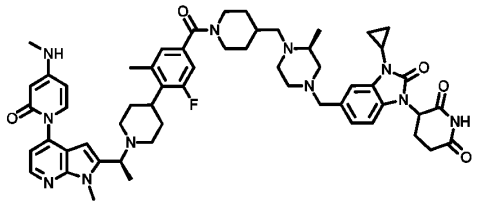
Example **3u194** and **3u195**. (S)-3-(6'-fluoro-5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(6'-fluoro-5'-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u193** (115 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u194** (40 mg, first peak) and Example **3u195** (40 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



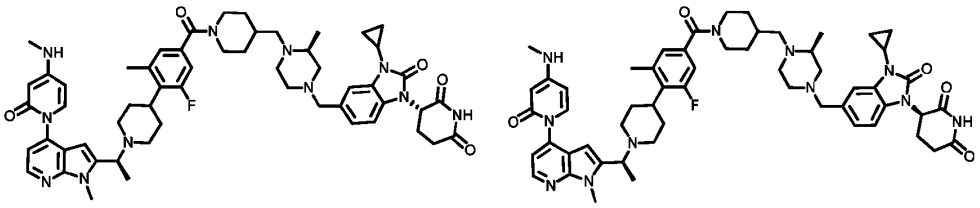
Example **3u196** 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione

Example **3u196** (90 mg) was prepared similarly to Example **3u166** from Ints. **3U131/3E78** (0.45 g/0.54 g).



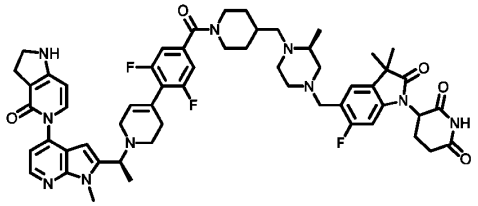
Example **3u197**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u184** (90 mg) was prepared similarly to Example **3u166** from Ints. **2G54/3C42** (0.30 g/0.40 g).



Example **3u198** and **3u199**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

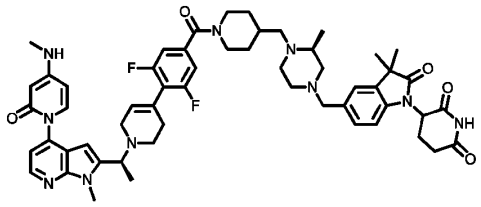
Example **3u197** (70 mg) was resolved by HPLC using a Chiralpak IK 10x250 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (5 mL/min) to give Example **3u198** (22 mg, first peak) and Example **3u199** (19 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u200**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-

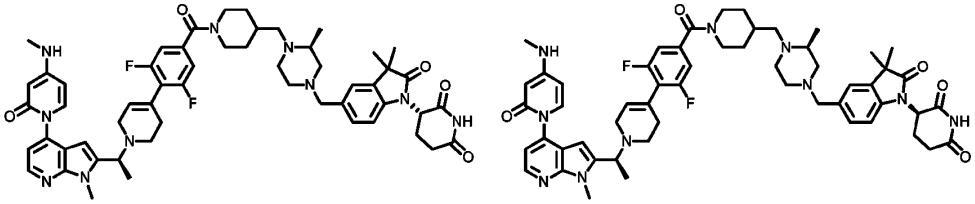
tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-6-fluoro-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u200** (90 mg) was prepared similarly to Example **3u166** from Ints. **3U122/3C47** (0.20 g/0.18 g).



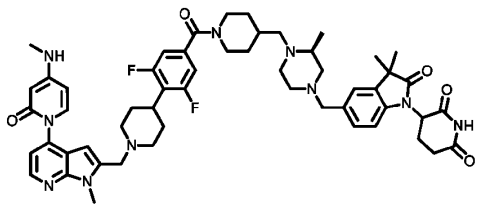
Example **3u201**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)-methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u201** (130 mg) was prepared similarly to Example **3u166** from Ints. **2G118/3E291** (0.30 g/0.45 g).



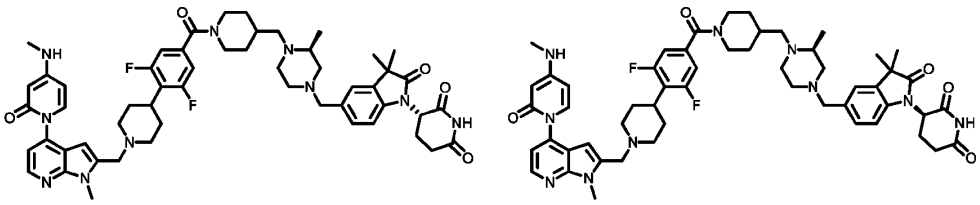
Example **3u202** and **3u203**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u201** (125 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u202** (50 mg, first peak) and Example **3u203** (43 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



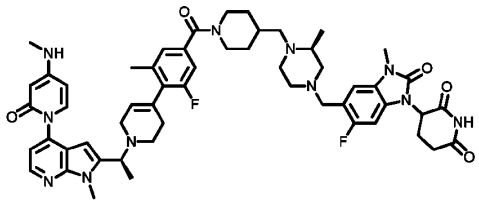
Example **3u204**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methyl-piperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u204** (110 mg) was prepared similarly to Example **3u201** from Ints. **2G108/3E291** (0.30 g/0.49 g).



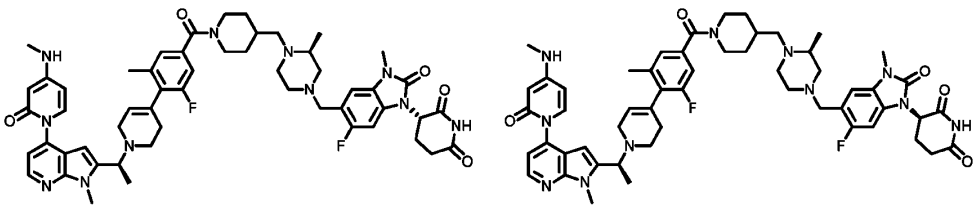
Example **3u205** and **3u206**. (S)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (R)-3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u204** (85 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (35 mL/min) to give Example **3u205** (21 mg, first peak) and Example **3u206** (26 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



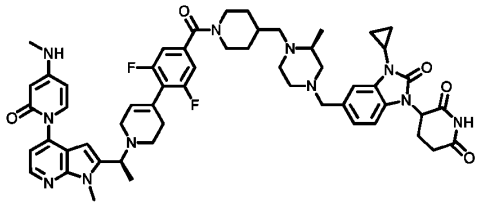
Example **3u207**. 3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u207** (0.20 g) was prepared similarly to Example **3u166** from Ints. **2G46/3E147** (0.32 g/0.48 g).



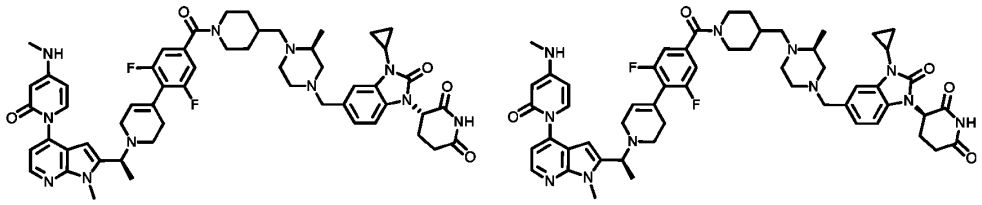
Example **3u208** and **3u209**. (S)-3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(6-fluoro-5-(((S)-4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u207** (175 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (30 mL/min) to give Example **3u208** (30 mg, first peak) and Example **3u209** (30 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



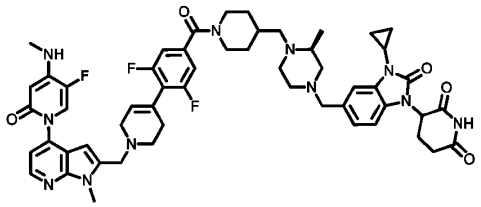
Example **3u210**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u210** (0.15 g) was prepared similarly to Example **3u166** Ints. **2G118/3E78** (0.30 g/0.40 g).



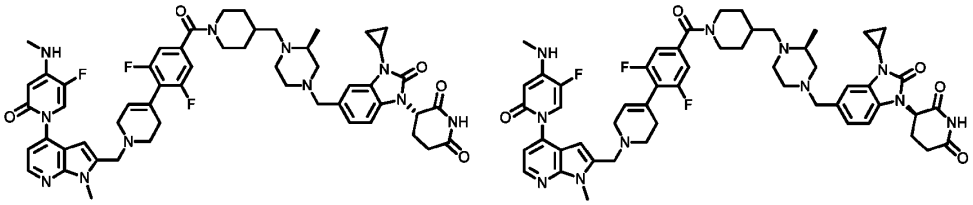
Example **3u211** and **3u212**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u210** (100 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u211** (37 mg, first peak) and Example **3u212** (30 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



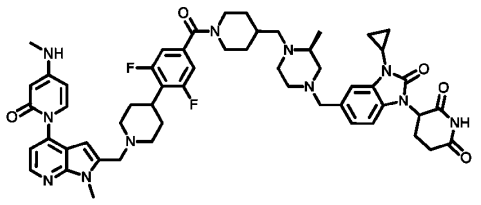
Example **3u213**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u213** (0.14 g) was prepared similarly to Example **3u166** from Ints. **2G48/3E78** (0.30 g/0.40 g).



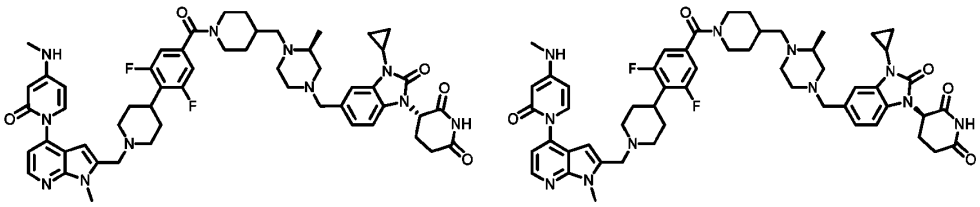
Example **3u214** and **3u215**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u213** (120 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (35 mL/min) to give Example **3u214** (26 mg, first peak) and Example **3u215** (28 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



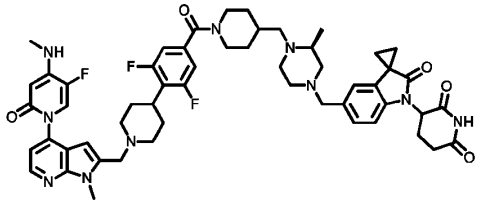
Example **3u216**. 3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)-methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u216** (0.14 g) was prepared similarly to Example **3u166** from Ints. **2G108/3E78** (0.30 g/0.41 g).



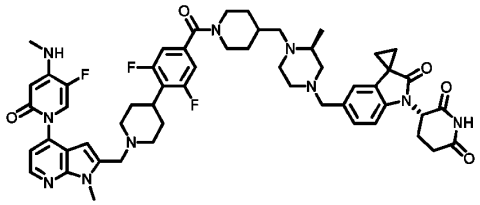
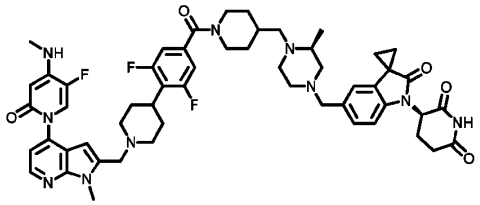
Example **3u217** and **3u218**. (S)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(3-cyclopropyl-5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)-piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u216** (100 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (50 mL/min) to give Example **3u217** (25 mg, first peak) and Example **3u218** (27 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



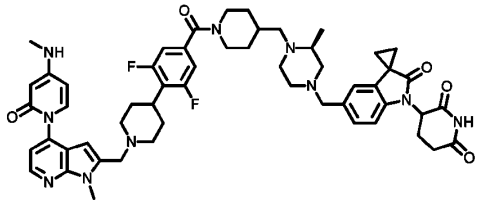
Example **3u219**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u219** (105 mg) was prepared similarly to Example **3u166** from Ints. **2G58/3C42** (0.30 g/0.44 g).

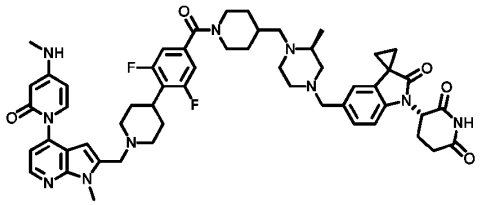
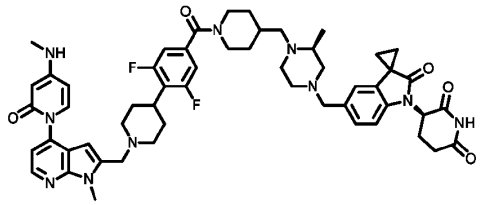
Example **3u220** and **3u221**. (S)-3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u219** (85 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u220** (37 mg, first peak) and Example **3u221** (30 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u222**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

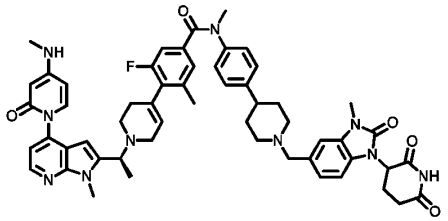
Example **3u222** (0.12 g) was prepared similarly to Example **3u166** from Ints. **2G108/3C42** (0.30 g/0.46 g).

Example **3u223** and **3u224**. (S)-3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (R)-3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-

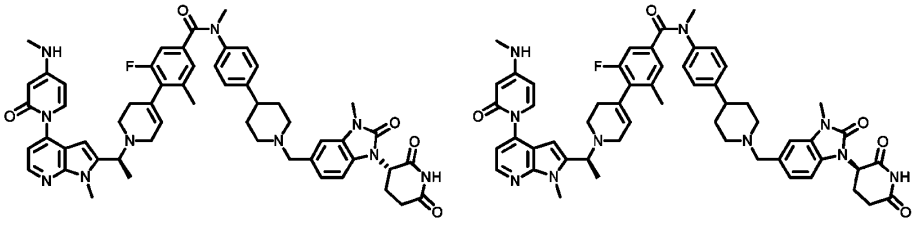
(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u222** (100 mg) was resolved by HPLC using a Chiralpak IK 30x250 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u223** (40 mg, first peak) and Example **3u224** (35 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



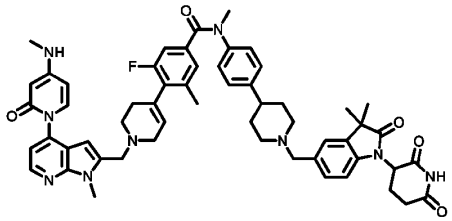
Example **3u225**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-benzamide

Example **3u225** (22 mg) was prepared similarly to Example **3u166** from Ints. **2G46/3U69** (0.24 g/0.35 g).



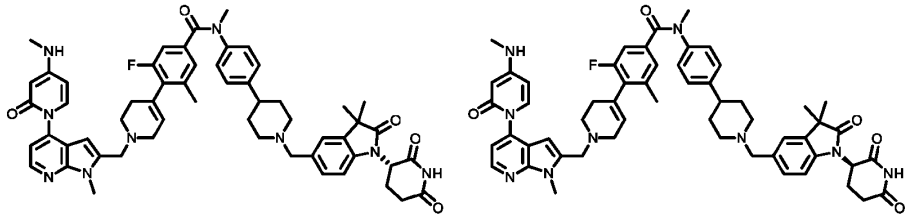
Example **3u226** and **3u227**. N-(4-(1-((1-((S)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzamide and N-(4-(1-((1-((R)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)benzamide

Example **3u225** (100 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (40 mL/min) to give Example **3u226** (7 mg, first peak) and Example **3u227** (7 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



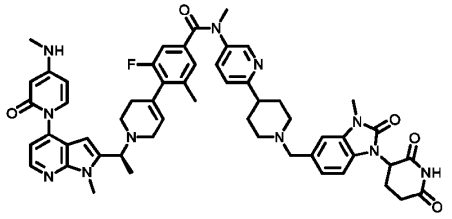
Example **3u228**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)-piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u228** (60 mg) was prepared similarly to Example **3u166** from Ints. **1M60/3U102** (0.20 g/0.24 g).



