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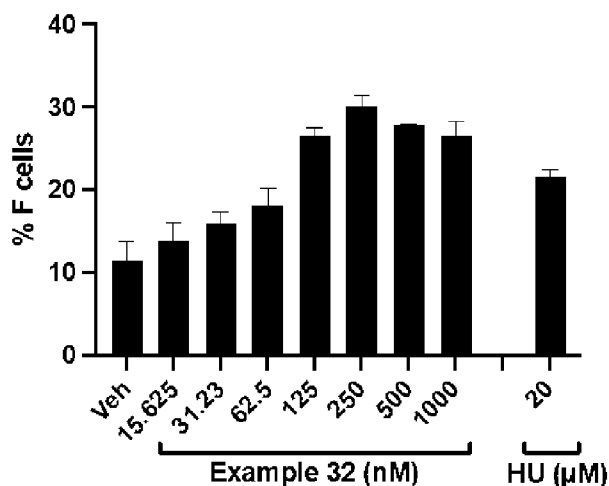
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(54) Title: PRC2 INHIBITORS FOR USE IN TREATING SICKLE CELL DISEASE

FIG. 1A

Donor A



(57) Abstract: The present disclosure relates to methods of treating a subject having sickle cell disease, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2). In certain embodiments of the disclosed methods, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has (a) been administered hydroxyurea; and/or (b) been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine.

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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**PRC2 INHIBITORS FOR USE IN TREATING SICKLE CELL DISEASE****CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/578,568 filed August 24, 2023, which is hereby incorporated by reference in its entirety.

**FIELD OF THE DISCLOSURE**

[0002] The present disclosure relates to compounds that inhibit the Polycomb Repressive Complex 2 (PRC2). In particular, the present disclosure relates to compounds, pharmaceutical compositions comprising the compounds and methods for use therefor in treating sickle cell disease.

**BACKGROUND OF THE DISCLOSURE**

[0003] The Polycomb Repressive Complex 2 (PRC2) is a multiprotein complex that contributes to the epigenetic silencing of target genes to regulate development and homeostasis. The PRC2 complex is comprised of three core subunits: enhancer of zeste homolog 2 (EZH2), embryonic ectoderm development protein (EED), and suppressor of zeste 12 (SUZ12). EED is a critical regulator of PRC2 in the silencing of expression of genes and gene clusters involved in development including but not limited to fetal orthologues (i.e. gamma globin), Hox genes, X chromosome inactivation, etc. Thus, EED provides a pharmacologic target for the treatment of diseases or disorders to impact transcription of specific target genes in blood and other tissues, including sickle cell disease.

**SUMMARY OF THE DISCLOSURE**

[0004] Disclosed herein are methods of treating sickle cell disease in a subject, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2), wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has (a) been administered hydroxyurea; and/or (b) been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine. In some embodiments are provided such methods wherein the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and hydroxyurea, voxelotor, crizanlizumab, or L-glutamine. In another embodiment is provided such methods, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is an inhibitor of embryonic ectoderm development protein (EED). In some embodiments disclosed herein, the inhibitor of embryonic ectoderm development protein (EED) is MAK683, pociredir (FTX-6058), APG-5918 (EEDi-5273), HJM-353, or BR-002. In other embodiments, the inhibitor of embryonic ectoderm development protein (EED) is a compound of Formula (I).

**BRIEF DESCRIPTION OF THE FIGURES**

[0005] FIG. 1A depicts the percentage of F cells (cells containing fetal hemoglobin) in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32, or hydroxyurea (HU) from Donor A.

[0006] FIG. 1B depicts the percentage of F cells (cells containing fetal hemoglobin) in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32 or hydroxyurea (HU) in Donor B.

[0007] FIG. 2A depicts HBG1 mRNA levels in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32 or hydroxyurea (HU) in Donor A.

[0008] FIG. 2B depicts HBG2 mRNA levels in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32 or hydroxyurea (HU) in Donor A.

[0009] FIG. 2C depicts HBG1 mRNA levels in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32 or hydroxyurea (HU) in Donor B.

[0010] FIG. 2D depicts HBG2 mRNA levels in 14-day differentiated cells post 7-day treatment with vehicle (veh), compound Example 32 or hydroxyurea (HU) in Donor B.

#### DETAILED DESCRIPTION OF THE DISCLOSURE

[0011] Unless defined otherwise, all terms and ranges used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs, unless expressly defined otherwise. All patents, patent applications, and publications referred to herein are incorporated by reference to the extent they are consistent with the present disclosure.

[0012] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms may also be used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an “alkyl” moiety generally refers to a monovalent radical (e.g. CH<sub>3</sub>-CH<sub>2</sub>-), in certain circumstances a bivalent linking moiety can be “alkyl,” in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., -CH<sub>2</sub>-CH<sub>2</sub>-), which is equivalent to the term “alkylene.” (Similarly, in circumstances in which a divalent moiety is required and is stated as being “aryl,” those skilled in the art will understand that the term “aryl” refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S).

[0013] As used herein, “Polycomb Repressive Complex 2” or “PRC2 complex” refers to a mammalian multiprotein complex comprising three core subunits: enhancer of zeste homolog 2 (EZH2), embryonic ectoderm development protein (EED), and suppressor of zeste 12 (SUZ12) and two additional non-essential subunits, AEBP2, and RbAp48.

[0014] As used herein, “EED” refers to the embryonic ectoderm development protein subunit of the PRC2 complex.

[0015] As used herein, an “PRC2 inhibitor” refers to compounds of the present disclosure that are represented by formula (I) as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of the PRC2 complex. While not wanting to be bound by any theory, we theorize that the inhibitors of the present disclosure may inhibit PRC2

enzymatic activity by binding to EED to prevent assembly of the PRC2 complex on histone H3 tails thereby inhibiting its activity.

[00016] As used herein, the term “vaso-occlusive crisis (VOC) events” means an event during which a subject suffering from sickle cell disease experiences an obstruction of microcirculation by sickled red blood cells, causing ischemic injury to the organ supplied. A subject experiencing a vaso-occlusive crisis (VOC) event may experience pain, and so such events may also be referred to by those of ordinary skill in the art as “sickle cell pain crises” or “SCD pain crises.”

[00017] The term “amino” refers to  $-\text{NH}_2$ .

[00018] The term “acetyl” refers to  $-\text{C}(\text{O})\text{CH}_3$ .

[00019] As herein employed, the term “acyl” refers to an alkylcarbonyl or arylcarbonyl substituent wherein the alkyl and aryl portions are as defined herein.

[00020] The term “alkyl” as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms. As such, “alkyl” encompasses  $\text{C}_1$ ,  $\text{C}_2$ ,  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$ ,  $\text{C}_7$ ,  $\text{C}_8$ ,  $\text{C}_9$ ,  $\text{C}_{10}$ ,  $\text{C}_{11}$  and  $\text{C}_{12}$  groups. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[00021] The term “alkenyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms. As such, “alkenyl” encompasses  $\text{C}_2$ ,  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$ ,  $\text{C}_7$ ,  $\text{C}_8$ ,  $\text{C}_9$ ,  $\text{C}_{10}$ ,  $\text{C}_{11}$  and  $\text{C}_{12}$  groups. Examples of alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[00022] The term “alkynyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms. As such, “alkynyl” encompasses  $\text{C}_2$ ,  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$ ,  $\text{C}_7$ ,  $\text{C}_8$ ,  $\text{C}_9$ ,  $\text{C}_{10}$ ,  $\text{C}_{11}$  and  $\text{C}_{12}$  groups. Examples of alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[00023] An “alkylene,” “alkenylene,” or “alkynylene” group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Examples of alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Exemplary alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Exemplary alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[00024] The term “alkoxy” refers to  $-\text{OC}_1-\text{C}_6$  alkyl.

[00025] The term “cycloalkyl” as employed herein is a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. As such, “cycloalkyl” includes  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$ ,  $\text{C}_7$ ,  $\text{C}_8$ ,  $\text{C}_9$ ,  $\text{C}_{10}$ ,  $\text{C}_{11}$  and  $\text{C}_{12}$  cyclic hydrocarbon groups. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[00026] The term “heteroalkyl” refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are independently replaced O, S, or  $\text{NR}^x$ , wherein  $\text{R}^x$  is hydrogen or  $\text{C}_1-\text{C}_3$  alkyl. Examples of heteroalkyl groups include methoxymethyl, methoxyethyl and methoxypropyl.

**[00027]** An “aryl” group is a C<sub>6</sub>-C<sub>14</sub> aromatic moiety comprising one to three aromatic rings. As such, “aryl” includes C<sub>6</sub>, C<sub>10</sub>, C<sub>13</sub>, and C<sub>14</sub> cyclic hydrocarbon groups. An exemplary aryl group is a C<sub>6</sub>-C<sub>10</sub> aryl group. Particular aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl.

**[00028]** An “aralkyl” or “arylalkyl” group comprises an aryl group covalently linked to an alkylene group wherein the moiety is linked to another group via the alkyl moiety. An exemplary aralkyl group is -(C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

**[00029]** A “heterocyclyl” or “heterocyclic” group is a mono- or bicyclic (fused or spiro) ring structure having from 3 to 12 atoms, (3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 atoms), for example 4 to 8 atoms, wherein one or more ring atoms are independently -C(O)-, N, NR<sup>5</sup>, O, or S, and the remainder of the ring atoms are quaternary or carbonyl carbons. Examples of heterocyclic groups include, without limitation, epoxy, oxiranyl, oxetanyl, azetidiny, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, thiazolidinyl, thiatanyl, dithianyl, trithianyl, azathianyl, oxathianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidonyl, thiomorpholinyl, dimethyl-morpholinyl, and morpholinyl. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

**[00030]** As used herein, “L-heterocyclyl” refers to a heterocyclyl group covalently linked to another group via an alkylene linker L, where L is C<sub>1</sub>-C<sub>4</sub> alkylene.

**[00031]** As used herein, the term “heteroaryl” refers to a group having 5 to 14 ring atoms, preferably 5, 6, 10, 13 or 14 ring atoms; having 6, 10, or 14  $\pi$  electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms that are each independently N, O, or S. “Heteroaryl” also includes fused multicyclic (*e.g.*, bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic and at least one ring contains an N, O, or S ring atom.

**[00032]** Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, furanyl, furazanyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl,

thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

**[00033]** A “L-heteroaryl,” “heteroaralkyl” or “heteroarylalkyl” group comprises a heteroaryl group covalently linked to another group via an alkylene linker. Examples of heteroaralkyl groups comprise a C<sub>1</sub>-C<sub>6</sub> alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Examples of heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, thiazolylethyl, benzimidazolylmethyl, benzimidazolylethyl, quinazolinylmethyl, quinolinylmethyl, quinolinylethyl, benzofuranylmethyl, indolinylethyl, isoquinolinylmethyl, isoinodolylmethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

**[00034]** An “arylene,” “heteroarylene,” or “heterocyclylene” group is an bivalent aryl, heteroaryl, or heterocyclyl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

**[00035]** As employed herein, when a moiety (e.g., cycloalkyl, aryl, heteroaryl, heterocyclyl, urea, etc.) is described as “optionally substituted” without expressly stating the substituents it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents.

**[00036]** The term “halogen” or “halo” as employed herein refers to chlorine, bromine, fluorine, or iodine.

**[00037]** The term “haloalkyl” refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Exemplary haloalkyls are trifluoromethyl, difluoromethyl, fluorchloromethyl, chloromethyl, and fluoromethyl.

**[00038]** The term “hydroxyalkyl” refers to an alkyl chain, as defined herein, wherein at least one hydrogen of the alkyl chain has been replaced by hydroxyl.

**[00039]** As used herein, “an effective amount” of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of PRC2 complex.

**[00040]** As used herein, a “therapeutically effective amount” of a compound is an amount that is sufficient to ameliorate or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of PRC2 complex. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

**[00041]** As used herein, “treatment” means any manner in which the symptoms or pathology of a condition, disorder or disease in a subject are ameliorated or otherwise beneficially altered.

**[00042]** Disclosed herein are methods of treating sickle cell disease in a subject, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2), wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has (a) been administered hydroxyurea; and/or (b) been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine. In some embodiments, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2

(PRC2) the subject has been administered hydroxyurea. In some embodiments, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has been administered hydroxyurea and been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine. In some embodiments, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has been administered hydroxyurea and been administered a stable dose of voxelotor. In some embodiments, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has been administered hydroxyurea and been administered a stable dose of crizanlizumab. In some embodiments, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has been administered hydroxyurea and been administered a stable dose of L-glutamine.

**[00043]** In other embodiments are provided such methods of treating sickle cell disease in a subject, wherein, prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced (a) one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea; or (b) one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.

**[00044]** In other embodiments are provided such methods of treating sickle cell disease in a subject, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea. In some embodiments, the subject further experienced continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose. In some embodiments, the subject further experienced an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea. In some embodiments, the subject further experienced

unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea. In some embodiments, the subject refused to continue the further administration of hydroxyurea.

**[00045]** In other embodiments are provided such methods of treating sickle cell disease in a subject, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine. In some embodiments, the subject further experienced continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months. In some embodiments, the subject further experienced a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor. In some embodiments, the subject further experienced continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine. In some embodiments, the subject further experienced an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine. In some embodiments, the subject further experienced unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine. In some embodiments, the subject refused to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.

**[00046]** In another embodiment is provided such methods of treating sickle cell disease in a subject, wherein the subject has been administered hydroxyurea prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2). In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject further experienced one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period; (b) episodes of acute chest syndrome (ACS); (c) an inability to tolerate continued administration of hydroxyurea; (d) unmanageable drug-drug interactions with the continued administration of hydroxyurea; and (e) the subject's refusal to continue the further administration of hydroxyurea. In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject further experienced the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period. In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject further experienced episodes of acute chest syndrome (ACS). In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2

(PRC2) the subject further experienced an inability to tolerate continued administration of hydroxyurea. In some embodiments, the inability to tolerate continued administration of hydroxyurea is characterized by one or more of the following: (a) allergic reaction to the administration of hydroxyurea; (b) hematologic toxicity; (c) inability to tolerate gastrointestinal side effects; (d) intolerable fatigue; (e) intolerable dizziness; (f) intolerable headaches; (g) intolerable fever; (h) intolerable leg ulcers; and (i) intolerable skin changes. In some embodiments, the hematologic toxicity is characterized by a decrease in one or more of red blood cells, white blood cells, and platelets. In some embodiments, the gastrointestinal side effects are selected from one or more of nausea, vomiting, diarrhea, and abdominal pain. In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject further experienced unmanageable drug-drug interactions with the continued administration of hydroxyurea. In some embodiments, in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject refused to continue the further administration of hydroxyurea.

**[00047]** In another embodiment is provided such methods of treating sickle cell disease in a subject, wherein the subject has been administered one or more of voxelotor, crizanlizumab, and L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[00048]** In some embodiments, the subject has been administered voxelotor prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2). In some embodiments, the subject has further exhibited one or more of (a) a failure to increase hemoglobin (Hb) by at least 1 g/dL, (b) an inability tolerate continued administration of voxelotor, (c) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, and (d) the subject's refusal to continue the further administration of voxelotor.

**[00049]** In some embodiments, the subject has been administered crizanlizumab prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2). In some embodiments, the subject has further exhibited one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period, (b) an inability tolerate continued administration of crizanlizumab, (c) unmanageable drug-drug interactions as a result of the continued administration to the subject of crizanlizumab, and (d) the subject's refusal to continue the further administration of crizanlizumab.

**[00050]** In some embodiments, the subject has been administered L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2). In some embodiments, the subject has further exhibited one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period, (b) an inability tolerate continued administration of L-glutamine, (c) unmanageable drug-drug interactions as a result of the continued administration to the subject of L-glutamine, and (d) the subject's refusal to continue the further administration of L-glutamine.

**[00051]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2

(PRC2) the subject has further experienced one or more of (a) 4 or more vaso-occlusive crisis (VOC) events over the prior 12-month period; (b) 2 or more vaso-occlusive crisis (VOC) events over the prior 6-month period; (c) 2 or more vaso-occlusive crisis (VOC) events over the prior 12-month period and at least one of one or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism; (d) 2 or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism over the prior 12-month period; (e) pulmonary hypertension; and (f) chronic kidney disease. In some embodiments, the pulmonary hypertension is characterized by one or more of (a) tricuspid regurgitant jet velocity (TRV) of greater than or equal to 3.0 m/s; (b) TRV of greater than or equal to 2.5 m/s and N-terminal pro b-type natriuretic peptide (NT-proBNP) plasma level of greater than or equal to 160 pg/mL; and (c) documented ongoing pulmonary hypertension diagnosed from previous echocardiogram or right-sided heart catheterization with mean pulmonary artery pressure greater than 25 mm Hg. In some embodiments, the chronic kidney disease is characterized by measurement on two separate and consecutive occasions of one or more of (a) an estimated glomerular filtration rate (eGFR) of greater than or equal to 30 mL/min/1.73 m<sup>2</sup> and less than 60 mL/min/1.73 m<sup>2</sup>; and (b) proteinuria characterized by an albumin to creatinine ratio greater than 300 mg/g or protein to creatinine ratio greater than 30 mg/mmol.

**[00052]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and hydroxyurea, voxelotor, crizanlizumab, or L-glutamine. In some embodiments, the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and hydroxyurea. the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and crizanlizumab. In some embodiments, the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and L-glutamine.

**[00053]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered one or more of hydroxyurea, voxelotor, crizanlizumab, and L-glutamine. In some embodiments, in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered hydroxyurea. In some embodiments, in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered voxelotor. In some embodiments, in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered crizanlizumab. In some embodiments, in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered L-glutamine.

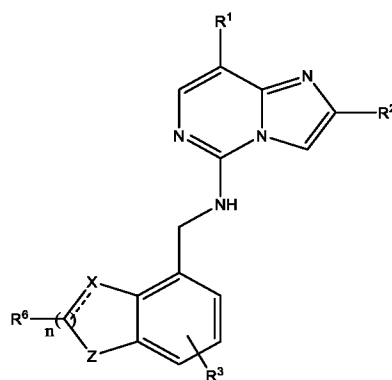
**[00054]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject (a) has not undergone major surgery, serious illness, infection, fever, significant

bleeding, cerebrovascular accident, or seizure within 14 days prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2); (b) is not being administered anticoagulants or medications that induce or inhibit cytochrome P450 (CYP) 3A4, inhibit P-glycoprotein, breast cancer resistance protein, or multidrug and toxin extrusion protein 2-K, or are substrates of CYP2B6 within 14 days prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2); (c) has not received a bone marrow transplant or human stem cell transplant or gene therapy; (d) has not received a vaccination in the 7 days prior to administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2); (e) is not exhibiting alanine aminotransferase of equal to or greater than 3 times the upper limit of normal (ULN), albumin less than 2.0 mg/dL, direct (conjugated) bilirubin greater than 1.5mg/dL, or prothrombin time greater than 1.5 ULN; (f) does not have severe renal disease defined as eGFR less than 30 mL/min/1.73 m<sup>2</sup>; (g) is not undergoing dialysis; (h) does not have a history of human immunodeficiency virus (HIV) infection, a history of hepatitis B infection, or active hepatitis C infection; (i) is not receiving regularly scheduled transfusions; (j) has not been transfused within the prior 60-day period; (k) has not tested positive for illicit drugs of abuse other than opioids, tetrahydrocannabinol, or cannabidiol; (l) is not pregnant, a lactating female, or a female of childbearing age unable or who is unwilling to comply with birth control or abstinence during the period during which the inhibitor of polycomb repressive complex 2 (PRC2) is administered to the subject; (m) has not exhibited a heart rate corrected QT interval-Fridericia's method (QTcF) of greater than 450 msec (male) or greater than 470 msec (female); (n) has not exhibited an active malignancy or history of cancer (except for squamous cell skin cancer, basal cell skin cancer, or stage 0 cervical carcinoma in situ, with no recurrence for the last 5 years); or (o) has not exhibited the presence of a chromosomal abnormality or genetic mutation that may put the subject at an increased risk of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

**[00055]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject is contraindicated for transfusions.

**[00056]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is an inhibitor of embryonic ectoderm development protein (EED). In some embodiments, the inhibitor of embryonic ectoderm development protein (EED) is MAK683. In some embodiments, the inhibitor of embryonic ectoderm development protein (EED) is pociredir (FTX-6058). In some embodiments, the inhibitor of embryonic ectoderm development protein (EED) is APG-5918 (EEDi-5273). In some embodiments, the inhibitor of embryonic ectoderm development protein (EED) is HJM-353. In some embodiments, the inhibitor of embryonic ectoderm development protein (EED) is BR-002.

**[00057]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein the inhibitor of embryonic ectoderm development protein (EED) is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

===== represents a single or a double bond;

Z is O or S;

X is O, CR<sup>5</sup>, CR<sup>5</sup>OH, or C(R<sup>5</sup>)<sub>2</sub>, wherein:

when X is O, ===== is a single bond;

when X is C(R<sup>5</sup>)<sub>2</sub>, ===== is a single bond;

when X is CR<sup>5</sup>OH, ===== is a single bond; or

when X is CR<sup>5</sup>, ===== is a double bond;

R<sup>1</sup> is aryl, heteroaryl, L-cycloalkyl, -N(R<sup>5</sup>)heterocyclyl, or L-heterocyclyl, wherein the aryl, the

heteroaryl and the cyclyl portion of the L-cycloalkyl, -N(R<sup>5</sup>)heterocyclyl, and L-heterocyclyl may be optionally substituted with one or more R<sup>4</sup>;

R<sup>2</sup> is cyano, -COOR<sup>5</sup> or -C(O)N(R<sup>5</sup>)<sub>2</sub>;

R<sup>3</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl or halogen;

each R<sup>4</sup> is independently oxo, cyano, halogen, -P(O)(OC<sub>1</sub>-C<sub>3</sub>)<sub>2</sub>, alkoxy, hydroxyl, hydroxyalkyl,

heteroalkyl, aralkyl, haloalkyl, -COOR<sup>5</sup>, -Y<sup>2</sup>-haloalkyl, -Y<sup>1</sup>-C<sub>1</sub>-C<sub>6</sub> alkyl, -Y<sup>2</sup>-C<sub>1</sub>-C<sub>6</sub> alkyl, -L-cycloalkyl, -L-heteroaryl, -L-heterocyclyl, -Y<sup>1</sup>-heterocyclyl, -Y<sup>2</sup>-heterocyclyl, -L-N(R<sup>5</sup>)<sub>2</sub>, -O-L-N(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)CO(R<sup>6</sup>), -O-L-OR<sup>5</sup>, -C(CF<sub>3</sub>)N(R<sup>5</sup>)<sub>2</sub>, -Y<sup>1</sup>-N(R<sup>5</sup>)<sub>2</sub>, -Y<sup>2</sup>-N(R<sup>5</sup>)<sub>2</sub> wherein the ring portion of the aralkyl, -L-cycloalkyl, -L-heteroaryl, -L-heterocyclyl and -Y<sup>1</sup>-heterocyclyl may be optionally substituted with one or more R<sup>7</sup>;

L is a bond or C<sub>1</sub>-C<sub>4</sub> alkylene;

Y<sup>1</sup> is a bond, -C(O)-, or -NHC(O)-;

Y<sup>2</sup> is a bond, -S-, -SO-, -SO<sub>2</sub>-, or -NR<sup>5</sup>SO<sub>2</sub>-;

each R<sup>5</sup> is independently hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl; or

each R<sup>5</sup> taken together with the nitrogen atom to which they are attached form a 5 – 8 membered heterocyclic ring optionally substituted with one or more R<sup>6</sup>;

R<sup>6</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, haloalkyl, hydroxyalkyl, or heteroalkyl;

each  $R^7$  is independently oxo, cyano, hydroxyl, alkoxy, halogen, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl,  $-L-N(R^5)_2$ ,  $C_1-C_6$  alkyl or  $-Y^1$ -heterocyclyl, wherein  $-Y^1$ -heterocyclyl may be optionally substituted with one or more  $R^6$ ; and

$n$  is 1 or 2.

**[00058]** In some embodiments are such methods wherein in the compound of Formula (I)  $Z$  is O. In some embodiments  $Z$  is S. In some embodiments  $n$  is 1. In some embodiments wherein  $R^2$  is cyano. In some embodiments  $R^2$  is  $-COOR^5$ . In some embodiments  $R^2$  is  $-C(O)N(R^5)_2$ . In some embodiments  $R^3$  is halogen, wherein in some embodiments the halogen is fluorine. In some embodiments  $X$  is  $C(R^5)_2$  and  $-----$  is a single bond. In some embodiments  $X$  is  $CR^5$  and  $=====$  is a double bond. In some embodiments  $X$  is O and  $-----$  is a single bond.

**[00059]** In some embodiments, in the compounds of Formula (I)  $R^1$  is aryl optionally substituted with one or more  $R^4$ . In some embodiments, the aryl is phenyl optionally substituted with one or more  $R^4$ . In some embodiments, the phenyl is substituted with one, two or three  $R^4$ . In some embodiments, the one, two or three  $R^4$  are each independently halogen, hydroxyl, haloalkyl,  $-COOR^5$ ,  $-Y^1-C_1-C_6$  alkyl,  $Y^2-C_1-C_6$  alkyl,  $-L-N(R^5)_2$ ,  $-O-L-N(R^5)_2$ ,  $-C(CF_3)N(R^5)_2$ ,  $-Y^1-N(R^5)_2$ ,  $-Y^2-N(R^5)_2$ ,  $Y^2$ -haloalkyl,  $-L$ -heterocyclyl, or  $-Y^1$ -heterocyclyl, wherein the heterocyclyl portion of the  $-L$ -heterocyclyl or  $-Y^1$ -heterocyclyl may be optionally substituted with one or more  $R^7$ . In some embodiments,  $R^4$  is  $-Y^1-C_1-C_6$  alkyl and  $Y^1$  is a bond and the  $C_1-C_6$  alkyl is methyl, ethyl, isopropyl, butyl or pentyl. In some embodiments,  $R^4$  is  $-Y^2-C_1-C_6$  alkyl and  $Y^2$  is a  $-SO_2-$  and the  $C_1-C_6$  alkyl is methyl. In some embodiments,  $R^4$  is  $-Y^2$ -haloalkyl and  $Y^2$  is  $-S-$  or  $-SO_2-$  and the haloalkyl is trifluoromethyl. In some embodiments,  $R^4$  is  $-L-N(R^5)_2$  and  $L$  is a bond and each  $R^5$  is hydrogen, each  $R^5$  is methyl, or one  $R^5$  is methyl and one  $R^5$  is hydrogen. In some embodiments,  $R^4$  is  $-L-N(R^5)_2$  and  $L$  is methylene or ethylene and each  $R^5$  is hydrogen, each  $R^5$  is methyl, or one  $R^5$  is methyl and one  $R^5$  is hydrogen. In some embodiments,  $R^4$  is  $-Y^1-N(R^5)_2$ ,  $Y^1$  is  $-C(O)-$  and each  $R^5$  independently is hydrogen, each  $R^5$  is independently methyl, or one  $R^5$  is methyl and one  $R^5$  is hydrogen. In some embodiments,  $R^4$  is  $-Y^2-N(R^5)_2$ ,  $Y^2$  is  $-SO_2-$  and each  $R^5$  independently is hydrogen, each  $R^5$  is methyl, or one  $R^5$  is methyl and one  $R^5$  is independently hydrogen. In some embodiments,  $R^4$  is  $-Y^1$ -heterocyclyl and  $Y^1$  is  $-C(O)-$  and the heterocyclyl portion of the  $L$ -heterocyclyl is piperazinyl or 4-methyl-piperazinyl. In some embodiments,  $R^4$  is  $-L$ -heterocyclyl and  $L$  is a bond and the heterocyclyl portion of the  $L$ -heterocyclyl is azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, or 3 $\lambda^2$ -azabicyclo[3.1.0]hexanyl, each optionally substituted with one or more  $R^7$  selected from oxo,  $C_1-C_3$  alkyl, alkoxy, hydroxyl and/or halogen. In some embodiments,  $R^4$  is  $-L$ -heterocyclyl, wherein  $L$  is a methylene and the heterocyclyl portion of the  $L$ -heterocyclyl is azetidiny, oxetanyl, pyrrolidinyl piperidinyl, each optionally substituted with one or more  $R^7$  selected from  $C_1-C_3$  alkyl, alkoxy, hydroxyl and/or halogen. In some embodiments,  $R^4$  is  $-Y^1$ -heterocyclyl and  $Y^1$  is  $-C(O)-$  and the heterocyclyl portion of the  $Y^1$ -heterocyclyl is morpholinyl optionally substituted with one or more  $C_1-C_3$  alkyl. In some embodiments,  $R^4$  is  $-L$ -heteroaryl optionally substituted with one or more  $R^7$ , wherein in some embodiments, the  $-L$ -heteroaryl is tetrazolyl. In some embodiments,  $R^4$  is  $-PO_3(C_1-C_3 \text{ alkyl})_2$ . In

some embodiments,  $R^4$  is  $-\text{COOR}^5$ . In some embodiments,  $R^4$  is hydroxyalkyl. In some embodiments,  $R^4$  is  $-\text{O-L-N(R}^5)_2$ . In some embodiments,  $R^4$  is aralkyl.

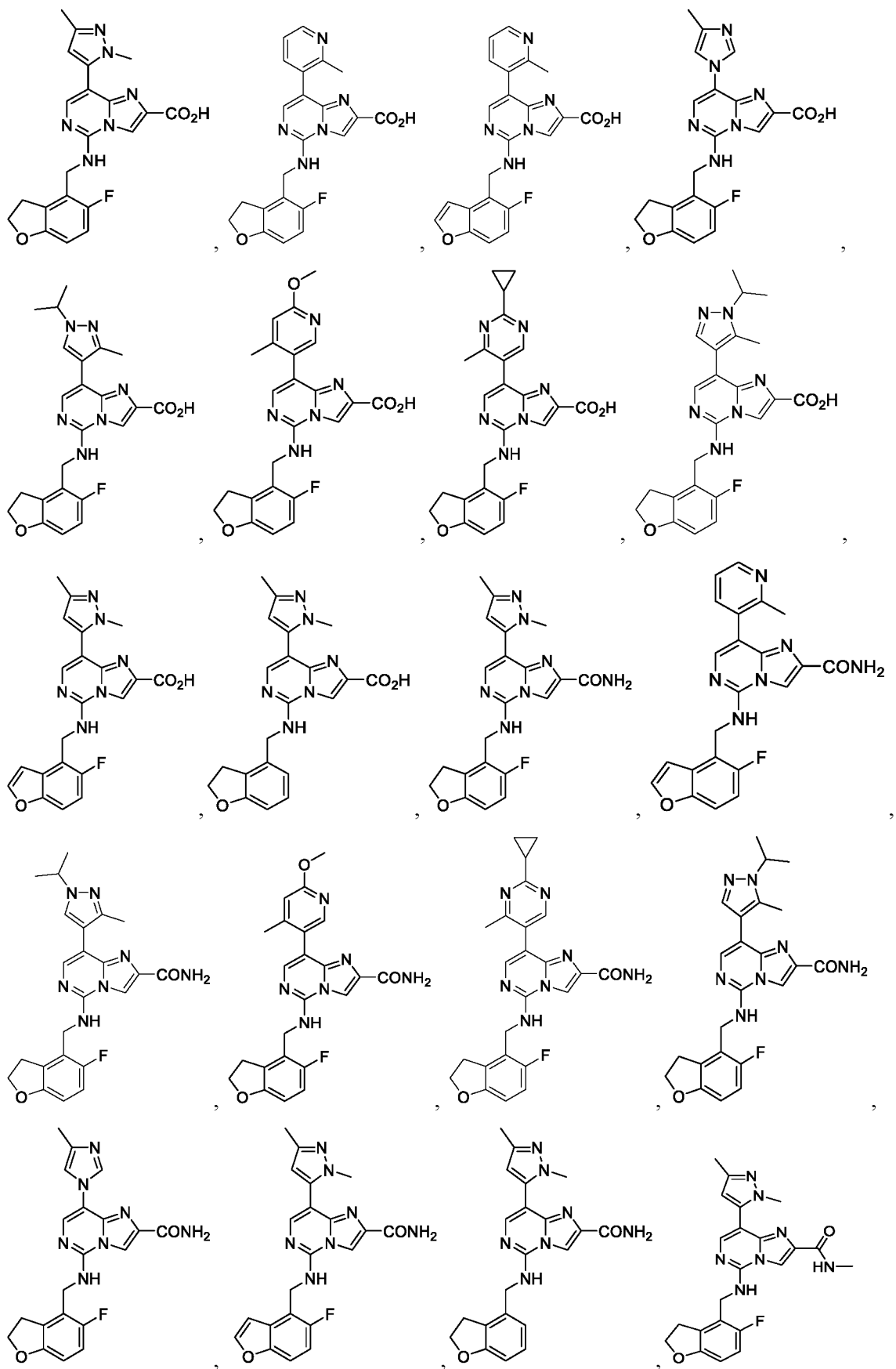
**[00060]** In some embodiments, in the compounds of Formula (I),  $R^1$  is heteroaryl optionally substituted with one or more  $R^4$ . In some embodiments, the heteroaryl is pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazinyl, pyridyl, pyridinyl-2-one, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, isoindolinyl, naphthridinyl, 1,2,3,4-tetrahydroisoquinolinyl, or 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, each optionally substituted with one or more  $R^4$ . In some embodiments, the heteroaryl is substituted with one or more  $R^4$ , wherein each  $R^4$  is independently cyano, halogen,  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl,  $-\text{Y}^2\text{-C}_1\text{-C}_6$  alkyl, alkoxy, hydroxyalkyl, heteroalkyl, haloalkyl,  $-\text{L-cycloalkyl}$ ,  $-\text{L-N(R}^5)_2$ ,  $-\text{Y}^1\text{-N(R}^5)_2$ ,  $-\text{L-heteroaryl}$ ,  $-\text{L-heterocyclyl}$ , or  $-\text{Y}^1\text{-heterocyclyl}$ , wherein the heteroaryl of the  $-\text{L-heteroaryl}$  or the heterocyclyl portion of the  $-\text{L-heterocyclyl}$ , or  $-\text{Y}^1\text{-heterocyclyl}$  may be optionally substituted with one or more  $R^7$ . In some embodiments, the heteroaryl is pyrazolyl optionally substituted with one  $R^4$  independently selected from hydroxyalkyl, heteroalkyl, haloalkyl,  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl,  $-\text{L-N(R}^5)_2$ ,  $-\text{L-heterocyclyl}$  or  $-\text{L-heteroaryl}$ , wherein the heteroaryl of the  $-\text{L-heteroaryl}$  or the heterocyclyl portion of the  $-\text{L-heterocyclyl}$  may be optionally substituted with one or more  $R^7$ . In some embodiments,  $R^4$  is  $-\text{L-heteroaryl}$  and L is methylene where the heteroaryl is pyridyl optional substituted with one or more  $R^7$ . In some embodiments,  $R^4$  is  $-\text{L-heterocyclyl}$  optionally substituted with one or more  $R^7$  where L is a bond and the heterocyclyl portion of the  $-\text{L-heterocyclyl}$  is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl or 4-methylpiperazinyl. In some embodiments,  $R^4$  is  $-\text{L-heterocyclyl}$  optionally substituted with one or more  $R^7$  where L is methylene and the heterocyclyl portion of the  $-\text{L-heterocyclyl}$  is azetidyl, oxetanyl, pyrrolidinyl, pyrrolidinone, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, piperazinyl or 4-methylpiperazinyl. In some embodiments,  $R^4$  is  $-\text{L-N(R}^5)_2$  where L is methylene and each  $R^5$  is independently hydrogen, each  $R^5$  is independently  $\text{C}_1\text{-C}_3$  alkyl, or one  $R^5$  is  $\text{C}_1\text{-C}_3$  alkyl and one  $R^5$  is hydrogen. In some embodiments,  $R^4$  is  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl where  $\text{Y}^1$  is a bond and the  $\text{C}_1\text{-C}_6$  alkyl is methyl, ethyl or isopropyl. In some embodiments, the heteroaryl is pyrazolyl optionally substituted with two  $R^4$  groups each independently selected from hydroxyalkyl, heteroalkyl, haloalkyl, and  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl. In some embodiments, the heteroaryl is pyridyl optionally substituted with one  $R^4$  independently selected from cyano, halogen, alkoxy, hydroxyalkyl, heteroalkyl, haloalkyl,  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl,  $-\text{L-N(R}^5)_2$ ,  $-\text{Y}^1\text{-N(R}^5)_2$ ,  $-\text{L-cycloalkyl}$ , or  $-\text{L-heterocyclyl}$  optionally substituted with one or more  $R^7$ .

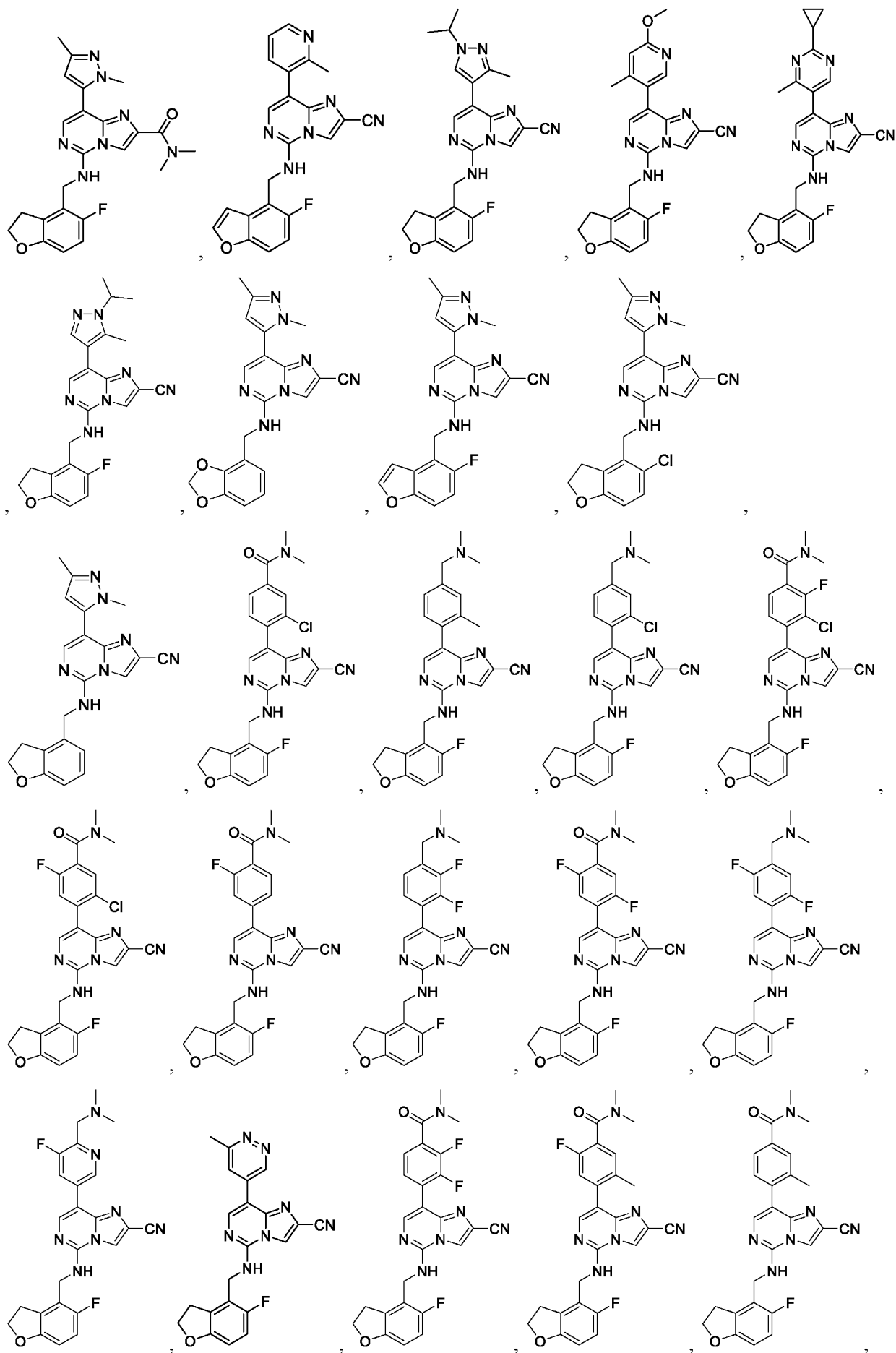
**[00061]** In some embodiments, in the compounds of Formula (I),  $R^1$  is  $-\text{L-cycloalkyl}$  optionally substituted with one or more  $R^4$ .

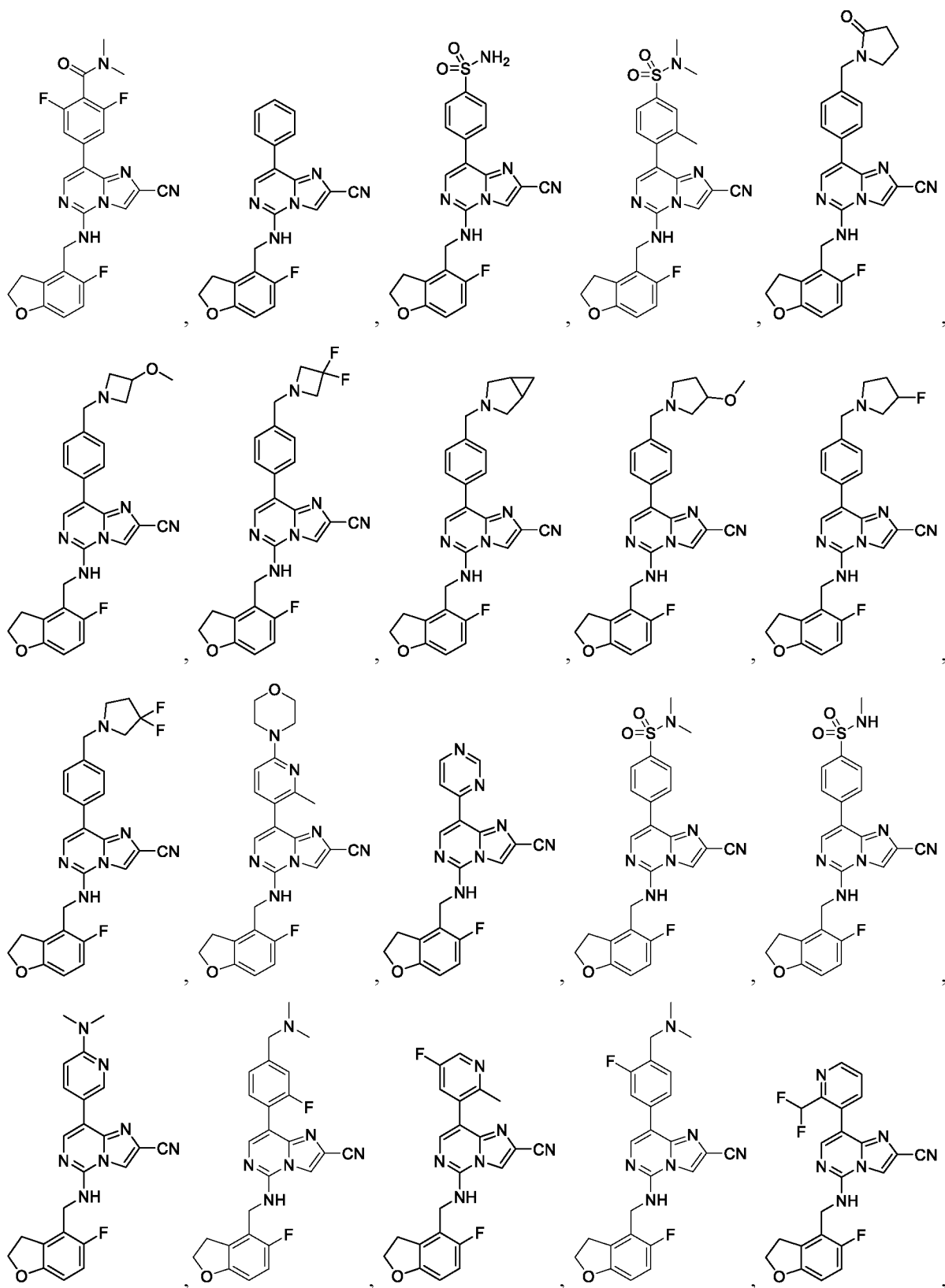
**[00062]** In some embodiments, in the compounds of Formula (I),  $R^1$  is  $-\text{L-heterocyclyl}$  optionally substituted with one or more  $R^4$ . In some embodiments, L is a bond and the heterocyclyl is piperidinyl or tetrahydropyranyl.

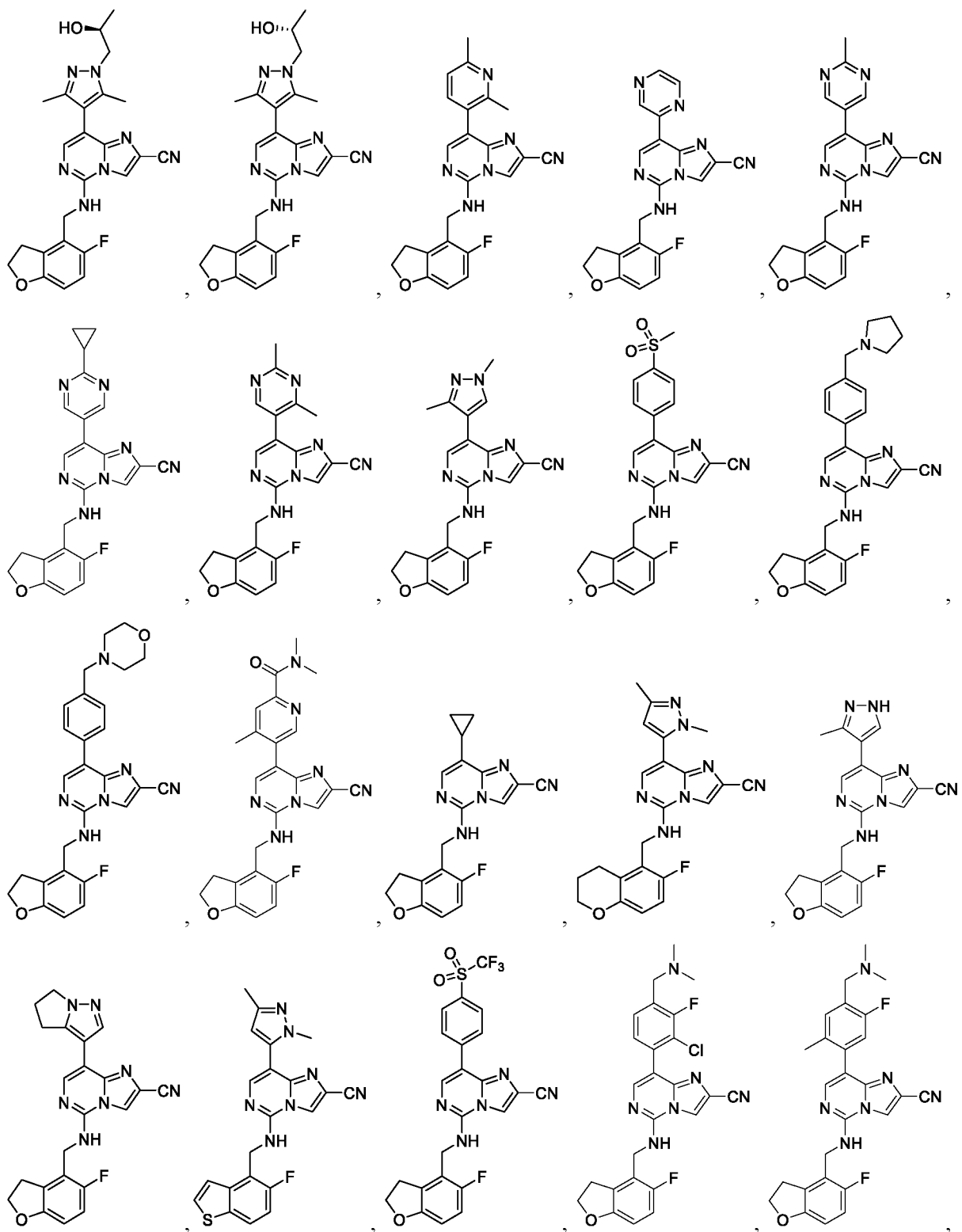
**[00063]** In some embodiments, in the compounds of Formula (I), wherein n is two.

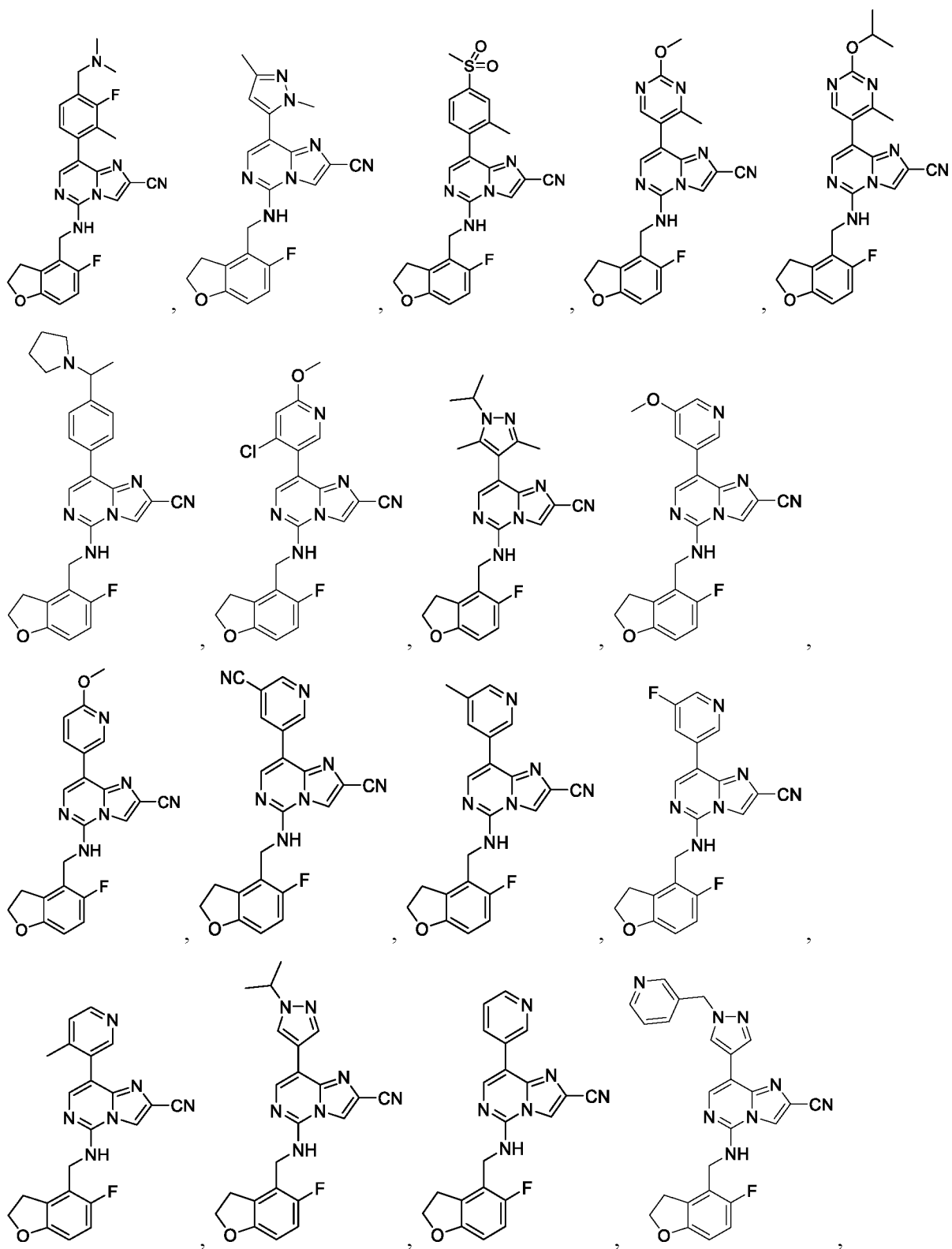
**[00064]** Further provided herein are the described methods of treating sickle cell disease in a subject, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is a compound selected from