Example **3u229** and **3u230**. (S)-N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide and (R)-N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

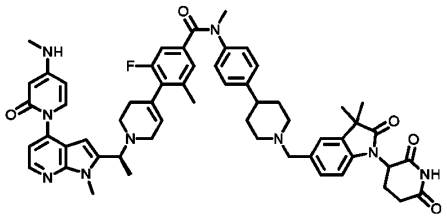
Example **3u228** (45 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (28 mL/min) to give Example **3u229** (17 mg, first peak) and Example **3u230** (18 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



Example **3u231**. N-(6-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)pyridin-3-yl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-

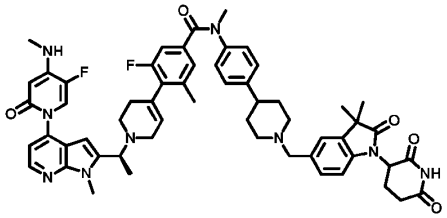
methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u231** (8 mg) was prepared similarly to Example **3u166** from Ints. **2G46/3U104** (0.10 g/0.12 g).



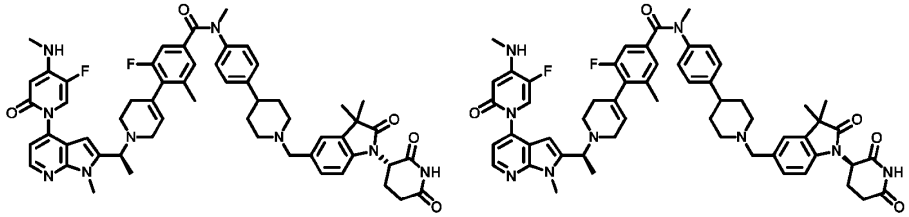
Example **3u232**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)-piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u232** (10 mg) was prepared similarly to Example **3u166** from Ints. **2G46/3U102** (50 mg/64 mg).



Example **3u233**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

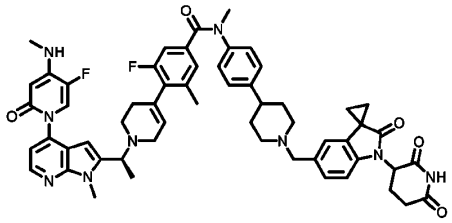
Int. **2G45** (0.30 g) was dissolved in DMF/Et_3N (13:1, 4.8 mL). Int. **3U102** (0.34 g) and BEP (0.23 g) were added at 0 °C and the mixture stirred for 12h at RT. The reaction mixture diluted with water to precipitate a solid that was HPLC-purified to give Example **3u233** (0.11 g).



Example **3u234** and **3u235**. N-(4-(1-((1-((S)-2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-

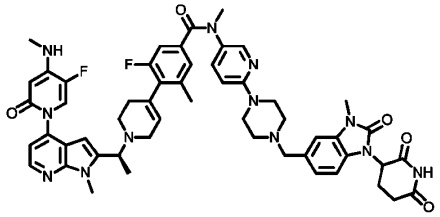
N,5-dimethylbenzamide and N-(4-(1-((1-((R)-2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

Example **3u233** (72 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (26 mL/min) to give Example **3u234** (26 mg, first peak) and Example **3u235** (22 mg, second peak). The absolute configurations for these compounds at the glutarimide chiral centers were not determined.



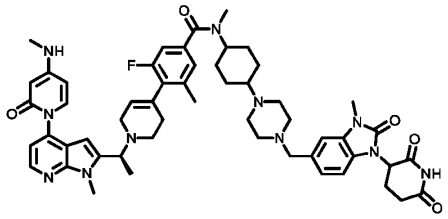
Example **3u236**. N-(4-(1-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

Ints. **2G45/3C55** (0.20 g/0.27 g) were mixed in DMF (5 mL). Et_3N (0.52 mL) and BEP (0.31 g) were added at 0 °C and the mixture stirred for 16h at RT. The reaction mixture diluted with water to precipitate a solid that was HPLC-purified to give Example **3u236** (20 mg).



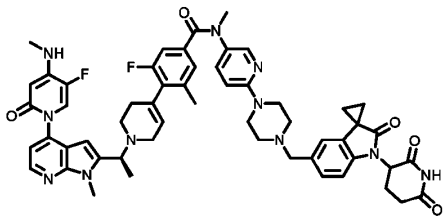
Example **3u237**. N-(6-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperazin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

Example **3u237** (0.1 g) was prepared similarly to Example **3u236** from Ints. **2G45/3U96** (0.15 g/0.18 g).



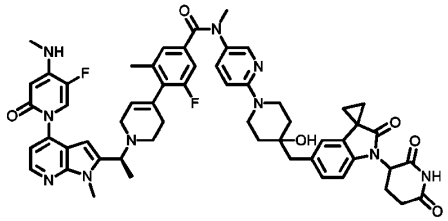
Example **3u238**. N-(4-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperazin-1-yl)cyclohexyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Int. **2G46** (21 mg) was added to a solution of Int. **3U97** (30 mg), HATU (21 mg) and DIPEA (52 µL) in DMF (1 mL) and stirred ON at RT. The reaction mixture was concentrated and HPLC-purified to give Example **3u238** (3 mg).



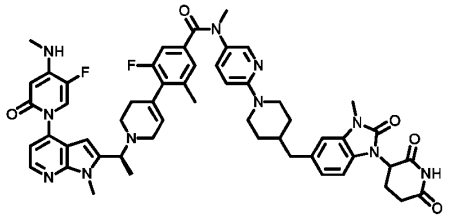
Example **3u239**. N-(6-(4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)-methyl)piperazin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethyl-benzamide

Example **3u239** (75 mg) was prepared similarly to Example **3u236** from Ints. **2G45/3U114** (0.12 g/0.17 g).



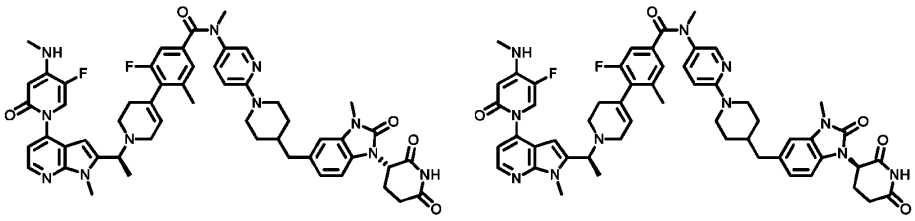
Example **3u240**. N-(6-(4-((1'-(2,6-dioxopiperidin-3-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-5'-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

Example **3u240** (7 mg) was prepared similarly to Example **3u236** from Ints. **2G45/3U108** (50 mg/68 mg).



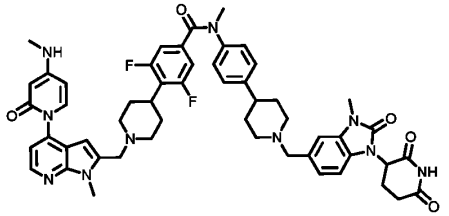
Example **3u241**. N-(6-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

Example **3u241** (0.12 g) was prepared similarly to Example **3u236** from Ints. **2G45/3U104** (0.20 g/0.24 g).



Example **3u242** and **3u243**. N-(6-(4-((1-((S)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-N,5-dimethylbenzamide and N-(6-(4-((1-((R)-2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

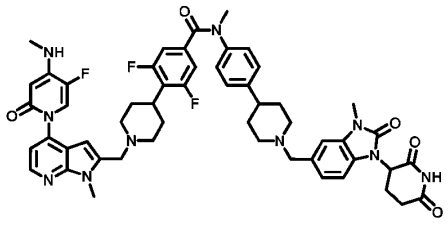
Example **3u241** (90 mg) was resolved by HPLC using a Chiralpak IK 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u242** (42 mg, first peak) and Example **3u243** (18 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



Example **3u244**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3,5-difluoro-N-methyl-4-(1-((1-methyl-4-(4-

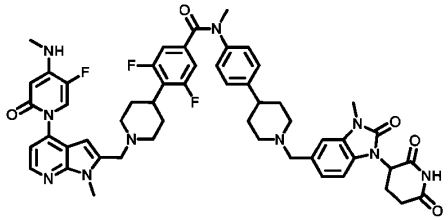
(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzamide

Example **3u244** (25 mg) was prepared similarly to Example **3u236** from Ints. **2G108/3U69** (0.10 g/0.13 g).



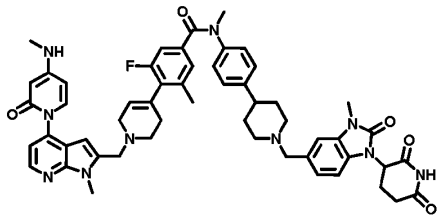
Example **3u245**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-N-methylbenzamide

Example **3u245** (22 mg) was prepared similarly to Example **3u236** from Ints. **2G58/3U69** (0.12 g/0.14 g).



Example **3u246**. N-(6-(4-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N,5-dimethylbenzamide

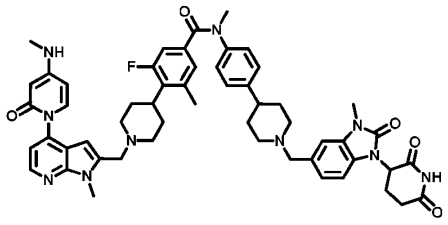
Example **3u246** (98 mg) was prepared similarly to Example **3u236** from Ints. **2G45/3U116** (0.20 g/0.25 g).



Example **3u247**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((1-methyl-4-(4-

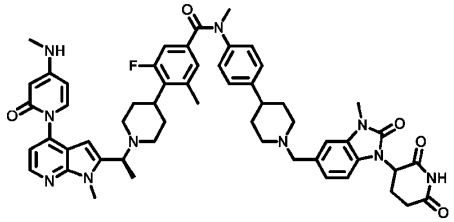
(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u247** (56 mg) was prepared similarly to Example **3u246** from Ints. **1M60/3U69** (0.10 g/0.13 g) in DMF (2 mL).



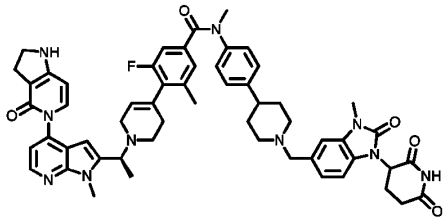
Example **3u248**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzamide

Example **3u248** (20 mg) was prepared similarly to Example **3u236** from Ints. **2G113/3U69** (0.13 g/0.15 g).



Example **3u249**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzamide

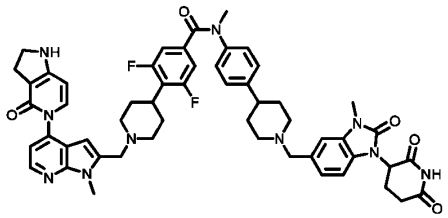
Example **3u249** (8 mg) was prepared similarly to Example **3u236** from Ints. **2G54/3U69** (0.10 g/0.13 g).



Example **3u250**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-

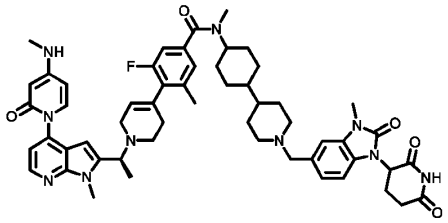
(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

Example **3u250** (25 mg) was prepared similarly to Example **3u236** from Ints. **2G53/3U69** (0.30 g/0.31 g).



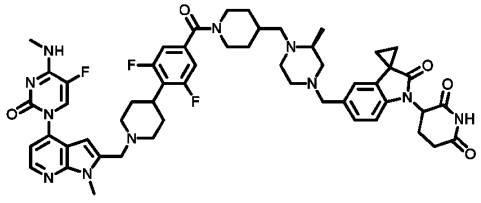
Example **3u251**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)phenyl)-3,5-difluoro-N-methyl-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-benzamide

Example **3u251** (25 mg) was prepared similarly to Example **3u236** from Ints. **2G57/3U69** (0.20 g/0.19 g).



Example **3u252**. N-(4-(1-((1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-5-yl)methyl)piperidin-4-yl)cyclohexyl)-3-fluoro-N,5-dimethyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzamide

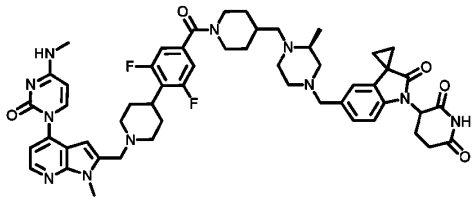
Ints. **3U67/3U135** (64 mg/0.15 g) and 4Å MS were stirred 24h in DCE/Et_3N (3 mL/50 microL). NaCNBH3 (19 mg) was added and stirring continued 24h. The mixture was filtered. The residue after concentration was HPLC-purified to give Example **3u252** (5.1 mg).



Example **3h10**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-

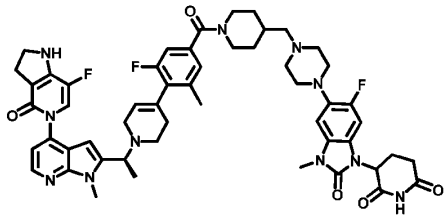
yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3h10** (26 mg) was prepared similarly to Example **3h2** from Ints. **3C40/3C42** (0.10 g/0.12 g).



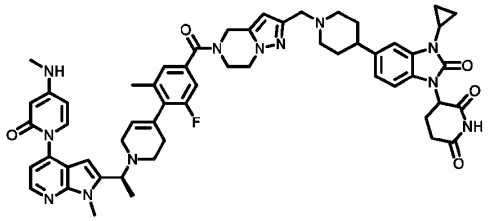
Example **3h12**. 3-(5'-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3h12** (27 mg) was prepared similarly to Example **3h2** from Ints. **3C10/3C42** (0.10 g/0.13 g).



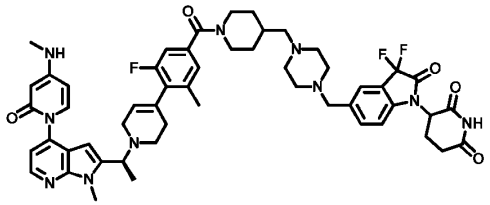
Example **3u253**. 3-(6-fluoro-5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u253** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G27/2T37** (0.12 g/0.15 g).



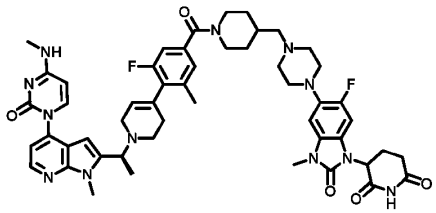
Example **3u254**. 3-(3-cyclopropyl-5-(1-((5-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u254** (10 mg) was prepared similarly to Example **3u35** from Ints. **2G46/2T52** (60 mg/60 mg).



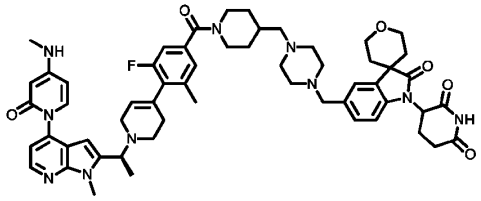
Example **3u255**. 3-(3,3-difluoro-5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u255** (4 mg) was prepared similarly to Example **3u35**from Ints. **2G46/2T70** (0.17 g/0.28 g).



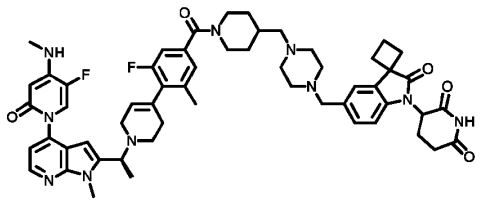
Example **3u256**. 3-(6-fluoro-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u256** (10 mg) was prepared similarly to Example **3u163** from Ints. **2G108/2T37** (90 mg/0.10 g).