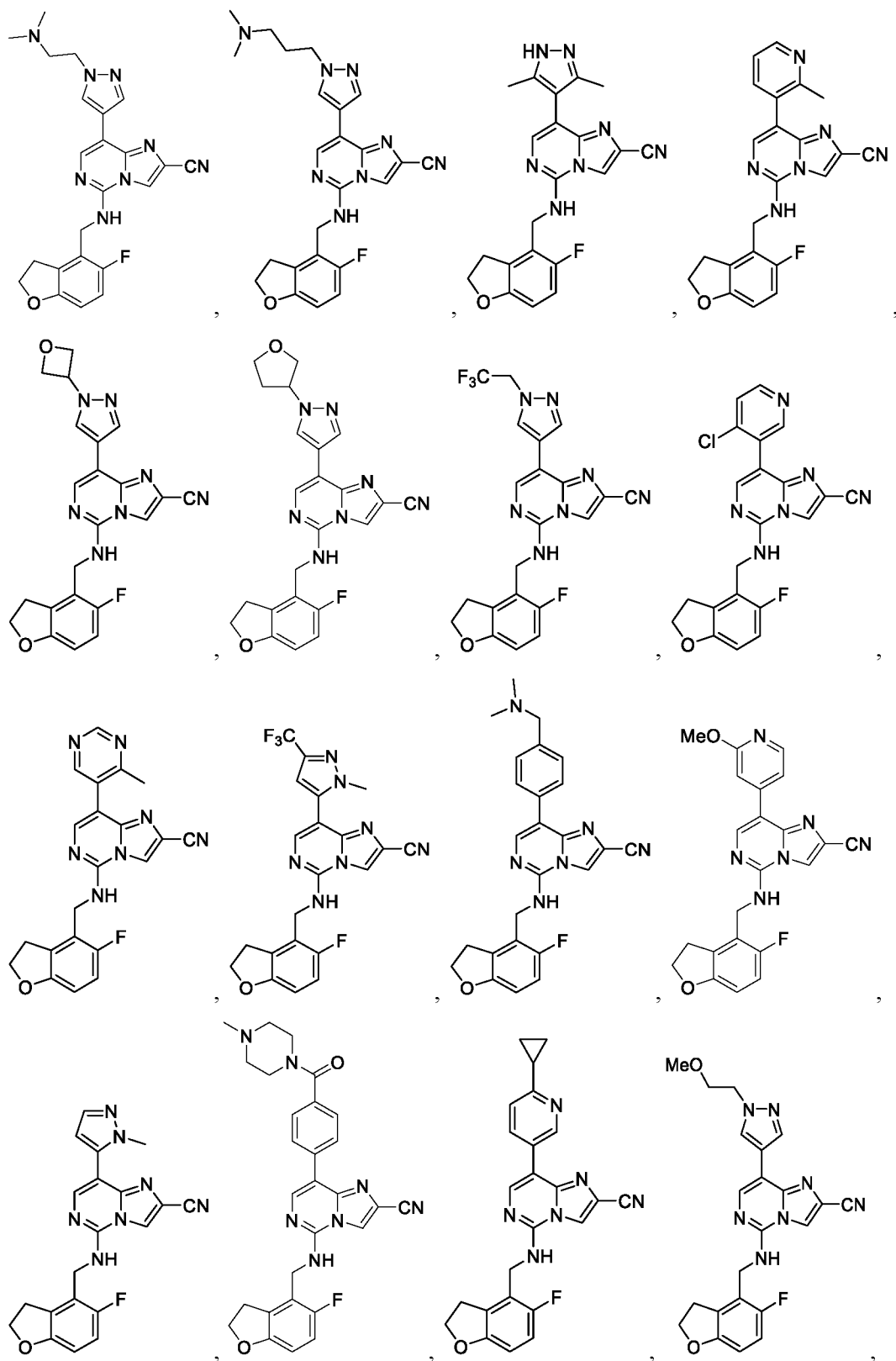


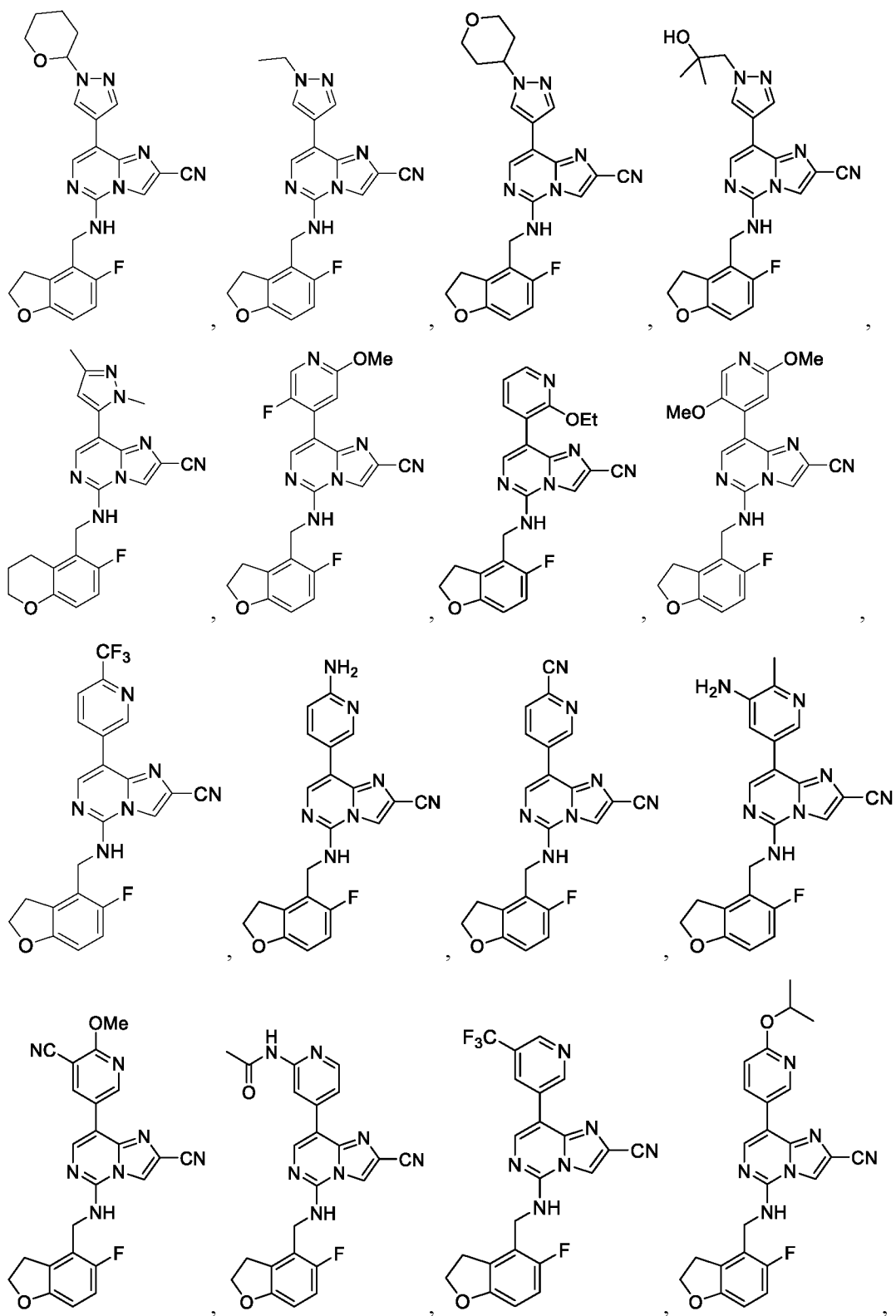


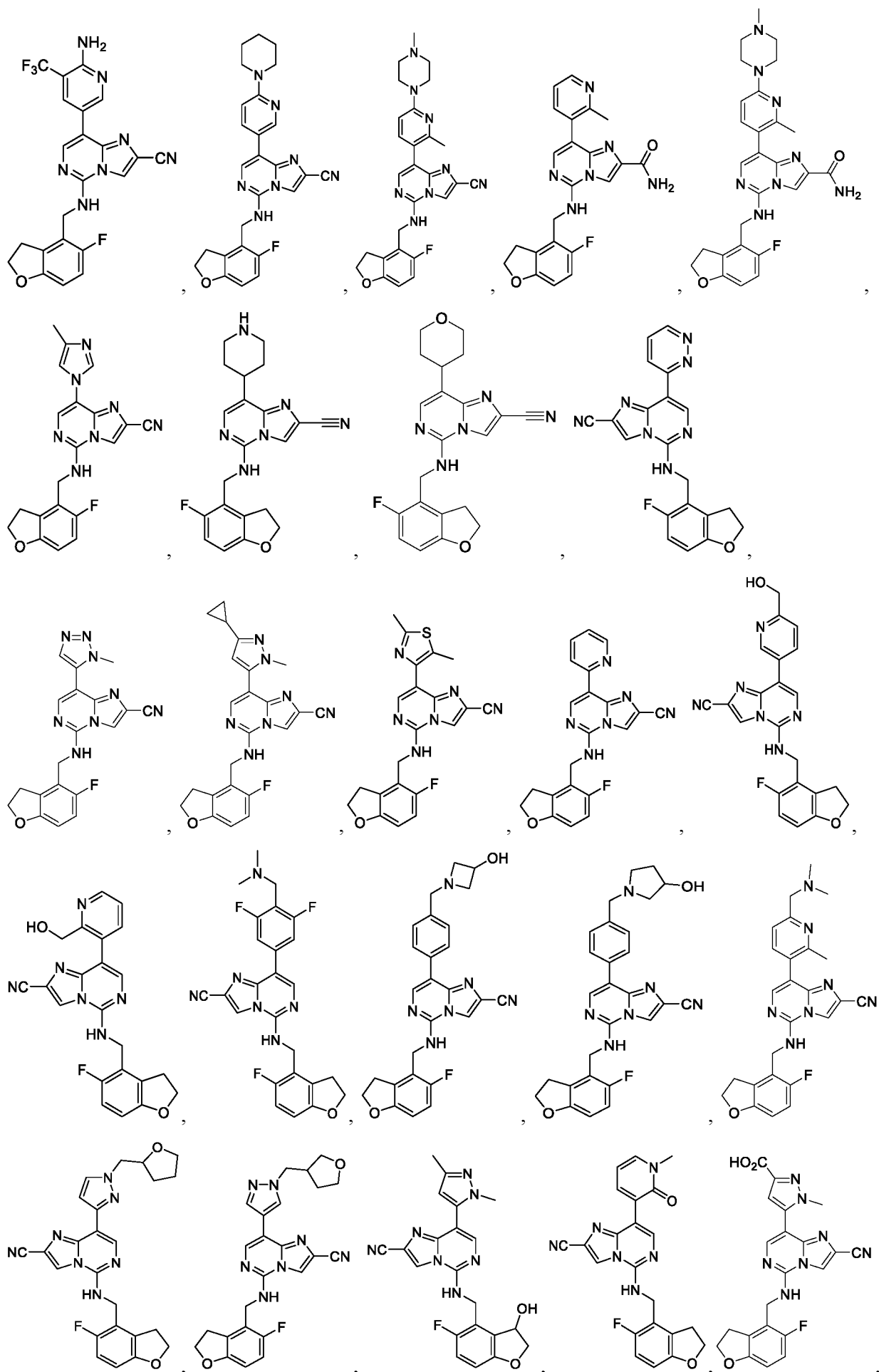


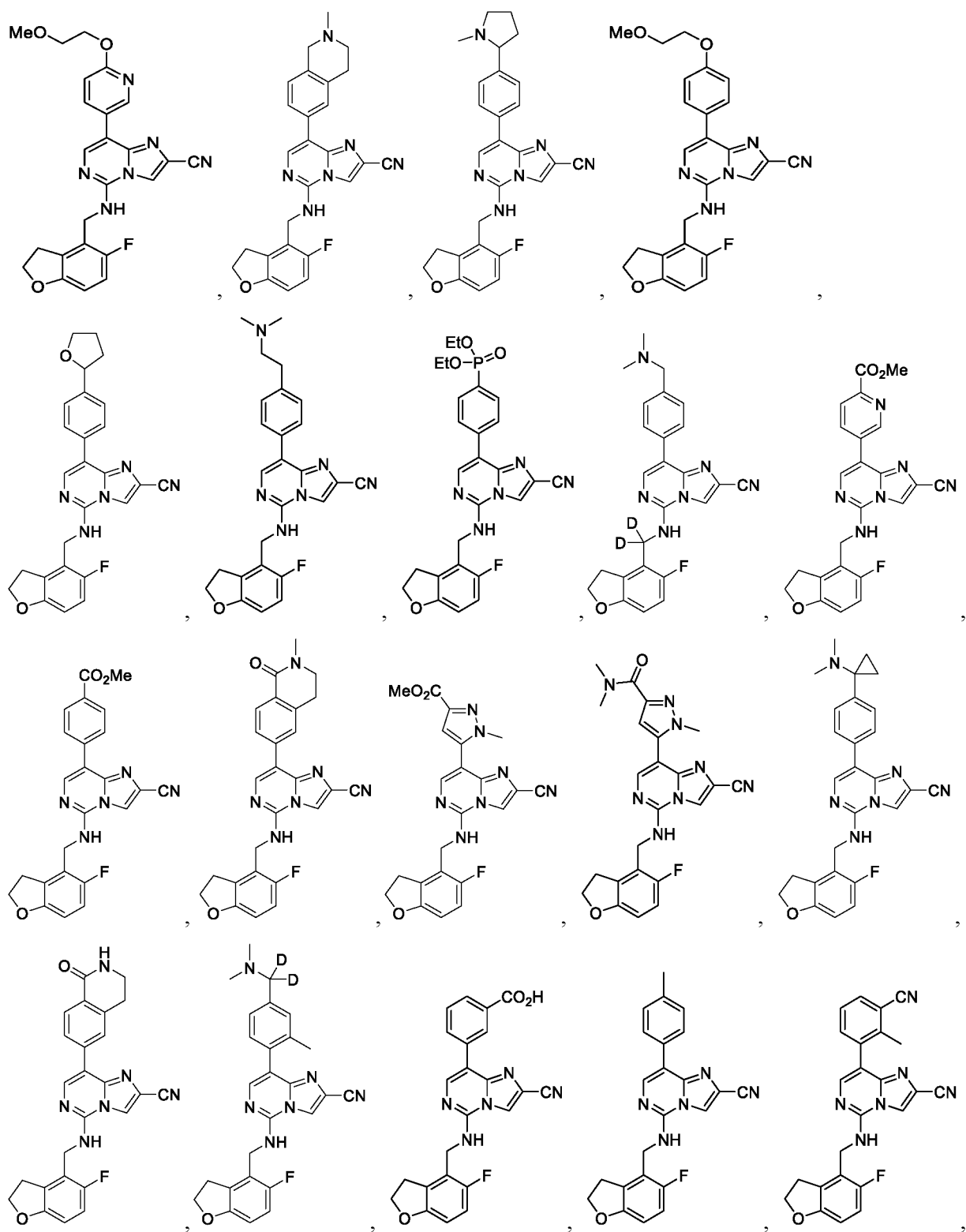


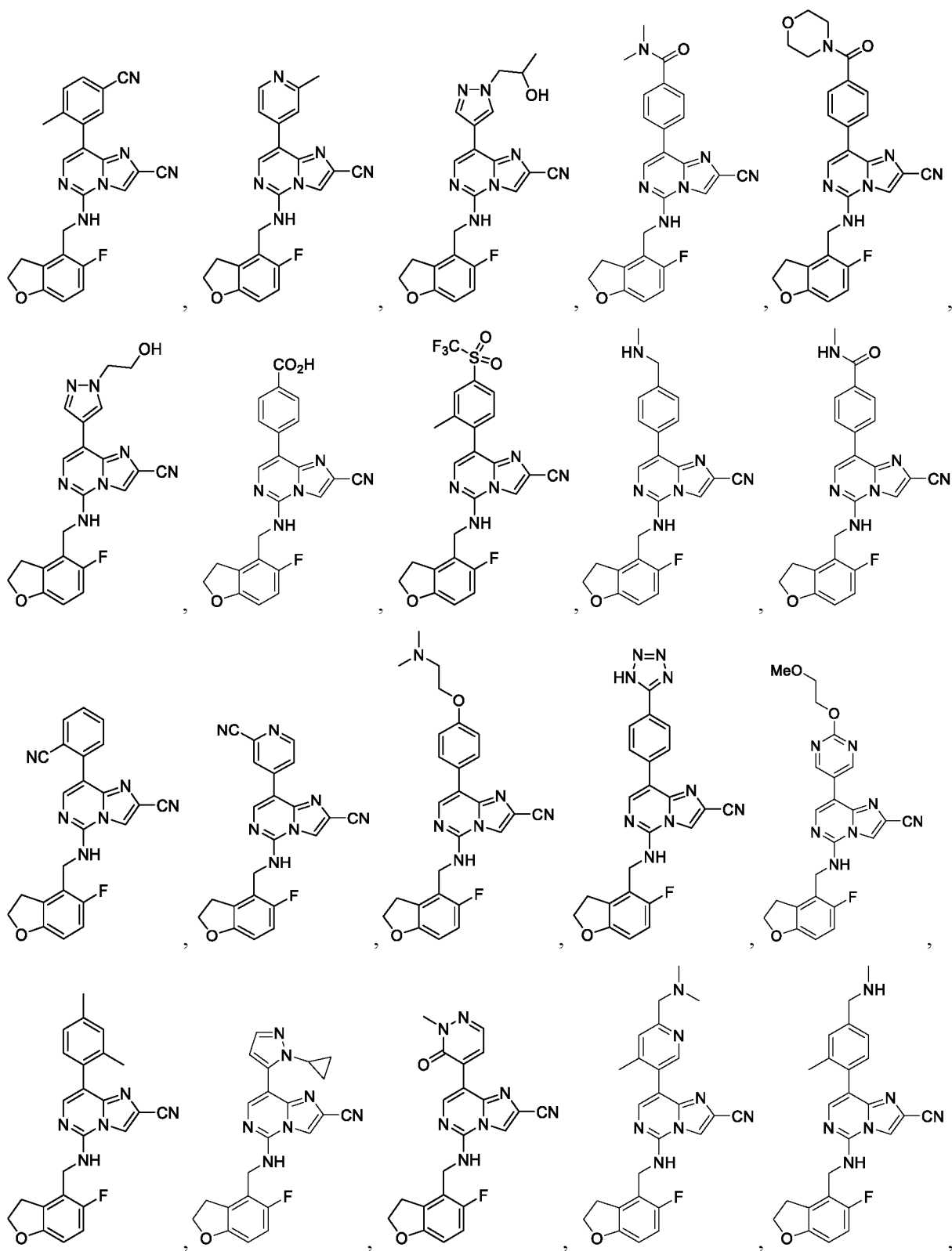


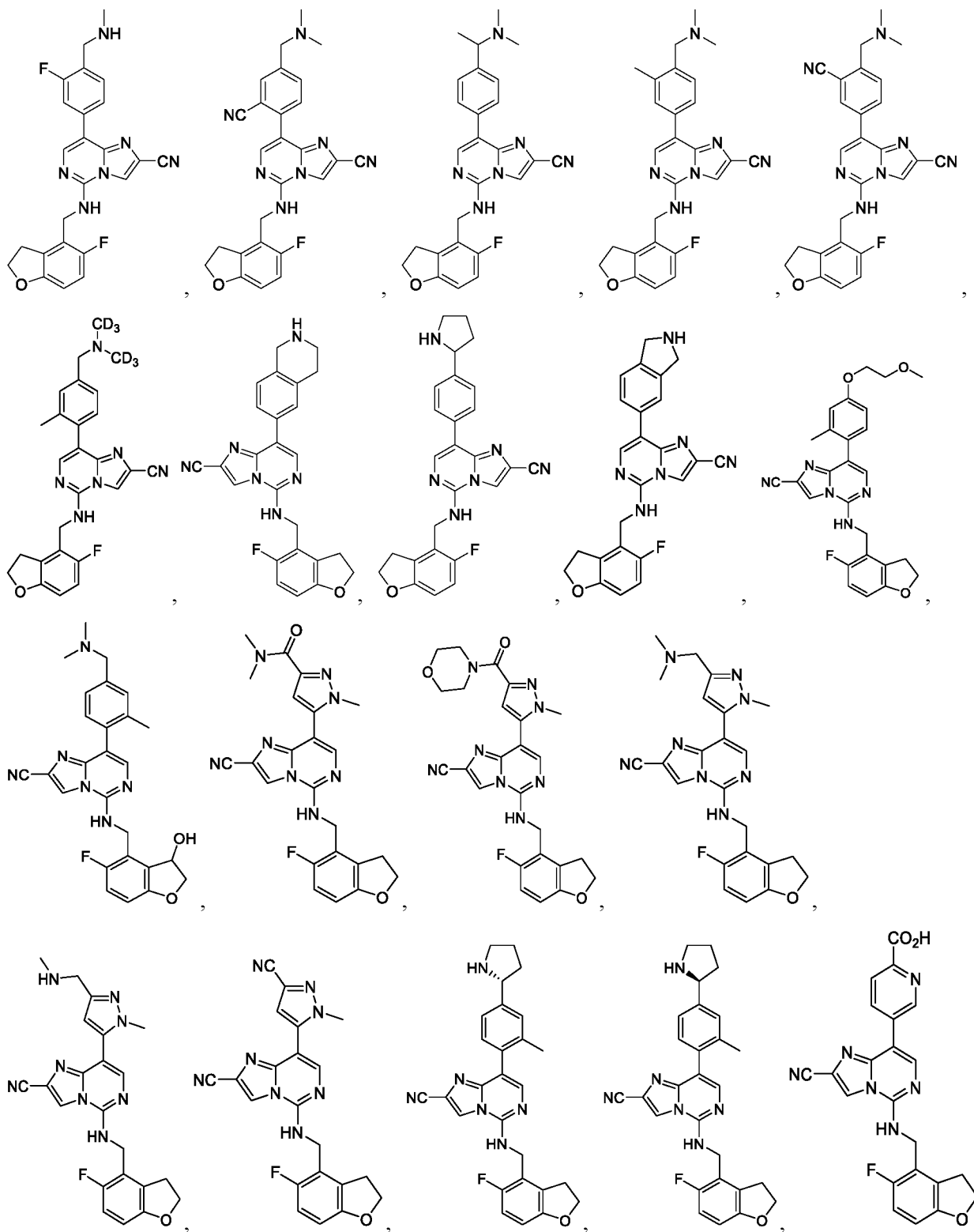


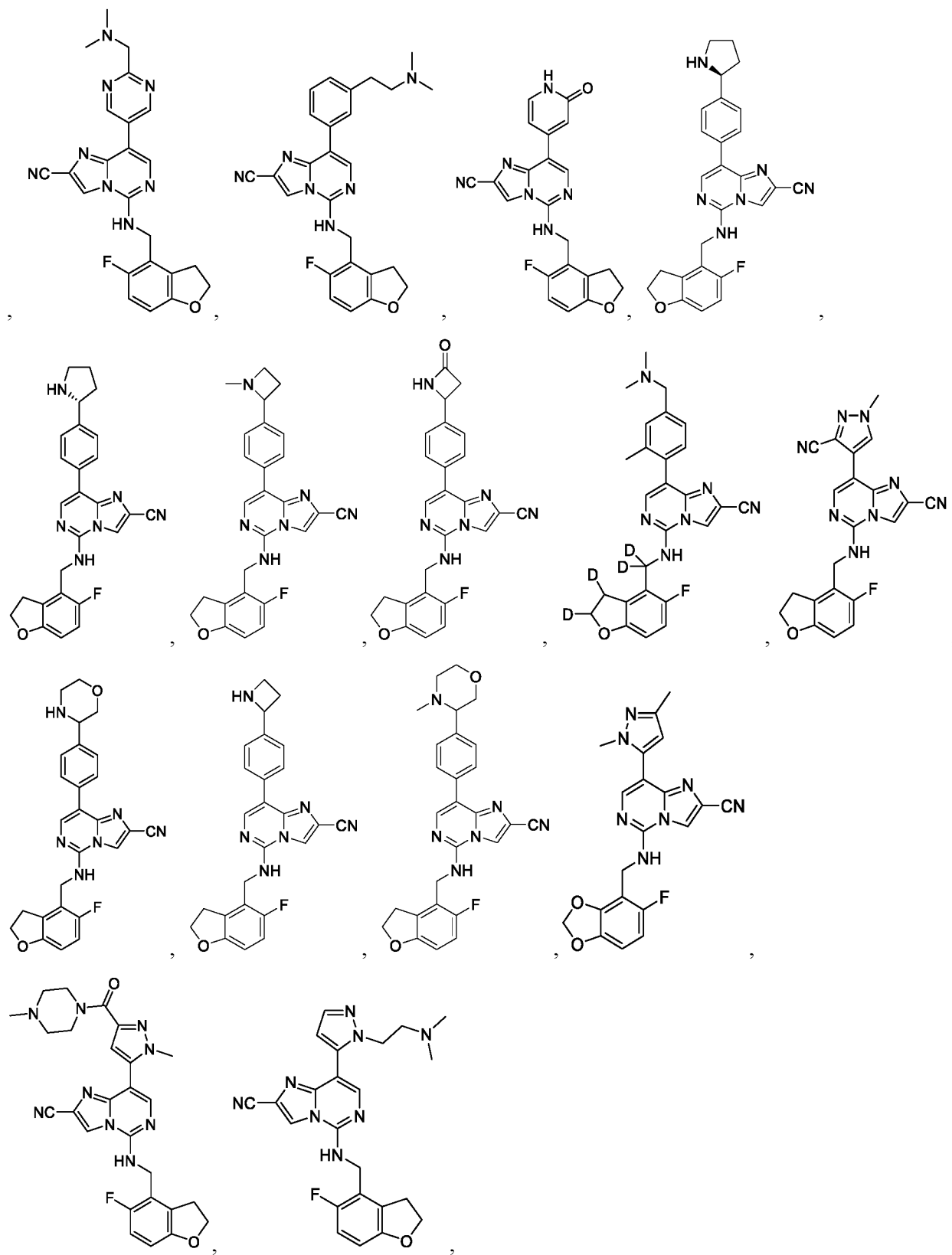


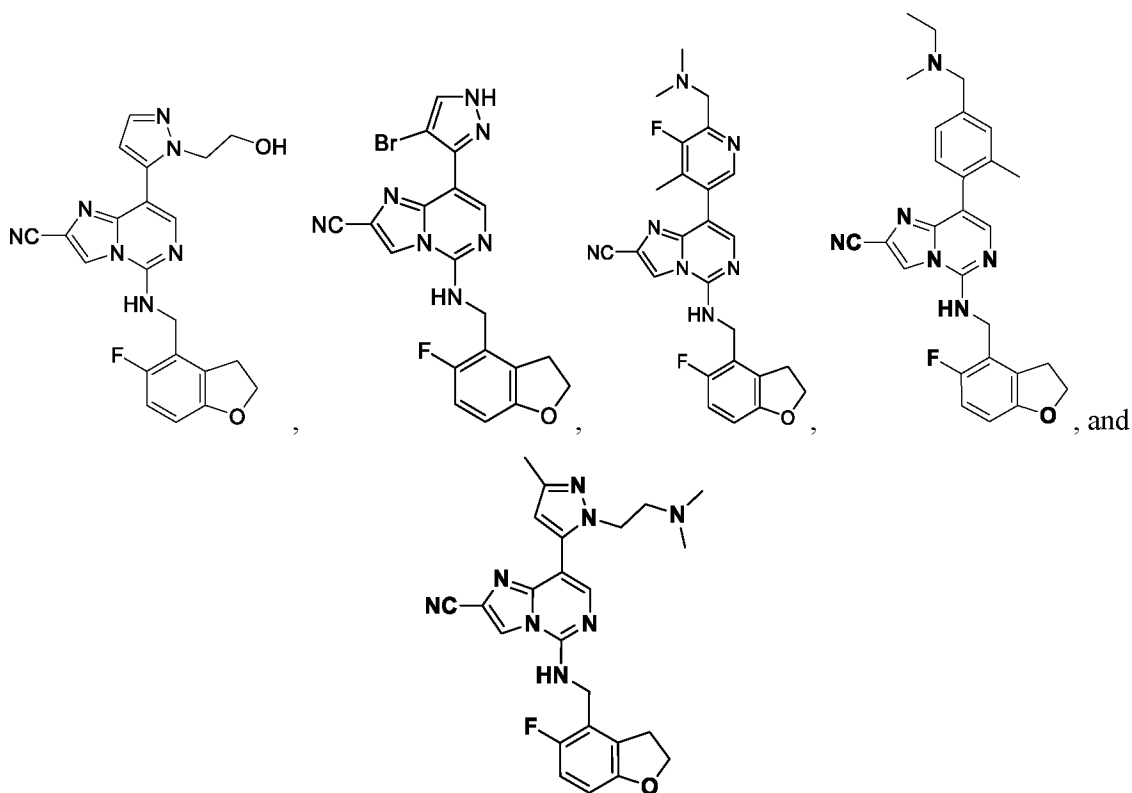




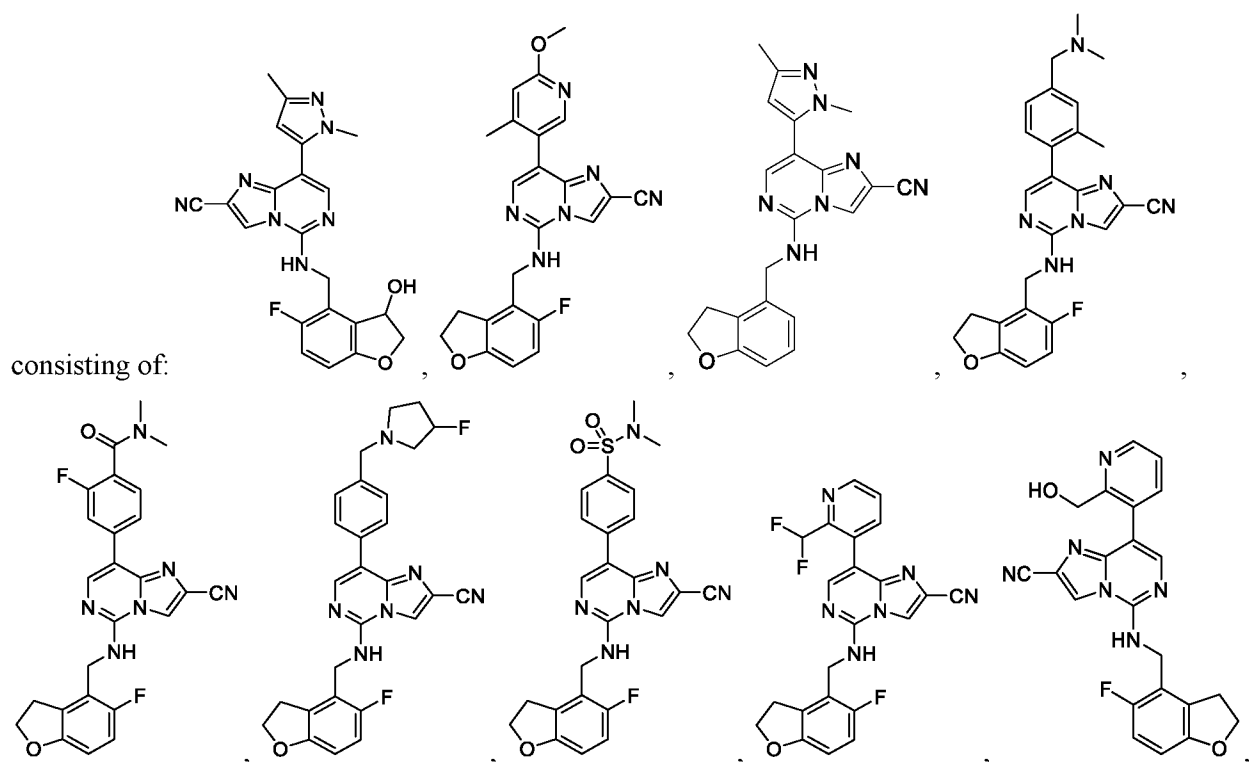


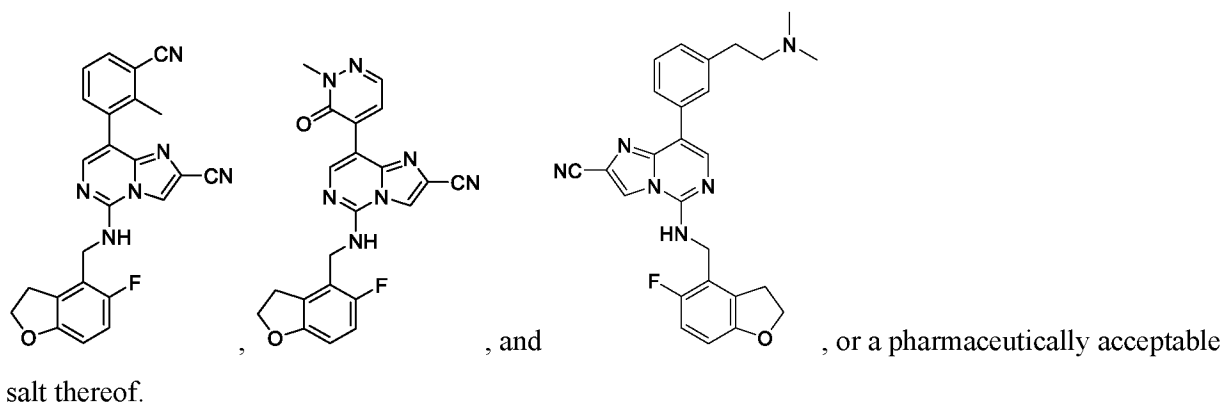




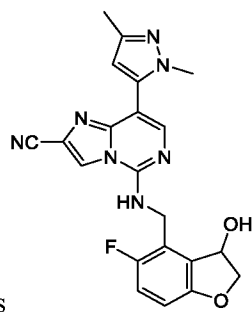


[00065] Further provided herein are the described methods of treating sickle cell disease in a subject, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is a compound selected from the group



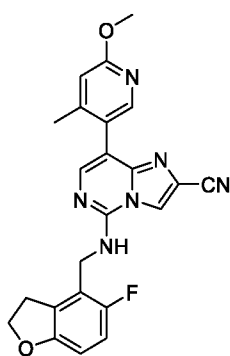


[00066] In other embodiments are provided the methods disclosed herein, wherein the compound of



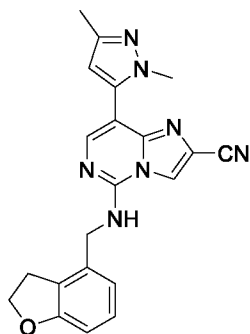
Formula (I) is , or a pharmaceutically acceptable salt thereof.

[00067] In other embodiments are provided the methods disclosed herein, wherein the compound of



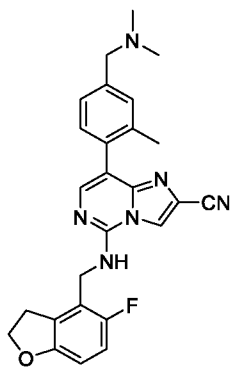
Formula (I) is , or a pharmaceutically acceptable salt thereof.

[00068] In other embodiments are provided the methods disclosed herein, wherein the compound of



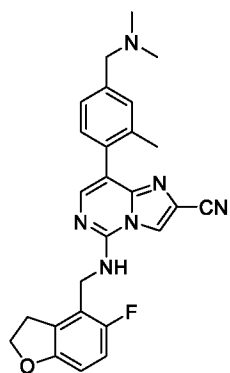
Formula (I) is , or a pharmaceutically acceptable salt thereof.

[00069] In other embodiments are provided the methods disclosed herein, wherein the compound of



Formula (I) is , or a pharmaceutically acceptable salt thereof.

[00070] Also provided herein are methods of treating sickle cell disease in a subject as disclosed herein, comprising administering to the subject a therapeutically effective amount of a compound which is



(Example 32), or a pharmaceutically acceptable salt thereof, wherein Example 32 is in crystalline form. Also provided herein are such methods wherein the crystalline form of Example 32 is an anhydrous form. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $8.1^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a further peak in an x-ray powder diffraction (XRPD) pattern at  $9.6^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $5.7^\circ \pm 0.2^\circ$  2-theta,  $19.7^\circ \pm 0.2^\circ$  2-theta, and  $22.0^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $9.8^\circ \pm 0.2^\circ$  2-theta,  $15.2^\circ \pm 0.2^\circ$  2-theta, and  $17.7^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of about 172 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 205 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 206 °C to about 210 °C, or from about 207 °C to about 210 °C, or from about 208 °C to about 210 °C, or from about 209 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 1% upon heating the sample from about 25 °C to a temperature prior to melting. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 1% upon heating the sample from about 25 °C to about 380 °C.

[00071] Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $13.7^{\circ} \pm 0.2^{\circ}$  2-theta and  $19.2^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $5.5^{\circ} \pm 0.2^{\circ}$  2-theta,  $8.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $15.9^{\circ} \pm 0.2^{\circ}$  2-theta,  $19.9^{\circ} \pm 0.2^{\circ}$  2-theta, and  $24.1^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $10.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $11.0^{\circ} \pm 0.2^{\circ}$  2-theta,  $15.4^{\circ} \pm 0.2^{\circ}$  2-theta,  $21.0^{\circ} \pm 0.2^{\circ}$  2-theta, and  $26.3^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 208 °C, or from about 203 °C to about 206 °C, or from about 203 °C to about 205 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 380 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 210 °C.

[00072] Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further a peak in an x-ray powder diffraction (XRPD) pattern at  $15.4^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further a peak in an x-ray powder diffraction (XRPD) pattern at  $19.2^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a further peak in an x-ray powder diffraction (XRPD) pattern at  $13.7^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $5.5^{\circ} \pm 0.2^{\circ}$  2-theta,  $8.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $15.9^{\circ} \pm 0.2^{\circ}$  2-theta,  $19.9^{\circ} \pm 0.2^{\circ}$  2-theta, and  $24.1^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $10.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $11.0^{\circ} \pm 0.2^{\circ}$  2-theta,  $21.0^{\circ} \pm 0.2^{\circ}$  2-theta, and  $26.3^{\circ} \pm 0.2^{\circ}$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 206 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 208 °C, or from about 203 °C to about 206 °C, or from about 203 °C to about 205 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample

from about 25 °C to about 380 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 210 °C.

**[00073]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits peaks in an x-ray powder diffraction (XRPD) pattern at  $7.7^\circ \pm 0.2^\circ$  2-theta and  $15.4^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $19.2^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a further peak in an x-ray powder diffraction (XRPD) pattern at  $13.7^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $5.5^\circ \pm 0.2^\circ$  2-theta,  $8.6^\circ \pm 0.2^\circ$  2-theta,  $15.9^\circ \pm 0.2^\circ$  2-theta,  $19.9^\circ \pm 0.2^\circ$  2-theta, and  $24.1^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $10.6^\circ \pm 0.2^\circ$  2-theta,  $11.0^\circ \pm 0.2^\circ$  2-theta,  $21.0^\circ \pm 0.2^\circ$  2-theta, and  $26.3^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 206 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 208 °C, or from about 203 °C to about 206 °C, or from about 203 °C to about 205 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 380 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 210 °C.

**[00074]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits peaks in an x-ray powder diffraction (XRPD) pattern at  $7.7^\circ \pm 0.2^\circ$  2-theta and  $19.2^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $15.4^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a further peak in an x-ray powder diffraction (XRPD) pattern at  $13.7^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $5.5^\circ \pm 0.2^\circ$  2-theta,  $8.6^\circ \pm 0.2^\circ$  2-theta,  $15.9^\circ \pm 0.2^\circ$  2-theta,  $19.9^\circ \pm 0.2^\circ$  2-theta, and  $24.1^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits further peaks in an x-ray powder diffraction (XRPD) pattern at  $10.6^\circ \pm 0.2^\circ$  2-theta,  $11.0^\circ \pm 0.2^\circ$  2-theta,  $21.0^\circ \pm 0.2^\circ$  2-theta, and  $26.3^\circ \pm 0.2^\circ$  2-theta. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 210 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 206 °C to about 210 °C. Also provided herein are

such methods wherein the crystalline form of Example 32 exhibits a peak in a differential scanning calorimetry pattern of from about 203 °C to about 208 °C, or from about 203 °C to about 206 °C, or from about 203 °C to about 205 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 380 °C. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits a loss in mass in a thermal gravimetric analysis of less than about 2% upon heating the sample from about 25 °C to about 210 °C.

**[00075]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 10% degradation when stored at 25 °C and 60% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days.

**[00076]** Also provided herein are such methods wherein the crystalline form of Example 32 (a) exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $8.1^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) exhibits less than about 10% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 (a) exhibits peaks in an x-ray powder diffraction (XRPD) pattern at  $9.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $5.7^{\circ} \pm 0.2^{\circ}$  2-theta,  $19.7^{\circ} \pm 0.2^{\circ}$  2-theta, and  $22.0^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days.

**[00077]** Also provided herein are such methods wherein the crystalline form of Example 32 (a) exhibits a peak in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) exhibits less than about 10% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits (a) peaks in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta,  $13.7^{\circ} \pm 0.2^{\circ}$  2-theta, and  $19.2^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 25 °C and 60% relative humidity for at least 7 days.

**[00078]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 10% degradation when the crystalline forms are stored at 40 °C and 75% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of

Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days.

**[00079]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits (a) a peak in an x-ray powder diffraction (XRPD) pattern at  $8.1^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days.

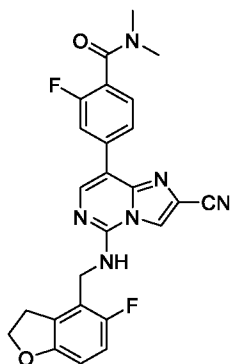
Also provided herein are such methods wherein the crystalline form of Example 32 exhibits (a) peaks in an x-ray powder diffraction (XRPD) pattern at  $9.6^{\circ} \pm 0.2^{\circ}$  2-theta,  $5.7^{\circ} \pm 0.2^{\circ}$  2-theta,  $19.7^{\circ} \pm 0.2^{\circ}$  2-theta, and  $22.0^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days.

**[00080]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits (a) a peak in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days.

Also provided herein are such methods wherein the crystalline form of Example 32 exhibits (a) peaks in an x-ray powder diffraction (XRPD) pattern at  $7.7^{\circ} \pm 0.2^{\circ}$  2-theta,  $13.7^{\circ} \pm 0.2^{\circ}$  2-theta, and  $19.2^{\circ} \pm 0.2^{\circ}$  2-theta, and (b) less than about 10% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 40 °C and 75% relative humidity for at least 7 days.

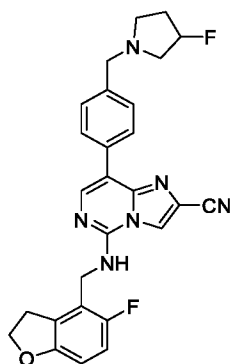
**[00081]** Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 10% degradation when the crystalline form is stored at 60 °C for at least one week. Also provided herein are such methods wherein the crystalline form of Example 32 exhibits less than about 1%, or less than about 2%, or less than about 3%, or less than about 4%, or less than about 5%, or less than about 6%, or less than about 7%, or less than about 8%, or less than about 9% degradation when the crystalline form is stored at 60 °C for at least one week.

[00082] In other embodiments are provided the methods disclosed herein, wherein the compound of



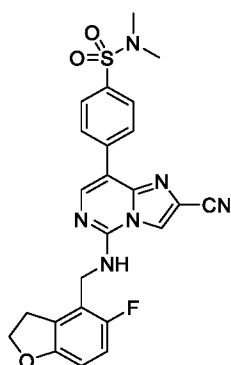
Formula (I) is \_\_\_\_\_, or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



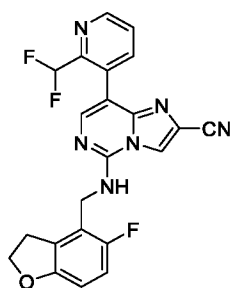
is \_\_\_\_\_, or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



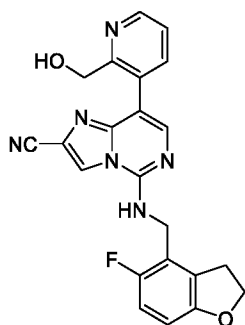
is \_\_\_\_\_, or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



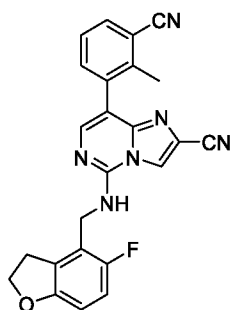
is \_\_\_\_\_, or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



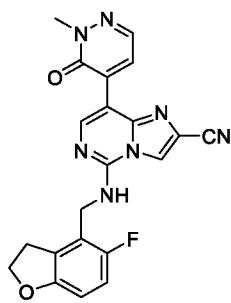
is , or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



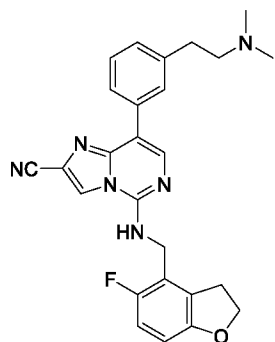
is , or a pharmaceutically acceptable salt thereof.

In other embodiments are provided the methods disclosed herein, wherein the compound of Formula (I)



is , or a pharmaceutically acceptable salt thereof.

**[00083]** In other embodiments are provided the methods disclosed herein, wherein the compound of



Formula (I) is , or a pharmaceutically acceptable salt thereof.

**[00084]** In another aspect, the disclosure provides pharmaceutical compositions comprising a PRC2 inhibitor as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent for use in the treatment of sickle cell disease in a subject. Compounds of the disclosure may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In

certain embodiments, compounds disclosed herein are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be by the oral route.

**[00085]** The characteristics of the carrier will depend on the route of administration. As used herein, the term “pharmaceutically acceptable” means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the disclosure may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

**[00086]** As used herein, the term “pharmaceutically acceptable salts” refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula  $--NR^+Z^-$ , wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide,  $--O-$ alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

**[00087]** The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a subject a therapeutically effective amount without causing serious toxic effects in the subject treated. A dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

## Embodiments

**[00088]** Embodiment 1: A method of treating sickle cell disease in a subject, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2), wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has:

- a. been administered hydroxyurea; and/or
- b. been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine.

**[00089]** Embodiment 2: The method of embodiment 1, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced:

- a. one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea; or
- b. one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.

**[00090]** Embodiment 3: The method of embodiment 2, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea.

**[00091]** Embodiment 4: The method of embodiment 2, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.

**[00092]** Embodiment 5: The method of embodiment 1, wherein the subject has been administered hydroxyurea prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[00093]** Embodiment 6: The method of embodiment 5, wherein in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period; (b) episodes of acute chest syndrome (ACS); (c) an inability to tolerate continued administration of hydroxyurea; (d) unmanageable drug-drug interactions with the continued administration of hydroxyurea; and (e) the subject's refusal to continue the further administration of hydroxyurea.

**[00094]** Embodiment 7: The method of embodiment 6, wherein the inability to tolerate continued administration of hydroxyurea is characterized by one or more of the following: (a) allergic reaction to the administration of hydroxyurea; (b) hematologic toxicity; (c) inability to tolerate gastrointestinal side effects; (d) intolerable fatigue; (e) intolerable dizziness; (f) intolerable headaches; (g) intolerable fever; (h) intolerable leg ulcers; and (i) intolerable skin changes.

**[00095]** Embodiment 8: The method of embodiment 7, wherein the hematologic toxicity is characterized by a decrease in one or more of red blood cells, white blood cells, and platelets.

**[00096]** Embodiment 9: The method of embodiment 7, wherein the gastrointestinal side effects are selected from one or more of nausea, vomiting, diarrhea, and abdominal pain.

**[00097]** Embodiment 10: The method of embodiment 1, wherein the subject has been administered one or more of voxelotor, crizanlizumab, and L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[00098]** Embodiment 11: The method of embodiment 10, wherein the subject has been administered voxelotor prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[00099]** Embodiment 12: The method of embodiment 11, wherein the subject has further exhibited one or more of (a) a failure to increase hemoglobin (Hb) by at least 1 g/dL, (b) an inability tolerate continued administration of voxelotor, (c) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, and (d) the subject's refusal to continue the further administration of voxelotor.

**[000100]** Embodiment 13: The method of embodiment 10, wherein the subject has been administered crizanlizumab prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[000101]** Embodiment 14: The method of embodiment 13, wherein the subject has further exhibited one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period, (b) an inability tolerate continued administration of crizanlizumab, (c) unmanageable drug-drug interactions as a result of the continued administration to the

subject of crizanlizumab, and (d) the subject's refusal to continue the further administration of crizanlizumab.

**[000102]** Embodiment 15: The method of embodiment 10, wherein the subject has been administered L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

**[000103]** Embodiment 16: The method of embodiment 15, wherein the subject has further exhibited one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period, (b) an inability tolerate continued administration of L-glutamine, (c) unmanageable drug-drug interactions as a result of the continued administration to the subject of L-glutamine, and (d) the subject's refusal to continue the further administration of L-glutamine.

**[000104]** Embodiment 17: The method of any one of embodiments 1 to 16, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of:

- a. 4 or more vaso-occlusive crisis (VOC) events over the prior 12-month period;
- b. 2 or more vaso-occlusive crisis (VOC) events over the prior 6-month period;
- c. 2 or more vaso-occlusive crisis (VOC) events over the prior 12-month period and at least one of one or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism;
- d. 2 or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism over the prior 12-month period;
- e. pulmonary hypertension; and
- f. chronic kidney disease.

**[000105]** Embodiment 18: The method of embodiment 17, wherein the pulmonary hypertension is characterized by one or more of (a) tricuspid regurgitant jet velocity (TRV) of greater than or equal to 3.0 m/s; (b) TRV of greater than or equal to 2.5 m/s and N-terminal pro b-type natriuretic peptide (NT-proBNP) plasma level of greater than or equal to 160 pg/mL; and (c) documented ongoing pulmonary hypertension diagnosed from previous echocardiogram or right-sided heart catheterization with mean pulmonary artery pressure greater than 25 mm Hg.

**[000106]** Embodiment 19: The method of embodiment 17, wherein the chronic kidney disease is characterized by measurement on two separate and consecutive occasions of one or more of (a) an estimated glomerular filtration rate (eGFR) of greater than or equal to 30 mL/min/1.73 m<sup>2</sup> and less than 60 mL/min/1.73 m<sup>2</sup>; and (b) proteinuria characterized by an albumin to creatinine ratio greater than 300 mg/g or protein to creatinine ratio greater than 30 mg/mmol.

**[000107]** Embodiment 20: The method of any one of embodiments 1 to 19, wherein the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and hydroxyurea, voxelotor, crizanlizumab, or L-glutamine.

[000108] Embodiment 21: The method of any one of embodiments 1 to 20, wherein in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered one or more of hydroxyurea, voxelotor, crizanlizumab, and L-glutamine.

[000109] Embodiment 22: The method of any one of embodiments 1 to 21, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject:

- a. has not undergone major surgery, serious illness, infection, fever, significant bleeding, cerebrovascular accident, or seizure within 14 days prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2);
- b. is not being administered anticoagulants or medications that induce or inhibit cytochrome P450 (CYP) 3A4, inhibit P-glycoprotein, breast cancer resistance protein, or multidrug and toxin extrusion protein 2-K, or are substrates of CYP2B6 within 14 days prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2);
- c. has not received a bone marrow transplant or human stem cell transplant or gene therapy;
- d. has not received a vaccination in the 7 days prior to administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2);
- e. is not exhibiting alanine aminotransferase of equal to or greater than 3 times the upper limit of normal (ULN), albumin less than 2.0 mg/dL, direct (conjugated) bilirubin greater than 1.5mg/dL, or prothrombin time greater than 1.5 ULN;
- f. does not have severe renal disease defined as eGFR less than 30 mL/min/1.73 m<sup>2</sup>;
- g. is not undergoing dialysis;
- h. does not have a history of human immunodeficiency virus (HIV) infection, a history of hepatitis B infection, or active hepatitis C infection;
- i. is not receiving regularly scheduled transfusions;
- j. has not been transfused within the prior 60-day period;
- k. has not tested positive for illicit drugs of abuse other than opioids, tetrahydrocannabinol, or cannabidiol;
- l. is not pregnant, a lactating female, or a female of childbearing age unable or who is unwilling to comply with birth control or abstinence during the period during which the inhibitor of polycomb repressive complex 2 (PRC2) is administered to the subject;
- m. has not exhibited a heart rate corrected QT interval-Fridericia's method (QTcF) of greater than 450 msec (male) or greater than 470 msec (female);
- n. has not exhibited an active malignancy or history of cancer (except for squamous cell skin cancer, basal cell skin cancer, or stage 0 cervical carcinoma in situ, with no recurrence for the last 5 years); or

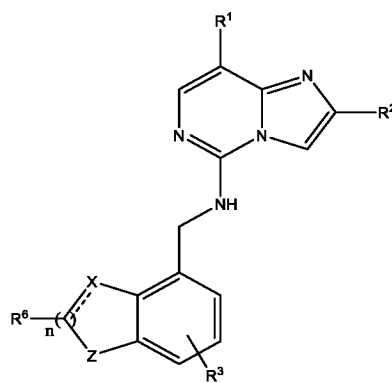
- o. has not exhibited the presence of a chromosomal abnormality or genetic mutation that may put the subject at an increased risk of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

[000110] Embodiment 23: The method of any one of embodiments 1 to 22, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject is contraindicated for transfusions.

[000111] Embodiment 24: The method of any one of embodiments 1 to 23, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is an inhibitor of embryonic ectoderm development protein (EED).

[000112] Embodiment 25: The method of embodiment 24, wherein the inhibitor of embryonic ectoderm development protein (EED) is MAK683, pociredir (FTX-6058), APG-5918 (EEDi-5273), HJM-353, or BR-002.

[000113] Embodiment 26: The method of embodiment 24, wherein the inhibitor of embryonic ectoderm development protein (EED) is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

===== represents a single or a double bond;

Z is O or S;

X is O, CR<sup>5</sup>, CR<sup>5</sup>OH, or C(R<sup>5</sup>)<sub>2</sub>, wherein:

when X is O, ===== is a single bond;

when X is C(R<sup>5</sup>)<sub>2</sub>, ===== is a single bond;

when X is CR<sup>5</sup>OH, ===== is a single bond; or

when X is CR<sup>5</sup>, ===== is a double bond;

R<sup>1</sup> is aryl, heteroaryl, L-cycloalkyl, -N(R<sup>5</sup>)heterocyclyl, or L-heterocyclyl, wherein the aryl, the

heteroaryl and the cyclyl portion of the L-cycloalkyl, -N(R<sup>5</sup>)heterocyclyl, and L-heterocyclyl may be optionally substituted with one or more R<sup>4</sup>;

R<sup>2</sup> is cyano, -COOR<sup>5</sup> or -C(O)N(R<sup>5</sup>)<sub>2</sub>;

R<sup>3</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl or halogen;

each  $R^4$  is independently oxo, cyano, halogen,  $-P(O)(OC_1-C_3)_2$ , alkoxy, hydroxyl, hydroxyalkyl, heteroalkyl, aralkyl, haloalkyl,  $-COOR^5$ ,  $-Y^2$ -haloalkyl,  $-Y^1-C_1-C_6$  alkyl,  $-Y^2-C_1-C_6$  alkyl,  $-L$ -cycloalkyl,  $-L$ -heteroaryl,  $-L$ -heterocyclyl,  $-Y^1$ -heterocyclyl,  $-Y^2$ -heterocyclyl,  $-L-N(R^5)_2$ ,  $-O-L-N(R^5)_2$ ,  $-N(R^5)CO(R^6)$ ,  $-O-L-OR^5$ ,  $-C(CF_3)N(R^5)_2$ ,  $-Y^1-N(R^5)_2$ ,  $-Y^2-N(R^5)_2$  wherein the ring portion of the aralkyl,  $-L$ -cycloalkyl,  $-L$ -heteroaryl,  $-L$ -heterocyclyl and  $-Y^1$ -heterocyclyl may be optionally substituted with one or more  $R^7$ ;

$L$  is a bond or  $C_1-C_4$  alkylene;

$Y^1$  is a bond,  $-C(O)-$ , or  $-NHC(O)-$ ;

$Y^2$  is a bond,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ , or  $-NR^5SO_2-$ ,

each  $R^5$  is independently hydrogen or  $C_1-C_3$  alkyl; or

each  $R^5$  taken together with the nitrogen atom to which they are attached form a 5 – 8 membered heterocyclic ring optionally substituted with one or more  $R^6$ ;

$R^6$  is hydrogen,  $C_1-C_3$  alkyl, halogen, haloalkyl, hydroxyalkyl, or heteroalkyl;

each  $R^7$  is independently oxo, cyano, hydroxyl, alkoxy, halogen, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl,  $-L-N(R^5)_2$ ,  $C_1-C_6$  alkyl or  $-Y^1$ -heterocyclyl, wherein  $-Y^1$ -heterocyclyl may be optionally substituted with one or more  $R^6$ ; and

$n$  is 1 or 2.

[000114] Embodiment 27: The method of embodiment 26, wherein  $Z$  is  $O$ .

[000115] Embodiment 28: The method of embodiment 26, wherein  $Z$  is  $S$ .

[000116] Embodiment 29: The method according to any of embodiments 26 to 28, wherein  $n$  is 1.

[000117] Embodiment 30: The method according to any of embodiments 26 to 29, wherein  $R^2$  is cyano.

[000118] Embodiment 31: The method according to any of embodiments 26 to 29, wherein  $R^2$  is  $-COOR^5$ .

[000119] Embodiment 32: The method according to any of embodiments 26 to 29, wherein  $R^2$  is  $-C(O)N(R^5)_2$ .

[000120] Embodiment 33: The method according to any of embodiments 26 to 32, wherein  $R^3$  is halogen.

[000121] Embodiment 34: The method of embodiment 33, wherein the halogen is fluorine.

[000122] Embodiment 35: The method according to any of embodiments 26 to 33, wherein  $X$  is  $C(R^5)_2$  and  $=====$  is a single bond.

[000123] Embodiment 36: The method according to any of embodiments 26 to 33, wherein  $X$  is  $CR^5$  and  $=====$  is a double bond.

[000124] Embodiment 37: The method according to any of embodiments 26 to 33, wherein  $X$  is  $O$  and  $=====$  is a single bond.

[000125] Embodiment 38: The method according to any of embodiments 26 to 37, wherein  $R^1$  is aryl optionally substituted with one or more  $R^4$ .

[000126] Embodiment 39: The method of embodiment 38, wherein the aryl is phenyl optionally substituted with one or more  $R^4$ .

[000127] Embodiment 40: The method of embodiment 39, wherein the phenyl is substituted with one, two or three  $R^4$ .

[000128] Embodiment 41: The method of embodiment 40, wherein the one, two or three  $R^4$  are each independently halogen, hydroxyl, haloalkyl,  $-\text{COOR}^5$ ,  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl,  $\text{Y}^2\text{-C}_1\text{-C}_6$  alkyl,  $-\text{L-N(R}^5)_2$ ,  $-\text{O-L-N(R}^5)_2$ ,  $-\text{C(CF}_3\text{)N(R}^5)_2$ ,  $-\text{Y}^1\text{-N(R}^5)_2$ ,  $-\text{Y}^2\text{-N(R}^5)_2$ ,  $\text{Y}^2\text{-haloalkyl}$ ,  $-\text{L-heterocyclyl}$ , or  $-\text{Y}^1\text{-heterocyclyl}$ , wherein the heterocyclyl portion of the  $-\text{L-heterocyclyl}$  or  $-\text{Y}^1\text{-heterocyclyl}$  may be optionally substituted with one or more  $R^7$ .

[000129] Embodiment 42: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^1\text{-C}_1\text{-C}_6$  alkyl and  $\text{Y}^1$  is a bond and the  $\text{C}_1\text{-C}_6$  alkyl is methyl, ethyl, isopropyl, butyl or pentyl.

[000130] Embodiment 43: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^2\text{-C}_1\text{-C}_6$  alkyl and  $\text{Y}^2$  is a  $-\text{SO}_2\text{-}$  and the  $\text{C}_1\text{-C}_6$  alkyl is methyl.

[000131] Embodiment 44: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^2\text{-haloalkyl}$  and  $\text{Y}^2$  is  $-\text{S-}$  or  $-\text{SO}_2\text{-}$  and the haloalkyl is trifluoromethyl.

[000132] Embodiment 45: The method of embodiment 41, wherein  $R^4$  is  $-\text{L-N(R}^5)_2$  and  $\text{L}$  is a bond and each  $\text{R}^5$  is hydrogen, each  $\text{R}^5$  is methyl, or one  $\text{R}^5$  is methyl and one  $\text{R}^5$  is hydrogen.

[000133] Embodiment 46: The method of embodiment 41, wherein  $R^4$  is  $-\text{L-N(R}^5)_2$  and  $\text{L}$  is methylene or ethylene and each  $\text{R}^5$  is hydrogen, each  $\text{R}^5$  is methyl, or one  $\text{R}^5$  is methyl and one  $\text{R}^5$  is hydrogen.

[000134] Embodiment 47: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^1\text{-N(R}^5)_2$ ,  $\text{Y}^1$  is  $-\text{C(O)-}$  and each  $\text{R}^5$  independently is hydrogen, each  $\text{R}^5$  is independently methyl, or one  $\text{R}^5$  is methyl and one  $\text{R}^5$  is hydrogen.

[000135] Embodiment 48: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^2\text{-N(R}^5)_2$ ,  $\text{Y}^2$  is  $-\text{SO}_2\text{-}$  and each  $\text{R}^5$  independently is hydrogen, each  $\text{R}^5$  is methyl, or one  $\text{R}^5$  is methyl and one  $\text{R}^5$  is independently hydrogen.

[000136] Embodiment 49: The method of embodiment 41, , wherein  $R^4$  is  $-\text{Y}^1\text{-heterocyclyl}$  and  $\text{Y}^1$  is  $-\text{C(O)-}$  and the heterocyclyl portion of the  $\text{L-heterocyclyl}$  is piperazinyl or 4-methyl-piperazinyl.

[000137] Embodiment 50: The method of embodiment 41, wherein  $R^4$  is  $-\text{L-heterocyclyl}$  and  $\text{L}$  is a bond and the heterocyclyl portion of the  $\text{L-heterocyclyl}$  is azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, or  $3\lambda^2\text{-azabicyclo[3.1.0]hexanyl}$ , each optionally substituted with one or more  $\text{R}^7$  selected from oxo,  $\text{C}_1\text{-C}_3$  alkyl, alkoxy, hydroxyl and/or halogen.

[000138] Embodiment 51: The method of embodiment 41, wherein  $R^4$  is  $-\text{L-heterocyclyl}$ , wherein  $\text{L}$  is a methylene and the heterocyclyl portion of the  $\text{L-heterocyclyl}$  is azetidiny, oxetanyl, pyrrolidinyl, piperidinyl, each optionally substituted with one or more  $\text{R}^7$  selected from  $\text{C}_1\text{-C}_3$  alkyl, alkoxy, hydroxyl and/or halogen.

[000139] Embodiment 52: The method of embodiment 41, wherein  $R^4$  is  $-\text{Y}^1\text{-heterocyclyl}$  and  $\text{Y}^1$  is  $-\text{C(O)-}$  and the heterocyclyl portion of the  $\text{Y}^1\text{-heterocyclyl}$  is morpholinyl optionally substituted with one or more  $\text{C}_1\text{-C}_3$  alkyl.

[000140] Embodiment 53: The method of embodiment 41, wherein  $R^4$  is  $-\text{L-heteroaryl}$  optionally substituted with one or more  $\text{R}^7$ .

- [000141] Embodiment 54: The method of embodiment 53, wherein the -L-heteroaryl is tetrazolyl.
- [000142] Embodiment 55: The method of embodiment 26, wherein  $R^4$  is  $-\text{PO}_3(\text{C}_1\text{--C}_3 \text{ alkyl})_2$ .
- [000143] Embodiment 56: The method of embodiment 41, wherein  $R^4$  is  $-\text{COOR}^5$ .
- [000144] Embodiment 57: The method of embodiment 26, wherein  $R^4$  is hydroxyalkyl.
- [000145] Embodiment 58: The method of embodiment 41, wherein  $R^4$  is  $-\text{O-L-N}(\text{R}^5)_2$ .
- [000146] Embodiment 59: The method of embodiment 26, wherein  $R^4$  is aralkyl.
- [000147] Embodiment 60: The method according to any of embodiments 26 to 37, wherein  $R^1$  is heteroaryl optionally substituted with one or more  $R^4$ .
- [000148] Embodiment 61: The method of embodiment 60, wherein the heteroaryl is pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazinyl, pyridyl, pyridinyl-2-one, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, isoindolinyl, naphthridinyl, 1,2,3,4-tetrahydroisoquinolinyl, or 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, each optionally substituted with one or more  $R^4$ .
- [000149] Embodiment 62: The method of embodiment 61, wherein the heteroaryl is substituted with one or more  $R^4$ , wherein each  $R^4$  is independently cyano, halogen,  $-\text{Y}^1\text{--C}_1\text{--C}_6$  alkyl,  $-\text{Y}^2\text{--C}_1\text{--C}_6$  alkyl, alkoxy, hydroxyalkyl, heteroalkyl, haloalkyl, -L-cycloalkyl, -L-N( $\text{R}^5$ )<sub>2</sub>,  $-\text{Y}^1\text{--N}(\text{R}^5)_2$ , -L-heteroaryl, -L-heterocyclyl, or  $-\text{Y}^1\text{--heterocyclyl}$ , wherein the heteroaryl of the -L-heteroaryl or the heterocyclyl portion of the L-heterocyclyl, or  $\text{Y}^1\text{--heterocyclyl}$  may be optionally substituted with one or more  $R^7$ .
- [000150] Embodiment 63: The method of embodiment 62, wherein the heteroaryl is pyrazolyl optionally substituted with one  $R^4$  independently selected from hydroxyalkyl, heteroalkyl, haloalkyl,  $-\text{Y}^1\text{--C}_1\text{--C}_6$  alkyl, -L-N( $\text{R}^5$ )<sub>2</sub>, L-heterocyclyl or L-heteroaryl, wherein the heteroaryl of the L-heteroaryl or the heterocyclyl portion of the L-heterocyclyl may be optionally substituted with one or more  $R^7$ .
- [000151] Embodiment 64: The method of embodiment 63, wherein  $R^4$  is -L-heteroaryl and L is methylene where the heteroaryl is pyridyl optional substituted with one or more  $R^7$ .
- [000152] Embodiment 65: The method of embodiment 63, wherein  $R^4$  is -L-heterocyclyl optionally substituted with one or more  $R^7$  where L is a bond and the heterocyclyl portion of the L-heterocyclyl is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl or 4-methylpiperazinyl.
- [000153] Embodiment 66: The method of embodiment 63, wherein  $R^4$  is -L-heterocyclyl optionally substituted with one or more  $R^7$  where L is methylene and the heterocyclyl portion of the L-heterocyclyl is azetidiny, oxetanyl, pyrrolidinyl, pyrrolidinone, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, piperazinyl or 4-methylpiperazinyl.
- [000154] Embodiment 67: The method of embodiment 63, wherein  $R^4$  is -L-N( $\text{R}^5$ )<sub>2</sub> where L is methylene and each  $\text{R}^5$  is independently hydrogen, each  $\text{R}^5$  is independently  $\text{C}_1\text{--C}_3$  alkyl, or one  $\text{R}^5$  is  $\text{C}_1\text{--C}_3$  alkyl and one  $\text{R}^5$  is hydrogen.
- [000155] Embodiment 68: The method of embodiment 63, wherein  $R^4$  is  $-\text{Y}^1\text{--C}_1\text{--C}_6$  alkyl where  $\text{Y}^1$  is a bond and the  $\text{C}_1\text{--C}_6$  alkyl is methyl, ethyl or isopropyl.
- [000156] Embodiment 69: The method of embodiment 63, wherein the heteroaryl is pyrazolyl optionally substituted with two  $R^4$  groups each independently selected from hydroxyalkyl, heteroalkyl, haloalkyl, and  $-\text{Y}^1\text{--C}_1\text{--C}_6$  alkyl.

[000157] Embodiment 70: The method of embodiment 63, wherein the heteroaryl is pyridyl optionally substituted with one  $R^4$  independently selected from cyano, halogen, alkoxy, hydroxyalkyl, heteroalkyl, haloalkyl,  $-Y^1-C_1-C_6$  alkyl,  $-L-N(R^5)_2$ ,  $-Y^1-N(R^5)_2$ ,  $-L$ -cycloalkyl, or  $-L$ -heterocyclyl optionally substituted with one or more  $R^7$ .

[000158] Embodiment 71: The method according to any of embodiments 26 to 37, wherein  $R^1$  is  $-L$ -cycloalkyl optionally substituted with one or more  $R^4$ .

[000159] Embodiment 72: The method according to any of embodiments 26 to 37, wherein  $R^1$  is  $-L$ -heterocyclyl optionally substituted with one or more  $R^4$ .

[000160] Embodiment 73: The method of embodiment 72, wherein  $L$  is a bond and the heterocyclyl is piperidinyl or tetrahydropyranyl.

[000161] Embodiment 74: The method according to any of embodiments 26 to 28, wherein  $n$  is two.

[000162] Embodiment 75: The method of any one of embodiments 1 to 24, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is a compound selected from a compound disclosed herein.

[000163] Embodiment 76: The method according to any one of embodiments 1 to 75, wherein the method results in induction of fetal hemoglobin expression in erythroid cells.

[000164] Embodiment 77: The method according to any one of embodiments 1 to 75, wherein the method results in upregulation of mRNA levels of fetal hemoglobin protein in the subject.

[000165] Embodiment 78: The method according to any one of embodiments 1 to 75, wherein the method results in increased levels of fetal hemoglobin protein in the subject.

## METHODS OF USE

[000166] In one embodiment is provided a method of treating sickle cell disease in a subject, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2) as disclosed herein.

[000167] In another embodiment is provided any of the methods disclosed herein, wherein the method results in induction of fetal hemoglobin expression in erythroid cells.

[000168] In another embodiment is provided any of the methods disclosed herein, wherein the method results in upregulation of mRNA levels of fetal hemoglobin protein.

[000169] In another embodiment is provided any of the methods disclosed herein, wherein the method results in increased levels of fetal hemoglobin protein in the subject.

[000170] The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively. The degree of mono- and dimethylation of histone H3K27 may be monitored in the subject using well known methods, including those described in Example A below, to assess the effectiveness of treatment, along with other prognostic or biological factors, and dosages may be adjusted accordingly by the attending medical practitioner.

## GENERAL REACTION SCHEME, INTERMEDIATES AND EXAMPLES

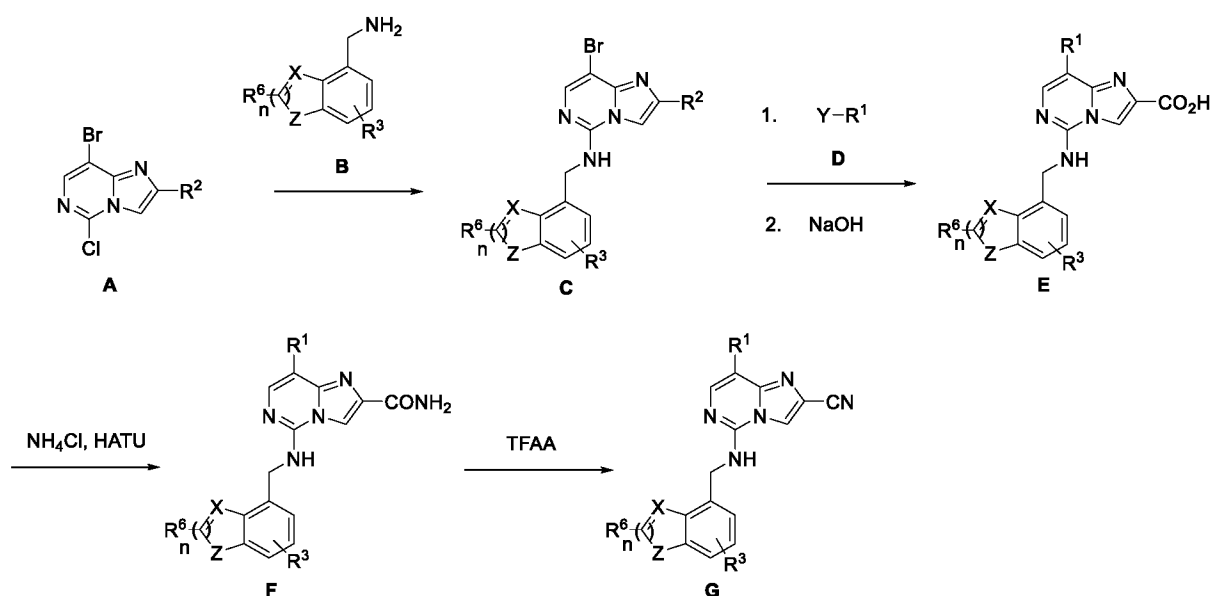
## GENERAL REACTION SCHEMES

[000171] Inhibitors of polycomb repressive complex 2 (PRC2) are known to those of ordinary skill in the art or may be prepared by methods known to those having ordinary skill in the art.

[000172] The compounds of Formula (I) disclosed herein may be prepared using methods described in United States Patent No. 11,091,495, the contents of which are incorporated by reference herein for that purpose. The compounds disclosed herein may also be prepared using methods known to those having ordinary skill in the art and commercially available reagents and intermediates in the synthetic methods and reaction schemes described herein, or may be prepared using other reagents and conventional methods well known to those skilled in the art.

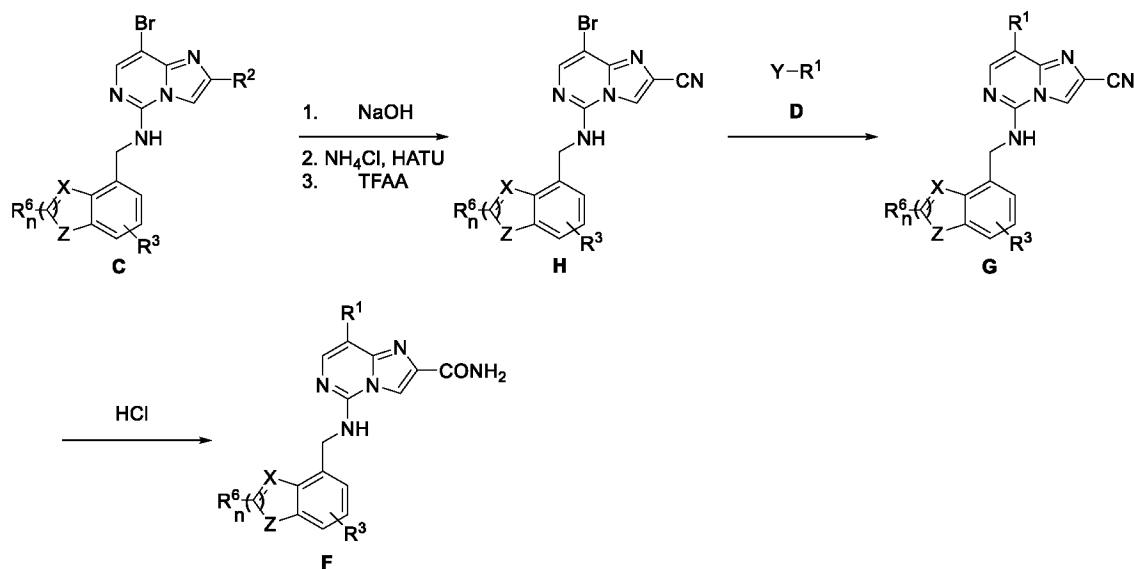
[000173] For instance, intermediates for compounds and compounds of Formula (I) of the present disclosure may be prepared according to General Reaction Schemes I or II:

## General Reaction Scheme I



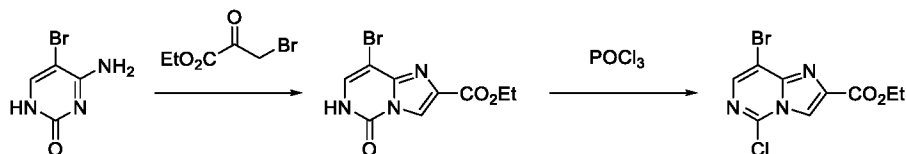
[000174] In General Reaction Scheme I, *R*<sup>2</sup>-ester substituted imidazo[1,2-*c*]pyrimidine A is coupled to *R*<sup>3</sup> optionally substituted intermediate amine B by nucleophilic substitution to yield Intermediate C. A boronic acid derivative (Y)-*R*<sup>1</sup> D is coupled via a Suzuki reaction with halogen substituted Intermediate C in the presence of a suitable base, e.g., sodium carbonate, and the *R*<sup>2</sup> ester is converted to the acid by saponification with NaOH to generate intermediate acid E. The acid is converted to the corresponding amide, which is dehydrated to form title compound nitrile G.

## General Reaction Scheme II



[000175] Halogenated Intermediate C containing a suitable  $\text{R}^2$  reactant, e.g., an ester, in the presence of a suitable base is converted to acid intermediate by saponification, then treated with  $\text{NH}_4\text{Cl}$  in the presence of HATU to form the amide which is subsequently dehydrated to form nitrile Intermediate H.  $\text{R}^1$  is coupled to Intermediate H via a Suzuki reaction using boronic acid derivative (Y) in the presence of base. The nitrile group of  $\text{R}^1$ -containing Intermediate G is hydrolyzed in the presence of acid and water to afford title compound amide F.

## INTERMEDIATE A-1

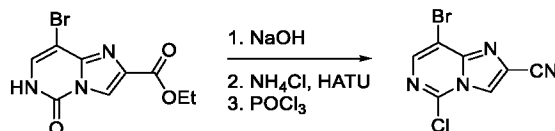


[000176] An exemplary Intermediate A, Intermediate A-1, may be used to synthesize compounds of formula (I). A mixture of 6-amino-5-bromo-1H-pyrimidin-2-one (2.00 g, 10.5 mmol, 1.00 equiv) and ethyl 3-bromo-2-oxopropanoate (3.12 g, 16.0 mmol, 2.00 mL, 1.52 equiv) in DMF (20.0 mL) was stirred at 80 °C for 3 h. The mixture was concentrated *in vacuo* to give a residue. To the residue was added water (50.0 mL), the mixture was extracted with ethyl acetate (80.0 mL  $\times$  3) and the organic layer was concentrated *in vacuo*. The crude material was heated in methanol (5.00 mL) and the solid was removed by filtration. The filtrate was concentrated under reduced pressure to provide ethyl 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxylate (1.00 g, 3.50 mmol, 33.2% yield) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 12.09 (br s, 1H), 8.32 (s, 1H), 7.73 (s, 1H), 4.30 (q,  $J$  = 7.2 Hz, 2H), 1.31 (t,  $J$  = 7.2 Hz, 3H).

[000177] A mixture of ethyl 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxylate (500 mg, 1.75 mmol, 1 equiv) and DIEA (564 mg, 4.37 mmol, 760  $\mu\text{L}$ , 2.50 equiv) in  $\text{POCl}_3$  (8.00 mL) was stirred for 15 h at 120 °C. The mixture was concentrated *in vacuo* to afford the crude residue. The crude material was purified by column chromatography (petroleum ether/ethyl acetate, 10/1 to 1/1) to provide ethyl 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2-carboxylate (380 mg, 1.25 mmol, 71.4% yield) as a yellow

solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.61 (s, 1H), 8.20 (s, 1H), 4.46 (q,  $J$  = 7.2 Hz, 2H), 1.43 (t,  $J$  = 7.2 Hz, 3H).

### INTERMEDIATE A-2



[000178] A second exemplary Intermediate A, Intermediate A-2, also may be used to synthesize compounds of formula (I). To a solution of ethyl 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxylate (3.00 g, 10.2 mmol, 1.00 equiv) in MeOH (60.0 mL) was added NaOH (1 M, 30.5 mL, 3.00 equiv). The resultant mixture was stirred at 60 °C for 1 h. Subsequently, the reaction mixture was concentrated and the pH was adjusted to 4 with 1M aq HCl at which time a precipitate formed. The solid was filtered and dried under vacuum to provide 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxylic acid (2.60 g, 10.1 mmol, 99.1% yield) as a brown solid.

[000179] To a solution of 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxylic acid (2.60 g, 10.1 mmol, 1.00 equiv) in DMF (60.0 mL) was added  $\text{NH}_4\text{Cl}$  (1.62 g, 30.2 mmol, 3.00 equiv), DIPEA (11.7 g, 90.7 mmol, 15.8 mL, 9.00 equiv) and HATU (5.75 g, 15.1 mmol, 1.50 equiv). The mixture was stirred at 15 °C for 12 h and was subsequently concentrated in vacuo. The resultant residue was triturated with MeOH (30 mL). The precipitate was washed with water 50 mL, filtered and the filtrate was concentrated in vacuo to afford 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxamide (1.78 g, 6.92 mmol, 68.7% yield) as a light-yellow solid. LC-MS  $[\text{M}+1]$ : 257.0.

[000180] To a solution of 8-bromo-5-oxo-6H-imidazo[1,2-c]pyrimidine-2-carboxamide (1.70 g, 6.61 mmol, 1.00 equiv) in  $\text{POCl}_3$  (20.0 mL) was added DIPEA (4.27 g, 33.1 mmol, 5.76 mL, 5.00 equiv) dropwise at 0 °C. The mixture was stirred at 120 °C for 12 h. The reaction mixture was filtered and concentrated at reduced pressure to provide the crude material. The crude residue was purified by column chromatography ( $\text{SiO}_2$ , Petroleum ether/Ethyl acetate = 10/1 to 4/1) to afford 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2-carbonitrile (950 mg, 3.69 mmol, 55.8% yield) as a light-yellow solid. LC-MS  $[\text{M}+1]$ : 258.9.

[000181] Alternatively, Intermediate A-2 may be prepared on a large scale as follows:

[000182] To a solution of cytosine (300 g, 2.70 mol, 1.00 equiv) in DMF (1.5 L) was added NBS (480 g, 2.70 mol, 1.00 equiv). The mixture was stirred at 25 °C for 10 h at which time the crude  $^1\text{H}$  NMR spectrum indicated that the reaction was complete. The reaction mixture was filtered and the filter cake was washed with water (1 L x 4). The solid was collected and dried under reduced pressure to afford 5-bromocytosine (480 g, 2.53 mol, 93.6% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.80 (br s, 1H), 11.36 - 10.16 (m, 1H), 7.74 (s, 1H), 6.83 (br s, 2H).

[000183] A mixture of compound 5-bromocytosine (150 g, 789 mmol, 1.00 equiv) and ethyl 3-bromo-2-oxo-propanoate (385 g, 1.97 mol, 247 mL, 2.50 equiv) in AcOH (1.5 L) was stirred at 120 °C for 2 h. The crude  $^1\text{H}$  NMR spectrum indicated that the reaction was complete. Three batches were concentrated to provide a residue that was triturated with MTBE (3 L) and filtered. The filter cake was washed with

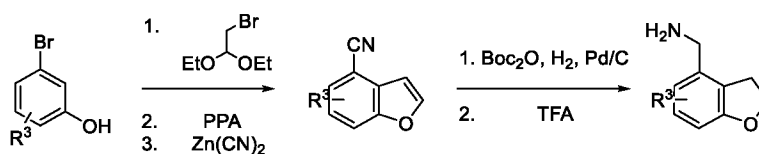
water (1 L x 4) and dried to afford ethyl 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxylate (300 g, 1.05 mol, 44.3% yield) as a brown solid.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  12.47 - 11.64 (m, 1H), 8.33 (s, 1H), 8.06 (s, 2H), 7.73 (s, 1H), 4.31 (q,  $J$  = 7.1 Hz, 2H), 1.32 (t,  $J$  = 7.1 Hz, 3H).

**[000184]** To a solution of ethyl 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxylate (150 g, 524 mmol, 1.00 equiv) in MeOH (1.5 L) was added NaOH (2 M, 786 mL, 3.00 equiv). The mixture was stirred at 65 °C for 2 h at which time the LCMS indicated that the reaction was complete. The reaction mixture was concentrated to give a residue that was acidified with HCl (2 M) to pH = 2~3. The solid was filtered and the filter cake was washed with water (800 mL x 4). The solid was collected and dried under vacuum to afford 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxylic acid (140 g, 543 mmol, 51.7% yield) as a brown solid. LCMS (M+1): 257.9.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  12.86 - 11.28 (m, 1H), 8.27 (s, 1H), 7.73 (s, 1H).

**[000185]** To a suspension of 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxylic acid (120 g, 465 mmol, 1.00 equiv) in  $\text{SOCl}_2$  (787 g, 6.62 mol, 480 mL, 14.2 equiv) was added DMF (340 mg, 4.65 mmol, 358  $\mu\text{L}$ , 0.01 equiv) and the mixture was stirred at 80 °C for 2 h. The solution was concentrated to give a residue that was dissolved in DCM (200 mL). The resulting mixture was added dropwise to conc. ammonium hydroxide (1.09 kg, 9.35 mol, 1.20 L, 20.1 equiv) at 0 °C and the mixture was subsequently stirred at 25 °C for 1 h. LCMS indicated that the reaction was complete. The mixture was filtered, the filter cake was washed with MeOH (200 mL), and the solid was dried under vacuum to afford 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxamide (120 g, crude) as a brown solid. LCMS (M+1): 257.0/259.0.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  8.05 (s, 1H), 7.66 (s, 1H), 7.56 (br s, 1H), 7.41 (br s, 1H).

**[000186]** To a solution of 8-bromo-5-oxo-5,6-dihydroimidazo[1,2-c]pyrimidine-2-carboxamide (20.0 g, 77.8 mmol, 1.00 equiv) in  $\text{POCl}_3$  (388 g, 2.53 mol, 235 mL, 32.5 equiv) was added DIEA (50.3 g, 389 mmol, 67.8 mL, 5.00 equiv) dropwise at 0 °C. The mixture was stirred at 120 °C for 12 h. The reaction mixture (4 identical batches combined) was cooled to room temperature and was concentrated to afford a residue. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 5:1) to provide 8-bromo-5-chloroimidazo[1,2-c]pyrimidine-2-carbonitrile (19.9 g, 76.1 mmol, 24.5% yield, 98.6% purity) as an off-white solid. LCMS (M+1): 388.0/390.0.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  9.19 (s, 1H), 8.36 (s, 1H).

#### INTERMEDIATE B-1



**[000187]** An exemplary Intermediate B, Intermediate B-1, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is  $\text{C}(\text{R}^5)_2$ , and  $\text{-----}$  is a single bond. A mixture of 3-bromophenol (10.0 g, 57.8 mmol, 1.00 equiv) and 2-bromo-1,1-diethoxy-ethane (13.7 g, 69.4 mmol, 10.4 mL, 1.20 equiv) in DMF (100 mL) was added potassium carbonate (24.0 g, 173 mmol, 3.00 equiv). The resultant mixture was stirred at 110 °C for 12 h under a nitrogen atmosphere. The reaction mixture was

diluted with petroleum ether (100 mL) and washed with brine (50.0 mL  $\times$  4), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether) to afford 1-bromo-3-(2,2-diethoxyethoxy)benzene (17.0 g, 48.2 mmol, 83.4% yield, 82.0% purity) as a light yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.17 - 7.07 (m, 3H), 6.88 - 6.84 (m, 1H), 4.82 (t,  $J$ =5.2 Hz, 1H), 3.99 (d,  $J$ =5.2 Hz, 2H), 3.80 - 3.74 (m, 1H), 3.80 - 3.73 (m, 2H), 3.68 - 3.61 (m, 2H), 1.25 (t,  $J$ =7.2 Hz, 6H).

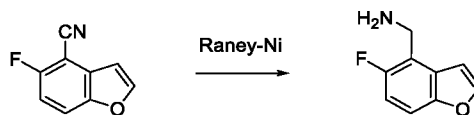
**[000188]** To a solution of polyphosphoric acid (21.5 g, 63.6 mmol, 1.50 equiv) in toluene (80.0 mL) was added 1-bromo-3-(2,2-diethoxyethoxy)benzene (15.0 g, 42.5 mmol, 1.00 equiv) at 90 °C. The mixture was stirred at 90 °C for 2 h and then concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether) to afford 4-bromobenzofuran (5.20 g, 13.2 mmol, 31.0% yield, 50.0% purity) as a yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.70 (s, 1H), 7.67 (d,  $J$ =2.0 Hz, 1H), 7.61 (d,  $J$ =2.4 Hz, 1H), 7.47 (d,  $J$ =8.4 Hz, 2H), 7.41 (d,  $J$ =8.0 Hz, 1H), 7.37 (dd,  $J$ =1.6, 8.4 Hz, 1H), 7.21 - 7.15 (m, 1H), 6.85 - 6.80 (m, 1H), 6.78 - 6.73 (m, 1H).

**[000189]** To a solution of 4-bromobenzofuran (5.20 g, 13.2 mmol, 1.00 equiv) in DMAC (50.0 mL) was added zinc cyanide (6.85 g, 58.3 mmol, 4.42 equiv) and  $\text{Pd}(\text{PPh}_3)_4$  (1.52 g, 1.32 mmol, 0.100 equiv). The mixture was stirred at 140 °C for 12 h under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (80.0 mL), washed with brine (50.0 mL  $\times$  3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether / ethyl acetate = 50 / 1 to 0 / 1) to afford benzofuran-4-carbonitrile (1.60 g, 10.1 mmol, 76.2% yield, 90.0% purity) as a light-yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.80 (d,  $J$ =2.0 Hz, 1H), 7.75 (d,  $J$ =8.4 Hz, 1H), 7.60 (d,  $J$ =8.0 Hz, 1H), 7.38 (t,  $J$ =8.4 Hz, 1H), 7.03 - 7.00 (m, 1H).

**[000190]** To a solution of benzofuran-4-carbonitrile (750 mg, 4.72 mmol, 1.00 equiv) in methyl alcohol (10.0 mL) was added  $\text{Boc}_2\text{O}$  (3.09 g, 14.2mmol, 3.00 equiv) and  $\text{Pd/C}$  (4.72 mmol, 10.0 w. %, 1.00 equiv). The mixture was stirred at 30 °C for 24 h under hydrogen (50.0 psi). The reaction mixture was filtered and concentrated under reduced pressure to give the crude material, which was purified by column chromatography (petroleum ether / ethyl acetate = 1 / 0 to 50 / 1) to afford *tert*-butyl *N*-(2,3-dihydrobenzofuran-4-ylmethyl) carbamate (140 mg, 562  $\mu\text{mol}$ , 11.9% yield) as a colorless oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.10 (t,  $J$ =8.0 Hz, 1H), 6.74 (dd,  $J$ =8.0, 14.0 Hz, 2H), 4.75 (br s, 1H), 4.59 (t,  $J$ =8.8 Hz, 2H), 4.28 (br d,  $J$ =5.6 Hz, 2H), 3.20 (t,  $J$ =8.8 Hz, 2H), 1.47 (s, 9H).

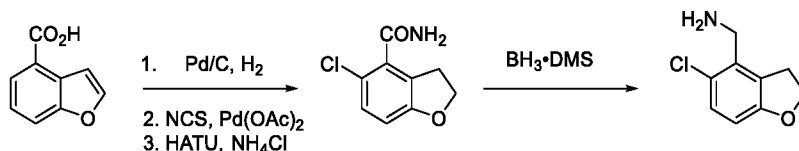
**[000191]** To a solution of *tert*-butyl *N*-(2,3-dihydrobenzofuran-4-ylmethyl) carbamate (140 mg, 562  $\mu\text{mol}$ , 1.00 equiv) in DCM (2.00 mL) was added TFA (640 mg, 5.62 mmol, 416  $\mu\text{L}$ , 10.0 equiv). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with DCM (10.0 mL) and was added to a saturated potassium carbonate aqueous solution (10.0 mL). The biphasic mixture was stirred at 25 °C for 0.5 h. The organic phase was separated, dried over sodium sulfate, concentrated *in vacuo* to afford 2,3-dihydrobenzofuran-4-ylmethanamine (80.0 mg, 483  $\mu\text{mol}$ , 85.9% yield, 90.0% purity) as a yellow solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.13 (t,  $J$ =8.0 Hz, 1H), 6.84 (d,  $J$ =7.6 Hz, 1H), 6.72 (d,  $J$ =8.0 Hz, 1H), 4.60 (t,  $J$ =8.8 Hz, 2H), 3.82 (s, 2H), 3.20 (t,  $J$ =8.8 Hz, 2H).

## INTERMEDIATE B-2



[000192] A second exemplary Intermediate B, Intermediate B-2, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is CR<sup>5</sup>,        is a double bond and one R<sup>3</sup> is fluorine. To a mixture of 5-fluorobenzofuran-4-carbonitrile (250 mg, 1.47 mmol, 1.00 equiv) and Raney-Ni (126 mg, 1.47 mmol, 1.00 equiv) in methyl alcohol (6.60 mL) was added ammonium hydroxide (1.60 mL). The mixture was purged with nitrogen and stirred at 25 °C for 12 h under a hydrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to afford (5-fluorobenzofuran-4-yl) methanamine (220 mg, 1.20 mmol, 81.3% yield, 90.0% purity) as a brown oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 7.67 (s, 1H), 7.33 (br d, *J*=5.6 Hz, 1H), 7.04 (br t, *J*=9.6 Hz, 1H), 6.90 (s, 1H), 4.54 - 3.78 (m, 2H).

## INTERMEDIATE B-3



[000193] A third exemplary Intermediate B, Intermediate B-3, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is C(R<sup>5</sup>)<sub>2</sub>,        is a single bond and one R<sup>3</sup> is chlorine. To a solution of benzofuran-4-carboxylic acid (900 mg, 5.55 mmol, 1 equiv) in MeOH (9.00 mL) was added palladium on activated carbon (20.0 mg, 555 μmol, 10.0 wt %, 0.10 equiv) under nitrogen. The vessel was evacuated and purged with hydrogen several times. The mixture was stirred at 25 °C for 12 h under hydrogen (50.0 psi). The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford 2,3-dihydrobenzofuran-4-carboxylic acid (750 mg, 3.66 mmol, 65.9% yield, 80.0% purity) as a white solid. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 7.38 (d, *J*=8.0 Hz, 1H), 7.20 (t, *J*=8.0 Hz, 1H), 6.97 (d, *J*=8.0 Hz, 1H), 4.54 (t, *J*=8.8 Hz, 2H), 3.45 (br t, *J*=8.8 Hz, 2H).

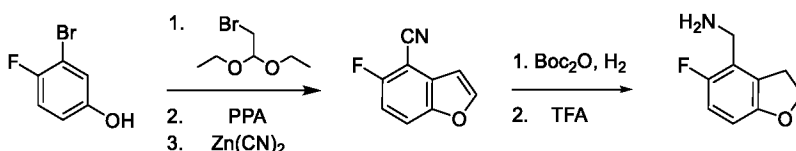
[000194] To a solution of 2,3-dihydrobenzofuran-4-carboxylic acid (750 mg, 3.66 mmol, 1.00 equiv) in DMF (1.00 mL) was added Pd(OAc)<sub>2</sub> (82.1 mg, 366 μmol, 0.10 equiv) and NCS (586 mg, 4.39 mmol, 1.20 equiv). The reaction was stirred at 110 °C for 12 h under an atmosphere of nitrogen. The reaction mixture was filtered and concentrated *in vacuo* and the resultant residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1 to dichloromethane/methanol = 10/1) to afford 5-chloro-2,3-dihydrobenzofuran-4-carboxylic acid (600 mg, crude) as a yellow oil. LC-MS: [M+1] 198.9.

[000195] To a solution of 5-chloro-2,3-dihydrobenzofuran-4-carboxylic acid (600 mg, 3.02 mmol, 1.00 equiv) in DMF (5.00 mL) was added ammonium chloride (242 mg, 4.53 mmol, 1.50 equiv), HATU (2.30 g, 6.04 mmol, 2.00 equiv), DIEA (1.17 g, 9.06 mmol, 1.58 mL, 3.00 equiv). The reaction mixture was stirred at 25 °C for 12 h and concentrated *in vacuo* to give the crude material, which was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford 5-chloro-2,3-dihydrobenzofuran-4-carboxamide (700 mg, 2.83 mmol, 93.8% yield, 80.0% purity) as a white solid. <sup>1</sup>H

NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 7.87 (br s, 1H), 7.63 (br s, 1H), 7.17 (d,  $J$ =8.4 Hz, 1H), 6.79 (d,  $J$ =8.4 Hz, 1H), 4.58 (t,  $J$ =8.8 Hz, 2H), 3.18 (t,  $J$ =8.8 Hz, 2H).

[000196] To a solution of 5-chloro-2,3-dihydrobenzofuran-4-carboxamide (300 mg, 1.21 mmol, 1.00 equiv) in THF (5.00 mL) was added dropwise  $BH_3$ -DMS (10.0 M, 607  $\mu$ L, 5.00 equiv). The reaction was stirred at 70 °C for 2.5 h, quenched with MeOH (5.00 mL) and concentrated *in vacuo* to provide a residue. To the residue was added water (20.0 mL) and the mixture was extracted with DCM (20.0 mL $\times$ 3). The combined organic phase was washed with brine (20.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, and concentrated to afford (5-chloro-2,3-dihydrobenzofuran-4-yl)methanamine (240 mg, crude) as a brown oil. LC-MS: [M-16] 167.1.