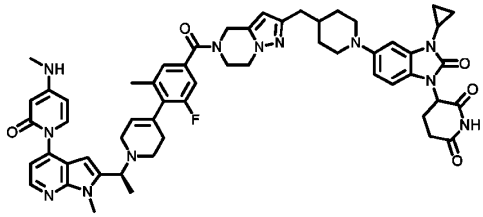
Example **3u257**. 3-(5-((4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-yl)piperidine-2,6-dione

Example **3u257** (4 mg) was prepared similarly to Example **3u35**from Ints. **2G46/2T74** (30 mg/30 mg).



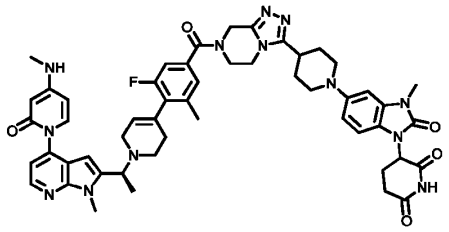
Example **3u258**. 3-(5'-((4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u258** (42 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T39** (90 mg/0.10 g).



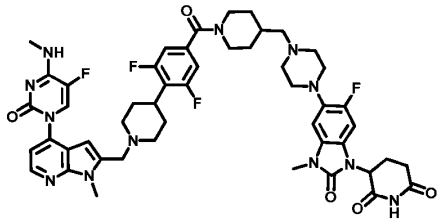
Example **3u259**. 3-(3-cyclopropyl-5-(4-((5-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperidin-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u259** (6 mg) was prepared similarly to Example **3u35**from Ints. **2G46/2T66** (26 mg/25 mg).



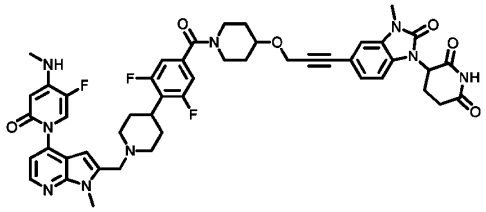
Example **3u260**. 3-(5-(4-(7-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)piperidin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u260** (3 mg) was prepared similarly to Example **3u35** from Ints. **2G46/2T82** (28 mg/25 mg).



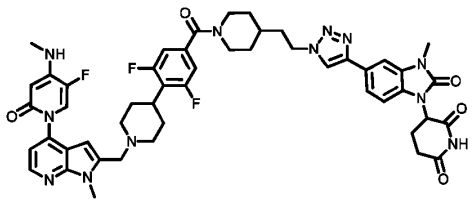
Example **3u261**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u261** (30 mg) was prepared similarly to Example **3u163** from Ints. **3C40/2T37** (0.10 g/0.12 g).



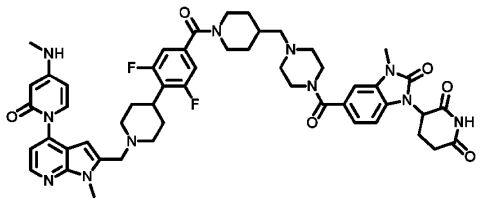
Example **3u262**. 3-(5-(3-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)oxy)prop-1-yn-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u262** (30 mg) was prepared similarly to Example **3u163** from Ints. **2G58/3B1** (0.13 g/0.25 g).



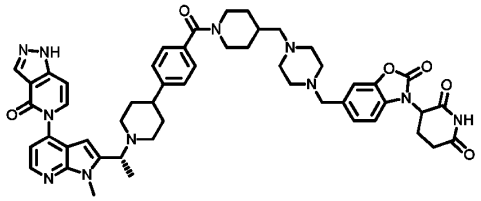
Example **3u263**. 3-(5-(1-(2-(1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u263** (52 mg) was prepared similarly to Example **3u163** from Ints. **2G58/2T63** (0.12 g/0.16 g).



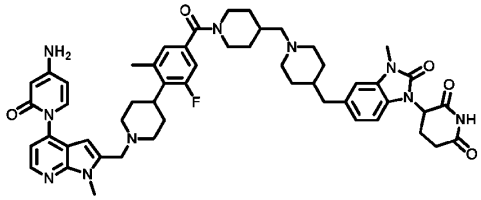
Example **3u264**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u264** (22 mg) was prepared similarly to Example **3u163** from Ints. **2G108/2T59** (0.10 g/0.15 g).



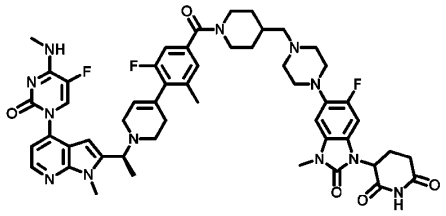
Example **3u265**. 3-(6-((4-((1-(4-(1-((R)-1-(1-methyl-4-(4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)piperidine-2,6-dione

Example **3u265** (36 mg) was prepared similarly to Example **3u163** from Ints. **2T77/2T57** (0.10 g/0.13 g).



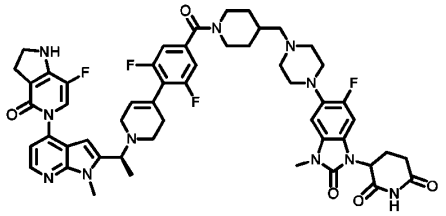
Example **3u267**. 3-(5-((1-((1-(4-(1-((4-(4-amino-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)-3-fluoro-5-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u267** (25 mg) was prepared similarly to Example **3u163** from Ints. **2T107/2T108** (20 mg/26 mg).



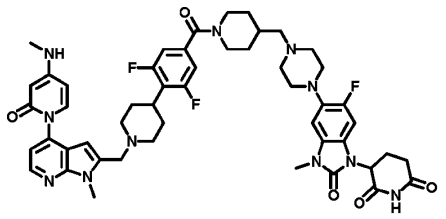
Example **3u268**. 3-(6-fluoro-5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

Example **3u268** (25 mg) was prepared similarly to Example **3u163** from Ints. **2G20/2T37** (80 mg/89 mg).



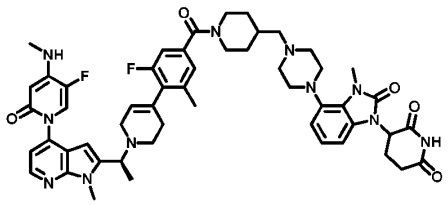
Example **3u269**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(7-fluoro-4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione

Example **3u269** (25 mg) was prepared similarly to Example **3u163** from Ints. **2G11/2T37** (0.10 g/0.13 g).



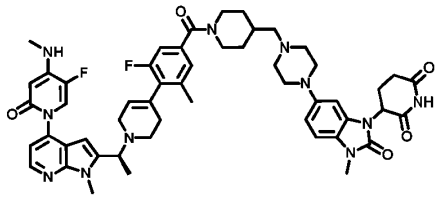
Example **3u270**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u270** (16 mg) was prepared similarly to Example **3u163** from Ints. **2G108/2T37** (0.12 g/0.15 g).



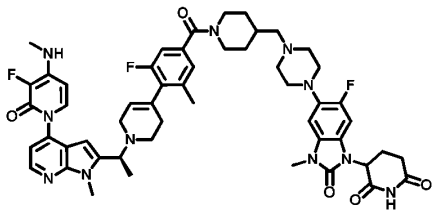
Example **3u271**. 3-(4-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione

Example **3u271** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G27/2T112** (0.12 g/0.14 g).



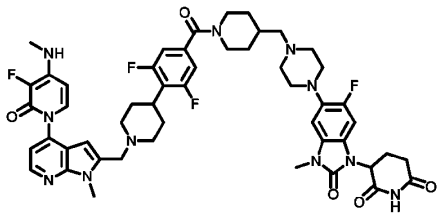
Example **3u272**. 3-(6-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u272** (45 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T115** (0.10 g/0.14 g).



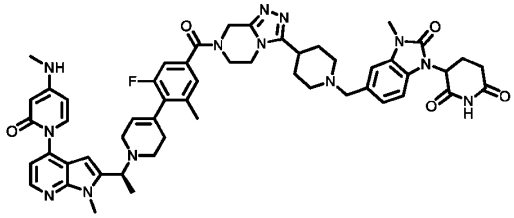
Example **3u273**. 3-(6-fluoro-5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u273** (15 mg) was prepared similarly to Example **3u163** from Ints. **3U39/2T37** (0.11 g/0.14 g).



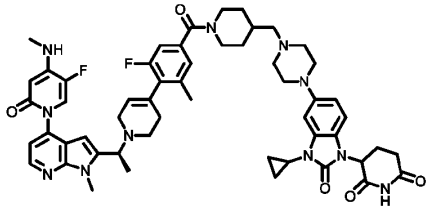
Example **3u274**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((4-(3-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u274** (29 mg) was prepared similarly to Example **3u163** from Ints. **3U78/2T73** (0.10 g/0.14 g).



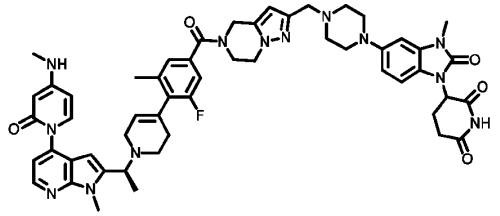
Example **3u275**. 3-(5-((4-(7-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)piperidin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Ints. **2T118/2G46** (34 mg/0.37 g) and HATU (0.37 g) were stirred ON in DMF/DIPEA (1 mL/0.55 mL). The residue after concentration was HPLC-purified to give Example **3u275** (12 mg).



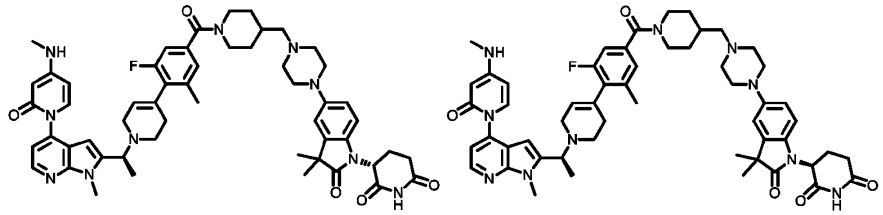
Int. **3u276**. 3-(3-cyclopropyl-5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methyl-benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u276** (20 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T86** (0.10 g/0.13 g).



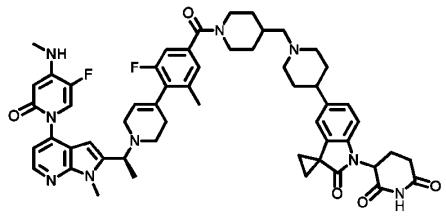
Example **3u277**. 3-(5-(4-((5-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Int. **2G46** (62 mg) and HATU (48 mg) were stirred 10 min in DMF/DIPEA (5 mL/0.04 mL). Int. **120** (58 mg) was added and stirring continued 15h. The residue after concentration was HPLC-purified to give Example **3u277** (11 mg).



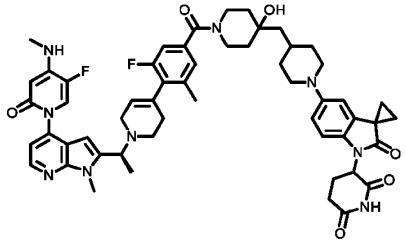
Example **3u281** and **3u280**. (R)-3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (S)-3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u304** (0.14 g) was resolved by HPLC using a Chiralpak IC 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (52 mL/min) to give Example **3u281** (28 mg, first peak) and Example **3u280** (26 mg, second peak) after a subsequent HPLC-purification. The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



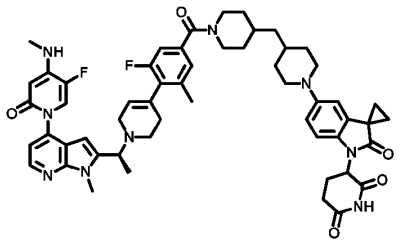
Example **3u282**. 3-(5'-(1-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)piperidin-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u282** (24 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T94** (0.10 g/0.14 g).



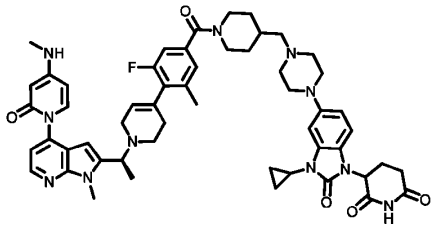
Example **3u283**. 3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-4-hydroxypiperidin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u283** (30 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T100** (0.10 g/0.16 g).



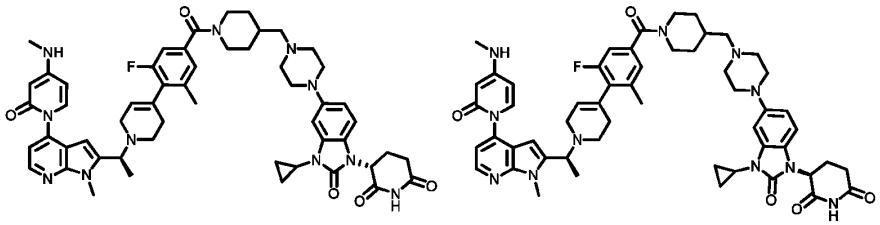
Example **3u284**. 3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperidin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u284** (30 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3C1** (80 mg/0.11 g).



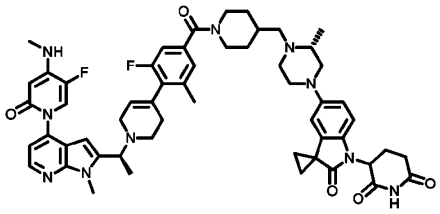
Example **3u287**. 3-(3-cyclopropyl-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione

Example **3u287** (0.12 g) was prepared similarly to Example **3u163** from Ints. **2G46/2T86** (0.30 g/0.35 g).



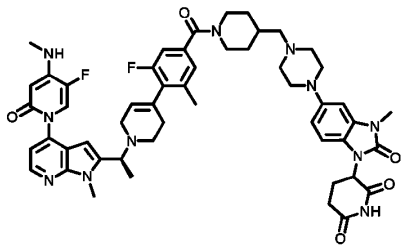
Example **3u279** and **3u278**. (R)-3-(3-cyclopropyl-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(3-cyclopropyl-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u287** (0.13 g) was resolved by HPLC using a CELLULOSE-SZ 250x30 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (42 mL/min) to give Example **3u279** (45 mg, first peak) and Example **3u278** (43 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



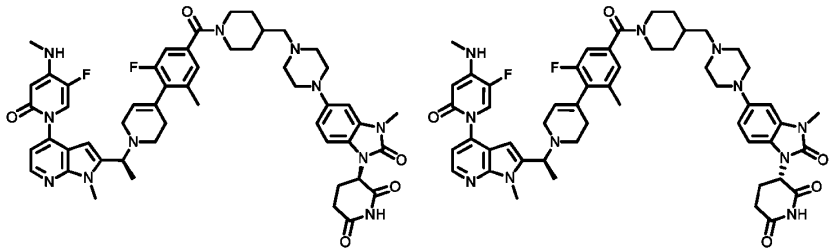
Example **3u295**. 3-(5'-((R)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u295** (75 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T89** (0.28 g/0.40 g).



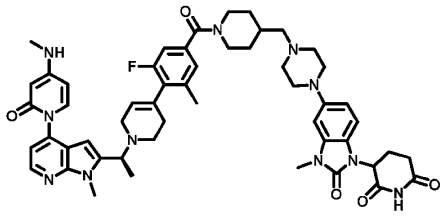
Example **3u298**. 3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione

Example **3u298** (0.16 g) was prepared similarly to Example **3u163** from Ints. **2G45/2T101** (0.25 g/0.31 g).



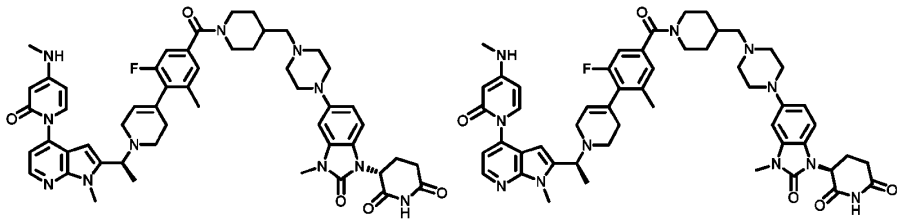
Example **3u297** and **3u296**. (R)-3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)piperidine-2,6-dione and (S)-3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methyl-amino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u298** (0.10 g) was resolved by HPLC using a CELLULOSE-SZ 250x10 mm 5µm column with an eluent of 35% ACN, 35% IPA and 30% DCM (4 mL/min) to give Example **3u297** (35 mg, first peak) and Example **3u296** (32 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



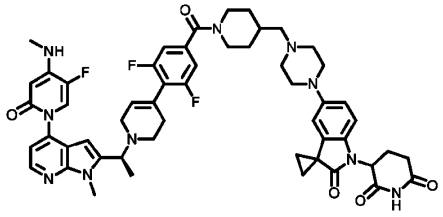
Example **3u299**. 3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u299** (0.17 g) was prepared similarly to Example **3u163** from Ints. **2G46/2T101** (0.25 g/0.32 g).



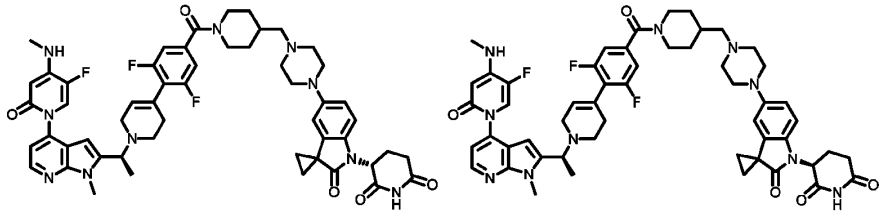
Example **3u294** and **3u293**. (R)-3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (S)-3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u299** (0.17 g) was resolved by HPLC using a CELLULOSE-SZ 250x10 mm 5µm column with an eluent of 40% ACN, 40% IPA and 20% DCM (6 mL/min) to give Example**3u294** (60 mg, first peak) and Example **3u293** (69 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



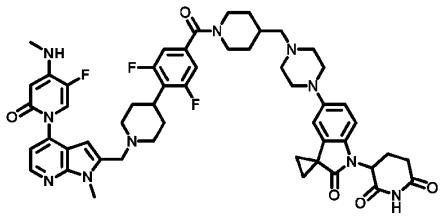
Example **3u300**. 3-(5'-(4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u300** (0.30 g) was prepared similarly to Example **3u163** from Ints. **2G74/3U1** (0.35 g/0.48 g).



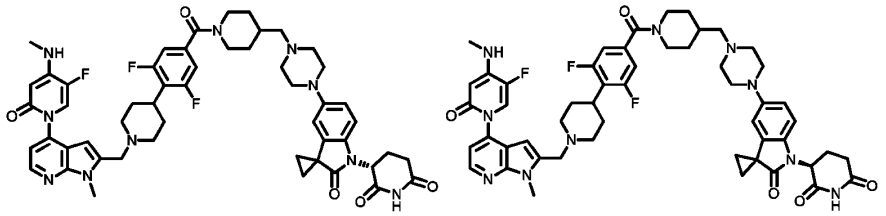
Example **3u290**. (R)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione or (S)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u300** (0.24 g) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 20% ACN, 40% IPA and 40% DCM (36 mL/min) to give Example **2u290** (27 mg, first peak). The second eluting peak was resolved by HPLC using a Chiralpak IC 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (52 mL/min) to give the other diastereomer (10 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



Example **3u301**. 3-(5'-(4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

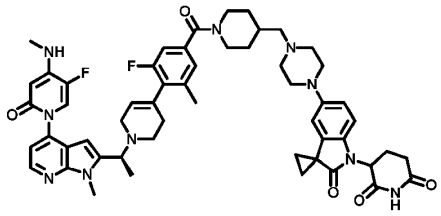
Example **3u301** (0.23 g) was prepared similarly to Example **3u163** from Ints. **2G58/3U1** (0.30 g/0.42 g).



Example **3u289** and **3u288**. (R)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-

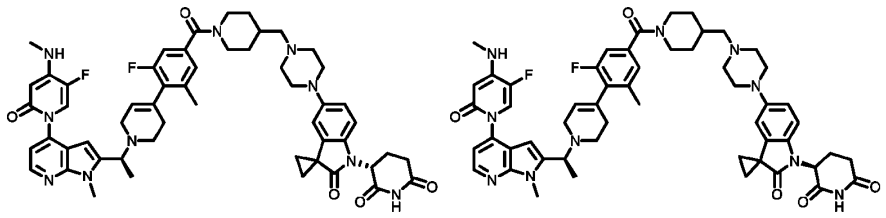
yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (S)-3-(5'-(4-((1-(3,5-difluoro-4-(1-((4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u301** (0.21 g) was resolved by HPLC using a CELLULOSE-SZ 250x30 mm 5μm column with an eluent of 40% ACN, 40% IPA and 20% DCM (36 mL/min) to give Example **3u289** (70 mg, first peak) and Example **3u288** (56 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



Example **3u302**. 3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

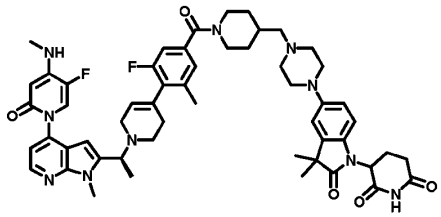
Example **3u302** (70 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3U1** (0.15 g/0.21 g).



Example **3u292** and **3u291**. (R)-3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione and (S)-3-(5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

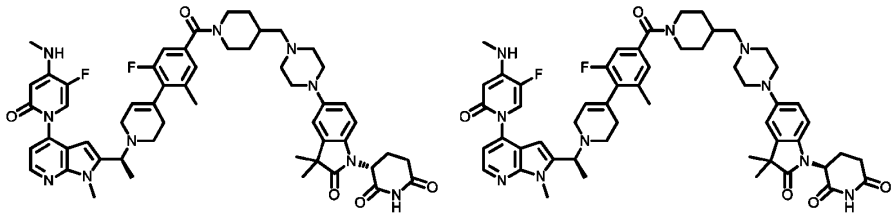
Example **3u302** (70 mg) was resolved by HPLC using a Chiralpak IK 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (26 mL/min) to give Example **3u292** (7

mg, first peak) and Example **3u291** (5 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



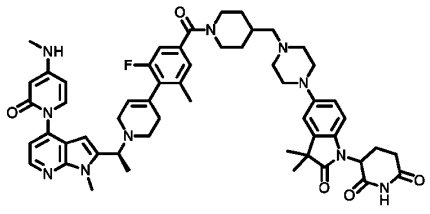
Example **3u303**. 3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u303** (0.11 g) was prepared similarly to Example **3u163** from Ints. **2G45/2T93** (0.26 g/0.33 g).



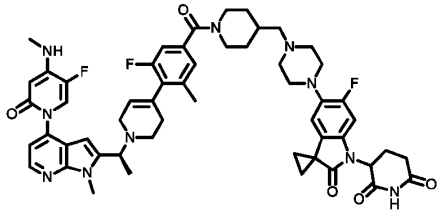
Example **3u286** and **3u285**. (R)-3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione and (S)-3-(5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u303** (0.19 g) was resolved by HPLC using a CELLULOSE-SC 250x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (52 mL/min) to give Example **3u286** (24 mg, first peak) and Example **3u285** (20 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



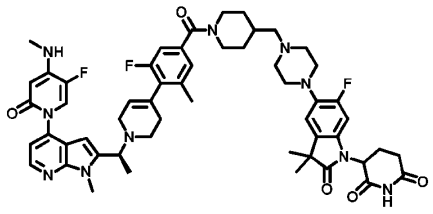
Example **3u304**. 3-(5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u304** (0.17 mg) was prepared similarly to Example **3u163** from Ints. **2G46/2T93** (0.30 g/0.40 g).



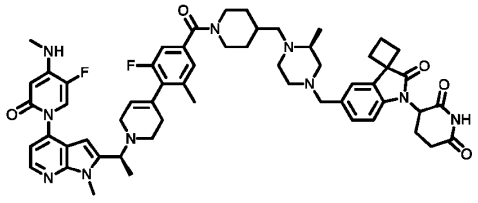
Example **3u305**. 3-(6'-fluoro-5'-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u305** (63 mg) was prepared similarly to Example **3u163** from Ints. **2G45/2T105** (0.12 g/0.17 g).



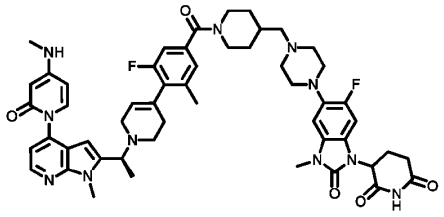
Example **3u306**. 3-(6-fluoro-5-(4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

Example **3u306** (14 mg) was prepared similarly to Example **3u163** from Ints. **2G45/TT73** (60 mg/74 mg).



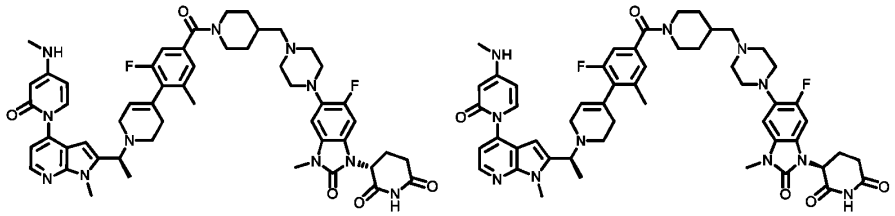
Example **3u309**. 3-(5'-(((S)-4-((1-(3-fluoro-4-(1-((S)-1-(4-(5-fluoro-4-(methylamino)-2-oxopyridin-1(2H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-methylbenzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)piperidine-2,6-dione

Example **3u309** (36 mg) was prepared similarly to Example **3u163** from Ints. **2G45/3U30** (0.11 g/0.15 g).



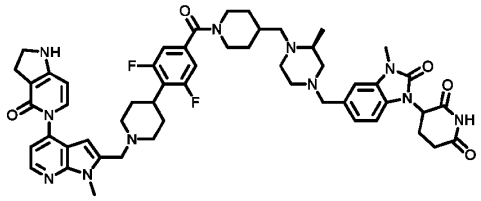
Example **3u310**. 3-(6-fluoro-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-piperidine-2,6-dione

Example **3u310** (0.21 g) was prepared similarly to Example **3u163** from Ints. **2G46-1/2T37** (0.30 g/0.35 g).



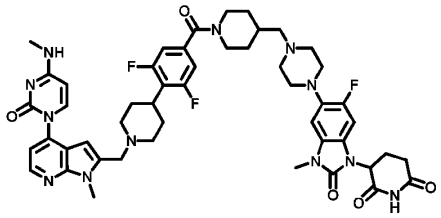
Example **3u308** and **3u307**. (R)-3-(6-fluoro-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and (R)-3-(6-fluoro-5-(4-((1-(3-fluoro-5-methyl-4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u310** (0.19 g) was resolved by HPLC using a Chiralpak IF PACKED 50x30 mm 5μm column with an eluent of 35% ACN, 35% IPA and 30% DCM (48 mL/min) to give Example **3u308** (14 mg, first peak) and Example **3u307** (20 mg, second peak). The absolute configurations were not determined at the glutarimide chiral centers for these compounds.



Example **3u311**. 3-(5-(((S)-4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3u311** (28 mg, TFA salt) was prepared similarly to Example **3u163** from Ints. **2G57/3E68** (0.15 g/0.15 g).



Example **3h43**. 3-(5-(4-((1-(3,5-difluoro-4-(1-((1-methyl-4-(4-(methylamino)-2-oxopyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

Example **3h43** (24 mg) was prepared similarly to Example **2h2** from Ints. **3C10/2T37** (0.10 g/0.12 g).

Characterization data

No.	Method	RT	Purity	MassObs	MassCalcd
3u99	34	3.91	96.12	995.55	994.5
3u97	18	1.35	98.47	991.99	990.5
3u96	34	3.82	99.76	991.5	990.5
3u95	34	3.77	98.49	991.5	990.5
3u94	34	3.78	97.75	991.54	990.5
3u93	34	3.78	98.04	991.56	990.5
3u92	34	3.7	98.83	984.63	983.5
3u91	34	3.72	94.51	984.59	983.5
3u90	34	3.74	99.34	982.53	983.5

3u9	34	3.97	98.32	1001.64	1000.5
3u89	34	3.86	97.51	983.56	982.5
3u88	34	3.86	97	983.52	982.5
3u87	34	3.85	99.3	983.67	982.5
3u86	33	7.34	97.2	983.18	982.5
3u85	34	3.67	97.5	982.51	981.5
3u84	34	3.89	98.62	987.51	986.5
3u83	34	3.61	94.02	986.46	985.5
3u82	34	3.95	97.47	985.6	984.5
3u81	34	3.95	99.14	985.64	984.5
3u80	34	3.46	98.72	985.6	984.5
3u8	34	3.8	97.01	1000.48	999.5
3u79	34	3.85	96.76	987.61	986.5
3u78	34	3.85	96.08	987.61	986.5
3u77	34	3.86	98.92	987.57	986.5
3u76	10	9.12	95.25	982.53	981.5
3u75	10	9.13	95.04	982.62	981.5
3u74	34	3.64	97.69	982.66	981.5
3u73	34	3.64	98.35	982.58	981.5
3u72	34	3.65	98.87	982.58	981.5
3u71	34	3.65	99.57	982.58	981.5
3u70	34	3.69	95.75	982.55	981.5
3u7	34	3.7	99.72	947.63	946.5
3u69	31	1.36	97.38	981.66	980.5
3u68	34	3.76	95.02	981.59	980.5
3u67	34	3.77	94.57	981.63	980.5
3u66	34	3.75	97.07	981.61	980.5
3u65	34	3.94	96.61	981.59	980.5
3u64	34	3.95	98.36	981.59	980.5
3u63	34	3.97	95.57	981.54	980.5
3u62	34	3.68	95.09	976.63	975.5
3u61	34	3.69	95.02	976.63	975.5
3u60	34	3.68	99.29	976.61	975.5
3u6	34	3.71	99.81	947.63	946.5
3u59	34	3.78	97.86	975.58	974.5

3u58	34	3.77	97.74	975.54	974.5
3u57	34	3.79	96.94	975.54	974.5
3u56	34	3.6	99.24	974.53	973.5
3u55	34	3.6	95.13	974.53	973.5
3u54	34	3.64	98.59	974.6	973.5
3u53	34	3.62	97.88	974.53	973.5
3u52	34	3.62	98.11	974.53	973.5
3u51	34	3.61	97.38	974.55	973.5
3u50	34	3.91	97.56	989.59	988.5
3u5	34	3.71	98.46	947.59	946.5
3u49	34	3.9	97.77	989.63	988.5
3u48	34	3.93	99.26	989.59	988.5
3u47	34	3.76	96.79	969.6	968.5
3u46	34	3.76	98	969.64	968.5
3u45	34	3.76	98.88	969.6	968.5
3u44	34	3.71	99.52	973.52	972.5
3u43	34	3.7	97.37	973.52	972.5
3u42	34	3.69	97.84	973.59	972.5
3u41	10	8.98	91.55	966.78	965.5
3u40	10	8.99	94.29	964.6	965.5
3u4	34	4.02	98.92	1013.54	1012.5
3u39	34	3.55	91.08	964.56	965.5
3u38	34	3.82	98.25	965.59	964.5
3u37	34	3.82	99.34	965.55	964.5
3u36	34	3.83	97.35	965.61	964.5
3u35	41	0.811	100	964.4	965.5
3u34	34	3.63	98.06	966.62	965.5
3u33	34	3.63	98.45	966.62	965.5
3u32	34	3.67	96.73	966.62	965.5
3u311	34	3.61	98.7	970.54	969.5
3u310	34	3.71	95.74	956.54	955.5
3u31	34	3.52	98.69	944.57	943.5
3u309	19	1.64	96.08	1009.62	1008.5
3u308	34	3.7	95	956.52	955.5
3u307	34	3.7	96.07	956.52	955.5