#### INTERMEDIATE B-4



[000197] A fourth exemplary Intermediate B, Intermediate B-4, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is  $C(R^5)_2$ , ----- is a single bond and one  $R^3$  is fluorine. To a solution of 3-bromo-4-fluorophenol (100 g, 524 mmol, 1.00 equiv) and 2-bromo-1,1-diethoxyethane (124 g, 628 mmol, 94.5 mL, 1.20 equiv) in DMF (600 mL) was added potassium carbonate (217 g, 1.57 mol, 3.00 equiv). The mixture was stirred at 110 °C for 12 h under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate (500 mL), washed with brine (500 mL  $\times$  5), and concentrated at reduced pressure to provide a residue. The residue was purified by column chromatography (petroleum ether / ethyl acetate = 1 / 0 to 20 / 1) to afford 2-bromo-4-(2,2-diethoxyethoxy)-1-fluorobenzene (171 g, 501 mmol, 95.7% yield, 90.0% purity) as a light-yellow oil.  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  = 7.12 (dd,  $J$ =2.8, 5.6 Hz, 1H), 7.06 - 6.98 (m, 1H), 6.84 (td,  $J$ =3.2, 9.2 Hz, 1H), 4.81 (t,  $J$ =5.2 Hz, 1H), 3.96 (d,  $J$ =5.2 Hz, 2H), 3.81 - 3.72 (m, 2H), 3.68 - 3.59 (m, 2H), 1.25 (t,  $J$ =7.2 Hz, 6H).

[000198] To a solution of PPA (254 g, 752 mmol, 1.50 equiv) in toluene (1.30 L) was added 2-bromo-4-(2,2-diethoxyethoxy)-1-fluorobenzene (171 g, 501 mmol, 1.00 equiv) at 90 °C. The mixture was stirred at 95 °C for 2 h and concentrated at reduced pressure to provide a residue. The residue was purified by column chromatography (petroleum ether) to give 4-bromo-5-fluorobenzofuran (87.3 g, 203 mmol, 40.5% yield, 50.0% purity) as a yellow oil. To a mixture of 4-bromo-5-fluorobenzofuran (85.5 g, 398 mmol, 1.00 equiv) and 6-bromo-5-fluorobenzofuran (85.5 g, 398 mmol, 1.00 equiv) in DMAC (1.50 L) was added zinc cyanide (31.1 g, 264 mmol, 0.67 equiv) and  $Pd(PPh_3)_4$  (23.0 g, 19.9 mmol, 0.05 equiv). The mixture was stirred at 90 °C for 12 h under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate (1.00 L) and filtered. The filtrate was washed with brine (1.00 L  $\times$  3) and the organic layer was concentrated at reduced pressure to provide a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 50/1) to afford 4-bromo-5-fluorobenzofuran (78 g, crude) as a white solid.

[000199] To a solution of 4-bromo-5-fluoro-benzofuran (87.3 g, 203 mmol, 1.00 equiv) in DMAC (600 mL) was added zinc cyanide (94.6 g, 805 mmol, 3.97 equiv) and Pd(PPh<sub>3</sub>)<sub>4</sub> (23.5 g, 20.3 mmol, 0.10 equiv). The mixture was stirred at 110 °C for 12 h under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate (500 mL), washed with brine (400 mL × 5), dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure to provide a residue. The residue was purified by column chromatography (petroleum ether / ethyl acetate = 1 / 0 to 50 / 1) to afford 5-fluorobenzofuran-4-carbonitrile (20.0 g, 118 mmol, 58.1% yield, 95.0% purity) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 7.84 (d, *J*=2.0 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.14 (t, *J*=9.2 Hz, 1H), 7.02 - 6.96 (m, 1H).

[000200] To a solution of 5-fluorobenzofuran-4-carbonitrile (19.6 g, 116 mmol, 1.00 equiv) in methyl alcohol (1.00 L) was added di-*tert*-butyl dicarbonate (75.7 g, 347 mmol, 3.00 equiv) and Pd/C 10 w. % (1.16 g). The mixture was stirred at 35 °C for 24 h under an atmosphere of hydrogen gas (50.0 psi). The reaction mixture was filtered and concentrated at reduced pressure to provide a residue. The residue was purified by column chromatography (petroleum ether / ethyl acetate = 1 / 0 to 3 / 1) to afford *tert*-butyl N-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl]carbamate (22.0 g, 78.2 mmol, 67.7% yield, 95.0% purity) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 6.82 - 6.76 (m, 1H), 6.62 (dd, *J*=4.0, 8.8 Hz, 1H), 4.88 (br s, 1H), 4.60 (t, *J*=8.8 Hz, 2H), 4.30 (br d, *J*=6.0 Hz, 2H), 3.30 (br t, *J*=8.8 Hz, 2H), 1.44 (s, 9H).

[000201] To a solution of *tert*-butyl N-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl] carbamate (22.0 g, 78.2 mmol, 1.00 equiv) in DCM (200 mL) was added TFA (89.2 g, 782 mmol, 57.9 mL, 10.0 equiv). The mixture was stirred at 25 °C for 0.5 h and subsequently quenched with satd aq potassium carbonate (200 mL). The mixture was allowed to stir at 25 °C for 0.5 hour. The organic phase was separated and dried over sodium sulfate, concentrated *in vacuo* to afford (5-fluoro-2,3-dihydrobenzofuran-4-yl)methanamine (13.0 g, 73.9 mmol, 94.5% yield, 95.0% purity) as a light yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 6.85 - 6.76 (m, 1H), 6.60 (dd, *J*=4.0, 8.8 Hz, 1H), 4.61 (t, *J*=8.8 Hz, 2H), 3.82 (s, 2H), 3.24 (t, *J*=8.8 Hz, 2H).

[000202] Alternatively, Intermediate A-2 may be prepared on a large scale as follows:

[000203] To a solution of 3-bromo-4-fluorophenol (1.00 kg, 5.24 mol, 1.00 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (3.41 kg, 10.5 mol, 2.00 equiv) in DMF (5.00 L) was added compound 2-bromo-1,1-diethoxyethane (1.24 kg, 6.28 mol, 1.20 equiv) in one portion. The suspension was stirred at 110°C for 12 h. TLC (petroleum ether/ethyl acetate = 10/1, R<sub>f</sub> = 0.50) indicated that the reaction was complete. The reaction mixture was filtered, diluted with water (15.0 L), and extracted with MTBE (5.00 L x 2). The combined organic layers were washed with brine (3.00 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give compound 2-bromo-4-(2,2-diethoxyethoxy)-1-fluorobenzene (1.61 kg, crude) as a yellow oil.

[000204] Two reactions were conducted in parallel on the same scale and combined during the workup. To a mixture of polyphosphoric acid (1.30 kg) in toluene (2.40 L) was added 2-bromo-4-(2,2-diethoxyethoxy)-1-fluorobenzene (800 g, 2.60 mol, 1.00 equiv) in one portion at 90 °C. The mixture was stirred at 90 °C for 3 h. TLC (petroleum ether/EtOAc = 10/1, R<sub>f</sub> = 0.6) indicated that the reaction was complete. The two reactions were combined prior to work up. The mixture was poured into water (6.00

L) and extracted with MTBE (6.00 L x 2). The combined organic layer was washed with brine (5.00 L x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/EtOAc = 1/0 to 100/1) to give a ~1:1 mixture of 4-bromo-5-fluorobenzofuran and 6-bromo-5-fluorobenzofuran (800 g, 3.72 mol, 71.4% yield) as a brown oil.

**[000205]** Two reactions were conducted in parallel on the same scale and combined during the workup. To a mixture of 4-bromo-5-fluorobenzofuran (150 g, 698 mmol, 1.00 equiv) and 6-bromo-5-fluorobenzofuran (150 g, 698 mmol, 1.00 equiv) in DMA (2.40 L) was added Zn(CN)<sub>2</sub> (49.2 g, 419 mmol, 0.60 equiv) and Pd(PPh<sub>3</sub>)<sub>4</sub> (40.3 g, 34.9 mmol, 0.05 equiv) in one portion at 25 °C under N<sub>2</sub>. The mixture was stirred at 90 °C for 12 h. TLC (petroleum ether/EtOAc = 10/1) indicated the consumption of the undesired isomer (6-bromo-5-fluorobenzofuran). The two reactions were combined prior to work up. The mixture was diluted with EtOAc (5.00 L) and filtered. The filtrate was poured into water (8.00 L) and the mixture was extracted with EtOAc (3.00 L x 2). The combined organic phase was washed with brine (4.00 L x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/EtOAc = 1/0 to 5/1) to give compound 4-bromo-5-fluorobenzofuran (340 g) as a yellow oil.

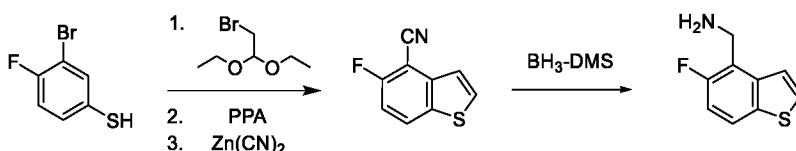
**[000206]** Two reactions were conducted in parallel on the same scale and combined during the workup. To a mixture of compound 4-bromo-5-fluorobenzofuran (170 g, 791 mmol, 1.00 equiv) in DMA (1.30 L) was added Zn(CN)<sub>2</sub> (92.8 g, 791 mmol, 1.00 eq.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (91.4 g, 79.1 mmol, 0.10 equiv) in one portion at 25 °C under N<sub>2</sub>. The resultant mixture was stirred at 120 °C for 12 h. TLC (petroleum ether/EtOAc = 10/1) indicated that the reaction was complete. The two reactions were combined prior to work up and the mixture was poured into water (3.00 L) and EtOAc (4.00 L), filtered, and the filtrate was extracted with EtOAc (2.00 L x 2). The combined organic layer was washed with brine (3.00 L x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/EtOAc = 1/0 to 50/1) to afford compound 5-fluorobenzofuran-4-carbonitrile (120 g, 745 mmol, 47.1% yield) as a yellow oil. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD) δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.82-7.86 (m, 1H), 7.23-7.28 (m, 1H), 7.02 (d, *J* = 2.0 Hz, 1H).

**[000207]** Two reactions were conducted in parallel on the same scale and combined during the workup. To a solution of compound 5-fluorobenzofuran-4-carbonitrile (60.0 g, 372 mmol, 1.00 equiv) in MeOH (1.50 L) was added Boc<sub>2</sub>O (122 g, 559 mmol, 1.50 equiv) and Pd/C (12.0 g, 10 wt %) under N<sub>2</sub>. The suspension was evacuated and purged with H<sub>2</sub> several times and the mixture was stirred under H<sub>2</sub> (50 psi) at 50 °C for 12 h. TLC (petroleum ether/EtOAc = 10/1) indicated that the reaction was complete. The two reactions were combined prior to work up and filtered. The filtrate was concentrated to afford a residue that was triturated with petroleum ether (500 mL), filtered, and dried at 45 °C under vacuum to provide *tert*-butyl ((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (100 g, 374 mmol, 50.2% yield) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 6.76-6.81 (m, 1H), 6.60-6.63 (m, 1H), 4.60 (t, *J* = 8.8 Hz, 2H), 4.29-4.31 (m, 2H), 3.30 (t, *J* = 8.8 Hz, 2H), 1.44 (s, 9H).

**[000208]** Two reactions were conducted in parallel on the same scale and combined during the workup. To a mixture of *tert*-butyl ((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (50.0 g, 187 mmol,

1.00 equiv) in EtOAc (400 mL) was added HCl/EtOAc (300 mL, 4M) in one portion at 25 °C under N<sub>2</sub>. The resultant mixture was stirred for 4 h at which time TLC (petroleum ether/EtOAc = 5/1) indicated that the reaction was complete. The two reactions were combined prior to work up, filtered, and the filter cake was washed by MTBE (100 mL x 2). The filter cake was dissolved in water (200 mL) and the pH was adjusted to 9 with sat.aq. K<sub>2</sub>CO<sub>3</sub> at 0 °C prior to extraction with DCM (200 mL x 4). The combined organic phase was washed with brine (200 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to afford (5-fluoro-2,3-dihydrobenzofuran-4-yl)methanamine (50.0 g, 299 mmol, 79.9% yield) as a brown oil. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 8.57 (br. s., 3H), 6.97 (m, 1H), 6.77-6.80 (m, 1H), 4.55-4.59 (m, 2H), 3.94 (s, 2H), 3.37-3.42 (m, 2H).

#### INTERMEDIATE B-5



[000209] A fifth exemplary Intermediate B, Intermediate B-5, may be used to synthesize compounds of formula I wherein Z is S, n is one, X is C(R<sup>5</sup>)<sub>2</sub>,        is a single bond and one R<sup>3</sup> is fluorine. A mixture of 3-bromo-4-fluorobenzenethiol (4.50 g, 21.7 mmol, 1.00 equiv), 2-bromo-1,1-diethoxyethane (4.71 g, 23.9 mmol, 3.60 mL, 1.10 equiv), and potassium carbonate (3.60 g, 26.1 mmol, 1.20 equiv) in DMF (50.0 mL) was purged with nitrogen. The mixture was stirred at 80 °C for 0.5 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* to provide a residue, which was purified by column chromatography (petroleum ether/ethyl acetate, 20/1 to 5/1) to afford 2-bromo-4-(2,2-diethoxyethylsulfanyl)-1-fluoro-benzene (6.2 g, 19.2 mmol, 88.3 % yield) as a colorless liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.63 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.32 (ddd, *J* = 2.4, 4.4, 8.8 Hz, 1H), 7.03 (t, *J* = 8.4 Hz, 1H), 4.63 (t, *J* = 5.6 Hz, 1H), 3.72 - 3.65 (m, 2H), 3.57 - 3.51 (m, 2H), 3.08 (d, *J* = 5.6 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 6H).

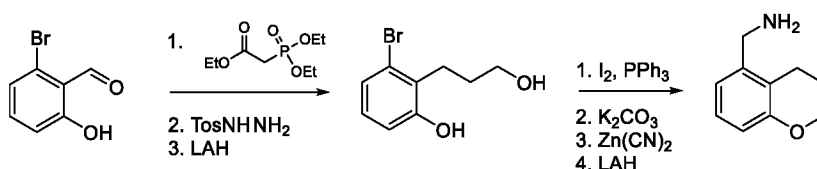
[000210] To a solution of polyphosphoric acid (39 g, 710 μL, 1.00 equiv) in chlorobenzene (70.0 mL) was added 2-bromo-4-(2,2-diethoxyethylsulfanyl)-1-fluoro-benzene (5.9 g, 18.3 mmol, 1.00 equiv) and the resultant mixture was stirred at 130 °C for 12 h. The mixture was concentrated *in vacuo* to provide a residue. The residue was purified by column chromatography (petroleum ether) to afford 4-bromo-5-fluoro-benzothiophene (2.50 g, 10.8 mmol, 29.8% yield, 50% purity) as a colorless liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.75 (dd, *J* = 4.4, 8.8 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 5.6 Hz, 1H), 7.17 (t, *J* = 8.8 Hz, 1H).

[000211] To a solution of 4-bromo-5-fluoro-benzothiophene (1.25 g, 5.41 mmol, 1.00 equiv) in DMAC (12.0 mL) was added zinc cyanide (953 mg, 8.11 mmol, 515 μL, 1.50 equiv) and Pd(PPh<sub>3</sub>)<sub>4</sub> (938 mg, 811 μmol, 0.150 equiv). The mixture was stirred at 100 °C for 12 h under an atmosphere of nitrogen. Water (50.0 mL) was added and the mixture was extracted with ethyl acetate (80.0 mL x 3). The combined organic layer was concentrated *in vacuo* to provide a residue. The residue was purified by column chromatography (petroleum ether) to afford 5-fluorobenzothiophene-4-carbonitrile (530 mg, 2.99 mmol,

27.7% yield) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.05 (dd,  $J$  = 4.4, 8.8 Hz, 1H), 7.80 (d,  $J$  = 5.6 Hz, 1H), 7.57 (d,  $J$  = 5.6 Hz, 1H), 7.23 (t,  $J$  = 8.8 Hz, 1H).

[000212] To a mixture of 5-fluorobenzothiophene-4-carbonitrile (300 mg, 1.69 mmol, 1.00 equiv) in THF (2.00 mL) was added  $\text{BH}_3\text{-Me}_2\text{S}$  (10 M, 677  $\mu\text{L}$ , 4.00 equiv) at 0 °C and the mixture was stirred for 6 h at 75 °C. The mixture was cooled to room temperature and was quenched with ethanol (10.0 mL) and the pH was adjusted to 3 with aq HCl (2 M). The mixture was concentrated *in vacuo* to provide a residue to which water (20.0 mL) was added. The aqueous mixture was extracted with ethyl acetate (40.0 mL  $\times$  4) and the combined organic layer was concentrated to afford (5-fluorobenzothiophen-4-yl)methanamine (150 mg, 828  $\mu\text{mol}$ , 48.9% yield) as a yellow solid.

#### INTERMEDIATE B-6



[000213] A sixth exemplary Intermediate B, Intermediate B-6, may be used to synthesize compounds of formula I wherein Z is O, n is two, X is  $\text{C}(\text{R}^5)_2$ , ===== is a single bond and one  $\text{R}^3$  is fluorine.

[000214] To a solution of 2-bromo-6-hydroxy-benzaldehyde (0.30 g, 1.49 mmol, 1.00 eq.) and ethyl 2-diethoxyphosphorylacetate (669 mg, 2.98 mmol, 592  $\mu\text{L}$ , 2.00 eq.) in DMF (3.00 mL) was added NaH (119 mg, 2.98 mmol, 60% purity, 2.00 eq.) at rt under a nitrogen atmosphere. The resultant mixture was stirred at 40 °C for 12 h. The reaction mixture was diluted with ethyl acetate (50.0 mL) and quenched with water (10.0 mL). The combined organic phase was washed with brine (30.0 mL  $\times$  3), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography ( $\text{SiO}_2$ , Petroleum ether/Ethyl acetate = 10/1 to 4/1) to afford ethyl (*E*)-3-(2-bromo-6-hydroxy-phenyl)prop-2-enoate (380 mg, 1.37 mmol, 92.0% yield, 98.0% purity) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.02 (d,  $J$ =16.0 Hz, 1H), 7.15 (dd,  $J$ =1.2, 8.0 Hz, 1H), 7.06 (t,  $J$ =8.0 Hz, 1H), 6.97 (d,  $J$ =16.0 Hz, 1H), 6.86 (d,  $J$ =8.0 Hz, 1H), 4.56 (s, 1H), 4.25 (q,  $J$ =7.2 Hz, 2H), 1.33 (t,  $J$ =7.2 Hz, 3H).

[000215] To a solution of ethyl (*E*)-3-(2-bromo-6-hydroxy-phenyl)prop-2-enoate (380 mg, 1.37 mmol, 1.00 eq.) in THF (5.00 mL) and water (5.00 mL) was added NaOAc (225 mg, 2.75 mmol, 2.00 eq.) and 4-methylbenzenesulfonohydrazide (512 mg, 2.75 mmol, 2.00 eq.). The mixture was stirred at 70 °C for 12 h. The mixture was cooled to rt and extracted with ethyl acetate (20.0 mL  $\times$  2). The combined organic phase was washed with brine (30.0 mL  $\times$  3), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 20/1 to 10/1) to afford ethyl 3-(2-bromo-6-hydroxy-phenyl)propanoate (380 mg, 1.32 mmol, 96.2% yield, 95.0% purity) as a light-yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.27 (s, 1H), 7.14 (dd,  $J$ =1.2, 8.0 Hz, 1H), 6.99 (t,  $J$ =8.0 Hz, 1H), 6.93 - 6.88 (m, 1H), 4.17 (q,  $J$ =7.2 Hz, 2H), 3.50 (s, 1H), 3.10 - 3.03 (m, 2H), 2.87 - 2.79 (m, 2H), 1.28 - 1.24 (m, 3H).

**[000216]** To a solution of ethyl 3-(2-bromo-6-hydroxy-phenyl)propanoate (0.10 g, 348  $\mu$ mol, 1.00 eq.) in THF (2.00 mL) was added LAH (39.6 mg, 1.04 mmol, 3.00 eq.) at 0 °C. The mixture was stirred at rt for 2 h. The reaction mixture was quenched with water (0.50 mL) and was diluted with DCM (30.0 mL). The mixture was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by prep-TLC (SiO<sub>2</sub>, PE: EA = 2:1) to afford 3-bromo-2-(3-hydroxypropyl)phenol (70.0 mg, 297  $\mu$ mol, 85.4% yield, 98.0% purity) as a yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.66 (br s, 1H), 7.14 (dd, *J*=1.2, 8.0 Hz, 1H), 6.97 (t, *J*=8.0 Hz, 1H), 6.84 (dd, *J*=1.2, 8.0 Hz, 1H), 3.64 (t, *J*=5.6 Hz, 2H), 3.03 - 2.94 (m, 2H), 2.01 - 1.90 (m, 2H).

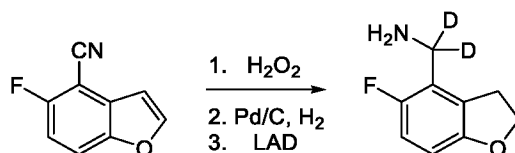
**[000217]** Iodine (3.30 g, 13.0 mmol, 2.62 mL, 1.65 eq.) was added to a solution of imidazole (2.42 g, 35.5 mmol, 4.50 eq.) and PPh<sub>3</sub> (3.72 g, 14.2 mmol, 1.80 eq.) in DCM (40.0 mL) at 0 °C. The reaction mixture was stirred for 15 min followed by the dropwise addition of a solution of 3-bromo-2-(3-hydroxypropyl)phenol (1.85 g, 7.89 mmol, 1.00 eq.) in DCM (10.0 mL). The reaction mixture was protected from light and stirred for 12 h at rt. The mixture was diluted with DCM (50.0 mL) and washed with brine (40.0 mL  $\times$  2). The combined organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/0 to 20/1) to afford 3-bromo-2-(3-iodopropyl)phenol (2.10 g, 6.16 mmol, 78.1% yield) as a white solid.

**[000218]** To a solution of 3-bromo-2-(3-iodopropyl)phenol (2.10 g, 6.16 mmol, 1.00 eq.) in acetone (50.0 mL) was added K<sub>2</sub>CO<sub>3</sub> (1.70 g, 12.3 mmol, 2.00 eq.). The mixture was stirred at 50 °C for 12 h. The reaction mixture was filtered and concentrated in vacuo. The crude material was purified by column chromatography (SiO<sub>2</sub>, petroleum ether) to afford 5-bromochromane (1.20 g, 5.63 mmol, 91.5% yield, 100% purity) as a light-yellow oil.

**[000219]** A mixture of 5-bromochromane (0.10 g, 469  $\mu$ mol, 1.00 eq.), Zn(CN)<sub>2</sub> (110 mg, 939  $\mu$ mol, 2.00 eq.), Pd(PPh<sub>3</sub>)<sub>4</sub> (81.4 mg, 70.4  $\mu$ mol, 0.15 eq.) in DMAC (1.00 mL) was purged with nitrogen. The mixture was stirred at 100 °C for 8 h. The reaction mixture was diluted with ethyl acetate (20.0 mL) and washed with brine (15.0 mL  $\times$  3). The combined organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by prep-TLC (SiO<sub>2</sub>, PE: EA = 10:1) to afford chromane-5-carbonitrile (60.0 mg, 377  $\mu$ mol, 80.3% yield) as a light-yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.22 - 7.18 (m, 1H), 7.18 - 7.13 (m, 1H), 7.02 (dd, *J*=1.2, 8.0 Hz, 1H), 4.28 - 4.19 (m, 2H), 2.97 (t, *J*=6.4 Hz, 2H), 2.16 - 2.02 (m, 2H).

**[000220]** To a solution of chromane-5-carbonitrile (60.0 mg, 377  $\mu$ mol, 1.00 eq.) in THF (3.00 mL) was added LAH (57.2 mg, 1.51 mmol, 4.00 eq.) at 0 °C. The mixture was stirred at rt for 2 h. The reaction mixture was quenched with water (1.00 mL) and diluted with DCM (30 mL). The mixture was dried with magnesium sulfate and filtered. The filtrate was concentrated in vacuo to afford chroman-5-ylmethanamine (70.0 mg, crude) as a light-yellow oil.

## INTERMEDIATE B-7

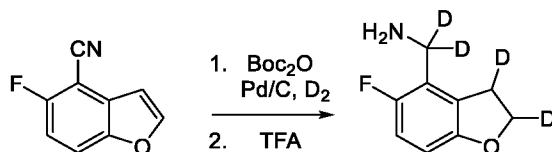


[000221] To a solution of 5-fluorobenzofuran-4-carbonitrile (2.00 g, 12.4 mmol, 1.00 equiv) in dimethyl sulfoxide (20.0 mL) was added hydrogen peroxide (7.04 g, 62.1 mmol, 5.96 mL, 30% purity, 5.00 equiv) and potassium carbonate (1.72 g, 12.4 mmol, 1.00 equiv) at 0 °C. The mixture was stirred at 25 °C for 1 h. The residue was poured into ice-water (5.00 mL) and stirred for 10 min. The mixture was filtered and concentrated under vacuum to give 5-fluorobenzofuran-4-carboxamide (1.80 g, 10.1 mmol, 81.0% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 8.11 (d, *J*=2.0 Hz, 1H), 7.81 (br s, 1H), 7.73 (dd, *J*=4.0, 8.8 Hz, 2H), 7.23 (dd, *J*=9.2, 10.4 Hz, 1H), 7.10 (d, *J*=1.2 Hz, 1H).

[000222] A solution of 5-fluorobenzofuran-4-carboxamide (1.80 g, 10.1 mmol, 1.00 equiv) in methyl alcohol (4.00 mL) was charged with hydrogen (50 psi) and Pd/C (500 mg, 50% purity). The mixture was stirred at 35 °C for 12 h. The mixture was filtered and concentrated under vacuum to give 5-fluoro-2,3-dihydrobenzofuran-4-carboxamide (1.60 g, 8.83 mmol, 87.9% yield) as a white solid. LCMS [*M*+1]: 182.2. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 7.82 - 7.55 (m, 2H), 6.96 (t, *J*=8.8 Hz, 1H), 6.79 (dd, *J*=4.0, 8.8 Hz, 1H), 4.54 (t, *J*=8.8 Hz, 2H), 3.25 (t, *J*=8.8 Hz, 2H).

[000223] To a solution of 5-fluoro-2,3-dihydrobenzofuran-4-carboxamide (1.60 g, 8.83 mmol, 1.00 equiv) in tetrahydrofuran (20.0 mL) was added lithium aluminumdeuteride (670 mg, 17.7 mmol, 911 μL, 2.00 equiv) at 0 °C. The mixture was stirred at 60 °C for 12 h. The mixture was quenched with water (1.60 mL) (stirred for 15 min), followed by sodium hydroxide (1.50 mL, 15% aq.) (15 min) and water (4.80 mL) (30 min). The suspension was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (basic conditions) to afford (5-fluoro-2,3-dihydrobenzofuran-4-yl)methan-d<sub>2</sub>-amine (0.80 g, 4.56 mmol, 51.6% yield, 96.4% purity) as a red oil. <sup>1</sup>H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.82 - 6.76 (m, 1H), 6.59 (dd, *J*=4.0, 8.8 Hz, 1H), 4.59 (t, *J*=8.8 Hz, 2H), 3.23 (t, *J*=8.8 Hz, 2H).

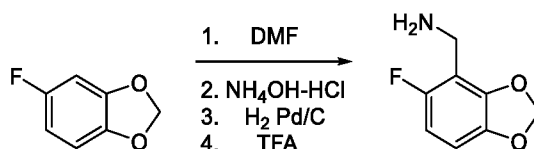
## INTERMEDIATE B-8



[000224] To a solution of 5-fluorobenzofuran-4-carbonitrile (100 mg, 620 μmol, 1.00 equiv) in methanol-*d*<sub>4</sub> (1.00 mL) was added di-*tert*-butyl dicarbonate (135 mg, 620 μmol, 143 μL, 1.00 equiv) and palladium on carbon (100 mg, 10.0 w%, 0.09 equiv). The mixture was stirred at 35 °C for 12 h under a deuterium gas atmosphere (15 psi). The reaction was filtered and concentrated at reduced pressure to give *tert*-butyl ((5-fluoro-2,3-dihydrobenzofuran-4-yl)-2,3-d<sub>2</sub>)methyl-d<sub>2</sub>)carbamate (45.0 mg, 166 μmol, 26.7% yield) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 6.82 - 6.76 (m, 1H), 6.62 (dd, *J*=3.6, 8.4 Hz, 1H), 4.86 (br s, 1H), 4.57 (br d, *J*=10.0 Hz, 1H), 3.27 (br d, *J*=6.8 Hz, 1H), 1.46 - 1.41 (s, 9H).

[000225] To a solution of *tert*-butyl ((5-fluoro-2,3-dihydrobenzofuran-4-yl-2,3-d2)methyl-d2)carbamate (40.0 mg, 147  $\mu$ mol, 1.00 equiv) in dichloromethane (2.00 mL) was added trifluoroacetic acid (109  $\mu$ L, 1.47 mmol, 10.0 equiv). The mixture was stirred at 25 °C for 1 h. and subsequently was concentrated at reduced pressure to give a residue. The residue was added to saturated sodium bicarbonate (2.00 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (2.00 mL  $\times$  3). The combined organic phase was washed with brine (2.00 mL  $\times$  3), dried with anhydrous sodium sulfate, filtered, and concentrated at reduced pressure to afford dideuterio-(2,3-dideuterio-5-fluoro-2,3-dihydrobenzofuran -4-yl)methanamine (25.0 mg, crude) as a white solid, which was used without further purification.

#### INTERMEDIATE B-9



[000226] To a solution of 5-fluoro-1,3-benzodioxole (500 mg, 3.57 mmol, 1.00 equiv) in THF (5.00 mL) was added *n*-BuLi (2.50 M, 1.57 mL, 1.10 equiv) dropwise at -78 °C. The mixture was stirred at -78 °C for 15 min followed by the dropwise addition of DMF (235 mg, 3.21 mmol, 247  $\mu$ L, 0.90 equiv) and continued stirring at -78 °C for 0.5 h. The mixture was poured into saturated ammonium chloride aqueous solution (5.00 mL) and stirred for 15 min. The aqueous phase was extracted with ethyl acetate (6.00 mL  $\times$  2). The combined organic phase was washed with brine (6.00 mL  $\times$  3), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5-fluoro-1,3-benzodioxole-4-carbaldehyde (370 mg, 2.20 mmol, 61.7% yield) as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 10.07 (s, 1H), 7.12 (dd,  $J$ =4.4, 8.4 Hz, 1H), 6.72 (dd,  $J$ =8.8, 11.6 Hz, 1H), 6.17 (s, 2H).

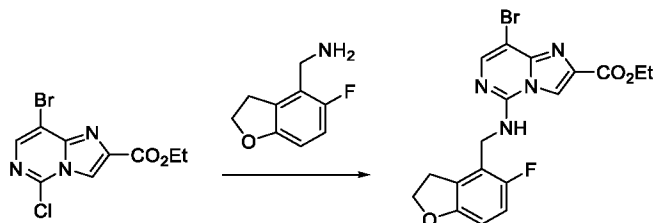
[000227] To a solution of 5-fluoro-1,3-benzodioxole-4-carbaldehyde (200 mg, 1.19 mmol, 1.00 equiv) in ethyl alcohol (6.00 mL) was added hydroxylamine-hydrochloride (248 mg, 3.57 mmol, 3.00 equiv) and triethylamine (827  $\mu$ L, 5.95 mmol, 5.00 equiv). The mixture was stirred at 15 °C for 0.5 h and the mixture was concentrated under reduced pressure to give a residue. The residue was triturated with water (3.00 mL  $\times$  2) and filtered, the filter cake was collected and dried under reduced pressure to give 5-fluoro-1,3-benzodioxole-4-carbaldehyde oxime (200 mg, 1.09 mmol, 91.8% yield) as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 11.68 (s, 1H), 8.08 (s, 1H), 6.91 (br dd,  $J$ =4.0, 8.4 Hz, 1H), 6.77 - 6.65 (m, 1H), 6.12 (s, 2H).

[000228] To a solution of 5-fluoro-1,3-benzodioxole-4-carbaldehyde oxime (280 mg, 2.07 mmol, 1.00 equiv) in methyl alcohol (3.00 mL) was added Pd/C (2.07 mmol, 10% purity, 1.00 equiv) and di-*tert*-butyl dicarbonate (906 mg, 4.15 mmol, 953  $\mu$ L, 2.00 equiv). The mixture was stirred at 25 °C for 12 h under a hydrogen atmosphere (15 psi). The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/0 to 2/1) to afford *tert*-butyl *N*-[(5-fluoro-1,3-benzodioxol-4-yl)methyl]carbamate (350 mg, 1.71 mmol, 82.3% yield) as a white solid. LCMS [M-55]: 214.1.

[000229] To a solution of *tert*-butyl ((5-fluorobenzo[d][1,3]dioxol-4-yl)methyl)carbamate (85.0 mg, 316  $\mu$ mol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.30 mL). The mixture was stirred at 25 °C for

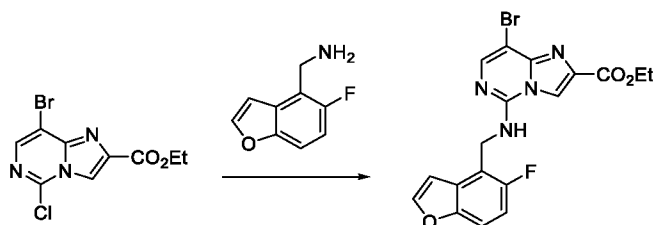
0.5 h. The reaction mixture was neutralized with saturated aq potassium carbonate (5.00 mL) and stirred for 30 min. The aqueous phase was extracted with DCM (5.00 mL  $\times$  2). The combined organic phase was washed with brine (5.00 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (5-fluorobenzo[d][1,3]dioxol-4-yl)methanamine (45.0 mg, 266  $\mu$ mol, 84.3% yield) as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.63 (dd,  $J$ =4.4, 8.4 Hz, 1H), 6.52 (dd,  $J$ =8.4, 10.4 Hz, 1H), 6.00 (s, 2H), 3.89 (s, 2H).

#### INTERMEDIATE C-1



[000230] An exemplary Intermediate C, Intermediate C-1, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is  $\text{C}(\text{R}^5)_2$ ,  $\text{-----}$  is a single bond and one  $\text{R}^3$  is fluorine. A mixture of ethyl 8-bromo-5-chloroimidazo[1,2-c]pyrimidine-2-carboxylate (380 mg, 1.25 mmol, 1.00 equiv), (5-fluoro-2,3-dihydrobenzofuran-4-yl)methanamine (250.34 mg, 1.50 mmol, 1.20 equiv), DIEA (322 mg, 2.50 mmol, 434  $\mu\text{L}$ , 2.00 equiv) in DMF (3.00 mL) was purged with nitrogen and was stirred at 85  $^\circ\text{C}$  for 0.5 h. To this mixture was added water (10.0 mL) and ethyl acetate (8.00 mL). The biphasic mixture was filtered to remove a solid impurity and the organic layer was concentrated *in vacuo* to provide ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (443 mg, 1.02 mmol, 81.5% yield) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 8.87 (s, 1H), 8.50 (t,  $J$  = 4.8 Hz, 1H), 7.90 (s, 1H), 6.93 (t,  $J$  = 9.6 Hz, 1H), 6.69 (dd,  $J$  = 4.0, 8.8 Hz, 1H), 4.65 (d,  $J$  = 4.8 Hz, 2H), 4.52 (t,  $J$  = 8.8 Hz, 2H), 4.32 (q,  $J$  = 7.2 Hz, 2H), 3.25 (t,  $J$  = 8.8 Hz, 2H), 1.32 (t,  $J$  = 7.2 Hz, 3H).

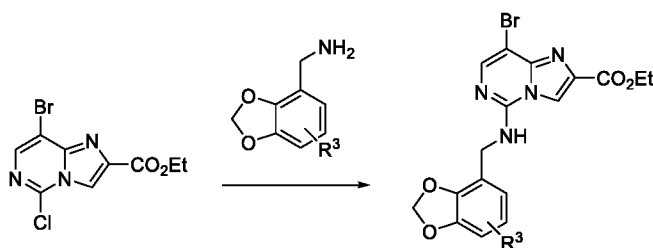
#### INTERMEDIATE C-2



[000231] A second exemplary Intermediate C, Intermediate C-2, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is  $\text{CR}^5$ ,  $\text{=====}$  is a double bond and one  $\text{R}^3$  is fluorine. A mixture of 8-bromo-5-chloroimidazo[1,2-c]pyrimidine-2-carboxylate (160 mg, 525  $\mu$ mol, 1.00 equiv), (5-fluorobenzofuran-4-yl)methanamine (116 mg, 630  $\mu$ mol, 1.20 equiv) and DIEA (136 mg, 1.05 mmol, 183  $\mu\text{L}$ , 2.00 equiv) in DMF (2.00 mL) was stirred at 85  $^\circ\text{C}$  for 0.5 h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether/ethyl acetate, 0/1 to 2/1) to afford ethyl 8-bromo-5-(((5-fluorobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (180 mg, 78.2%

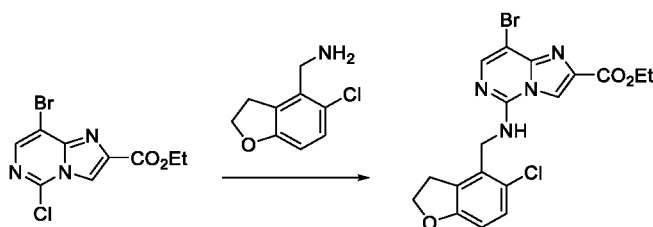
yield) as a brown solid. LCMS [M+1]: 433.1.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.63 (s, 1H), 7.92 (s, 1H), 7.80 (d,  $J$ =2.0 Hz, 1H), 7.45 (dd,  $J$ =3.6, 8.8 Hz, 1H), 7.13 - 7.07 (m, 1H), 7.06 (d,  $J$ =1.2 Hz, 1H), 5.04 (s, 2H), 4.38 (q,  $J$ =6.8 Hz, 2H), 1.38 (t,  $J$ =7.2 Hz, 3H).