3u306	34	3.98	97.01	987.51	986.5
3u305	34	3.93	95.42	985.49	984.5
3u304	31	1.4	98.14	951.54	950.5
3u303	31	1.43	98.8	969.56	968.5
3u302	19	4.45	98.74	967.73	966.5
3u301	32	1.75	99.48	959.56	958.4
3u300	30	4.24	97.32	971.58	970.4
3u30	34	3.52	98.68	944.57	943.5
3u3	34	3.57	85.19	956.45	955.5
3u299	30	4.12	95.42	938.6	937.5
3u298	34	3.71	95.01	956.52	955.5
3u297	38	2.79	98.15	956.62	955.5
3u296	38	2.81	96.26	956.75	955.5
3u295	30	1.45	95.83	981.62	980.5
3u294	34	3.62	98.45	938.54	937.5
3u293	34	3.6	98.16	938.54	937.5
3u292	34	3.82	98.23	967.56	966.5
3u291	34	3.83	98.23	967.52	966.5
3u290	34	3.82	98.54	971.51	970.4
3u29	34	3.48	99.04	944.61	943.5
3u289	34	3.77	97.74	959.54	958.4
3u288	34	3.77	96.7	959.5	958.4
3u287	34	3.7	98.45	964.58	963.5
3u286	34	3.91	95.12	969.58	968.5
3u285	34	3.91	95.06	969.53	968.5
3u284	34	4.07	95.18	966.55	965.5
3u283	34	3.69	98.07	982.51	981.5
3u282	34	3.98	95.21	966.51	965.5
3u281	34	3.81	95.98	951.6	950.5
3u280	34	3.81	97.68	951.56	950.5
3u28	34	3.56	98.22	962.54	961.5
3u279	34	3.7	98.21	964.54	963.5
3u278	34	3.69	98.24	964.54	963.5
3u277	41	0.897	100	974.4	975.5
3u276	34	3.82	95.44	982.55	981.5

3u275	41	0.806	100	976.6	975.5
3u274	34	3.77	99.67	966.47	965.4
3u273	34	3.8	96.92	974.49	973.5
3u272	34	3.79	99.69	956.52	955.5
3u271	34	3.91	96.11	956.52	955.5
3u270	34	3.66	98.68	948.45	947.4
3u27	34	3.57	97.3	962.54	961.5
3u269	34	3.88	97.64	990.45	989.4
3u268	34	3.69	99.07	975.46	974.5
3u267	34	3.58	98.79	925.42	924.5
3u265	34	3.62	97	920.42	919.4
3u264	34	3.42	98.67	958.47	957.4
3u263	30	1.57	98.6	945.57	944.4
3u262	30	1.66	99.78	904.53	903.4
3u261	16	1.74	99.66	967.69	966.4
3u260	41	0.917	97.4	963.4	961.5
3u26	34	3.55	99.01	960.48	961.5
3u259	41	0.919	97.83	1002.4	1000.5
3u258	34	3.9	97.73	995.59	994.5
3u257	41	0.884	91.01	1005.6	1006.5
3u256	34	3.58	95.74	957.52	956.5
3u255	41	0.944	95.36	971	972.5
3u254	41	0.903	97.93	1002.4	1000.5
3u253	34	3.82	95.92	986.5	985.5
3u252	41	0.93	100	963.2	964.5
3u251	34	3.83	98.75	963.49	962.4
3u250	19	4.53	93.08	971.61	970.5
3u25	10	8.93	94.23	964.6	963.5
3u249	10	9.96	99.65	961.56	960.5
3u248	34	3.83	97.68	947.53	946.5
3u247	34	3.8	98.38	945.47	944.4
3u246	34	3.62	96.46	994.48	993.4
3u245	34	3.93	97.38	969.49	968.4
3u244	34	3.82	96.66	951.48	950.4
3u243	34	3.96	96.38	978.52	977.5

3u242	34	3.98	96.64	978.52	977.5
3u241	34	3.99	97.4	978.48	977.5
3u240	34	3.76	98.37	1005.48	1004.5
3u24	10	8.92	93.42	964.6	963.5
3u239	34	3.84	98.19	990.49	989.5
3u238	41	0.861	98.81	964.4	965.5
3u237	34	3.73	98.43	979.55	978.4
3u236	34	4.14	95.07	988.54	987.5
3u235	34	4.2	95.18	990.55	989.5
3u234	34	4.21	96.67	990.6	989.5
3u233	34	4.23	98.22	990.55	989.5
3u232	34	4.07	97.84	972.5	971.5
3u231	34	3.62	94.04	960.44	959.5
3u230	34	3.99	95.82	958.51	957.5
3u23	10	8.92	92.35	964.6	963.5
3u229	34	3.97	96.65	958.47	957.5
3u228	34	3.99	98	958.47	957.5
3u227	34	3.95	97.68	959.48	958.5
3u226	34	3.86	97.68	959.48	958.5
3u225	34	3.89	95.05	959.48	958.5
3u224	34	3.74	98.16	969.68	968.5
3u223	34	3.73	97.58	969.56	968.5
3u222	34	3.74	98.39	969.56	968.5
3u221	34	3.83	97.82	987.57	986.5
3u220	34	3.83	97.43	987.61	986.5
3u22	10	8.89	92.46	962.58	963.5
3u219	34	3.83	98.29	987.57	986.5
3u218	34	3.67	98.52	984.59	983.5
3u217	34	3.7	98.38	984.59	983.5
3u216	34	3.7	97.96	984.55	983.5
3u215	34	3.74	99.57	1000.59	999.5
3u214	34	3.75	99.17	1000.55	999.5
3u213	34	3.72	99.69	1000.51	999.5
3u212	34	3.75	95.01	996.56	995.5
3u211	34	3.74	97.96	996.64	995.5

3u210	34	3.72	96.72	996.52	995.5
3u21	34	4.17	95.22	964.5	963.5
3u209	34	3.72	95.89	984.55	983.5
3u208	34	3.7	96.79	984.55	983.5
3u207	34	3.7	98.85	984.51	983.5
3u206	34	3.81	98.25	971.57	970.5
3u205	34	3.19	97.92	971.53	970.5
3u204	34	3.77	98.91	971.49	970.5
3u203	34	3.86	98.47	983.58	982.5
3u202	34	3.87	96.9	983.58	982.5
3u201	34	3.73	98.09	983.5	982.5
3u200	35	1.65	96.58	1013.55	1012.5
3u20	34	4.05	98.12	984.53	983.5
3u2	34	3.57	90.15	956.45	955.5
3u199	34	3.8	97.33	994.54	993.5
3u198	34	3.78	98.07	994.54	993.5
3u197	34	3.79	96.24	994.59	993.5
3u196	34	3.82	95.01	1010.55	1009.5
3u195	34	3.84	97.97	995.51	994.5
3u194	34	3.84	98.46	995.51	994.5
3u193	34	3.85	98.3	995.59	994.5
3u192	34	3.76	98.63	977.49	976.5
3u191	8	3.76	98.02	977.54	976.5
3u190	34	3.77	98.43	977.54	976.5
3u19	34	3.63	96.95	958.53	957.5
3u189	34	3.78	96.1	949.52	948.5
3u188	34	3.8	97.24	949.57	948.5
3u187	34	3.77	94.34	949.57	948.5
3u186	34	3.79	96.94	961.58	960.5
3u185	34	3.81	95.01	961.62	960.5
3u184	34	3.74	96.24	961.58	960.5
3u183	34	3.94	97.42	997.57	996.5
3u182	34	3.93	95.13	997.57	996.5
3u181	34	3.95	96.53	997.61	996.5
3u180	34	3.76	96.89	965.57	964.5

3u18	34	3.69	98.06	957.52	956.5
3u179	34	3.4	97.16	965.61	964.5
3u178	22	3.96	99.24	965.49	964.5
3u177	34	3.87	96.85	979.68	978.5
3u176	34	3.84	97.91	979.55	978.5
3u175	34	3.88	96.44	979.68	978.5
3u174	34	3.97	98..00	997.61	996.5
3u173	34	3.99	97.44	997.61	996.5
3u172	34	10.07	99.46	997.69	996.5
3u171	34	3.95	99.49	983.63	982.5
3u170	34	3.95	97.98	983.67	982.5
3u17	34	3.69	98.01	957.52	956.5
3u169	34	3.85	98.48	983.96	982.5
3u168	34	3.81	99.22	1010.63	1009.5
3u167	34	3.81	99.16	1010.63	1009.5
3u166	34	3.87	96.85	1010.55	1009.5
3u165	34	3.92	97.86	991.56	990.5
3u164	34	3.93	98.9	995.61	994.5
3u163	34	3.43	97.51	938.56	937.5
3u162	34	3.43	95.31	938.52	937.5
3u161	8	3.44	92.24	938.52	937.5
3u160	34	3.44	95.38	940.54	939.5
3u16	34	3.68	98.28	957.52	956.5
3u159	34	3.52	99.6	940.58	939.5
3u158	34	3.46	99.22	940.54	939.5
3u157	34	3.52	98.57	952.59	951.5
3u156	34	3.53	97.71	952.55	951.5
3u155	10	8.92	99.09	952.55	951.5
3u154	34	3.84	96.46	999.6	998.5
3u153	34	3.85	97.69	999.6	998.5
3u152	34	3.85	99.39	999.58	998.5
3u151	34	3.69	95.9	941.53	940.5
3u150	34	3.7	97.94	941.48	940.5
3u15	34	3.63	96.25	970.56	969.5
3u149	32	1.72	98.98	941.51	940.5

3u148	34	3.71	98.24	1008.61	1007.5
3u147	34	3.71	96.44	1008.7	1007.5
3u146	10	9.37	90.7	1008.66	1007.5
3u145	33	7.2	41.92	1004.8	1003.5
3u144	10	9.5	93.17	1002.61	1003.5
3u143	10	9.49	95.16	1002.61	1003.5
3u142	34	3.62	95.06	990.6	989.5
3u140	10	9.16	91.49	990.64	989.5
3u14	34	3.63	98.41	970.61	969.5
3u139	23	4.56	52.05	978.74	977.5
3u138	34	3.65	89.72	978.8	977.5
3u137	10	9.2	92.12	978.71	977.5
3u136	34	3.97	95.33	985.49	984.5
3u135	34	3.94	98.03	1022.61	1021.5
3u134	34	3.82	98.02	1022.57	1021.5
3u133	34	3.87	93.7	1022.56	1021.5
3u132	34	3.87	95.47	1022.56	1021.5
3u131	8	3.86	95.53	1022.56	1021.5
3u130	34	3.86	97.17	1014.53	1013.5
3u13	34	3.64	98.3	970.56	969.5
3u129	34	3.85	97.67	1014.53	1013.5
3u128	34	3.84	97.85	1014.62	1013.5
3u127	34	3.92	96	1011.48	1010.5
3u126	34	3.98	95.37	981.46	980.4
3u125	34	3.67	99.01	978.81	977.5
3u124	10	9.18	98.64	978.63	977.5
3u123	10	9.18	98.37	978.63	977.5
3u122	34	3.61	98.86	978.59	977.5
3u121	34	3.89	95.36	999.56	998.5
3u120	34	3.85	96.27	1010.6	1009.5
3u12	34	3.6	99.22	970.61	969.5
3u119	34	3.88	97.62	1010.64	1009.5
3u118	34	3.88	98.7	1010.67	1009.5
3u117	34	3.85	96.02	1007.58	1006.5
3u116	34	3.93	95.84	1007.54	1006.5

3u115	34	3.98	98.74	1005.52	1004.5
3u114	34	3.96	98.3	995.53	994.5
3u113	10	9.5	98.62	992.65	991.5
3u112	34	3.74	98.49	992.61	991.5
3u111	34	3.74	99.35	992.74	991.5
3u110	41	0.969	97.71	992	990.5
3u11	34	3.6	97.38	970.56	969.5
3u109	34	3.78	97.48	996.54	995.5
3u108	10	9.36	95.01	996.7	995.5
3u107	10	9.36	97.06	996.7	995.5
3u106	28	6.86	95.11	996.84	995.5
3u105	10	9.4	99.04	996.64	995.5
3u104	10	9.4	99.1	996.64	995.5
3u103	34	3.72	99.26	996.77	995.5
3u102	34	3.79	98.34	996.58	995.5
3u101	34	3.92	98.05	995.57	994.5
3u100	34	3.91	96.44	995.55	994.5
3u10	34	3.57	99.48	970.56	969.5
3u1	34	3.55	97.19	956.58	955.5
3h12	34	3.62	98.68	970.58	969.5
3h10	34	3.74	98.42	988.56	987.5
3e44	3	3.72	99.1	948.7	947.5
3e39	8	3.62	99.6	936.7	935.5
3h43	34	3.5	96.6	948.4	949.5

Method refers to one of LC/MS methods 1-41

RT = retention time in min

Purity is based on LC/MS (UV) or by ^{1}H NMR (if indicated with *)

Example 3 - Pharmacology data for the compounds of the disclosure

No.	Eotaxin-3 EC_{50} (nM)	STAT6 degradation DC_{50} (nM)	STAT6 degradation E_{max} (%)
3e39	0.5	0.5	
3e44	0.3	0.7	
3h10	4.8	3.2	
3h12	1.3	3.2	

3u1	1.0	0.9	
3u10		0.6	
3u100	3.1	1.7	
3u101	2.4	2.3	
3u102	1.9	3.4	
3u103		2.5	
3u104		0.9	
3u105		1.4	
3u106	0.8	2.3	
3u107	2.8	2.5	
3u108	4.1	3.4	
3u109	2.8	1.4	
3u11	0.2	0.5	
3u110		2.5	
3u111	0.3	0.4	
3u112		0.5	
3u113		0.6	
3u114		9.9	
3u115	9.1	8.3	
3u116	6.0	8.7	
3u117	1210		
3u118	2.2	1.2	
3u119	2.2	2.1	
3u12	0.5	0.6	
3u120	3.7	1.0	
3u121	2.0	2.5	
3u122 (3u124)*	0.6	1.2	
3u123 (3u124)*		0.9	
3u125	0.6	0.8	
3u126	0.2	0.4	
3u127	14.8	5.4	
3u128	1.6	1.1	
3u129	1.4	1.0	

3u13	1.0	0.7	
3u130	1.8	1.3	
3u131		0.8	
3u132		0.5	
3u133		0.8	
3u134			20-30
3u135	185		
3u136	16.4		
3u137	0.4	0.2	
3u139 (3u138)*		0.2	
3u14	1.2	0.6	
3u140	1.0	1.4	
3u142		2.4	
3u143		0.7	
3u144		0.4	
3u145		2.0	
3u146	1.4	1.7	
3u147		1.6	
3u148		2.7	
3u149	27.6	33.8	
3u15	2.2	0.8	
3u150	39.2		
3u151			30-40
3u152	13.2	6.6	
3u153	8.7	4.1	
3u154	10.1	6.4	
3u155	0.5	0.3	
3u156		0.6	
3u157	0.4	0.3	
3u158		24.1	
3u159	52.6	12.8	
3u16	12.1	11.2	
3u160	27.5	10.9	

3u161	1.7	3.1	
3u162	2.3	3.3	
3u163		4.4	
3u164	2.0	1.0	
3u165 (3u97)*		1.4	
3u166	1.3	1.1	
3u167		0.8	
3u168		2.1	
3u169	14.6	4.1	
3u17	6.3	6.0	
3u170	7.5	2.5	
3u171	15.4	3.5	
3u172	13.2	2.9	
3u173	7.8	3.1	
3u174	11	3.8	
3u175	3.8	1.3	
3u176	9.8	2.3	
3u177	3.1	1.8	
3u178	7.7	5.6	
3u179	12.4	6.1	
3u18	18.6	8.4	
3u180	17.3	8.8	
3u181	16.3	3.4	
3u182	7.0	5.9	
3u183	8.0	5.9	
3u184	7.0	2.4	
3u185	2.3	2.8	
3u186	4.6	3.5	
3u187	4.2	3.1	
3u188	3.7	3.4	
3u189	7.7	4.7	
3u19	0.3	0.7	
3u190	0.9	0.5	

3u191	0.5	0.4	
3u192	0.9	0.6	
3u193	2.4	1.9	
3u194	0.9	1.7	
3u195	2.2	1.6	
3u196	0.5	0.3	
3u197	2.7	1.2	
3u198	1.6	1.2	
3u199	2.7	1.1	
3u2		4.3	
3u20	11.7	4.7	
3u200	9.9	2.0	
3u201	3.8	1.3	
3u202	2.6	1.9	
3u203	5.2	3.4	
3u204	4.6	2.5	
3u205	5.9	3.0	
3u206	10.9	0.4	
3u207	0.2	0.3	
3u208	0.8	0.6	
3u209	0.7	7.3	
3u21		0.4	
3u210	1.1	0.5	
3u211	0.5	0.5	
3u212	0.8	7.5	
3u213	13.2	8.6	
3u214	4.5	13.7	
3u215	5.6	3.5	
3u216	1.5	3.5	
3u217	0.6	1.8	
3u218	0.8	2.6	
3u219	2.2	1.8	
3u22	0.8	0.7	

3u220	2.4	1.3	
3u221	4.5	1.9	
3u222	1.1	1.5	
3u223	1.3	0.9	
3u224	1.5	1.3	
3u225	0.3	0.1	
3u226	0.2	0.05	
3u227	0.3	0.04	
3u228	1.2	0.2	
3u229	1.6	0.3	
3u23		1.3	
3u230	2.0	0.4	
3u231	0.8	0.1	
3u232	0.8	0.1	
3u233	1.3	0.2	
3u234		0.1	
3u235	1.4	0.1	
3u236	0.9	0.1	
3u237	1.7	0.1	
3u238	3.2	1.4	
3u239	1.2	0.1	
3u24		1.2	
3u240	1.3	1.1	
3u241	0.2	0.1	
3u242	0.2	0.2	
3u243	0.4	0.3	
3u244	0.3	0.1	
3u245	0.1	0.1	
3u246	1.1	2.7	
3u247	0.3	0.04	
3u248	0.3	0.2	
3u249	1.4	0.6	
3u25	1.0	1.3	

3u250	0.4	0.1	
3u251	0.9	0.2	
3u252		0.4	
3u253	8.1		
3u254	0.2	0.4	
3u255		13.7	
3u256	0.8	2.5	
3u257	24.2		
3u258	7.0	3.1	
3u259		0.5	
3u26	3.4	2.9	
3u260	11.2		
3u261			<20
3u262			30-40
3u263			70-80
3u264		5.9	
3u265			<20
3u267			50-60
3u268	5.6		
3u269	96.3		
3u27	5.7	2.0	
3u270	26.8		
3u271	3.3		
3u272			<20
3u273	31.8		
3u274			<20
3u275		57.4	
3u276		4.3	
3u277		0.4	
3u278	3.1	3.1	
3u279	1.7	1.4	
3u28	24.3	2.9	
3u280	12.8		

3u281	4.2	4.0	
3u282	6.9		
3u283	126		
3u284	24	22.6	
3u285	101	7.8	
3u286	25.2	12.5	
3u287	2.9	2.7	
3u288	88.3		
3u289	18.9		
3u29	0.9	1.7	
3u291	21.7	5.7	
3u292	6.9	5.1	
3u293	0.8	1.0	
3u294	0.3	0.8	
3u295	18.9	4.5	
3u296	5.8	2.7	
3u297	3.2	2.2	
3u298	2.6	1.8	
3u299	0.5	0.9	
3u3		1.8	
3u30	1.6	2.2	
3u300 (3u290)*	24.1	13	
3u301	90.5		20-30
3u302	29.2	4.9	
3u303	37.1	21.7	
3u304	10.8	6.5	
3u305	24.9		
3u306	194		
3u307	1.1	1.4	
3u308	1.3	0.7	
3u309	4.8	2.2	
3u31	2.0	2.4	
3u310	0.4	0.7	

3u311	0.4	0.5	
3u32	0.3	0.2	
3u33	0.3	0.2	
3u34		0.3	
3u35	5.5	9.6	
3u36	3.3	1.4	
3u37	1.7	0.5	
3u38	1.5	1.3	
3u39	2.3	4.3	
3u4		4.0	
3u40		2.3	
3u41		6.0	
3u42	13.8	13.2	
3u43	9.1	8.5	
3u44	10.1	10.2	
3u45	4.5	3.9	
3u46	10.1	5.8	
3u47	8.0	0.8	
3u48	7.7	11.2	
3u49	12.9	1.7	
3u5	0.8	1.0	
3u50	30.2	0.9	
3u51	1.9	1.8	
3u52	1.1	4.3	
3u53	1.1	8.7	
3u54	2.7	12	
3u55	3.1	7.6	
3u56	3.5	8.7	
3u57	25.4	12	
3u58	12.6	7.6	
3u59	25.8	11.4	
3u6	19.3	0.7	
3u60	1.6	0.7	

3u61	1.2	1.9	
3u62	1.2	1.2	
3u63	67.3	12.9	
3u64	50.3	7.3	
3u65	93.5		
3u66	4.3	1.6	
3u67	5.8	1.4	
3u68	7.8	1.0	
3u69	2.4	1.5	
3u7		0.6	
3u70		5.8	
3u71	1.8	5.3	
3u72	1.9	4.5	
3u73	2.4	6.8	
3u74	1.1	0.6	
3u75	1.0	0.6	
3u76	1.3	3.2	
3u77	24.1	16.1	
3u78	45.9	9.8	
3u79	107	15.4	
3u8	5.9		
3u80	5.0	0.8	
3u81		0.8	
3u82	1.1	1.1	
3u83	8.0		
3u84		26	
3u85	5.2	3.1	
3u86	5.1	3.4	
3u87	15.2	3.5	
3u88	12.9	3.3	
3u89	43.7	4.1	
3u9	4.9	3.8	
3u90	0.9	0.3	

3u91	1.4	0.6	
3u92	1.8	0.4	
3u93	16.6	26.9	
3u94	23.8	10.2	
3u95	12.4	18.6	
3u96	1.0	4.1	
3u99	1.7	1.1	
3h43	7.4		

Eotaxin-3 EC_{50} values provided for test compounds with >80% E_{max}

STAT6 degradation DC_{50} values provided for test compounds with >80% E_{max}
Data is provided as geometric mean values across multiple assay runs and compound batches to the extent possible

* The activity of diastereomeric mixtures and their corresponding pure diastereomers is illustrated for several cases in this table such as **3u118/3u119/3u120** and **3u90/3u91/3u92** and also shown graphically for **3u118/3u119/3u120** in the method descriptions below.

STAT6 degrader assay

This was a HiBit based assay. A HeLa cell line stably transfected with a small protein, LgBit (Large Bit) was obtained from Promega. These cells express endogenous STAT6. A small 11 amino acid gene sequence (HiBiT) was inserted in the STAT6 gene using CRISPR technology. Once STAT6 protein is expressed in the cells, the HiBiT sequence will bind the LgBit in the cells resulting in a functional NanoBiT protein, giving a luminescent tag to STAT6, see figure 2.

Single cell clones were prepared and the clone 4.14 was selected for the assay based on that clone showing high luminescence, high STAT6 phosphorylation upon stimulation with IL-4, and inhibition of luminescence when cells were treated with STAT6 siRNA.

HeLa LgBiT clone 4.14 cells were suspended in DMEM with 10% FCS, 1% Pen/Strep, Na-pyrovate and Hygromycin B, at a concentration of 1.25 * 105 cells pr mL. 5000 cells were added pr well of a 384 well plate and 20 nL of compound was added by Echo® liquid handler. NN6394A (terfenadine, a toxic compound) was added to control wells at 50 µM concentration to establish the assay window. In these wells the cells are dead which equals 100% degradation of STAT6.

After 4-24h of incubation at 37°C under 5% CO_2/95% air, 5 µL substrate (Nano-GLO®) was added to the wells and the plates were centrifuged and incubated for 0.5h.

The luminescence in the wells as a measure of non-degraded STAT6 was measured in a plate reader (BMG Pherastar FSX). The measured DC_{50} (in nM) was determined and reported in figure 3.

The dose-response curves for Examples **3u208**, **3u246**, **3u118**, **3u119**, **3u120**, and **3u74** are shown in **FIG. 1** (where percent degradation is plotted *vs.* test compound concentration in M on a log-scale).

Human whole blood eotaxin-3 assay

This was a human whole blood assay using recombinant human Interleukin 4 to stimulate the blood and measuring the ability of the test compounds to inhibit eotaxin-3 release. The biological activities of the test compounds have been tested in human whole blood stimulated with IL-4 measuring Eotaxin-3 release. The test compounds were added to 384 well clear flat-bottom plate in a 4-fold serial dilution in triplicates using a liquid handler. Human whole blood stabilized in lithium-heparin tubes was added in a volume of 65 µL per well, resulting in a final DMSO concentration of 0.5 %. The plate is incubated for 2h at 37°C under 5% CO_2/95% air. Subsequently, 5 µL of recombinant human IL-4 (R&D Systems, cat# 204-ILB) was added to the wells to a final concentration of 400 pM. The plate was incubated for 48h at 37°C under 5% CO_2/95% air. The plate was spun down for 10 minutes at 500xg and 20 µL supernatant was harvested and transferred to a 384 well v-bottom plate using a liquid handler and stored at -20 ° C until further analysis. 10 µL supernatant was used to measure the level of Eotaxin-3 (CCL26) using Human Eotaxin-3 MSD kit from Mesocsale (Cat# K251UEK-4). The assay was performed according to the manufacture instructions.

The data from the human whole blood eotaxin-3 assay is shown in **FIG. 2** for Examples **3u208**, **3u246**, **3u118**, **3u119**, **3u120**, and **3u74** (where the effect in % is plotted against the test concentration in M on a log scale).

* * *

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

The disclosure illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure.

Thus, it should be understood that although the present disclosure has been specifically disclosed by certain embodiments and optional features, modification, improvement and variation of the disclosure embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this disclosure. The materials, methods, and examples provided here are representative of certain embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure.

The disclosure has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the disclosure with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

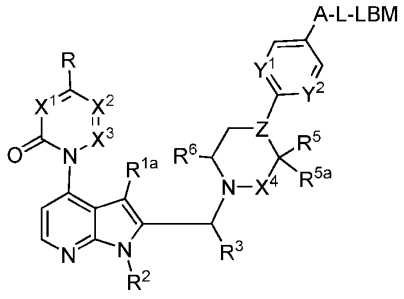
In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

Embodiments:

1.A compound having the formula (I'')



(I'')

wherein:

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is CR^4 or CO;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl-C_{1-4}alkyl, halo-C_{1-4}alkyl, -$(CH_2)_n$-O-C_{1-4}alkyl, -$(CH_2)_n$-CO-R', and -$(CH_2)_n$-CO_2R, wherein said phenyl is optionally substituted one or more times with a substituents independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, - NR'R'', -CON R'R'' and -CO_2R', and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1 or 2;

R^{1a} is hydrogen;

R^2 is selected from hydrogen, C_{1-5}alkyl and deuterated C_{1-4}alkyl; wherein said C_{1-4}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl and deuterated C_{1-4}alkyl;

R^4 and R^6 are independently selected from hydrogen and C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted with one or more halogens;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogens;

R^{5a} is hydrogen;

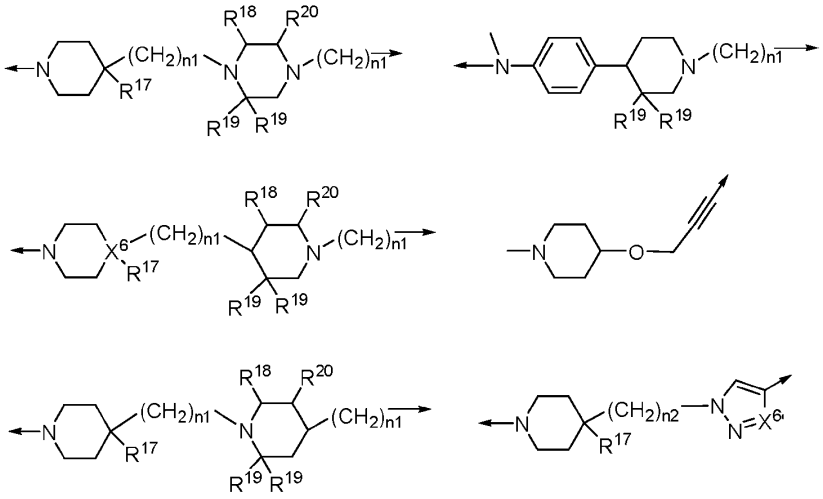
or R^5 and R^{10} together form a bond;

or R^5 and R^{5a} are both fluoro;

R^7 and R^8 is independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

A is CO;

L is selected from



wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

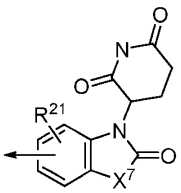
R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

$X^{6'}$ is C or N;

LBM is



wherein X^7 is O, NR^{22}, $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro and chloro;

R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy and C_{3-4} cycloalkyl;

R^{23} is independently selected from hydrogen and C_{1-4}alkyl;

R^{10} is selected from hydrogen and fluoro; or R^5 and R^{10} together form a bond;

R^{11} is selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', -CO_2R', -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R´ and R´´ are each independently selected from hydrogen and C_{1-4}alkyl; or

R^{11} and R^0 may together form a 5-6 membered heteroaromatic ring containing one to two heteroatoms selected from N, wherein said 5-6 membered heteroaromatic ring containing one to two heteroatoms selected from N is optionally be substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R'', -CONR'R'', and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R''are each independently selected from hydrogen and C_{1-4}alkyl;

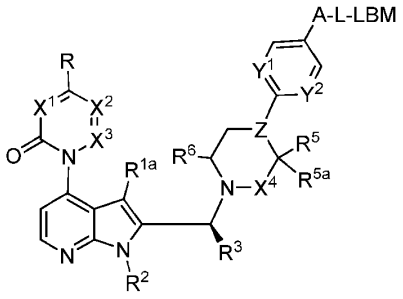
R^{12} and R^{13} are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', -CO_2R', -CO-CO_2R', and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R'' are each independently selected from hydrogen and C_1;

R^{14} is selected from hydrogen and C_{1-4}alkyl;

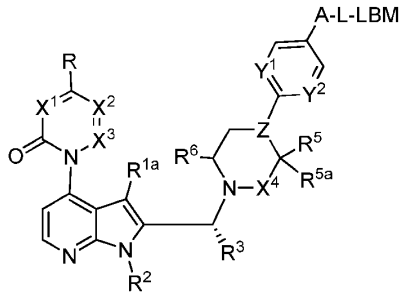
R^{15} is independently selected from C_{1-4}alkyl and C_{3-4} cycloalkyl ;

or pharmaceutically acceptable salts thereof.

Embodiment 2. A compound according to embodiment 1 having the formula (II) or (II´)



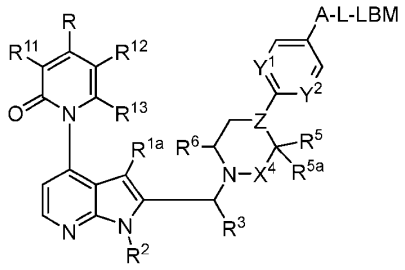
(II)



(II′)

wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Z, R, R^{1a}, R^2, R^5, R^{5a}, R^6, a, L and LBM are as defined in embodiment 1 and R^3 is C_{1-4}alkyl; or pharmaceutically acceptable salts thereof.

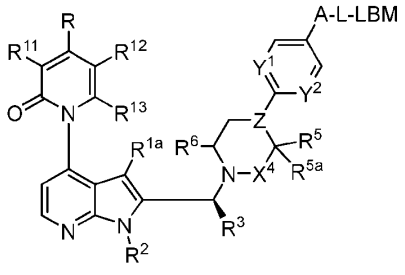
Embodiment 3. The compound according to embodiment 1 having the formula (III)



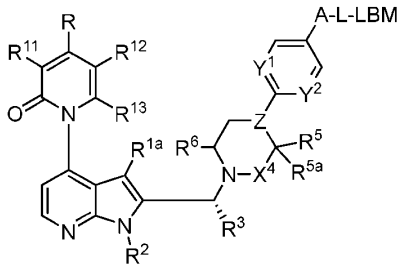
(III)

wherein Y^1, Y^2, X^4, Z, R, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^9, R^{11}, R^{12}, R^{13}, A, L and LBM are as defined in Embodiment 1 or pharmaceutically acceptable salts thereof.