### INTERMEDIATE C-3



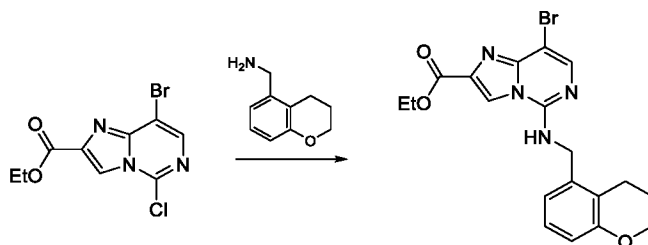
[000232] A third exemplary Intermediate C, Intermediate C-3, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is O, and ----- is a single bond. To a solution of ethyl 8-bromo-5-chloro-imidazo[1,2-c] pyrimidine -2-carboxylate (103 mg, 328  $\mu\text{mol}$ , 1.00 equiv), 1,3-benzodioxol-4-ylmethanamine (54.6 mg, 361  $\mu\text{mol}$ , 1.10 equiv) in DMF (2.00 mL) was added DIEA (42.4 mg, 328  $\mu\text{mol}$ , 57.2  $\mu\text{L}$ , 1.00 equiv). The resultant mixture was stirred at 85  $^\circ\text{C}$  for 1 h and was subsequently concentrated to afford the crude material. The residue was washed with water (3.00 mL  $\times$  2) to provide ethyl 5-((benzo[d][1,3]dioxol-4-ylmethyl)amino)-8-bromoimidazo[1,2-c]pyrimidine-2-carboxylate (120 mg, 286.24  $\mu\text{mol}$ , 87.2% yield) as a brown solid. LCMS: [M+1] 421.2.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 8.87 (s, 1H), 8.65 (br s, 1H), 7.88 (s, 1H), 6.90 - 6.77 (m, 3H), 6.03 (s, 2H), 4.66 (d,  $J$ =4.8 Hz, 2H), 4.36 - 4.31(m, 2H), 1.33 (t,  $J$ =7.2 Hz, 3H).

### INTERMEDIATE C-4



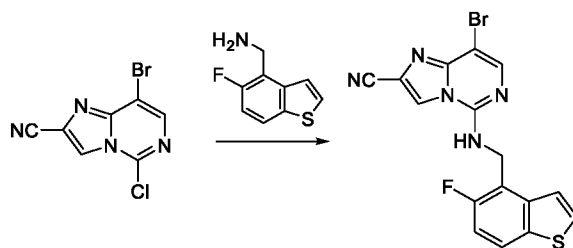
[000233] A fourth exemplary Intermediate C, Intermediate C-4, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is  $\text{C}(\text{R}^5)_2$ , ----- is a single bond and one  $\text{R}^3$  is chlorine. To a solution of ethyl 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2-carboxylate (230 mg, 755  $\mu\text{mol}$ , 1.00 equiv), (5-chloro-2,3-dihydrobenzofuran-4-yl)methanamine (118 mg, 642  $\mu\text{mol}$ , 0.850 equiv) in DMF (2.00 mL) was added DIEA (195 mg, 1.51 mmol, 263  $\mu\text{L}$ , 2.00 equiv) and the reaction mixture was stirred at 85  $^\circ\text{C}$  for 1 h. The solution was concentrated *in vacuo* to give the crude material, which was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to afford ethyl 8-bromo-5-(((5-chloro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (320 mg) as a brown solid. LCMS: [M+3] 453.1.

## INTERMEDIATE C-4A



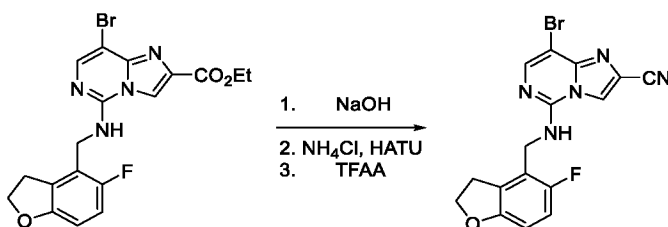
[000234] Another Intermediate C, Intermediate C-4A, may be used to synthesize compounds of formula I wherein Z is O, n is two, X is C(R<sup>5</sup>)<sub>2</sub>, and        is a single bond. To a solution of ethyl 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2-carboxylate (250 mg, 802  $\mu$ mol, 1.00 eq.) in DMF (3.00 mL) was added DIPEA (207 mg, 1.60 mmol, 279  $\mu$ L, 2.00 eq.) and chroman-5-ylmethanamine (170 mg, 1.04 mmol, 1.30 eq.). The mixture was stirred at 85 °C for 30 min. The reaction mixture was diluted with water (40 mL) and filtered. The solid was dried under vacuum to afford ethyl 8-bromo-5-((chroman-5-ylmethyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (320 mg, 742  $\mu$ mol, 92.5% yield) as a yellow solid. LC-MS: [M+1] 433.3.

## INTERMEDIATE C-4B



[000235] Yet another exemplary Intermediate C, Intermediate C-4B, may be used to synthesize compounds of formula I wherein Z is S, n is one, X is C(R<sup>5</sup>)<sub>2</sub>,        is a single bond and one R<sup>3</sup> is fluorine. To a solution of (5-fluorobenzothiophen-4-yl)methanamine (39.4 mg, 218  $\mu$ mol, 1.40 eq.) and 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2-carbonitrile (40.0 mg, 155  $\mu$ mol, 1.00 eq.) in DMF (2.00 mL) was added DIEA (60.2 mg, 466  $\mu$ mol, 81.2  $\mu$ L, 3.00 eq.). The reaction mixture was stirred at 85 °C for 1 h. The mixture was diluted with ethyl acetate (10.0 mL), washed with brine (10.0 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude residue. The crude material was purified by prep-TLC(petroleum ether/ethyl acetate = 1/1) to give 8-bromo-5-((5-fluorobenzo[b]thiophen-4-yl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (35.0 mg, 87.0  $\mu$ mol, 56.0% yield) as a brown solid. LCMS [M+1]: 404.0.

## INTERMEDIATE C-5



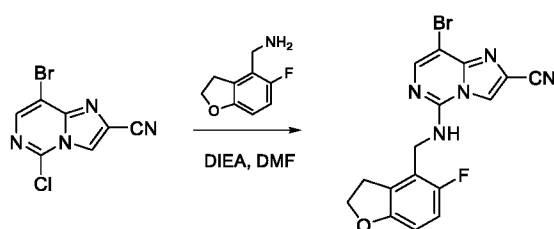
[000236] A fifth exemplary Intermediate C, Intermediate C-5, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is C(R<sup>5</sup>)<sub>2</sub>,        is a single bond and one R<sup>3</sup> is fluorine. A

mixture of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (160 mg, 367  $\mu$ mol, 1 equiv) and sodium hydroxide (1 M, 1.10 mL, 3 equiv) in methanol (3.30 mL) was stirred at 55 °C for 0.5 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* and the residue was diluted with water (1.00 mL). The pH was adjusted to pH = 2 with HCl (1 M) and the solid was collected by filtration. The resultant solid was dried under reduced pressure to afford 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (124 mg, 304  $\mu$ mol, 82.8% yield) as a white solid. LC-MS: [M+1] 408.8.

**[000237]** A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (124 mg, 304.  $\mu$ mol, 1.00 equiv), ammonium chloride (48.8 mg, 913  $\mu$ mol, 3.00 equiv), HATU (173 mg, 1.50 equiv), DIEA (314 mg, 2.44 mmol, 424  $\mu$ L, 8 equiv) in DMF (1.00 mL) was stirred at 30 °C for 1 h under an atmosphere of nitrogen. Subsequently, the mixture was concentrated *in vacuo*. To the crude material was added water (1.00 mL) and the resultant solid was collected by filtration. The solid was dried under reduced pressure to provide 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide (100 mg) as a white solid, which was used without further purification.

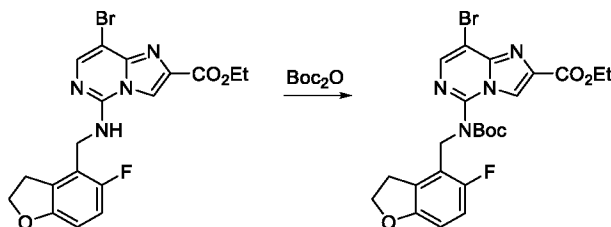
**[000238]** To a mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide (100 mg, 246.  $\mu$ mol, 1.00 equiv), TEA (484 mg, 4.79 mmol, 666  $\mu$ L, 19.4 equiv) in THF (2.00 mL) was added TFAA (302 mg, 1.44 mmol, 200  $\mu$ L, 5.84 equiv) at 0 °C. Subsequently, the mixture was stirred at 0–30 °C for 40 min under an atmosphere of nitrogen. The mixture was concentrated to provide the crude residue, which was purified by column chromatography (petroleum ether/ethyl acetate, 5/1 to 0/1) to afford 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 245  $\mu$ mol, 99.7% yield) as a yellow solid. LC-MS: [M+1] 387.8.

**[000239]** Alternatively, Intermediate C-5 may be prepared as follows:



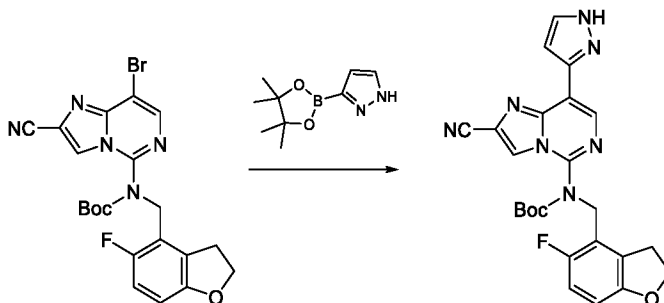
**[000240]** To a solution of 8-bromo-5-chloro-imidazo[1,2-c]pyrimidine-2- carbonitrile (3.00 g, 11.7 mmol, 1.00 equiv) and (5-fluoro-2,3-dihydrobenzofuran-4-yl) methanamine (2.14 g, 12.8 mmol, 1.10 equiv) in DMF (30.0 mL) was added DIEA (3.01 g, 23.3 mmol, 4.06 mL, 2.00 equiv). The resultant mixture was stirred at 85 °C for 1 h, cooled to rt, and poured into water (100 mL). The mixture was extracted with ethyl acetate (50.0 mL  $\times$  3). The combined organic phase was washed with brine (50.0 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (4.00 g, 10.3 mmol, 88.4% yield) as a yellow solid. LCMS [M+1]: 390.1.

## INTERMEDIATE C-6



[000241] A sixth exemplary Intermediate C, Intermediate C-6, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is C(R<sup>5</sup>)<sub>2</sub>, ===== is a single bond and one R<sup>3</sup> is fluorine. A mixture of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (204 mg, 460  $\mu$ mol, 1.00 equiv), di-*tert*-butyl dicarbonate (201 mg, 919  $\mu$ mol, 2.00 equiv), 4-(dimethylamino)pyridine (561  $\mu$ g, 4.60  $\mu$ mol, 0.01 equiv) in tetrahydrofuran (2.00 mL) was purged with nitrogen and subsequently allowed to stir at 25 °C for 2 h under an atmosphere of nitrogen. The mixture was diluted with water (3.00 mL) and extracted with ethyl acetate (2.00 mL  $\times$  3). The combined organic layers were washed with brine (2.00 mL  $\times$  3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide a residue. The crude material was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 3/1) to afford ethyl 8-bromo-5-((*tert*-butoxycarbonyl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (160 mg, 198  $\mu$ mol, 43.0% yield, 66. 2% purity) as a white solid. LC-MS [M+1]: 537.2. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 8.11 (s, 1H), 7.93 (s, 1H), 6.67 - 6.61 (m, 1H), 6.59 - 6.54 (m, 1H), 5.08 (s, 2H), 4.58 (t, *J*=8.8 Hz, 2H), 4.47 (q, *J*=7.2 Hz, 2H), 3.32 (br t, *J*=8.8 Hz, 2H), 1.43 (t, *J*=7.2 Hz, 3H), 1.36 (s, 9H).

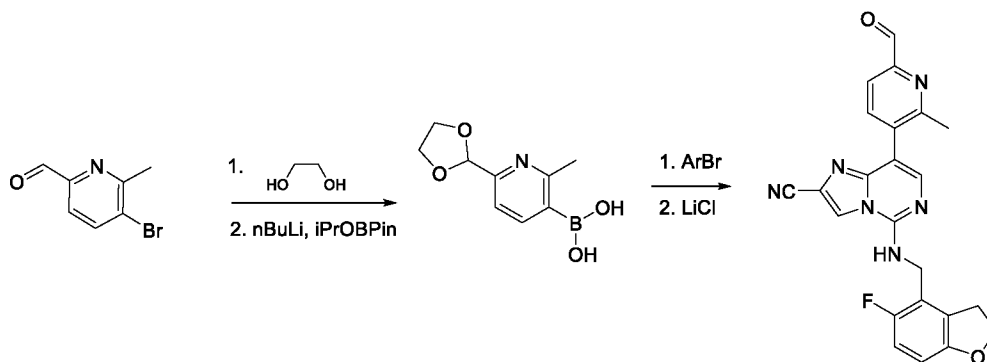
## INTERMEDIATE C-7



[000242] A seventh exemplary Intermediate C, Intermediate C-7, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is C(R<sup>5</sup>)<sub>2</sub>, ===== is a single bond, one R<sup>3</sup> is fluorine and R<sup>1</sup> is heteroaryl which may then be further substituted with one or more R<sup>4</sup>. To a solution of *tert*-butyl (8-bromo-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (500 mg, 1.01 mmol, 1.00 eq.), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (295 mg, 1.52 mmol, 1.50 eq.) and sodium bicarbonate (170 mg, 2.03 mmol, 2.00 eq.) in a mixture of dioxane (4.00 mL) and water (0.80 mL) was added Pd(dppf)Cl<sub>2</sub> (80.0 mg, 109  $\mu$ mol, 0.01 eq). The mixture was purged with nitrogen and stirred at 105 °C for 2 h. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/methanol = 10/1) to afford *tert*-butyl (2-cyano-8-(1*H*-pyrazol-3-

yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (120 mg, 230  $\mu$ mol, 22.7% yield, 91% purity) as a yellow solid.

### INTERMEDIATE C-8



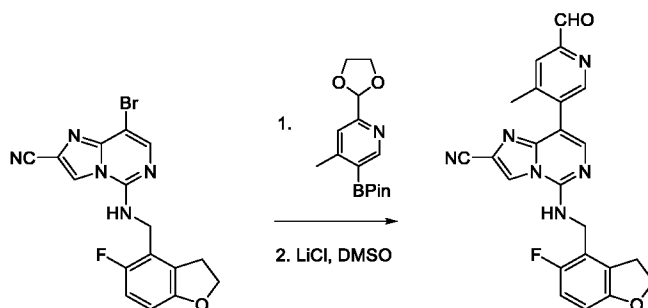
[000243] An eighth exemplary Intermediate C, Intermediate C-8, may be used to synthesize compounds of formula I wherein Z is O, n is one, X is C(R<sup>5</sup>)<sub>2</sub>, ===== is a single bond, one R<sup>3</sup> is fluorine and R<sup>1</sup> is heteroaryl which is substituted two R<sup>4</sup> groups, one of which serves as an intermediate to generate various R<sup>4</sup> groups, e.g., L-N(R<sup>5</sup>)<sub>2</sub>. To a solution of 5-bromo-6-methyl-pyridine-2-carbaldehyde (300 mg, 1.50 mmol, 1.00 eq.) in toluene (10.0 mL) was added TsOH•H<sub>2</sub>O (28.5 mg, 150  $\mu$ mol, 0.10 eq.) and ethylene glycol (186 mg, 3.00 mmol, 168  $\mu$ L, 2.00 eq.). The mixture was stirred at 120 °C for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to give compound 3-bromo-6-(1,3-dioxolan-2-yl)-2-methyl-pyridine (260 mg, 1.07 mmol, 71.0% yield) as a yellow oil.

[000244] To a solution of 3-bromo-6-(1,3-dioxolan-2-yl)-2-methyl-pyridine (0.30 g, 1.23 mmol, 1.00 eq.) in Et<sub>2</sub>O (15.0 mL) was added *n*-BuLi (2.50 M, 737  $\mu$ L, 1.50 eq.) dropwise at -78 °C. The mixture was stirred at -78 °C for 30 min prior to the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (457 mg, 2.46 mmol, 501  $\mu$ L, 2.00 eq.). The mixture was stirred at -78 °C for an additional hour. The reaction mixture was quenched with water (2.00 mL) and the resulting mixture was extracted with ethyl acetate (30.0 mL  $\times$  2). The combined organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to give [6-(1,3-dioxolan-2-yl)-2-methyl-3-pyridyl]boronic acid (160 mg, 766  $\mu$ mol, 62.3% yield) as yellow oil. LC-MS [M+1]: 209.9.

[000245] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (0.20 g, 515  $\mu$ mol, 1.00 eq.), [6-(1,3-dioxolan-2-yl)-2-methyl-3-pyridyl]boronic acid (162 mg, 773  $\mu$ mol, 1.50 eq.), sodium bicarbonate (130 mg, 1.55 mmol, 3.00 eq.) and Pd(dppf)Cl<sub>2</sub> (56.6 mg, 77.3  $\mu$ mol, 0.15 eq.) in water (0.60 mL) and dioxane (1.80 mL) was purged with nitrogen and the resultant mixture was stirred at 100 °C for 2 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane: methanol = 20:1) to give 8-(6-(1,3-dioxolan-2-yl)-2-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (150 mg, 317  $\mu$ mol, 61.6% yield) as a yellow oil. LC-MS [M+1]: 473.3.

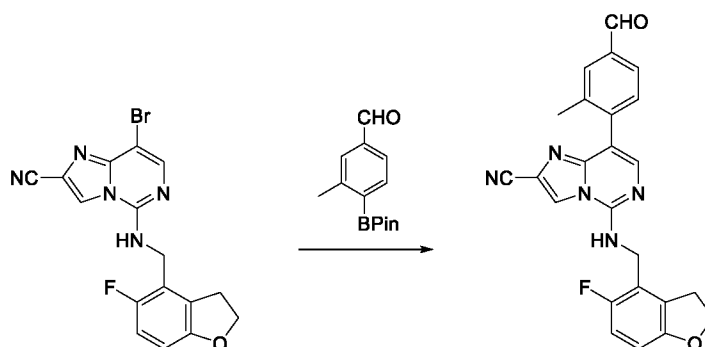
[000246] To a solution of 8-(6-(1,3-dioxolan-2-yl)-2-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (120 mg, 254  $\mu$ mol, 1.00 eq.) in DMSO (3.00 mL) and water (0.30 mL) was added lithium chloride (53.8 mg, 1.27 mmol, 5.00 eq.) and the mixture was stirred at 130 °C for 3 h. The mixture was cooled to rt and diluted with water (15.0 mL). The mixture was extracted with ethyl acetate (20.0 mL $\times$ 3) and the combined organic phase was washed with brine (20.0 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-formyl-2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 233  $\mu$ mol, 91.9% yield) as a brown solid. LC-MS [M+1]: 429.1.

## INTERMEDIATE C-9



[000247] To a solution of 2-(1,3-dioxolan-2-yl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (45.0 mg, 155  $\mu$ mol, 1.00 equiv), 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (60.0 mg, 155  $\mu$ mol, 1.00 equiv) in dioxane (1.00 mL) and water (0.30 mL) was added Pd(dppf)Cl<sub>2</sub> (11.3 mg, 15.5  $\mu$ mol, 0.10 equiv) and sodium bicarbonate (26.0 mg, 309  $\mu$ mol, 2.00 equiv) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 1 h. The mixture was concentrated in vacuo to provide the crude residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 0/1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-formyl-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (32.0 mg, 67.7  $\mu$ mol, 43.8% yield) as a yellow solid. LCMS [M+1]: 473.2.

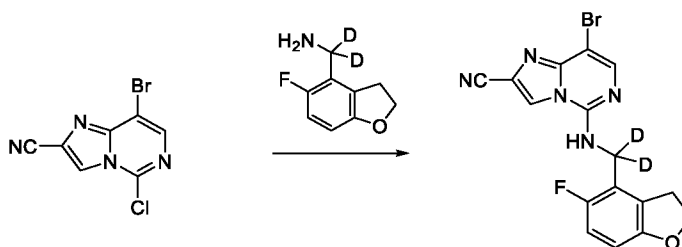
## INTERMEDIATE C-10



[000248] A mixture of (4-formyl-2-methyl-phenyl)boronic acid (80.0 mg, 488  $\mu$ mol, 1.50 eq), 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (126 mg, 325  $\mu$ mol, 1.00 eq.), sodium bicarbonate (54.7 mg, 651  $\mu$ mol, 2.00 eq.) and Pd(dppf)Cl<sub>2</sub> (23.8 mg, 32.5  $\mu$ mol, 0.10 eq.) in dioxane (1.00 mL) and water (0.30 mL) was purged with nitrogen 3 times and subsequently stirred at 100 °C for 2 h under a nitrogen atmosphere. The reaction mixture was diluted

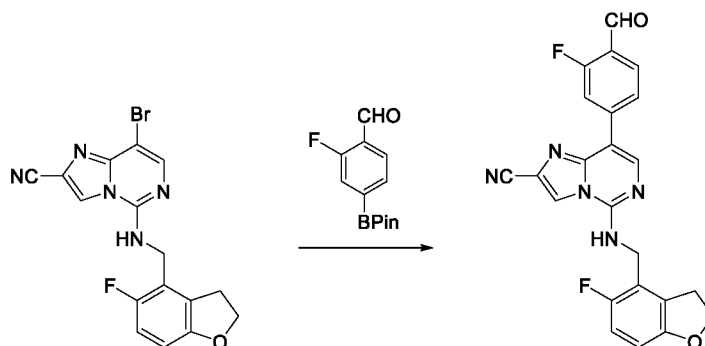
with water (10.0 mL) and extracted with ethyl acetate (10.0 mL  $\times$  3). The combined organic layer was washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide a residue. The residue was purified by prep-TLC (dichloromethane/methanol = 10/1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-formyl-2-methylphenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (74 mg, crude) as a yellow solid.  $^1\text{H}$  NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.04 (s, 1H), 8.93 (s, 1H), 8.55 (t, *J*=4.8 Hz, 1H), 7.85 (s, 1H), 7.82 - 7.77 (m, 2H), 7.54 (d, *J*=7.6 Hz, 1H), 7.01 - 6.90 (m, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 4.73 (d, *J*=4.4 Hz, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.38 - 3.32 (m, 2H), 2.27 (s, 3H).

## INTERMEDIATE C-11



[000249] To a solution of (5-fluoro-2,3-dihydrobenzofuran-4-yl)methan-*d*<sub>2</sub>-amine (50.0 mg, 284  $\mu\text{mol}$ , 1.00 equiv), 8-bromo-5-chloroimidazo[1,2-c]pyrimidine-2-carbonitrile (73.1 mg, 284  $\mu\text{mol}$ , 1.00 equiv) in DMF (1.00 mL) was added DIEA (110 mg, 851  $\mu\text{mol}$ , 148  $\mu\text{L}$ , 3.00 equiv). The mixture was stirred at 85  $^{\circ}\text{C}$  for 1 h. The reaction mixture was diluted with water (1.00 mL) and extracted with ethyl acetate (1.00 mL  $\times$  3). The combined organic layer was washed with brine (3.00 mL  $\times$  2), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl-*d*<sub>2</sub>)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (20.0 mg, crude) as a white solid. LCMS [*M*+1]: 390.0.

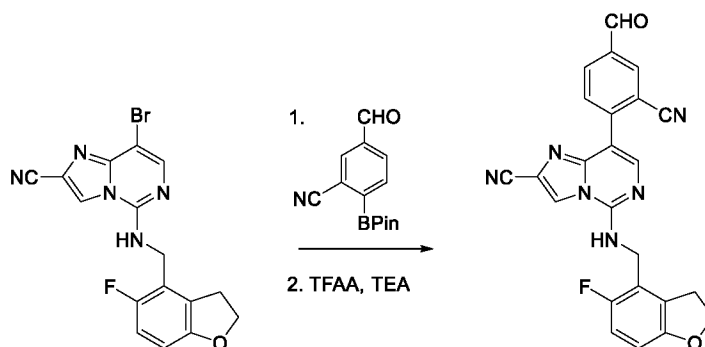
## INTERMEDIATE C-12



[000250] A mixture of (3-fluoro-4-formyl-phenyl)boronic acid (80.0 mg, 476  $\mu\text{mol}$ , 1.50 equiv), 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (123 mg, 318  $\mu\text{mol}$ , 1.00 equiv), sodium bicarbonate (53.4 mg, 635  $\mu\text{mol}$ , 2.00 equiv) and Pd(dppf)Cl<sub>2</sub> (23.2 mg, 31.8  $\mu\text{mol}$ , 0.10 equiv) in dioxane (1.00 mL) and water (0.30 mL) was purged with nitrogen and subsequently allowed to stir at 100  $^{\circ}\text{C}$  for 2 h under a nitrogen atmosphere. The reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate (10.0 mL  $\times$  3). The combined organic layer was washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide a residue that was purified by prep-TLC (dichloromethane/methanol = 10/1)

to afford 5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl) methylamino]-8-(3-fluoro-4-formyl-phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (87.0 mg, crude) as a yellow solid. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 10.24 (s, 1H), 8.97 (s, 1H), 8.81 (t, *J*=5.2 Hz, 1H), 8.44 (s, 1H), 8.22 - 8.16 (m, 2H), 7.95 - 7.91 (m, 1H), 6.99 - 6.93 (m, 1H), 6.72 (dd, *J*=4.0, 8.8 Hz, 1H), 4.77 (d, *J*=4.8 Hz, 2H), 4.56 (t, *J*=8.8 Hz, 2H), 3.36 - 3.33 (m, 2H).

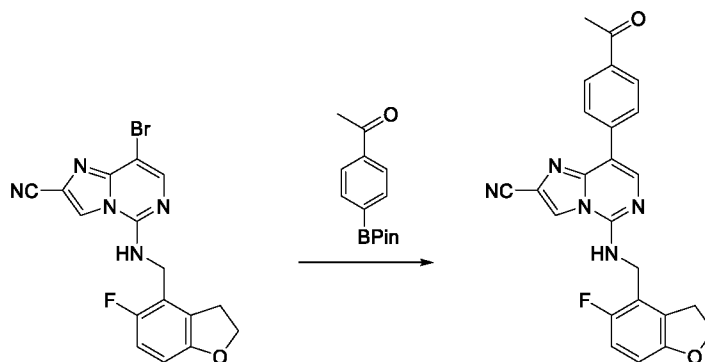
### INTERMEDIATE C-13



**[000251]** A mixture of 5-formyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (100 mg, 388 μmol, 1.00 equiv), 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (31.7 mg, 81.7 μmol, 0.21 equiv), Pd(dppf)Cl<sub>2</sub> (28.5 mg, 38.9 μmol, 0.10 equiv) and sodium bicarbonate (98.0 mg, 1.17 mmol, 3.00 equiv) in dioxane (1.50 mL) and water (0.30 mL) was purged with nitrogen and subsequently stirred at 95 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to afford 2-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-5-formylbenzamide (70 mg, 31.5% yield, 80% purity) as a yellow solid. LCMS [M+1]: 457.2. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 10.09 (s, 1H), 8.92 (s, 1H), 8.60 (br s, 1H), 8.06 (s, 1H), 8.03 (br d, *J*=8.4 Hz, 1H), 7.93 (br s, 1H), 7.88 - 7.77 (m, 2H), 7.38 (br s, 1H), 6.95 (br t, *J*=9.2 Hz, 1H), 6.71 (dd, *J*=3.6, 8.4 Hz, 1H), 4.72 (br s, 2H), 4.55 (br t, *J*=8.8 Hz, 2H), 3.53 - 3.48 (m, 2H).

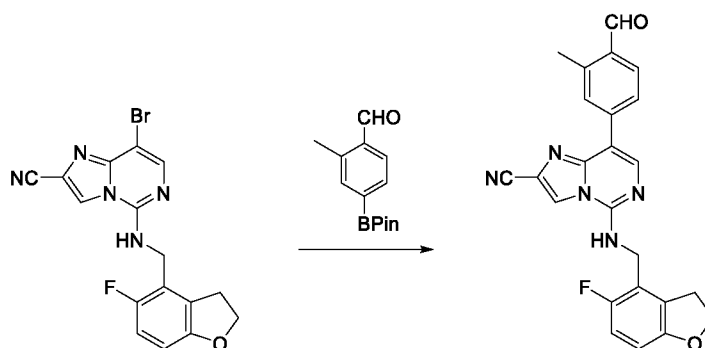
**[000252]** To a solution of 2-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-5-formylbenzamide (70.0 mg, 123 μmol, 1.00 equiv) in THF (1.00 mL) was added TEA (248mg, 2.45 mmol, 341 μL, 20.0 equiv) followed by TFAA (258 mg, 1.23 mmol, 171 μL, 10 equiv) dropwise at 0 °C. The mixture was stirred at 25 °C for 2 h and was subsequently concentrated under reduced pressure. The resultant residue was diluted with dichloromethane (6 mL) and the combined organic layer was washed with brine (3 mL × 2), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (ethyl acetate) to afford 8-(2-cyano-4-formylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 50.2% yield, 90.0% purity) as a yellow solid. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 10.09 (s, 1H), 8.99 (s, 1H), 8.86 (br s, 1H), 8.50 (d, *J*=1.2 Hz, 1H), 8.26 (dd, *J*=1.6, 8.0 Hz, 1H), 8.14 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 6.96 (t, *J*=9.6 Hz, 1H), 6.72 (dd, *J*=4.0, 8.8 Hz, 1H), 4.77 (br s, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.39 - 3.35 (m, 2H).

## INTERMEDIATE C-14



[000253] To a solution of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone (41.2 mg, 167  $\mu\text{mol}$ , 1.30 equiv) and 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (50.0 mg, 129  $\mu\text{mol}$ , 1.00 equiv) in dioxane (1.00 mL) and water (0.20 mL) was added Pd(dppf)Cl<sub>2</sub> (9.42 mg, 12.9  $\mu\text{mol}$ , 0.10 equiv) and sodium bicarbonate (21.6 mg, 258  $\mu\text{mol}$ , 2.00 equiv). The mixture was purged with nitrogen and subsequently stirred at 100 °C for 1 h. The mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to afford 8-(4-acetylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 54.5% yield) as a yellow solid. LCMS [M+1]: 428.0. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.96 (s, 1H), 8.24 (s, 1H), 8.19 (d, *J*=8.4 Hz, 2H), 8.02 (d, *J*=8.8 Hz, 2H), 6.93 (t, *J*=9.2 Hz, 1H), 6.68 (dd, *J*=3.6, 8.4 Hz, 1H), 4.74 (s, 2H), 4.53 (t, *J*=8.4 Hz, 2H), 3.31 - 3.28 (m, 2H), 2.60 (s, 3H).

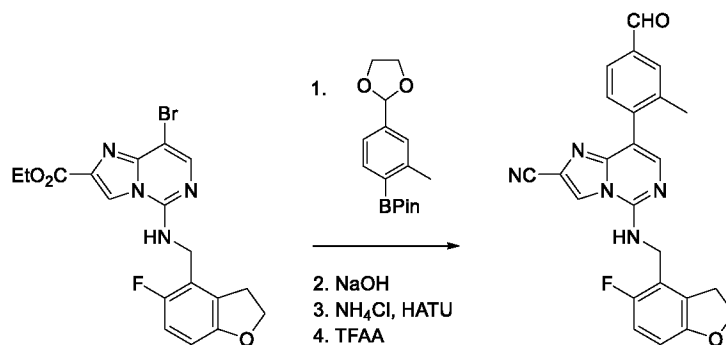
## INTERMEDIATE C-15



[000254] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (50.0 mg, 129  $\mu\text{mol}$ , 1.00 equiv), (4-formyl-3-methylphenyl)boronic acid (31.7 mg, 193  $\mu\text{mol}$ , 1.50 equiv), sodium bicarbonate (21.6 mg, 258  $\mu\text{mol}$ , 2.00 *eq*) and Pd(dppf)Cl<sub>2</sub>.CH<sub>2</sub>Cl<sub>2</sub> (10.5 mg, 12.9  $\mu\text{mol}$ , 0.10 equiv) and in dioxane (1 mL) and water (0.30 mL) was purged with nitrogen and then stirred at 95 °C for 2 h. The reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate (10.0 mL  $\times$  3). The combined organic layer was washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-formyl-3-methylphenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (25.0 mg, 58.5  $\mu\text{mol}$ , 45.4% yield) as a yellow solid. <sup>1</sup>H NMR (400MHz,

DMSO-*d*<sub>6</sub>)  $\delta$  = 10.25 (s, 1H), 8.96 (s, 1H), 8.69 (br t, *J*=4.8 Hz, 1H), 8.29 (s, 1H), 8.12 (dd, *J*=1.2, 8.4 Hz, 1H), 8.01 (s, 1H), 7.91 (d, *J*=8.4 Hz, 1H), 6.96 (t, *J*=9.2 Hz, 1H), 6.71 (dd, *J*=4.0, 8.4 Hz, 1H), 4.76 (br d, *J*=4.8 Hz, 2H), 4.56 (t, *J*=8.8 Hz, 2H), 3.31 - 3.29 (m, 2H), 2.70 (s, 3H).

### INTERMEDIATE C-16



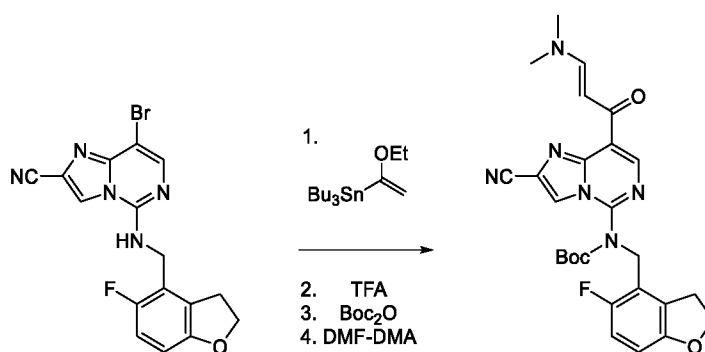
[000255] A mixture of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (3.00 g, 6.89 mmol, 1.00 equiv), 2-[4-(1,3-dioxolan-2-yl)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.60 g, 8.96 mmol, 1.3 equiv), NaHCO<sub>3</sub> (1.74 g, 20.7 mmol, 3.00 equiv), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (338 mg, 414  $\mu$ mol, 0.06 equiv) in dioxane (35.0 mL) and H<sub>2</sub>O (7.00 mL) was purged with N<sub>2</sub> and then stirred at 100 °C for 4 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified column chromatography (SiO<sub>2</sub>, dichloromethane/methyl alcohol = 100/1 to 30/1) to afford ethyl 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (1.70 g, 3.28 mmol, 47.6% yield) as a yellow solid. LCMS [M+1]: 519.2.

[000256] To a solution of ethyl 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (1.60 g, 3.09 mmol, 1.00 equiv) in methanol (16.0 mL) was added NaOH (1 M in water, 9.28 mL, 3.01 equiv) until the solution was adjusted to pH >12. The mixture was stirred at 50 °C for 2 h and was subsequently acidified to pH = 6 with 1M HCl. The formed precipitate was filtered and dried under vacuum to give the crude product 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (1.55 g). LCMS [M+1]: 491.0.

[000257] To a solution of 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (1.53 g, 3.12 mmol, 1.00 equiv) and ammonium chloride (536 mg, 10.0 mmol, 3.21 equiv) in DMF (15 mL) was added HATU (1.77 g, 4.67 mmol, 1.50 equiv) and DIEA (1.21 g, 9.35 mmol, 1.63 mL, 3.00 equiv). The mixture was stirred at 25 °C for 1 h and was subsequently diluted with water (20.0 mL). The suspension was filtered and the solid was dried under reduced pressure to give the crude product. The crude product diluted with water (60.0 mL) and extracted with ethyl acetate (60.0 mL  $\times$  2). The combined organic layer was washed with brine (80.0 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide (1.1 g, crude) as a yellow solid. LCMS [M+1]: 490.3.

**[000258]** To a solution of 8-(4-(1,3-dioxolan-2-yl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide (500 mg, 1.02 mmol, 1.00 equiv) and triethylamine (2.07 g, 20.4 mmol, 2.84 mL, 20.0 equiv) in THF (2.00 mL) was added dropwise TFAA (1.82 g, 8.68 mmol, 1.21 mL, 8.50 equiv) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h and was subsequently concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate=5/1 to 1/1) to provide the crude product. The crude product was triturated with methanol (5.00 mL) and the solid was collected by filtration to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-formyl-2-methylphenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (740 mg, 1.73 mmol, 84.8% yield) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 10.04 (s, 1H), 8.93 (s, 1H), 8.55 (t, *J*=4.8 Hz, 1H), 7.86 (s, 1H), 7.86 (s, 1H), 7.55 (d, *J*=7.6 Hz, 1H), 7.03 - 6.88 (m, 1H), 6.72 (dd, *J*=4.0, 8.8 Hz, 1H), 4.73 (d, *J*=4.8 Hz, 2H), 4.56 (t, *J*=8.8 Hz, 2H), 3.30 - 3.28 (m, 2H), 2.27 (s, 3H).