Embodiment 4. The compound according to embodiment 3 having the formula (IV) or (IV´)



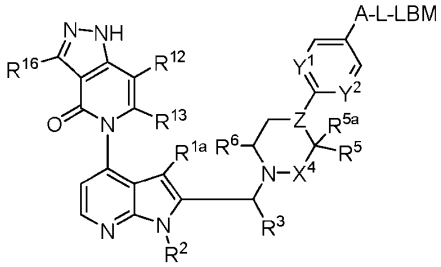
(IV)



(IV')

wherein Y^1, Y^2, X^4, Z, R, R^{11}, R^{12}, R^{13}, R^{1a}, R^2, R^5, R^{5a}, R^6, R^9, R^{11}, R^{12}, R^{13}, A, L and LBM are as defined in embodiment 3 and R^3 is C_{1-4}alkyl; or pharmaceutically acceptable salts thereof.

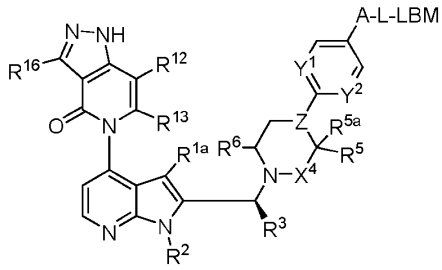
Embodiment 5. The compound according to embodiment 1 having the formula (VII)



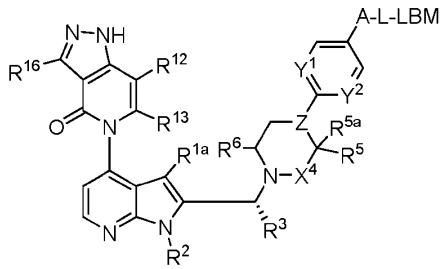
(VII)

wherein Z, X^4, Y^1, Y^2, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^9 R^{12}, R^{13}, A, L and LBM are as defined in embodiment 1 and R^{16} is selected from hydrogen, C_{1-4}alkyl and trifluoromethyl.

Embodiment 6. The compound according to embodiment 5 having the formula (VIII) or (VIII´)



(VIII)



(VIII')

wherein Z, X^4, Y^1, Y^2, R^{1a}, R^2, R^3, R^5, R^{5a}, R^6, R^9 R^{12}, R^{13}, A, L and LBM are as defined in embodiment 1 and R^{16} is selected from hydrogen, C_{1-4}alkyl and trifluromethyl.

Embodiment 7. The compound according to any one of embodiments 1-2, wherein X^1 is N, X^2 is CR^{12} and X^3 is CR^{13}.

Embodiment 8. The compound according to any one of embodiments 1-2, wherein X^1 is CR^{11} and X^2 is N, and X^3 is CR^{13}.

Embodiment 9. The compound according to any one of embodiments 1-2, wherein X^1 is CR^{11} and X^2 is CR^{12} and X^3 is N.

Embodiment 10. The compound according to any one of embodiments 1-9, wherein X^4 is CR^4 and R^4 is as defined in claim 1.

Embodiment 11. The compound according to any one of embodiments 1-10, wherein Z is N.

Embodiment 12. The compound according to any one of embodiments 1-10, wherein Z is CR^{10} and R^5 and R^{10} together form a bond.

Embodiment 13. The compound according to any one of embodiments 1-10, wherein Z is CR^{10} and R^{10} is hydrogen.

Embodiment 14. The compound according to any one of claims 1-13, wherein Y^1 is N and Y^2 is N.

Embodiment 15. The compound according to any one of claims 1-13, wherein Y^1 is N and Y^2 is CR^8.

Embodiment 16. The compound according to any one of claims 1-13, wherein Y^1 is CR^7 and Y^2 is CR^8.

Embodiment 17. The compound according to any one of embodiment 16, wherein

(a) both of R^7 and R^8 is C_{1-4}alkyl;
(b) both of R^7 and R^8 is halogen;
(c) one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen;
(d) one of R^7 and R^8 is C_{1-4}alkyl and the other is hydrogen; or
(e) one of R^7 and R^8 is halogen and the other is hydrogen.

Embodiment 18. The compound according to embodiment 17, wherein R^7 is halogen and R^8 is methyl.

Embodiment 19. The compound according to any one of embodiments 18 or 19, wherein the halogen is fluoro.

Embodiment 20. The compound according to any one of embodiments 1-4 and 7-19, wherein R is selected from $-NH_2$ and $NHCH_3$.

Embodiment 21. The compound according to any one of embodiments 1-20, wherein R^{12} and R^{13} is hydrogen.

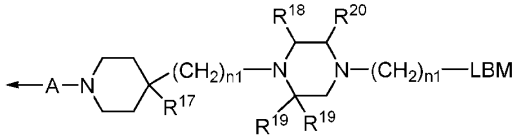
Embodiment 22. The compound according to any one of embodiments 1-4 and 7-19, wherein R^{11} is C_{1-4}alkyl, and R^{12} and R^{13} is hydrogen.

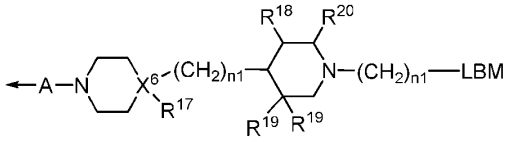
Embodiment 23. A compound according to any one of embodiments 1-22 wherein R^2 is methyl.

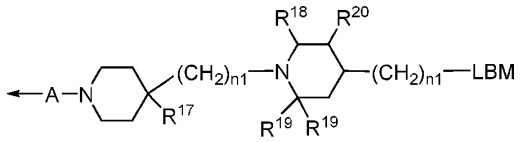
Embodiment 24. A compound according to any one of embodiments 1-23 wherein R^3 is methyl.

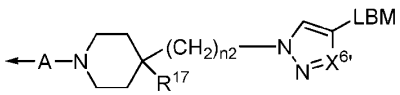
Embodiment 25. A compound according to any one of embodiments 1-24 wherein R^{5a} is hydrogen.

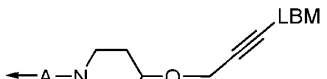
Embodiment 26. The compound according to any of embodiments 1-25, wherein -A-L-LBM is selected from

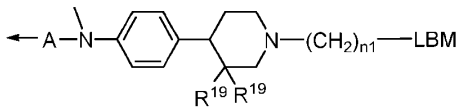












wherein A is CO;

n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

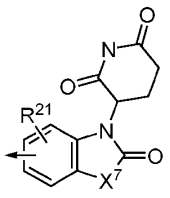
R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

$X^{6'}$ is C or N;

LBM is



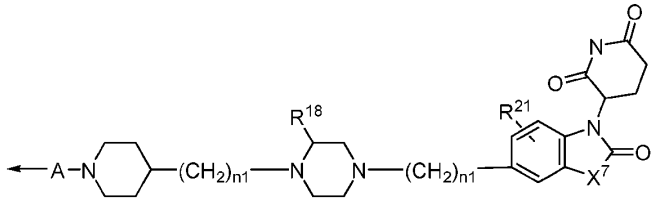
wherein X^7 is O, NR^{22}, $CR^{23}R^{23}$;

R^{21} is selected from hydrogen , fluoro and chloro;

R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy and C_{3-4} cycloalkyl; and

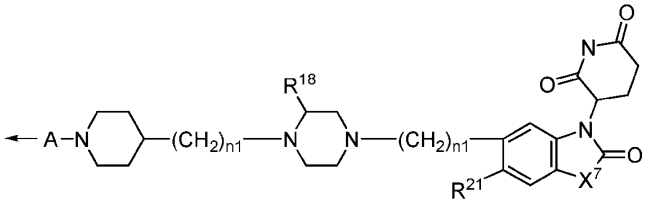
R^{23} is independently selected from hydrogen and C_{1-4}alkyl.

Embodiment 27. The compound according to embodiment 26, wherein A-L-LBM is



wherein A is CO, n1 is 1 and R^{18} and R^{21} is as defined in claim 1.

Embodiment 28. The compound according to embodiment 26, wherein A-L-LBM is



wherein A is CO, n is 1 and R^{18} is hydrogen or C_{1-4}alkyl and R^{21} is hydrogen and fluoro.

Embodiment 29. The compound according to embodiment 1, which is selected from 3-(3-methyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-(methylamino)-2-oxopyridin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione and 3-(3-methyl-5-(((S)-3-methyl-4-((1-(4-(1-((S)-1-(1-methyl-4-(4-oxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)piperidin-4-yl)benzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione or pharmaceutically acceptable salts thereof.

Embodiment 30. A compound according to any one of embodiments 1-29 for use in therapy.

Embodiment 31. A compound according to embodiment 30 for use in the treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of STAT6.

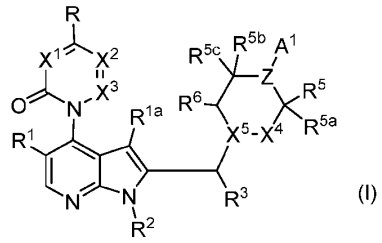
Embodiment 32. A compound according to embodiment 30 for use in the treatment of autoimmune diseases.

Embodiment 33. A compound according to embodiment 30 for use in the treatment of autoimmune diseases, characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors.

Embodiment 34. A pharmaceutical composition comprising a compound according to any one of Embodiments 1-29 together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

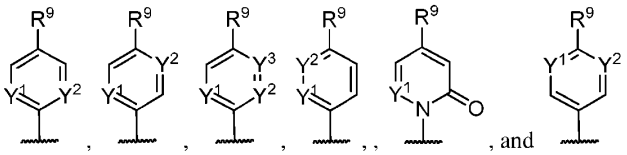
CLAIMS:

1. A compound having the formula (I)



(I)

wherein:

A^1 is selected from  ;

R^9 is -A-L-LBM;

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is selected from CR^4R^4 and CO;

X^5 is selected from N and oxidized N;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Y^3 is selected from N and CR^{17};

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl- C_{1-4}alkyl, halo-C_{1-4}alkyl, $-(CH_2)_n$-O-C_{1-4}alkyl, $-(CH_2)_n$-CO-R', and $-(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituents independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R", -CONR'R", and $-CO_2$R', and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1 or 2;

R^1 and R^{1a} are independently selected from hydrogen, fluoro, and C_{1-4}alkyl;

R^2 is selected from hydrogen, C_{1-5}alkyl, $-SO_2$-C_{1-4}alkyl and deuterated C_{1-4}alkyl, wherein said C_{1-5}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

each of R^4 and R^6 is independently selected from hydrogen, C_{1-4}alkyl, and C_{1-4} alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen;

or R^5 and R^{5a} are both fluoro or R^5 and R^{5a} together with the atom attached thereto form a CO group;

R^{5b} and R^{5c} are each independently selected from hydrogen and fluoro;

R^7, R^8, and R^{17} are each independently selected from hydrogen, halogen, cyano, C_{1-4}alkyl and C_{1-4}alkoxy, and C_{3-4}cycloalkyl, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

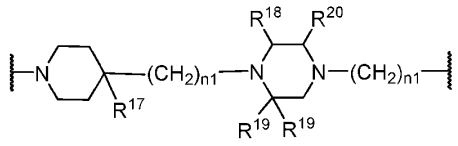
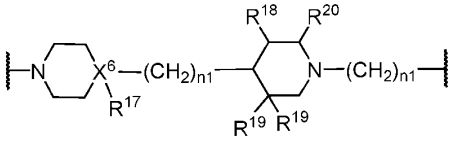
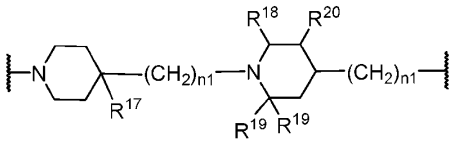
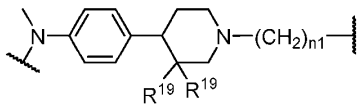
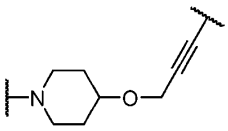
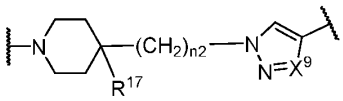
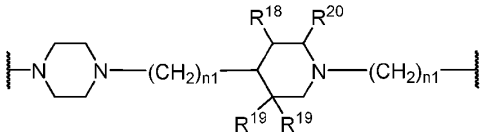
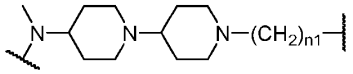
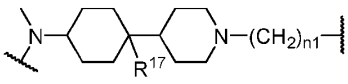
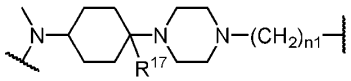
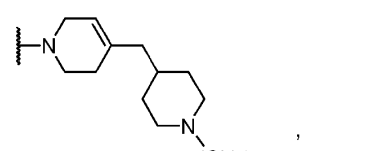
R^{11}, R^{12}, and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", -CO_2R', and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl; or

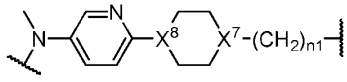
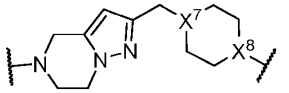
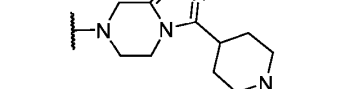
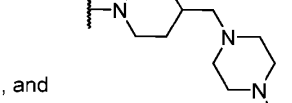
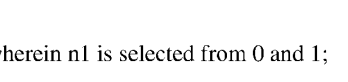
R^{11} and R^0 together with the atoms attached thereto form a 5-6 membered heteroaromatic or heterocyclic ring containing one or two N atoms, wherein said 5-6 membered heteroaromatic ring or heterocyclic ring containing one or two N atoms is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -$COCF_3$, -NR'R", -CONR'R", and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl; and

R^{12} and R^{13} are each independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R", -CONR'R", -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R" are each independently selected from hydrogen and C_{1-4}alkyl;

A is CO;

L is selected from


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wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

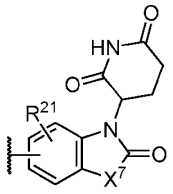
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

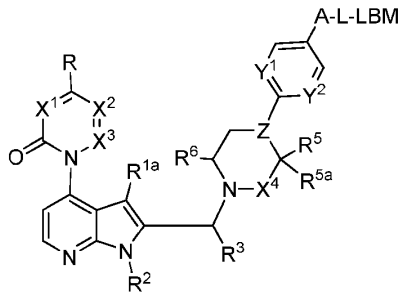
R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. A compound having the formula (I')



(I')

wherein:

X^1 is selected from N and CR^{11}; X^2 is selected from N and CR^{12}; and X^3 is selected from N and CR^{13}, provided that only one of X^1, X^2 and X^3 may be N;

X^4 is CR^4R^4 or CO;

Y^1 is selected from N and CR^7;

Y^2 is selected from N and CR^8;

Z is selected from N and CR^{10};

R is NHR^0;

R^0 is selected from hydrogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-4}alkyl, phenyl-C_{1-4}alkyl, halo-C_{1-4}alkyl, $-(CH_2)_n$-O-C_{1-4}alkyl, $-(CH_2)_n$-CO-R', and $-(CH_2)_n$-CO_2R', wherein said phenyl is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, - NR'R'', -CONR'R'', and $-CO_2$R', and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl, and n is 0, 1, or 2;

R^{1a} is hydrogen;

R^2 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl; wherein said C_{1-4}alkyl may optionally be substituted one or more times with halogen;

R^3 is selected from hydrogen, C_{1-4}alkyl, and deuterated C_{1-4}alkyl;

R^4 and R^6 are independently selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted with one or more halogens;

R^5 is selected from hydrogen, halogen, C_{1-4}alkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may optionally be substituted with one or more halogen;

R^{10} is selected from hydrogen and fluoro;

or R^5 and R^{10} together form a bond between the two carbons to which they are attached;

R^{5a} is hydrogen; or R^5 and R^{5a} are both fluoro;

R^7 and R^8 are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, and C_{1-4}alkoxy, wherein said C_{1-4}alkyl and C_{1-4}alkoxy may independently optionally be substituted with one or more halogen;

R^{11} is selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', $-CO_2$R', $-CO-(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl; or

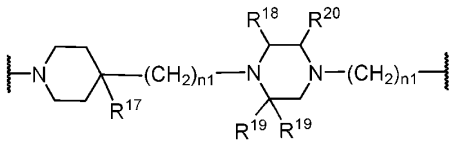
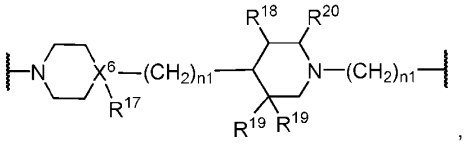
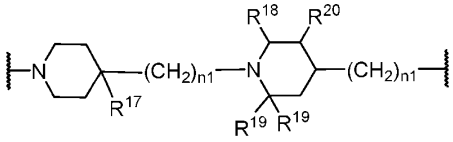
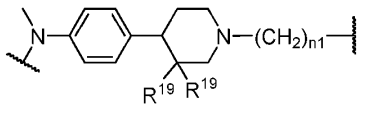
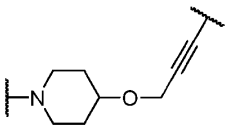
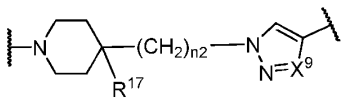
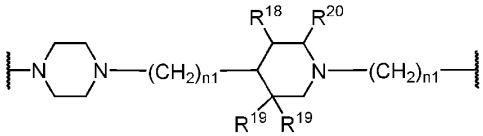
R^{11} and R^0 together with the atoms attached thereto may form a 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N, wherein said 5-6 membered heterocyclic or heteroaromatic ring containing one to two heteroatoms selected from N is optionally substituted one or more times with a substituent independently selected from halogen, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{3-4} cycloalkyl, hydroxy, C_{1-4}alkoxy, cyano, -NR'R'',

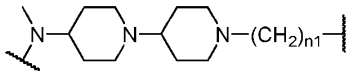
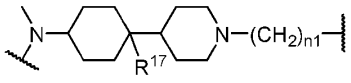
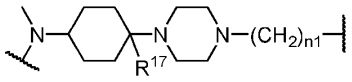
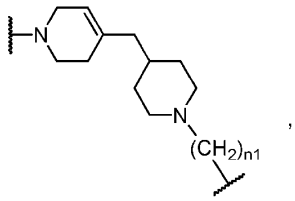
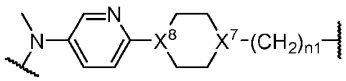
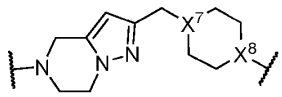
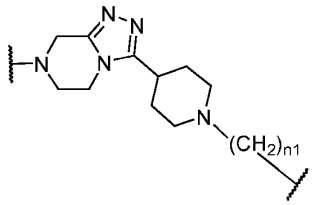
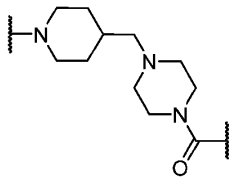
-CONR'R'' and -CO_2R', wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen and C_{1-4}alkoxy, and wherein R' and R'' are each independently selected from hydrogen and C_{1-4}alkyl;

R^{12} and R^{13} are independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{3-4} cycloalkyl, C_{1-4}alkoxy, hydroxy, cyano, -NR'R'', -CONR'R'', -CO_2R', -CO-CO_2R' and -CO-$(CH_2)_m$OH, wherein said C_{1-4}alkyl is optionally substituted one or more times with a substituent independently selected from halogen, hydroxy, and C_{1-4}alkoxy, and wherein m is 1, 2 or 3 and wherein R' and R''are each independently selected from hydrogen and C_{1-4}alkyl;

A is CO;

L is selected from


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, and ;

wherein n1 is selected from 0 and 1;

n2 is selected from 1 and 2;

R^{17} is selected from hydrogen and fluoro;

R^{18} is selected from hydrogen, fluoro, C_{1-4}alkyl wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro or C_{1-4}alkoxy;

R^{19} is independently selected from hydrogen, C_{1-4}alkyl and fluoro;

R^{20} is selected from hydrogen and C_{1-4}alkyl;

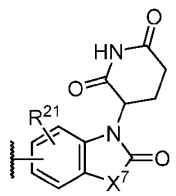
X^6 is C;

X^7 is CR^{24} or N;

R^{24} is selected from hydrogen and hydroxy;

X^8 and X^9 are independently CH or N; and

LBM is



wherein X^7 is O, NR^{22}, or $CR^{23}R^{23}$;

R^{21} is selected from hydrogen, fluoro, and chloro;

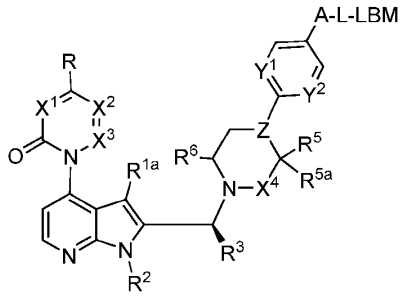
R^{22} is selected from hydrogen, C_{1-4}alkyl, deuterated C_{1-4}alkyl, and C_{3-4} cycloalkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with fluoro, hydroxy, C_{1-4}alkoxy, or C_{3-4} cycloalkyl;

each R^{23} is independently selected from hydrogen, halogen, and C_{1-4}alkyl; or

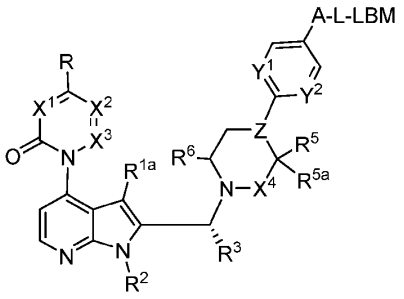
both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl or 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one to two heteroatoms selected from O;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. A compound according to claim 2, having the formula (II) or (II´)



(II)

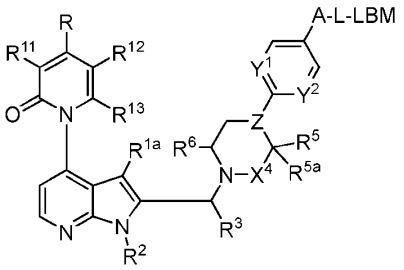


(II′)

wherein R^3 is C_{1-4}alkyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

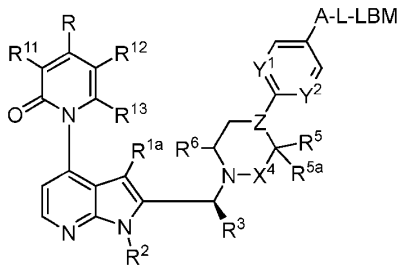
4. The compound according to claim 2 having the formula (III)



(III)

or a pharmaceutically acceptable salt or stereoisomer thereof.

5. The compound according to claim 4 having the formula (IV)



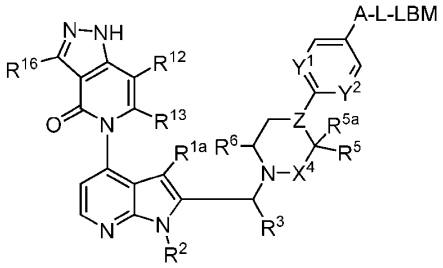
(IV)

wherein R^3 is C_{1-4}alkyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

6. The compound according to any one of claims 1-5, wherein R is NHR^0 and R^0 is selected from hydrogen and C_{1-4}alkyl.

7. The compound according to claim 2 having the formula (VII)

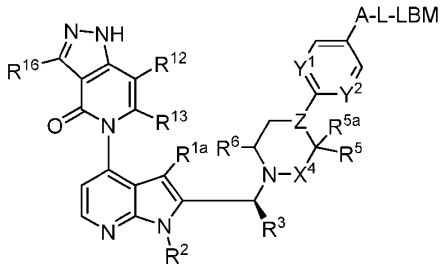


(VII)

wherein R^{16} is selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen;

or a pharmaceutically acceptable salt or stereoisomer thereof.

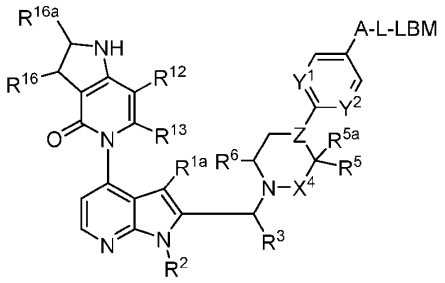
8. The compound according to claim 7 having the formula (VIII)



(VIII)

wherein R^{16} is selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen;
or a pharmaceutically acceptable salt or stereoisomer thereof.

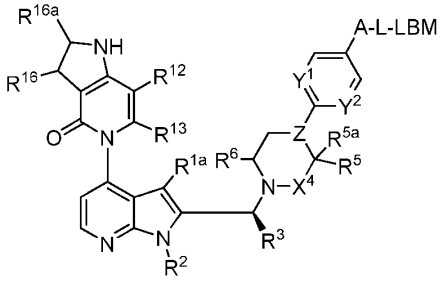
9. The compound according to claim 2, wherein the compound is of formula (IX):



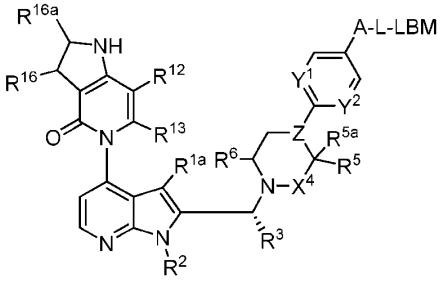
(IX)

wherein R^{16} and R^{16a} are selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen;
or a pharmaceutically acceptable salt or stereoisomer thereof.

10. The compound according to claim 2, wherein the compound is of formula (IXa), or (IXb):



(IXa) or



(IXb)

wherein R^{16} and R^{16a} are selected from hydrogen and C_{1-4}alkyl, wherein said C_{1-4}alkyl may optionally be substituted one or more times with a substituent independently selected from halogen;
or a pharmaceutically acceptable salt or stereoisomer thereof.

11. The compound according to any one of claims 1-10, wherein X^7 is NR^{22} and R^{22} is methyl.

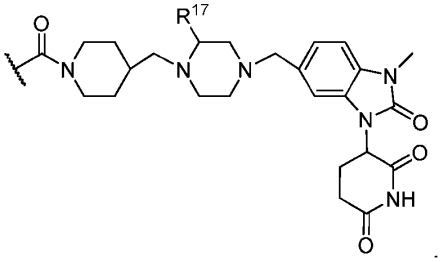
12. The compound according to any one of claims 1-10, wherein X^7 is NR^{22} and R^{22} is cyclopropyl.

13. The compound according to any one of claims 1-10, wherein X^7 is $CR^{23}R^{23}$, and both R^{23} are methyl or both R^{23} are fluoro.

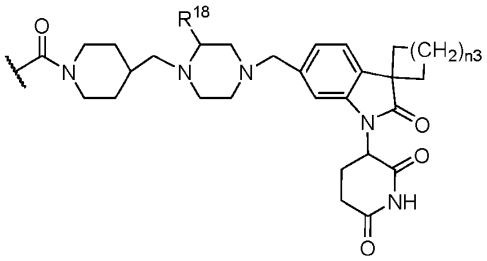
14. The compound according to any one of claims 1-10, wherein X^7 is $CR^{23}R^{23}$, and both R^{23} together with the carbon they are attached to form a C_{3-6} cycloalkyl.

15. The compound according to any one of claims 1-10, wherein X^7 is $CR^{23}R^{23}$, and both R^{23} together with the carbon they are attached to form a 3-6 membered heterocyclic ring, wherein the heterocyclic ring contains one heteroatom that is O.

16. The compound according to any one of claims 1-10, wherein A-L-LBM is



17. The compound according to any one of claims 1-10, wherein A-L-LBM is



wherein n3 is 0, 1, 2 or 3.

18. The compound according to any one of claims 1-17, wherein Z is N.

19. The compound according to any one of claims 1-17, wherein Z is CR^{10} and R^5 and R^{10} together form a bond.

20. The compound according to any one of claims 1-17, wherein Z is CR^{10} and R^{10} is hydrogen.

21. The compound according to any one of claims 1-20, wherein Y^1 is N and Y^2 is CR^8.

22. The compound according to any one of claims 1-20, wherein Y^1 is N and Y^2 is N.

23. The compound according to any one of claims 1-20, wherein Y^1 is CR^7 and Y^2 is CR^8.

24. The compound according to claim 23, wherein

(a) both of R^7 and R^8 is C_{1-4}alkyl;

(b) both of R^7 and R^8 is halogen;

(c) one of R^7 and R^8 is C_{1-4}alkyl and the other is halogen;

(d) one of R^7 and R^8 is C_{1-4}alkyl and the other is hydrogen; or

(e) one of R^7 and R^8 is halogen and the other is hydrogen.

25. The compound according to claim 24, wherein R^7 is halogen and R^8 is methyl.

26. The compound according to claim 24, wherein the halogen in b) c) and e) is fluoro.

27. The compound according to any one of claims 1-26, wherein R^{12} and R^{13} are hydrogen.

28. The compound according to any one of claims 1-7 and 16-27, wherein R^{11}, R^{12} and R^{13} are hydrogen.

29. A compound according to any one of claims 1-28, wherein X^4 is CR^4R^4 and each R^4 is independently selected from hydrogen and C_{1-4}alkyl.

30. A compound according to any one of claims 1-29, wherein R^2 is methyl.

31. A compound according to any one of claims 1-30, wherein R^3 is hydrogen or C_{1-4}alkyl.

32. A compound according to any one of claims 1-31, wherein R^3 is methyl.

33. A compound according to any one of claims 1-32, wherein R^{5a} is hydrogen.

34. The compound according to claim 1 or 2, which is selected from Table 1,or a pharmaceutically acceptable salt or stereoisomer thereof.

35. A compound according to any one of claims 1-34 for use in therapy.

36. A compound according to any one of claims 1-34 for use in the treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of STAT6.

37. A compound according to any one of claims 1-34 for use in the treatment of autoimmune diseases.

38. A compound according to any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, for use in the treatment of prophylaxis, treatment or amelioration of any of the following diseases characterized by Th2-mediated inflammation such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, urticaria, rhinitis, eosinophilic esophagitis, food allergy, diffuse cutaneous systemic sclerosis, alopecia areata and/or COPD (chronic obstructive pulmonary disease) and different cancers such as lymphomas, triple negative breast cancer and solid fibrous cancers either as a stand-alone treatment or in combination with other anticancer drugs such as check point inhibitors.

39. Use of the compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, for the manufacture of a medicament for the treatment of a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject.

40. A pharmaceutical composition comprising a compound according to any one of claims 1-33, or a pharmaceutically acceptable salt or stereoisomer thereof, together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

41. A pharmaceutical composition comprising a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient.

42. The pharmaceutical composition of claim 40 or 41, further comprising one or more additional therapeutic agents.

43. A method of treating an immune mediated disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of any one of claims 40-42.

44. A method of modulating a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of any one of claims 40-42.

45. The method of claim 44, the method comprising degrading STAT6 protein in a subject in need thereof.

46. A method of treating a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of any one of claims 40-42.

47. The method of claim 46, wherein the STAT6-mediated disorder or disease is from the class of diseases or rheumatology, gastroenterology, pulmonology, hepatology, nephrology, dermatology or an allergic disease.

48. The method of claim 46, wherein the STAT6-mediated disorder or disease is rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), lupus nephritis (LN), osteoarthritis (OA), ulcerative colitis (UC), Crohn's disease (CD), idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD), metabolic dysfunction-associated steatohepatitis (MASH), Diabetic kidney disease (DKD), diabetic nephropathy (DN), or atopic dermatitis (AD).

49. The method of claim 46, wherein the STAT6-mediated disorder or disease is atopic dermatitis, contact dermatitis, vitiligo, alopecia areata, acne, psoriasis, dermatomyositis, scleroderma, or morphea.

50. The method of claim 46, wherein the STAT6-mediated disorder or disease is atopic dermatitis.

51. A method of treating a disease or condition mediated by interleukin 4 (IL-4) or interleukin 3 (IL-3) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of any one of claims 40-42.

52. A method for manufacturing a medicament for treating a disease or condition mediated by a signal transducer and activator of transcription 6 (STAT6) protein activity in a subject in need thereof, characterized in that a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, is used.