### INTERMEDIATE C-17



**[000259]** To a solution of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (300 mg, 773 μmol, 1.00 equiv) and tributyl(1-ethoxyvinyl)stannane (279 mg, 773 μmol, 261 μL, 1.00 equiv) in dioxane (5.00 mL) was added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (54.2 mg, 77.3 μmol, 0.10 equiv). The reaction was stirred at 100 °C for 2 h under nitrogen. The reaction was quenched with saturated aqueous potassium fluoride (20.0 mL) and extracted with ethyl acetate (20.0 mL×2). The combined organic phase was washed with brine (20.0 mL×2), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 to 3/1) to afford 8-(1-ethoxyvinyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 264 μmol, 34.1% yield) as a brown solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.21 (s, 1H), 7.88 (s, 1H), 6.87 - 6.80 (m, 1H), 6.66 (dd, *J*=4.0, 8.4 Hz, 1H), 5.80 (d, *J*=2.4 Hz, 1H), 5.55 (br t, *J*=5.6 Hz, 1H), 4.81 (d, *J*=5.6 Hz, 2H), 4.63 (t, *J*=8.8 Hz, 2H), 4.59 (d, *J*=2.4 Hz, 1H), 4.03 - 3.95 (m, 2H), 3.41 (t, *J*=8.8 Hz, 2H), 1.44 (t, *J*=6.8 Hz, 3H).

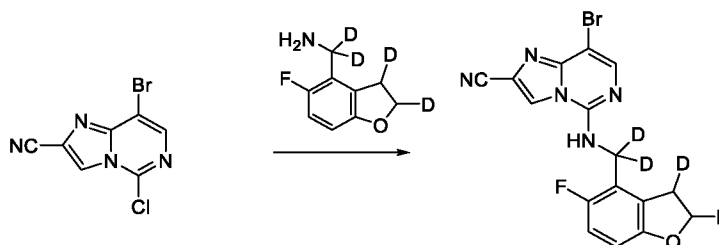
**[000260]** To a solution of 8-(1-ethoxyvinyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 264 μmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL). The reaction was stirred at 25 °C for 1 h. The reaction was concentrated under vacuum to give 8-acetyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (90.0 mg, 256 μmol, 97.2% yield) as a brown solid. <sup>1</sup>H NMR (400 MHz,

DMSO-*d*<sub>6</sub>)  $\delta$  = 9.16 (br s, 1H), 8.95 (s, 1H), 8.44 (s, 2H), 6.98 - 6.91 (m, 1H), 6.71 (dd, *J*=4.4, 8.8 Hz, 1H), 4.78 (s, 2H), 4.54 (t, *J*=8.8 Hz, 2H), 3.28 (t, *J*=8.8 Hz, 2H), 2.72 (s, 3H).

**[000261]** To a solution of 8-acetyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (50.0 mg, 142  $\mu$ mol, 1.00 equiv) in THF (2.00 mL) was added di-*tert*-butyl dicarbonate (62.1 mg, 285  $\mu$ mol, 2.00 equiv) and DMAP (1.74 mg, 14.2  $\mu$ mol, 0.10 equiv). The reaction was stirred at 80 °C for 1 h. The reaction was concentrated under vacuum to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 3/1) to afford *tert*-butyl (8-acetyl-2-cyanoimidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (40.0 mg, 88.6  $\mu$ mol, 62.3% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.87 (s, 1H), 8.60 (s, 1H), 6.83 - 6.77 (m, 1H), 6.64 (dd, *J*=3.6, 8.4 Hz, 1H), 5.09 (s, 2H), 4.54 (t, *J*=8.8 Hz, 2H), 3.30 - 3.25 (m, 2H), 2.86 (s, 3H), 1.33 (s, 9H).

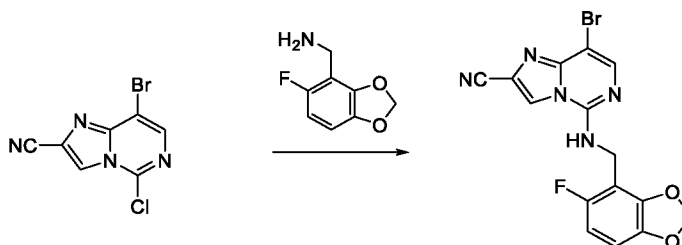
**[000262]** A solution of *tert*-butyl (8-acetyl-2-cyanoimidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 66.5  $\mu$ mol, 1.00 equiv) in DMF-DMA (209 mg, 1.76 mmol, 233  $\mu$ L, 26.5 equiv) was stirred at 100 °C for 1 h. The reaction was concentrated under vacuum to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to give *tert*-butyl (*E*)-(2-cyano-8-(3-(dimethylamino)acryloyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (20.0 mg, 39.5  $\mu$ mol, 59.4% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.71 (s, 1H), 8.01 (br d, *J*=12.8 Hz, 1H), 7.81 (s, 1H), 6.76 (br d, *J*=12.0 Hz, 1H), 6.70 - 6.63 (m, 1H), 6.56 (dd, *J*=4.0, 8.8 Hz, 1H), 5.12 (s, 2H), 4.56 (t, *J*=8.8 Hz, 3H), 3.28 (t, *J*=8.4 Hz, 2H), 3.23 (s, 3H), 3.06 (s, 3H), 1.38 (s, 9H).

#### INTERMEDIATE C-18



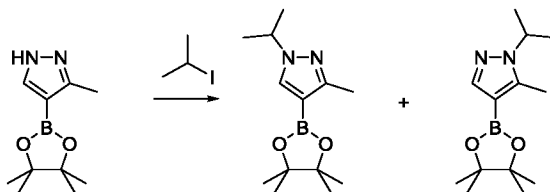
**[000263]** To a solution of dideuterio-(2,3-dideuterio-5-fluoro-2,3-dihydrobenzofuran-4-yl)methanamine (31.9 mg, 186  $\mu$ mol, 1.20 equiv) and 8-bromo-5-chloroimidazo[1,2-*c*]pyrimidine-2-carbonitrile (40.0 mg, 155  $\mu$ mol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (108  $\mu$ L, 621  $\mu$ mol, 4.00 equiv) and the mixture was stirred at 85 °C for 0.5 h. The mixture was concentrated at reduced pressure to give a residue, which was poured into water (3.00 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3.00 mL  $\times$  3). The combined organic phase was washed with brine (3.00 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)-2,3-*d*<sub>2</sub>)methyl-*d*<sub>2</sub>)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (25.0 mg, 63.7  $\mu$ mol, 41.0% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.30 (s, 1H), 7.94 (s, 1H), 7.93 (s, 1H), 6.83 - 6.76 (m, 1H), 6.64 (dd, *J*=4.0, 8.8 Hz, 1H), 4.59 (br d, *J*=10.0 Hz, 1H), 3.33 (br d, *J*=8.4 Hz, 1H).

## INTERMEDIATE C-19



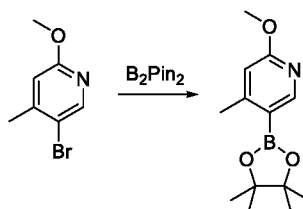
[000264] To a solution of 8-bromo-5-chloroimidazo[1,2-c]pyrimidine-2-carbonitrile (40.0 mg, 155  $\mu\text{mol}$ , 1.00 equiv) and (5-fluorobenzo[d][1,3]dioxol-4-yl)methanamine (31.5 mg, 186  $\mu\text{mol}$ , 1.20 equiv) in DMF (0.50 mL) was added DIEA (54.1  $\mu\text{L}$ , 310  $\mu\text{mol}$ , 2.00 equiv). The mixture was stirred at 85  $^{\circ}\text{C}$  for 0.5 h under a nitrogen atmosphere. The mixture was poured into water (3.00 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3.00 mL  $\times$  2). The combined organic phase was washed with brine (3.00 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 8-bromo-5-(((5-fluorobenzo[d][1,3]dioxol-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (50.0 mg, 128  $\mu\text{mol}$ , 82.5% yield) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 8.92 (s, 1H), 8.567 (br s, 1H), 7.95 (s, 1H), 6.88 (dd,  $J$ =4.4, 8.4 Hz, 1H), 6.69 (dd,  $J$ =8.8, 10.4 Hz, 1H), 6.04 (s, 2H), 4.67 (br d,  $J$ =2.0 Hz, 2H).

## INTERMEDIATE D-1



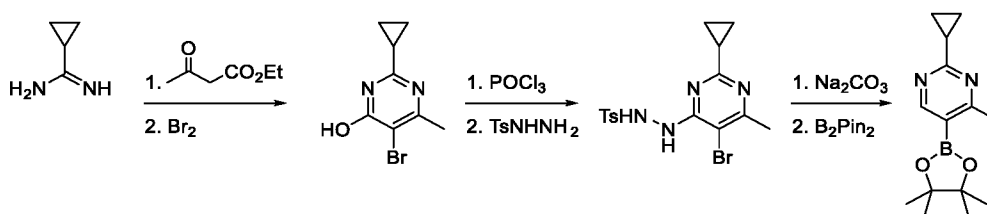
[000265] An exemplary Intermediate D, Intermediate D-1, may be used to synthesize compounds of formula I wherein  $\text{R}^1$  is a disubstituted heteroaryl. A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (370 mg, 1.78 mmol, 1.00 equiv), 2-iodopropane (907 mg, 5.33 mmol, 533  $\mu\text{L}$ , 3.00 equiv) and cesium carbonate (2.32 g, 7.11 mmol, 4.00 equiv) in acetonitrile (7.00 mL) was purged with nitrogen and subsequently stirred at 90  $^{\circ}\text{C}$  for 4 h. The reaction mixture was filtered and concentrated under reduced pressure to provide a residue. The crude material was purified by column chromatography (petroleum ether / ethyl acetate, 1 / 0 to 3 / 1) to afford a mixture of 1-isopropyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (170 mg, 34.4% yield, 90.0% purity) and 1-isopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (170 mg, 34.4% yield, 90.0% purity) as a light yellow oil. LCMS  $[\text{M}+1]$ : 251.4.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.73 (s, 0.6H), 7.65 (s, 1H), 4.50 - 4.36 (m, 2H), 2.45 (s, 2H), 2.40 (s, 3H), 1.50-1.44 (m, 12H), 1.31 (s, 22H).

## INTERMEDIATE D-2



[000266] A second exemplary Intermediate D, Intermediate D-2, may be used to synthesize compounds of formula I, wherein  $R^1$  is heteroaryl substituted with two  $R^4$  substituents. A mixture of 5-bromo-2-methoxy-4-methyl-pyridine (350 mg, 1.73 mmol, 1.00 equiv), bis(pinacolato)diboron (2.20 g, 8.66 mmol, 5.00 equiv), potassium acetate (527 mg, 5.37 mmol, 3.10 equiv), Pd(dppf)Cl<sub>2</sub> (127 mg, 173  $\mu$ mol, 0.10 equiv) in dioxane (5.00 mL) was purged with nitrogen and stirred at 90 °C for 3 h. The residue was diluted with ethyl acetate (3.00 mL) and extracted with ethyl acetate (2.00 mL  $\times$  3). The combined organic layers were washed with brine (2.00 mL  $\times$  3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate, 100/1 to 20/1) to afford 2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (150 mg, 546  $\mu$ mol, 31.5% yield, 90.6% purity) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 8.47 (s, 1H), 6.51 (s, 1H), 3.93 (s, 3H), 2.45 (s, 3H), 1.33 (s, 12H).

### INTERMEDIATE D-3



[000267] A third exemplary Intermediate D, Intermediate D-3, may be used to synthesize compounds of formula I or formula II wherein  $R^1$  is heteroaryl substituted with two  $R^4$  substituents. A mixture of cyclopropanecarboxamidine-HCl (5.00 g, 59.4 mmol, 1.00 equiv), ethyl 3-oxobutanoate (7.74 g, 59.4 mmol, 7.51 mL, 1.00 equiv), sodium ethoxide (8.09 g, 119 mmol, 2.00 equiv) in ethanol (500 mL) was purged with nitrogen and subsequently stirred at 25 °C for 12 h. The residue was dissolved in water (25.0 mL) and the pH was adjusted to ~4 with HCl (1 M). After cooling to 5 °C, the solid was collected and dried under reduced pressure to give 2-cyclopropyl-6-methyl-pyrimidin-4-ol (4.00 g, 26.6 mmol, 44.8% yield, 100% purity) as a white solid. LC-MS [M+1]: 151.3. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>)  $\delta$  = 12.45 (s, 1H), 5.93(s, 1H), 2.07 (s, 3H), 1.90 - 1.85 (m, 1H), 1.00 - 0.97 (m, 4H).

[000268] A mixture of 2-cyclopropyl-6-methyl-pyrimidin-4-ol (4.00 g, 26.6 mmol, 1.00 equiv), bromine (4.34 g, 27.2 mmol, 1.40 mL, 1.00 equiv), potassium hydroxide (1.49 g, 26.6 mmol, 1.00 equiv) in water (32.6 mL) was stirred at 25 °C for 2 h under a nitrogen atmosphere. The solid was filtered to give 5-bromo-2-cyclopropyl-6-methyl-pyrimidin-4-ol (2.76 g, 9.31 mmol, 35.0% yield, 77.3% purity) as a white solid. LC-MS [M+3]: 231.0.

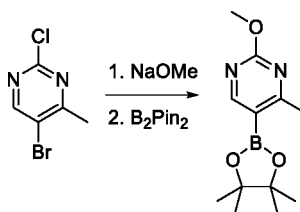
[000269] A mixture of 5-bromo-2-cyclopropyl-6-methyl-pyrimidin-4-ol (2.50 g, 8.44 mmol, 1.00 equiv) and dimethyl formamide (1.54 g, 21.1 mmol, 1.62 mL, 2.50 equiv) in toluene (36.9 mL) was added dropwise a solution of phosphorus oxychloride (1.57 g, 10.2 mmol, 951  $\mu$ L, 1.21 equiv) in toluene (9.20 mL) at 0 °C. The mixture was subsequently stirred at 25 °C for 3 h under a nitrogen atmosphere. The mixture was poured into sodium carbonate (1.00 M, 55.2 mL) and extracted with ethyl acetate (10.0 mL  $\times$  3). The combined organic phase was concentrated to afford compound 5-bromo-4-chloro-2-cyclopropyl-6-methyl-pyrimidine (2.31 g, 4.51 mmol, 53.5% yield, 48.4% purity) as a yellow oil. LC-MS [M+3]: 249.1.

[000270] A mixture of 5-bromo-4-chloro-2-cyclopropyl-6-methyl-pyrimidine (2.31 g, 9.33 mmol, 1.00 equiv), 4-methylbenzenesulfonohydrazide (5.91 g, 31.7 mmol, 3.40 equiv) in chloroform (4.30 mL) was stirred at 90 °C for 16 h under a nitrogen atmosphere. The solid was filtered and rinsed with dichloromethane (20.0 mL) to afford *N'*-(5-bromo-2-cyclopropyl-6-methyl-pyrimidin-4-yl)-4-methylbenzenesulfonohydrazide (1.60 g, 4.02 mmol, 43.1% yield, 99.8% purity) as a white solid. LC-MS [M+3]: 399.2. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 10.08 (br s, 1 H), 7.64 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 2.44 (br s, 3H), 2.37 (s, 3H), 2.05 - 1.83 (m, 1 H), 1.05 - 0.90 (m, 2H), 0.87-0.75 (m, 2H).

[000271] A mixture of *N'*-(5-bromo-2-cyclopropyl-6-methyl-pyrimidin-4-yl)-4-methylbenzenesulfonohydrazide (1.60 g, 4.02 mmol, 1.00 equiv) and aqueous sodium carbonate (0.57 M, 90.6 mL, 12.8 equiv) was stirred at 90 °C for 1 h under a nitrogen atmosphere. The mixture was diluted with ethyl acetate (50.0 mL) and the organic phase was separated and concentrated to afford 5-bromo-2-cyclopropyl-4-methyl-pyrimidine (620 mg, 2.59 mmol, 64.6% yield, 89.2% purity) as a brown oil. LC-MS [M+1]: 213.2. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 8.49 (s, 1H), 2.56 (s, 3H), 2.25 - 2.08 (m, 1H), 1.19 - 0.99 (m, 4H).

[000272] A mixture of 5-bromo-2-cyclopropyl-4-methyl-pyrimidine (580 mg, 2.43 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (863 mg, 3.40 mmol, 1.40 equiv), potassium acetate (715 mg, 7.28 mmol, 3.00 equiv), and Pd(dppf)Cl<sub>2</sub> (88.8 mg, 121 μmol, 0.05 equiv) in dioxane (5.00 mL) was purged with nitrogen and was subsequently stirred at 90 °C for 4 h under a nitrogen atmosphere. The residue was diluted with water (3.00 mL) and extracted with ethyl acetate (2.00 mL × 3). The combined organic layers were washed with brine (2.00 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate, 100/1 to 10/1) to afford 2-cyclopropyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (1.00 g, 1.92 mmol, 79.2% yield, 50.0% purity) as a yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 8.73 (s, 1H), 2.62 (s, 3H), 2.27 - 2.14 (m, 1H), 1.34 (s, 12H), 1.18 - 1.13 (m, 2H), 1.07 - 1.01 (m, 2H).

#### INTERMEDIATE D-4



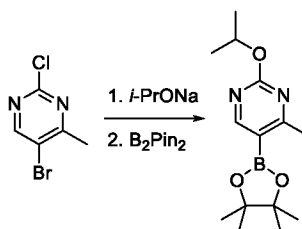
[000273] A fourth exemplary Intermediate D, Intermediate D-4, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with two R<sup>4</sup> substituents. A mixture of sodium (111 mg, 4.82 mmol, 1.00 equiv) in methanol (772 mg, 24.1 mmol, 975. μL, 5.00 equiv) was stirred at 25 °C for 0.5 h. To this solution was added 5-bromo-2-chloro-4-methyl-pyrimidine (1.00 g, 4.82 mmol, 1.00 equiv) and the mixture was stirred at 25 °C for 2 h. The reaction was quenched upon the addition of water (5 mL). The aqueous phase was extracted with ethyl acetate (10.0 mL × 3) and the combined organic phase was washed with brine (10.0 mL × 3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*

to afford 5-bromo-2-methoxy-4-methyl-pyrimidine (500 mg, 2.46 mmol, 51.1% yield) as a red oil.

LCMS: [M+1] 203.1.

[000274] To a solution of 5-bromo-2-methoxy-4-methyl-pyrimidine (500 mg, 2.46 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (813 mg, 3.20 mmol, 1.30 equiv) and potassium acetate (483 mg, 4.93 mmol, 2.00 equiv) in dioxane (5.00 mL) was added Pd(dppf)Cl<sub>2</sub> (180 mg, 246 μmol, 0.10 equiv) under nitrogen. The resultant mixture was stirred at 105 °C for 2 h. The mixture was concentrated *in vacuo* to give the crude material, which was purified by column chromatography (petroleum ether/ethyl acetate, 1/0 to 1:1) to afford 2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (150 mg, 539 μmol, 21.9% yield, 90.0% purity) as a red oil. <sup>1</sup>H NMR (400MHz, MeOD) δ = 8.69 (s, 1H), 4.03 (s, 3H), 2.65 (s, 3H), 1.38 (s, 12H).

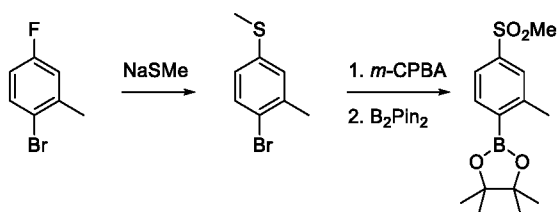
#### INTERMEDIATE D-5



[000275] A fifth exemplary Intermediate D, Intermediate D-5, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with two R<sup>4</sup> substituents. To a solution of isopropanol (869 mg, 14.5 mmol, 1.11 mL, 3.00 equiv) in THF (10.0 mL) was added portionwise NaH (578 mg, 14.5 mmol, 60.0 % purity, 3.00 equiv) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Subsequent to the addition of 5-bromo-2-chloro-4-methyl-pyrimidine (1.00 g, 4.82 mmol, 1.00 equiv) the mixture was allowed to stir at 25 °C for 3 h. The mixture was poured into water (20.00 mL) and the aqueous phase was extracted with ethyl acetate (20.0 mL × 3). The combined organic phase was washed with brine (20.0 mL × 3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to provide 5-bromo-2-isopropoxy-4-methyl- pyrimidine (600 mg, 2.60 mmol, 53.9 % yield) as a yellow oil.

[000276] To a solution of 5-bromo-2-isopropoxy-4-methyl-pyrimidine (300 mg, 1.30 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2- dioxaborolane (429 mg, 1.69 mmol, 1.30 equiv) and potassium acetate (255 mg, 2.60 mmol, 2.00 equiv) in dioxane (5.00 mL) was added Pd(dppf)Cl<sub>2</sub> (95.0 mg, 130 μmol, 0.10 equiv). The mixture was stirred at 105 °C for 2 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* to provide the crude material, which was purified by column chromatography (petroleum ether/ethyl acetate, 1/1 to dichloromethane: methanol, 10/1) to afford 2-isopropoxy-4-methyl-5-(4,4,5,5 -tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (60.0 mg, 216 μmol, 16.6% yield) as a white oil. LCMS: [M+1] 279.3.

#### INTERMEDIATE D-6

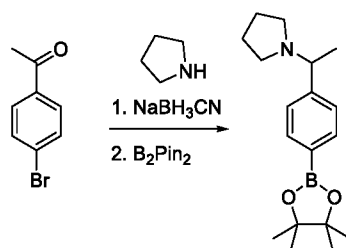


[000277] A sixth exemplary Intermediate D, Intermediate D-6, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is aryl substituted with two R<sup>4</sup> substituents. To a solution of 1-bromo-4-fluoro-2-methyl-benzene (1.00 g, 5.29 mmol, 1.00 equiv) in DMF (10.0 mL) was added NaSMe (869 mg, 5.29 mmol, 1.00 equiv). The mixture was stirred at 50 °C for 12 h. The reaction mixture was diluted with ethyl acetate (50.0 mL) and the organic layer was washed with brine (40.0 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-bromo-2-methyl-4-methylsulfanyl-benzene (900 mg, crude) as a light yellow oil. <sup>1</sup>H NMR (400MHz, MeOD) δ = 7.42 (d, *J*=8.4 Hz, 1H), 7.17 (d, *J*=2.0 Hz, 1H), 6.97 (dd, *J*=2.0, 8.4 Hz, 1H), 2.45 (s, 3H), 2.35 (s, 3H).

[000278] To a solution of 1-bromo-2-methyl-4-methylsulfanyl-benzene (900 mg, 4.15 mmol, 1.00 equiv) in DCM (9.00 mL) was added *m*-CPBA (1.43 g, 8.29 mmol, 2.00 equiv) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with DCM (20.0 mL), washed with satd aq potassium carbonate (20.0 mL × 3), brine (20.0 mL × 2), and the organic phase was concentrated under reduced pressure to give a residue. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate, 1 / 0 to 3 / 1) to afford 1-bromo-2-methyl-4-methylsulfonyl-benzene (370 mg, 1.41 mmol, 34.0% yield, 95.0% purity) as a white solid. <sup>1</sup>H NMR (400MHz, MeOD) δ = 7.87 (d, *J*=1.6 Hz, 1H), 7.82 (d, *J*=8.4 Hz, 1H), 7.66 (dd, *J*=2.0, 8.4 Hz, 1H), 3.12 (s, 3H), 2.50 (s, 3H).

[000279] A mixture of 1-bromo-2-methyl-4-methylsulfonyl-benzene (170 mg, 648 μmol, 1.00 equiv), potassium acetate (127 mg, 1.30 mmol, 2.00 equiv), Pd(dppf)Cl<sub>2</sub> (47.4 mg, 64.8 μmol, 0.100 equiv) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (247 mg, 972 μmol, 1.50 equiv) in dioxane (3.00 mL) was purged with nitrogen. The resultant reaction mixture was stirred at 105 °C for 1 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The crude material was purified by prep-TLC (petroleum ether / ethyl acetate, 5 / 1) to afford 4,4,5,5-tetramethyl-2-(2-methyl-4-methylsulfonyl-phenyl)-1,3,2-dioxaborolane (110 mg, 338 μmol, 52.1% yield, 90.9% purity) as a colorless oil. LCMS [M+1]: 296.9.

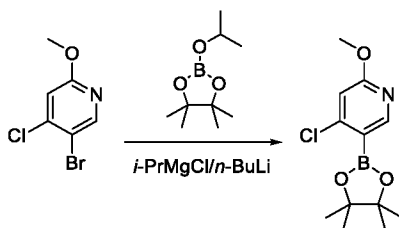
#### INTERMEDIATE D-7



[000280] A seventh exemplary Intermediate D, Intermediate D-7, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is aryl substituted with an R<sup>4</sup> substituent. To a solution of 1-(4-bromophenyl)ethanone (1.00 g, 5.02 mmol, 1.00 equiv), pyrrolidine (1.79 g, 25.1 mmol, 2.10 mL, 5.00 equiv) in methanol (16.0 mL) was added NaBH<sub>3</sub>CN (347 mg, 5.53 mmol, 1.10 equiv). The mixture was stirred at 20 °C for 24 h. To the mixture was added water (4.00 mL) and the aqueous phase was extracted with ethyl acetate (5.00 mL). The combined organic phase was washed with brine (2.00 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford 1-[1-(4-bromophenyl)ethyl]pyrrolidine (1.00 g, 3.93 mmol, 78.3% yield) as a yellow oil.

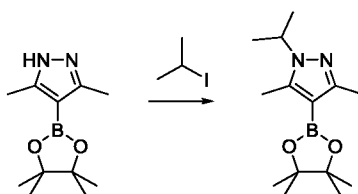
[000281] To a solution of 1-[1-(4-bromophenyl)ethyl]pyrrolidine (400 mg, 1.57 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (799 mg, 3.15 mmol, 2.00 equiv) and potassium acetate (308 mg, 3.15 mmol, 2.00 equiv) in dioxane (2.00 mL) was added Pd(dppf)Cl<sub>2</sub> (115 mg, 157 μmol, 0.100 equiv). The reaction mixture was stirred at 105 °C for 2 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* to give a residue. The crude material was purified by column chromatography (petroleum ether/ethyl acetate, 1/0 to 1/1) to afford 1-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl]pyrrolidine (110 mg) as a red oil.

#### INTERMEDIATE D-8



[000282] An eighth exemplary Intermediate D, Intermediate D-8, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with two R<sup>4</sup> substituents. To a solution of *n*-butyllithium (2.50 M, 1.80 mL, 1.00 equiv) was added dropwise over one min to *i*-PrMgCl (2.00 M, 1.12 mL, 0.500 equiv) in THF (12 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 5 min followed by the addition of 5-bromo-4-chloro-2-methoxy-pyridine (1.00 g, 4.50 mmol, 1.00 equiv) after which the mixture was stirred at 0 °C for 45 min. To this solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (836 mg, 4.50 mmol, 917 μL, 1.00 equiv) and the mixture stirred for an additional 15 min prior to stirring at 20 °C for 3 h. The reaction mixture was quenched by the addition of satd aq ammonium chloride (20.0 mL) at 20 °C and was extracted with ethyl acetate (20.0 mL × 3). The combined organic layers were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 4-chloro-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.00 g, 3.71 mmol, 82.5% yield) as a gray solid, which used for the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.47 (s, 1H), 6.77 (s, 1H), 3.97 (s, 3H), 1.38 (s, 12H).

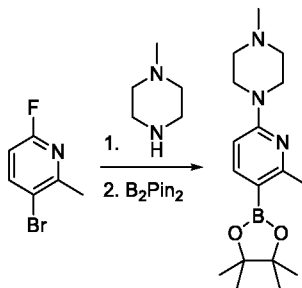
#### INTERMEDIATE D-9



[000283] A ninth exemplary Intermediate D, Intermediate D-9 may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with three R<sup>4</sup> substituents. A mixture of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg, 450 μmol, 1.00 equiv), isopropyl iodide (306 mg, 1.80 mmol, 180 μL, 4.00 equiv) and cesium carbonate (587 mg, 1.80 mmol, 4.00 equiv) in acetonitrile (3.00 mL) was purged with nitrogen and subsequently stirred at 65 °C for 4 h. The mixture was filtered and the solvent was removed *in vacuo* to afford 1-isopropyl-3,5-dimethyl-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (100 mg, 368  $\mu$ mol, 81.8% yield, 97.3% purity) as a green oil. LC-MS [M+1]: 265.

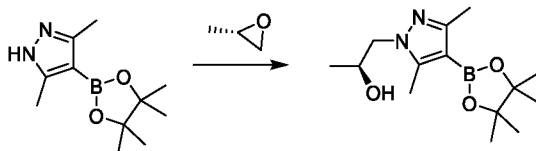
#### INTERMEDIATE D-10



[000284] A tenth exemplary Intermediate D, Intermediate D-10, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with two R<sup>4</sup> substituents. A mixture of 3-bromo-6-fluoro-2-methyl-pyridine (1.00 g, 5.26 mmol, 1.00 equiv) and *N*-methylpiperazine (685 mg, 6.84 mmol, 759  $\mu$ L, 1.30 equiv) was stirred at 110 °C for 12 h. The mixture was diluted with ethyl acetate (50.0 mL), washed with brine (20.0 mL  $\times$  3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to provide 1-(5-bromo-6-methyl-2-pyridyl)-4-methyl-piperazine (1.10 g, 4.07 mmol, 77.4% yield) as a yellow solid. LCMS [M+1]: 272.1.

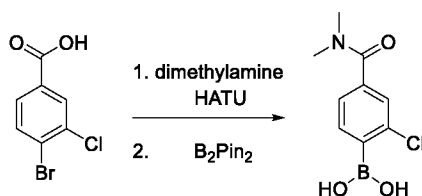
[000285] To a solution of 1-(5-bromo-6-methyl-2-pyridyl)-4-methyl-piperazine (400 mg, 1.48 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (752 mg, 2.96 mmol, 2.00 equiv) and potassium acetate (291 mg, 2.96 mmol, 2.00 equiv) in dioxane (2.00 mL) was added Pd(dppf)Cl<sub>2</sub> (108 mg, 148  $\mu$ mol, 0.100 equiv). The reaction was stirred at 105 °C for 2 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* to give a residue. The crude material was purified by prep-TLC (DCM/ MeOH = 10/1) to afford compound 1-methyl-4-(6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (210 mg, 662  $\mu$ mol, 44.7% yield) as a brown oil. LCMS [M+1]: 318.3.

#### INTERMEDIATE D-11



[000286] An eleventh exemplary Intermediate D, Intermediate D-11, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is heteroaryl substituted with three R<sup>4</sup> substituents. To a solution of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (100 mg, 450  $\mu$ mol, 1.00 equiv), (2*S*)-2-methyloxirane (392 mg, 6.75 mmol, 473  $\mu$ L, 15.0 equiv) was added cesium carbonate (29.3 mg, 90.1  $\mu$ mol, 0.20 equiv). The reaction mixture was stirred at 50 °C for 16 h and was subsequently concentrated under vacuum to give a residue. The crude residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether: ethyl acetate = 1:1) to afford (2*S*)-1-[3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]propan-2-ol (56.0 mg, 44.4% yield) as a yellow oil. LCMS [M + 1]: 281.3.

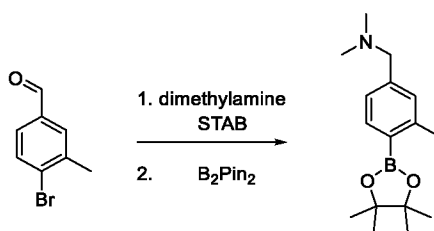
## INTERMEDIATE D-12



[000287] A twelfth exemplary Intermediate D, Intermediate D-12, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is aryl substituted with two R<sup>4</sup> substituents. To a solution of 4-bromo-3-chlorobenzoic acid (300 mg, 1.27 mmol, 1.00 equiv), DIEA (490 mg, 3.79 mmol, 660  $\mu$ L, 3.00 equiv) and *N,N*-dimethylamine (2.00 M in THF, 1.27 mL, 2.00 equiv) in DMF (3.00 mL) was added HATU (727 mg, 1.91 mmol, 1.50 equiv). The mixture was stirred at room temperature for 2 h and the reaction mixture was subsequently quenched upon the addition water (15.0 mL). The mixture was extracted with dichloromethane (20.0 mL  $\times$  3). The combined organic layer was washed with water (30.0 mL) and concentrated to provide the crude mixture. The resultant residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 5/1 to 2/1) to afford 4-bromo-3-chloro-*N,N*-dimethylbenzamide (430 mg, 983  $\mu$ mol, 77.0% yield, 60.0% purity) as a white solid. LCMS [M + 1]: 264.0. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.67 (d, *J*=8.2 Hz, 1H), 7.53 (d, *J*=1.6 Hz, 1H), 7.18 (dd, *J*=2.0, 8.4 Hz, 1H), 3.11 (s, 3H), 2.99 (s, 3H).

[000288] To a solution of 4-bromo-3-chloro-*N,N*-dimethylbenzamide (150 mg, 343  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (870 mg, 3.43 mmol, 10.0 equiv) and potassium acetate (67.0 mg, 683  $\mu$ mol, 2.00 equiv) in dioxane (10.0 mL) was added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (24.0 mg, 34.2  $\mu$ mol, 0.10 equiv). The vessel was flushed with nitrogen and the mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to rt and filtered through a pad of Celite. Purification by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 2/1) afforded [2-chloro-4-(dimethylcarbamoyl)phenyl]boronic acid (200 mg) as a yellow solid. LCMS [M + 1]: 228.0.

## INTERMEDIATE D-13

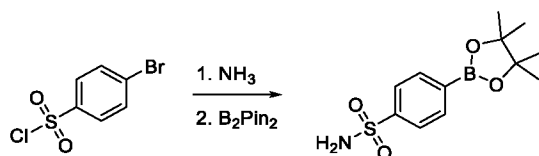


[000289] A thirteenth exemplary Intermediate D, Intermediate D-13, may be used to synthesize compounds of formula I, wherein R<sup>1</sup> is aryl substituted with two R<sup>4</sup> substituents. A mixture of 4-bromo-3-methylbenzaldehyde (500 mg, 2.51 mmol, 1.00 equiv) and *N,N*-dimethylamine (2 M in THF, 6.3 mL, 12.6 mmol, 5.00 equiv) in methanol (10.0 mL) was stirred at 40 °C for 30 min. Subsequently, sodium triacetoxymethylborohydride (1.60 g, 7.54 mmol, 3.00 equiv) was added and the mixture was stirred for another

3 h. The solution was concentrated under reduced pressure to give a residue. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 0/1 then dichloromethane/methanol = 20/1 to 10/1) to afford 1-(4-bromo-3-methyl-phenyl)-*N,N*-dimethyl-methanamine (570 mg) as a brown oil.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 7.61 (d,  $J$ =8.0 Hz, 1H), 7.38 (d,  $J$ =1.6 Hz, 1H), 7.16 (dd,  $J$ =1.6, 8.0 Hz, 1H), 3.96 (s, 2H), 2.63 (s, 6H), 2.42 (s, 3H).

[000290] A mixture of 1-(4-bromo-3-methyl-phenyl)-*N,N*-dimethyl-methanamine (470 mg, 2.06 mmol, 1.00 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (785 mg, 3.09 mmol, 1.50 equiv), potassium acetate (404 mg, 4.12 mmol, 2.00 equiv) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (151 mg, 206  $\mu\text{mol}$ , 0.100 equiv) in dioxane (8.00 mL) was purged with nitrogen and allowed to stir at 105 °C for 2 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (dichloromethane/methanol = 50/1 to 10/1) to afford *N,N*-dimethyl-1-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanamine (70.0 mg, 185  $\mu\text{mol}$ , 8.99% yield, 72.8% purity) as a brown oil. LCMS  $[\text{M}+1]$ : 275.6.

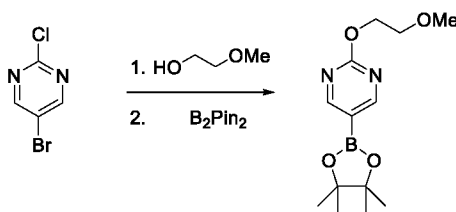
#### INTERMEDIATE D-14



[000291] A fourteenth exemplary Intermediate D, Intermediate D-14, may be used to synthesize compounds of formula I, wherein  $\text{R}^1$  is aryl substituted with one  $\text{R}^4$  substituent. To a solution of 4-bromobenzenesulfonyl chloride (200 mg, 783  $\mu\text{mol}$ , 1.00 equiv) in THF (2.00 mL) was added ammonia (7 N in MeOH, 224  $\mu\text{L}$ , 1.57 mmol, 2.00 equiv). The reaction mixture was stirred at 25 °C for 30 min. The mixture was concentrated in vacuo to provide a residue that was poured into water (10.0 mL). The aqueous phase was extracted with ethyl acetate (10.0 mL  $\times$  3) and the combined organic phase was washed with brine (3.00 mL  $\times$  3), dried with anhydrous sodium sulfate, filtered, and concentrated to give 4-bromobenzenesulfonamide (180 mg, 762  $\mu\text{mol}$ , 97.4% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.82 - 7.72 (m, 4H), 7.46 (s, 2H).

[000292] To a solution of 4-bromobenzenesulfonamide (100 mg, 424  $\mu\text{mol}$ , 1.00 equiv) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (129 mg, 508  $\mu\text{mol}$ , 1.20 equiv) in DMSO (2.00 mL) was added potassium acetate (83.1 mg, 847  $\mu\text{mol}$ , 2.00 equiv) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (31.0 mg, 42.4  $\mu\text{mol}$ , 0.10 equiv) under an atmosphere of nitrogen. The mixture was stirred at 80 °C for 3 h and was subsequently concentrated under vacuum to give a residue. The residue was poured into water (10.0 mL) and the aqueous phase was extracted with ethyl acetate (10.0 mL  $\times$  3). The combined organic phase was washed with brine (5.00 mL  $\times$  3), dried with anhydrous sodium sulfate, filtered, and concentrated to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (95.0 mg, 336  $\mu\text{mol}$ , 79.2% yield) as a red solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.96 - 7.88 (m, 4H), 7.26 (s, 2H), 1.35 (s, 12H).

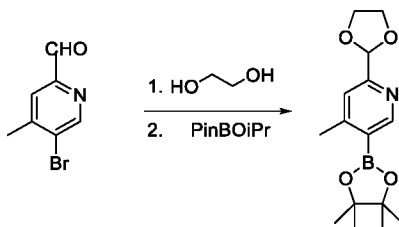
## INTERMEDIATE D-15



[000293] To a solution of 2-methoxyethanol (236 mg, 3.10 mmol, 245  $\mu$ L, 1.50 equiv) in tetrahydrofuran (2.00 mL) was added portionwise sodium hydride (99.3 mg, 60.0%, 2.48 mmol, 1.20 equiv) at 0 °C. The mixture was stirred at this temperature for 45 min followed by the dropwise addition of 5-bromo-2-chloropyrimidine (400 mg, 2.07 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for an additional 4 h. The mixture was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 10/1) to afford 5-bromo-2-(2-methoxyethoxy)pyrimidine (150 mg, 644  $\mu$ mol, 31.1% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.54 (s, 2H), 4.42 - 4.37 (m, 2H), 3.68 - 3.62 (m, 2H), 3.30 (s, 3H).

[000294] A mixture of 5-bromo-2-(2-methoxyethoxy)pyrimidine (150 mg, 644  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (327 mg, 1.29 mmol, 2.00 equiv), potassium acetate (126 mg, 1.29 mmol, 2.00 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (47.1 mg, 64.4  $\mu$ mol, 0.10 equiv) in dioxane (1.00 mL) was purged with nitrogen stirred at 100 °C for 2 h. The reaction was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1) to afford 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (130 mg, 464  $\mu$ mol, 72.1% yield) as a yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.83 - 8.79 (m, 2H), 4.61 - 4.54 (m, 2H), 3.82 - 3.76 (m, 2H), 3.44 (s, 3H), 1.36 (s, 12H).

## INTERMEDIATE D-16

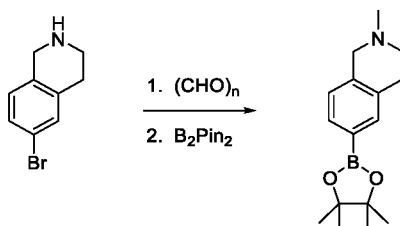


[000295] To a solution of ethylene glycol (310 mg, 5.00 mmol, 280  $\mu$ L, 2.00 equiv), 5-bromo-4-methylpyridine-2-carbaldehyde (500 mg, 2.50 mmol, 1.00 equiv) in toluene (20.0 mL) was added *p*-toluenesulfonic acid (47.6 mg, 250  $\mu$ mol, 0.10 equiv). The mixture was stirred at 110 °C for 12 h and was subsequently concentrated in vacuo to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 1/0 to 5/1) to afford 5-bromo-2-(1,3-dioxolan-2-yl)-4-methylpyridine (320 mg, 1.24 mmol, 49.6% yield) as a colorless oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.64 (s, 1H), 7.42 (s, 1H), 5.80 (s, 1H), 4.19 - 4.14 (m, 2H), 4.10 - 4.05 (m, 2H), 2.42 (s, 3H).

[000296] To a solution of 5-bromo-2-(1,3-dioxolan-2-yl)-4-methylpyridine (300 mg, 1.23 mmol, 1.00 equiv) in diethyl ether (20.0 mL) was added *n*-butyllithium (2.5 M, 737  $\mu$ L, 1.50 equiv) at -78 °C under a nitrogen atmosphere. The mixture was stirred at -78 °C for 0.5 h followed by the addition of 2-

isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (457 mg, 2.46 mmol, 501  $\mu$ L, 2.00 equiv). The mixture was warmed to 0 °C and stirred for an additional 1.5 h. The mixture was quenched with water (15.0 mL) and the resulting mixture was extracted with ethyl acetate (20.0 mL  $\times$  2). The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-(1,3-dioxolan-2-yl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (150 mg, crude) as a yellow oil. LCMS  $[M+1]$ : 292.15.

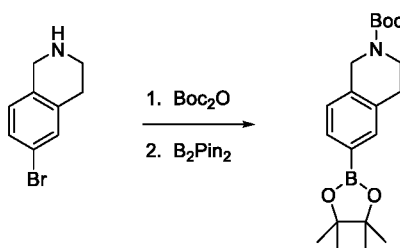
#### INTERMEDIATE D-17



[000297] A mixture of paraformaldehyde (350 mg, 3.63 mmol, 2.20 equiv) in methanol (1.00 mL) was stirred at 60 °C for 1 h and then cooled to 40 °C. To the mixture was added AcOH (1 drop) and 6-bromo-1,2,3,4-tetrahydroisoquinoline (350 mg, 1.65 mmol, 1.00 equiv) followed by NaCNBH<sub>3</sub> (114 mg, 1.82 mmol, 1.1 equiv). The mixture was stirred at 40 °C for 1 h and was subsequently filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 2/1) to afford 6-bromo-2-methyl-3,4-dihydro-1*H*-isoquinoline (360 mg, 1.59 mmol, 96.5% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  = 7.32 (s, 1H), 7.28 (dd,  $J$ =2.0, 8.4 Hz, 1H), 7.00 (d,  $J$ =8.0 Hz, 1H), 3.57 (s, 2H), 2.94 (t,  $J$ =6.0 Hz, 2H), 2.75 - 2.72 (m, 2H), 2.46 (s, 3H).

[000298] A mixture of 6-bromo-2-methyl-3,4-dihydro-1*H*-isoquinoline (220 mg, 973  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (494 mg, 1.95 mmol, 2.00 equiv), potassium acetate (191 mg, 1.95 mmol, 2.00 equiv), Pd(dppf)Cl<sub>2</sub> (71.2 mg, 97.3  $\mu$ mol, 0.10 equiv) in dioxane (3.00 mL) was purged with nitrogen and subsequently stirred at 100 °C for 2 h. The mixture was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 2/1) to afford 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinoline (150 mg, crude) as a white solid.

#### INTERMEDIATE D-18

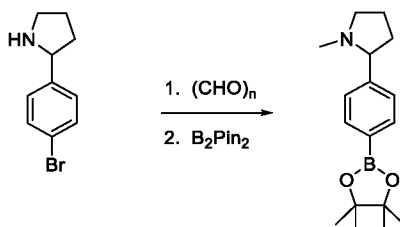


[000299] To a solution of 6-bromo-1,2,3,4-tetrahydroisoquinoline (400 mg, 1.89 mmol, 1.00 equiv) in tetrahydrofuran (2.00 mL) was added Boc<sub>2</sub>O (617 mg, 2.83 mmol, 1.50 equiv) and dimethylaminopyridine (46.1 mg, 377  $\mu$ mol, 0.20 equiv). The mixture was stirred at 25 °C for 3 h and was subsequently filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, Petroleum ether/Ethyl acetate = 20/1 to 3/1) to afford *tert*-butyl 6-bromo-

3,4-dihydro-1*H*-isoquinoline-2-carboxylate (150 mg, 480  $\mu$ mol, 25.5% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 7.38 - 7.32 (m, 2H), 7.07 (d,  $J$ =8.0 Hz, 1H), 4.52 (br s, 2H), 3.64 (br t,  $J$ =6.0 Hz, 2H), 2.84 (t,  $J$ =6.0 Hz, 2H), 1.51 (s, 9H).

**[000300]** A mixture of *tert*-butyl 6-bromo-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (140 mg, 448  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (228 mg, 897  $\mu$ mol, 2.00 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (32.8 mg, 44.8  $\mu$ mol, 0.10 equiv), potassium acetate (88.0 mg, 897  $\mu$ mol, 2.00 equiv) in dioxane (1.00 mL) was purged with nitrogen and subsequently stirred at 100  $^\circ\text{C}$  for 2 h. The mixture was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 2/1) to afford *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (100 mg, 278  $\mu$ mol, 62.1% yield) as a yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 7.58 - 7.54 (m, 2H), 7.13 (d,  $J$ =8.0 Hz, 1H), 4.58 (br s, 2H), 3.65 (br t,  $J$ =6.0 Hz, 2H), 2.84 (t,  $J$ =6.0 Hz, 2H), 1.35 (s, 12H), 1.19 (br s, 1H), 1.22 (s, 9H).

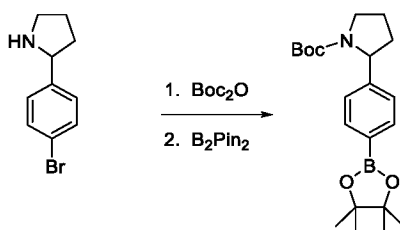
#### INTERMEDIATE D-19



**[000301]** A mixture of paraformaldehyde (133 mg, 4.42 mmol, 122  $\mu$ L, 10.0 equiv) and methyl alcohol (1.00 mL) was stirred at 60  $^\circ\text{C}$  for 1 h and then cooled to 0  $^\circ\text{C}$ . To the mixture was added acetic acid (52.5 mg, 874  $\mu$ mol, 0.05 mL, 1.98 equiv) and 2-(4-bromophenyl)pyrrolidine (100 mg, 442  $\mu$ mol, 1.00 equiv). The mixture was allowed to stir for 1 h at room temperature prior to the addition of sodium cyanoborohydride (83.4 mg, 1.33 mmol, 3.00 equiv) and an additional hour of stirring. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 3/1) to afford 2-(4-bromophenyl)-1-methyl-pyrrolidine (100 mg, 413  $\mu$ mol, 93.3% yield, 99.1% purity) as a white solid. LC-MS  $[\text{M}+1]$ : 240.1.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.48 - 7.41 (m, 2H), 7.26 - 7.21 (m, 2H), 3.33 - 3.14 (m, 1H), 3.02 (t,  $J$ =8.4 Hz, 1H), 2.29 (q,  $J$ =9.2 Hz, 1H), 2.16 (s, 3H), 2.06 - 1.89 (m, 1H), 1.86 - 1.77 (m, 1H), 1.76 - 1.69 (m, 2H).

**[000302]** A mixture of 2-(4-bromophenyl)-1-methyl-pyrrolidine (48.0 mg, 200  $\mu$ mol, 1.00 equiv), bis(pinacolato)diboron (76.1 mg, 300  $\mu$ mol, 1.50 equiv), potassium acetate (58.9 mg, 600  $\mu$ mol, 3.00 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (14.6 mg, 20.0  $\mu$ mol, 0.10 equiv) in dioxane (1.00 mL) was purged with nitrogen and then stirred at 90  $^\circ\text{C}$  for 2 h. The mixture was filtered and concentrated under reduced pressure to provide a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 3/1) to afford 1-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine (23.0 mg, 73.3  $\mu$ mol, 36.7% yield, 91.5% purity) as a white solid. LC-MS  $[\text{M}+1]$ : 288.0.

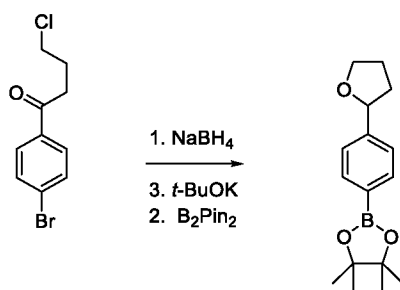
## INTERMEDIATE D-20



[000303] A mixture of 2-(4-bromophenyl)pyrrolidine (50.0 mg, 221  $\mu\text{mol}$ , 1.00 equiv), di-*tert*-butyl dicarbonate (57.9 mg, 265  $\mu\text{mol}$ , 1.20 equiv) and dimethylaminopyridine (2.70 mg, 22.1  $\mu\text{mol}$ , 0.10 equiv) in tetrahydrofuran (1.00 mL) was purged with nitrogen and then was stirred at 25 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The resultant residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 10/1) to afford *tert*-butyl 2-(4-bromophenyl)pyrrolidine-1-carboxylate (55.0 mg, 163  $\mu\text{mol}$ , 73.6% yield, 96.5% purity) as a yellow oil. LC-MS [M-55]: 272.1.

[000304] A mixture of *tert*-butyl 2-(4-bromophenyl)pyrrolidine-1-carboxylate (46.6 mg, 138  $\mu\text{mol}$ , 1.00 equiv), bis(pinacolato)diboron (52.5 mg, 207  $\mu\text{mol}$ , 1.50 equiv), potassium acetate (40.6 mg, 414  $\mu\text{mol}$ , 3.00 equiv) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (10.1 mg, 13.8  $\mu\text{mol}$ , 0.10 equiv) in dioxane (1.00 mL) was purged with nitrogen and then stirred at 90 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 5/1) to afford *tert*-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-1-carboxylate (45.0 mg, 102  $\mu\text{mol}$ , 74.3% yield, 85.0% purity) as a yellow solid. LC-MS [M-55]: 318.2.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.75 (br d,  $J$ =7.6 Hz, 2H), 7.17 (br d,  $J$ =7.6 Hz, 2H), 4.80 (br s, 1H), 3.63 (br s, 2H), 2.32 (br s, 1H), 1.98 - 1.75 (m, 3H), 1.58 (s, 9H), 1.35 (br s, 12H).

## INTERMEDIATE D-21



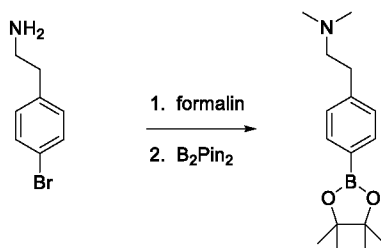
[000305] To a solution of a 1-(4-bromophenyl)-4-chloro-butan-1-one (1.00 g, 3.82 mmol, 1.00 equiv) in methanol (13.0 mL) was added portionwise  $\text{NaBH}_4$  (300 mg, 7.93 mmol, 2.07 equiv) at room temperature. The mixture was allowed to stir at room temperature for 2 h and was subsequently quenched by the addition of water (10.0 mL). The mixture was diluted with dichloromethane (20 mL) and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude product 1-(4-bromophenyl)-4-chloro-butan-1-ol (1.00 g, 3.79 mmol, 99.2% yield) as a light yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.49 (d,  $J$ =8.4 Hz, 2H), 7.24 (d,  $J$ =8.4 Hz, 2H), 4.71 (br t,  $J$ =6.0 Hz, 1H), 3.54 (s, 2H), 2.01 - 1.72 (m, 4H).

[000306] A solution of 1-(4-bromophenyl)-4-chloro-butan-1-ol (500 mg, 1.90 mmol, 1.00 equiv) and *t*-BuOK (1.0 M in THF, 1.90 mL, 1.00 equiv) was stirred for 2 h at room temperature. The reaction was

quenched with water and extracted with ether ( $2 \times 20.0$  mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide 2-(4-bromophenyl)tetrahydrofuran (420 mg, 1.85 mmol, 97.5% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.49 - 7.42 (m, 2H), 7.24 - 7.18 (m, 2H), 4.85 (t,  $J$ =7.2 Hz, 1H), 4.13 - 4.05 (m, 1H), 3.97 - 3.90 (m, 1H), 2.38 - 2.27 (m, 1H), 2.06 - 1.95 (m, 2H), 1.80 - 1.70 (m, 1H).

[000307] To a mixture of 2-(4-bromophenyl)tetrahydrofuran (150 mg, 661  $\mu\text{mol}$ , 1.00 equiv) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (252 mg, 992  $\mu\text{mol}$ , 1.50 equiv), potassium acetate (195 mg, 1.99 mmol, 3.01 equiv) in dioxane (5.00 mL) was added  $\text{Pd}(\text{dppf})\text{Cl}_2$  (48.3 mg, 66.0  $\mu\text{mol}$ , 0.10 equiv). The mixture was stirred at 105  $^\circ\text{C}$  for 1 h, cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated to give a residue that was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 2/1) to afford 4,4,5,5-tetramethyl-2-(4-tetrahydrofuran-2-ylphenyl)-1,3,2-dioxaborolane (240 mg, 639  $\mu\text{mol}$ , 96.8% yield, 73% purity) as a colorless oil. LCMS  $[\text{M}+1]$ : 275.1.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.78 (d,  $J$ =8.4 Hz, 2H), 7.34 (d,  $J$ =7.6 Hz, 2H), 4.92 (t,  $J$ =7.2 Hz, 1H), 4.17 - 4.06 (m, 1H), 4.00 - 3.90 (m, 1H), 2.41 - 2.27 (m, 1H), 2.09 - 1.91 (m, 2H), 1.85 - 1.73 (m, 1H), 1.35 (s, 12H).

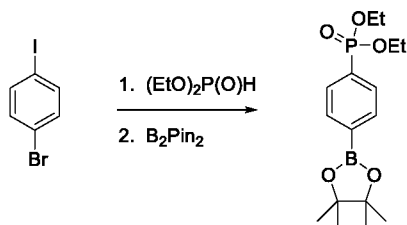
#### INTERMEDIATE D-22



[000308] To a cooled solution of 2-(4-bromophenyl)ethanamine (200 mg, 1.0 mmol, 155  $\mu\text{L}$ , 1.00 equiv) in formalin (300 mg, 9.99 mmol, 275  $\mu\text{L}$ , 10.0 equiv) was added  $\text{HCOOH}$  (5.00 mL) and the solution was stirred at 110  $^\circ\text{C}$  for 16 h under nitrogen. The reaction mixture was concentrated to give a residue. To the residue was added  $\text{HCl}$  (3 N, 1.00 mL) and the mixture was washed with ethyl acetate (310 mL). The aqueous phase was basified to pH = 14 with  $\text{NaOH}$  (10 N, 1.00 mL) and then extracted with ethyl acetate ( $3 \times 15.0$  mL). The combined organic phase was washed with brine ( $2 \times 15.0$  mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 2-(4-bromophenyl)-*N,N*-dimethylethanamine (200 mg, 877  $\mu\text{mol}$ , 87.7% yield) as a colorless oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.40 (d,  $J$ =8.4 Hz, 2H), 7.09 (d,  $J$ =8.4 Hz, 2H), 2.73 (d,  $J$ =8.4 Hz, 2H), 2.56 - 2.48 (m, 2H), 2.29 (s, 6H).

[000309] A mixture of 2-(4-bromophenyl)-*N,N*-dimethylethanamine (160 mg, 701  $\mu\text{mol}$ , 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (268mg, 1.06 mmol, 1.50 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (51.2 mg, 70.0  $\mu\text{mol}$ , 0.10 equiv), potassium acetate (206 mg, 2.10 mmol, 3.00 equiv) in dioxane (8.00 mL) was purged with nitrogen and was stirred at 100  $^\circ\text{C}$  for 1 h. The mixture was concentrated to give a residue that was purified by prep-TLC ( $\text{SiO}_2$ , dichloromethane/methanol = 10/1) to afford *N,N*-dimethyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanamine (350 mg, crude) as a black oil. LCMS  $[\text{M}+1]$ : 276.2.

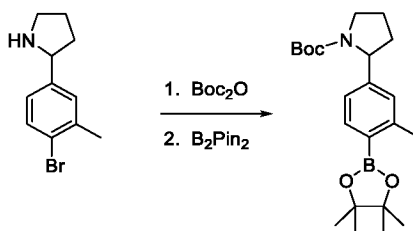
## INTERMEDIATE D-23



[000310] To a solution of 1-bromo-4-iodo-benzene (200 mg, 707  $\mu$ mol, 1.00 equiv), diethyl phosphite (97.6 mg, 707  $\mu$ mol, 91.2  $\mu$ L, 1.00 equiv) in tetrahydrofuran (2.00 mL) was added Pd(OAc)<sub>2</sub> (4.76 mg, 21.2  $\mu$ mol, 0.03 equiv), potassium acetate (9.02 mg, 91.9  $\mu$ mol, 0.13 equiv), DPPF (23.5 mg, 42.4  $\mu$ mol, 0.06 equiv) and triethylamine (107 mg, 1.06 mmol, 147  $\mu$ L, 1.50 equiv). The vessel was flushed with nitrogen and stirred at 68 °C for 1 h. The mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to afford 1-bromo-4-diethoxyphosphoryl -benzene (110 mg, 341  $\mu$ mol, 48.2% yield, 90.8% purity) as a red solid. LCMS [M+3]: 294.9. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.73 - 7.57 (m, 4H), 4.22 - 3.99 (m, 4H), 1.32 (t, *J*=7.2 Hz, 6H).

[000311] To a solution of 1-bromo-4-diethoxyphosphoryl-benzene (100 mg, 341  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1,3,2-dioxaborolane (104 mg, 409  $\mu$ mol, 1.20 equiv) in dioxane (2.00 mL) was added Pd(dppf)Cl<sub>2</sub> (24.9 mg, 34.1  $\mu$ mol, 0.10 equiv) and potassium acetate (67.0 mg, 682  $\mu$ mol, 2.00 equiv) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 2 h and was subsequently concentrated in vacuo to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to afford 2-(4-diethoxyphosphorylphenyl)-4,4,5,5- tetramethyl-1,3,2-dioxaborolane (55.0 mg, 162  $\mu$ mol, 47.4% yield) as a red oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.93 - 7.87 (m, 2H), 7.85 - 7.76 (m, 2H), 4.21 - 4.01 (m, 4H), 1.36 (s, 12H), 1.32 (t, *J*=7.2 Hz, 6H).

## INTERMEDIATE D-24

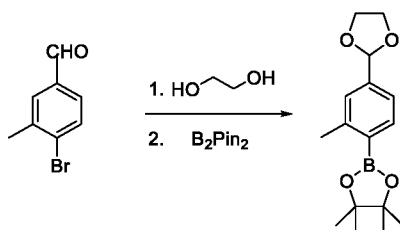


[000312] To a solution of 2-(4-bromo-3-methyl-phenyl)pyrrolidine (500 mg, 2.08 mmol, 1.00 equiv) in dichloromethane (5.00 mL) was added Boc<sub>2</sub>O (1.05 g, 4.79 mmol, 1.10 mL, 2.30 equiv) and dimethylaminopyridine (25.4 mg, 208  $\mu$ mol, 0.10 equiv). The mixture was stirred at 25 °C for 1 h and was subsequently filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate=30/1 to 20/1) to afford tert-butyl 2-(4-bromo-3-methyl-phenyl)pyrrolidine-1- carboxylate (600 mg, 84.7% yield) as a yellow oil. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 7.46 (br d, *J*=8.4 Hz, 1H), 7.10 (d, *J*=1.6 Hz, 1H), 6.92 (dd, *J*=1.6, 8.0 Hz,

1H), 4.73 (br s, 1H), 3.65 - 3.51 (m, 2H), 2.37 (s, 3H), 2.34 - 2.27 (m, 1H), 1.93 - 1.82 (m, 2H), 1.82 - 1.73 (m, 1H), 1.45 (br s, 3H), 1.24 - 1.13 (m, 6H).

**[000313]** A mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (268 mg, 1.06 mmol, 1.20 equiv), *tert*-butyl 2-(4-bromo-3-methyl-phenyl)pyrrolidine-1-carboxylate (300 mg, 882  $\mu$ mol, 1.00 equiv), Pd(dppf)Cl<sub>2</sub> (64.1 mg, 88.2  $\mu$ mol, 0.10 equiv) and potassium acetate (173 mg, 1.76 mmol, 2.00 equiv) in dioxane (3.00 mL) was purged with nitrogen and then the mixture was stirred at 100 °C for 1.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate=20/1 to 10/1) to afford *tert*-butyl 2-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-1-carboxylate (260 mg, 76.1% yield) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.68 (br d, *J*=7.6 Hz, 1H), 7.0 - 6.94 (m, 2H), 4.98 - 4.66 (m, 1H), 3.61 (br s, 2H), 2.52 (s, 3H), 2.36 (br s, 1H), 1.93 - 1.76 (m, 3H), 1.35 (br s, 12H), 1.29 - 1.25 (m 3H), 1.21 (br s, 6H).

#### INTERMEDIATE D-25

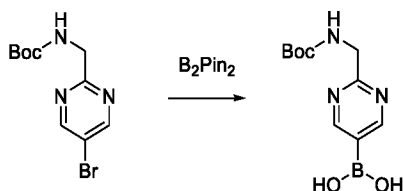


**[000314]** To a solution of 4-bromo-3-methyl-benzaldehyde (2.00 g, 10.1 mmol, 1.00 equiv) in toluene (100 mL) was added TsOH-H<sub>2</sub>O (191 mg, 1.00 mmol, 0.10 equiv) and ethylene glycol (1.25 g, 20.1 mmol, 1.12 mL, 2.00 equiv). The mixture was stirred at 130 °C for 12 h prior to cooling to room temperature. The pH was adjusted to 9 with DMAP and then concentrated in vacuo. The residue was purified by column chromatography (neutral Al<sub>2</sub>O<sub>3</sub>, petroleum ether/ethyl acetate = 1/0 to 100/1) to afford 2-(4-bromo-3-methyl-phenyl)-1,3-dioxolane (2.30 g, 9.46 mmol, 94.2% yield) as a yellow oil.

**[000315]** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.54 (d, *J*=8.4 Hz, 1H), 7.36 (d, *J*=1.6 Hz, 1H), 7.17 (dd, *J*=2.4, 8.0 Hz, 1H), 5.76 (s, 1H), 4.15 - 4.08 (m, 2H), 4.08 - 4.00 (m, 2H), 2.42 (s, 3H).

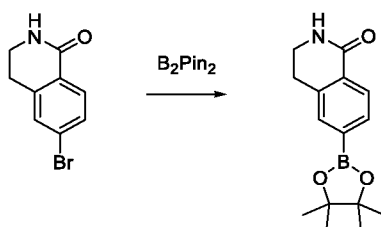
**[000316]** A mixture of 2-(4-bromo-3-methyl-phenyl)-1,3-dioxolane (2.50 g, 10.3 mmol, 1.00 equiv), Pin<sub>2</sub>B<sub>2</sub> (3.39 g, 13.4 mmol, 1.30 equiv), KOAc (2.02 g, 20.6 mmol, 2.00 equiv) and Pd(dppf)Cl<sub>2</sub> (376 mg, 514  $\mu$ mol, 0.05 equiv) in dioxane (30.0 mL) was purged with N<sub>2</sub> and then stirred at 100 °C for 6 h. The mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography (neutral Al<sub>2</sub>O<sub>3</sub>, petroleum ether/ethyl acetate = 1/0 to 50/1) to afford 2-[4-(1,3-dioxolan-2-yl)-2-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.60 g, 8.96 mmol, 87.1% yield) as a green oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.78 (d, *J*=7.6 Hz, 1H), 7.29 - 7.25 (m, 2H), 5.81 (s, 1H), 4.15 - 4.08 (m, 2H), 4.07 - 4.01 (m, 2H), 2.56 (s, 3H), 1.35 (s, 12H).

## INTERMEDIATE D-26



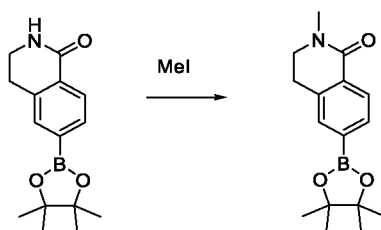
[000317] A mixture of *tert*-butyl *N*-[(5-bromopyrimidin-2-yl)methyl]carbamate (100 mg, 347  $\mu$ mol, 1.00 equiv), Pin<sub>2</sub>B<sub>2</sub> (176 mg, 694  $\mu$ mol, 2.00 equiv), KOAc (68.1 mg, 694  $\mu$ mol, 2.00 equiv) and Pd(dppf)Cl<sub>2</sub> (25.4 mg, 34.7  $\mu$ mol, 0.10 equiv) in dioxane (2.00 mL) was purged with N<sub>2</sub> and then stirred at 100 °C for 2 h. The reaction mixture was filtered and concentrated in vacuo to afford [2-[(*tert*-butoxycarbonylamino)methyl]pyrimidin-5-yl]boronic acid (100 mg, crude) as a red oil. LCMS [M-55]: 198.1.

## INTERMEDIATE D-27



[000318] A mixture of 6-bromo-3,4-dihydro-2H-isoquinolin-1-one (150 mg, 664  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (253 mg, 996  $\mu$ mol, 1.50 equiv), Pd(dppf)Cl<sub>2</sub> (48.55 mg, 66.35  $\mu$ mol, 0.10 equiv), potassium acetate (195 mg, 1.99 mmol, 3.00 equiv) in dioxane (5.00 mL) was purged with nitrogen and then stirred at 95 °C for 2 h. The reaction mixture was cooled and filtered through a pad of Celite and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 3/1 to 1/1) to afford 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (180 mg, 659  $\mu$ mol, 99.32% yield) as an off-white solid. LCMS [M+1]: 274.1. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  = 8.07 (d, *J*=8.0 Hz, 1H), 7.80 (d, *J*=7.6 Hz, 1H), 7.67 (s, 1H), 6.04 (s, 1H), 3.57 (dt, *J*=2.8, 6.4 Hz, 2H), 3.02 (t, *J*=6.4 Hz, 2H), 1.37 (s, 12H).

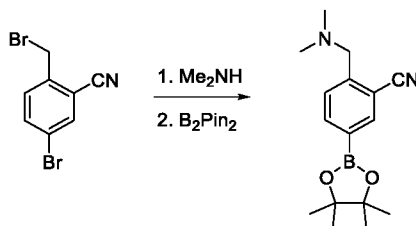
## INTERMEDIATE D-28



[000319] To a suspension of NaH (79.1 mg, 60%, 1.98 mmol, 2.00 equiv) in DMF (3.00 mL) at 0 °C was added dropwise a solution of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (270 mg, 989  $\mu$ mol, 1.00 equiv) in DMF. The mixture was stirred at this temperature for an additional 30 min prior to the dropwise addition of CH<sub>3</sub>I (1.40 g, 9.89 mmol, 615  $\mu$ L, 10.0 equiv) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was

quenched upon the addition of 20.0 mL of water followed by extraction with diethyl ether (3×30.0 mL). The combined organic layer was washed with water (50.0 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1-one (300 mg, crude) as a black oil. LCMS [M+1]: 288.1. <sup>1</sup>H NMR (400MHz, CHCl<sub>3</sub>-d) δ = 8.07 (d, *J*=7.6 Hz, 1H), 7.77 (d, *J*=7.6 Hz, 1H), 7.63 (s, 1H), 3.56 (t, *J*=6.8 Hz, 2H), 3.16 (s, 3H), 3.01 (t, *J*=6.8 Hz, 2H), 1.36 (s, 12H).

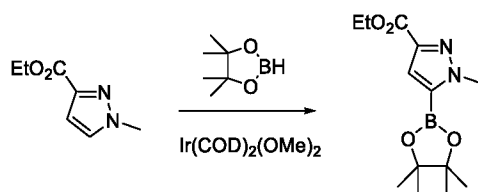
#### INTERMEDIATE D-29



[000320] A mixture of 5-bromo-2-(bromomethyl)benzonitrile (100 mg, 364 μmol, 1.00 equiv), diisopropylethylamine (141 mg, 1.09 mmol, 190 μL, 3.00 equiv) and dimethylamine (2.00 M, 1.82 mL, 10.0 equiv) in dimethyl formamide (2.00 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water 5.00 mL and extracted with ethyl acetate (5.00 mL × 3). The combined organic layer was washed with brine (3.00 mL × 3), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 3/1) to afford 5-bromo-2-[(dimethylamino)methyl]benzonitrile (50.0 mg, 209 μmol, 57.5% yield) as a yellow oil. LC-MS [M+1]: 239.2. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 7.77 (d, *J*=2.0 Hz, 1H), 7.69 (dd, *J*=2.0, 8.4 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 3.59 (s, 2H), 1.59 (br s, 6H).

[000321] A mixture of 5-bromo-2-[(dimethylamino)methyl]benzonitrile (30.0 mg, 125 μmol, 1.00 equiv), bis(pinacolato)diboron (63.7 mg, 251 μmol, 2.00 equiv), potassium acetate (36.9 mg, 376 μmol, 3.00 equiv) and Pd(dppf)Cl<sub>2</sub>.CH<sub>2</sub>Cl<sub>2</sub> (3.07 mg, 3.76 μmol, 0.03 equiv) in dioxane (1.00 mL) was purged with nitrogen and then stirred at 90 °C for 4 h. The mixture was filtered and concentrated under reduced pressure to give the crude product 2-[(dimethylamino)methyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (40.0 mg) as a black oil which was used in the next step without further purification.

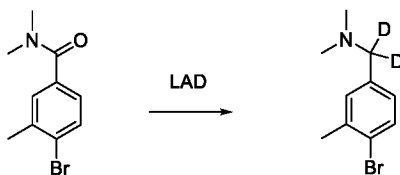
#### INTERMEDIATE D-30



[000322] To a solution of Ir(COD)<sub>2</sub>(OMe)<sub>2</sub> (5.00 mg, 7.54 μmol, 0.02 equiv) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (68.5 mg, 535 μmol, 77.7 μL, 1.50 equiv) in *n*-pentane (0.50 mL) was added 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (5.00 mg, 18.6 μmol, 0.05 equiv) and the mixture was stirred at 25 °C for 20 minutes. To this mixture was added a solution of methyl 1-methylpyrazole-3-carboxylate (50.0 mg, 357 μmol, 1.00 equiv) in *n*-pentane (0.50 mL) and THF (0.50 mL) and the mixture was stirred at 25 °C for 24 h. The mixture was partitioned between ethyl acetate (10.0 mL) and water (10.0 mL). The

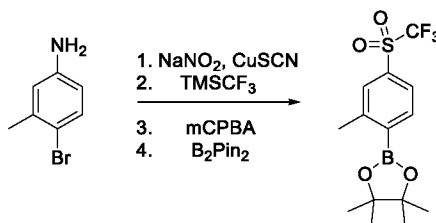
organic phase was dried over anhydrous sodium sulfate and concentrated to afford the crude product methyl 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-3-carboxylate (50.0 mg, 113  $\mu$ mol, 31.6% yield, 60.0% purity) as a black oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.28 (s, 1H), 4.15 (s, 3H), 3.93 (s, 3H), 1.35 (s, 12H).

#### INTERMEDIATE D-31



[000323] To a solution of 4-bromo-*N,N*,3-trimethylbenzamide (500 mg, 2.07 mmol, 1.00 equiv) in THF (5.00 mL) was added lithium tetradeuterioaluminumide (235 mg, 6.20 mmol, 3.00 equiv). The mixture was stirred at 0 °C for 1.5 h and subsequently was warmed to room temperature and allowed to stir for another hour. The reaction mixture was cooled to 0 °C and diluted with THF (10.0 mL). The reaction was quenched upon the dropwise addition of deuterium oxide (0.24 mL), 15% NaOD solution in deuterium oxide (0.24 mL) at 0 °C, and finally deuterium oxide (0.72 mL). The mixture was stirred at room temperature for 10 min, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , dichloromethane/methanol = 50/1 to 20/1) to afford 1-(4-bromo-3-methylphenyl)-1,1-dideuterio-*N,N*-dimethylmethanamine (220 mg, crude) as a brown oil. LCMS [ $\text{M}+1$ ]: 232.1.

#### INTERMEDIATE D-32



[000324] To a solution of 4-bromo-3-methyl-aniline (4.00 g, 21.5 mmol, 1.00 equiv) in concentrated sulfuric acid (40.0 mL) and water (40.0 mL) was added sodium nitrite (1.62 g, 23.4 mmol, 1.09 equiv) at 0 °C and the mixture was stirred for 90 min. Subsequently, potassium thiocyanate (2.82 g, 29.0 mmol, 2.82 mL, 1.35 equiv) in water (16.0 mL) and thiocyanatocopper (6.80 g, 55.9 mmol, 2.60 equiv) was then added to the suspension at 5 °C. After stirring at 5 °C for 2 h, the mixture was allowed to stir at room temperature for 10 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether) to afford (4-bromo-3-methyl-phenyl) thiocyanate (2.00 g, 8.77 mmol, 40.8% yield) as a yellow oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.52 (d,  $J$ =8.4 Hz, 1H), 7.33 (d,  $J$ =2.4 Hz, 1H), 7.14 (dd,  $J$ =2.4, 8.4 Hz, 1H), 2.36 (s, 3H).

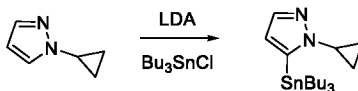
[000325] A mixture of (4-bromo-3-methyl-phenyl) thiocyanate (500 mg, 2.19 mmol, 1.00 equiv), trimethyl(trifluoromethyl)silane (1.00 g, 7.04 mmol, 3.21 equiv) and tetrabutylammonium fluoride (1.00 M, 701  $\mu$ L, 0.32 equiv) in tetrahydrofuran (1.00 mL) was stirred at room temperature for 4 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether) to afford 1-bromo-2-methyl-4-(trifluoromethylsulfanyl)benzene

(450 mg, 1.66 mmol, 75.7% yield) as a colorless oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.59 (d,  $J$ =8.0 Hz, 1H), 7.52 (d,  $J$ =2.0 Hz, 1H), 7.34 (dd,  $J$ =2.4, 8.0 Hz, 1H), 2.44 (s, 3H).

**[000326]** A mixture of 1-bromo-2-methyl-4-(trifluoromethylsulfonyl)benzene (450 mg, 1.66 mmol, 1.00 *equiv*) and *m*-chloroperbenzoic acid (2.02 g, 85.0%, 9.96 mmol, 6.00 *equiv*) in chloroform (10.0 mL) was stirred at room temperature for 2 h. The mixture was heated to 60 °C and allowed to stir for an additional 10 h. The mixture was diluted with saturated sodium bicarbonate (15.0 mL) and extracted with dichloromethane (5.00 mL  $\times$ 3). The combined organic phase was washed with sodium sulfite (5.00 mL), brine (5.00 mL), dried over sodium sulfate, filtered, and concentrated under pressure to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether) to afford 1-bromo-2-methyl-4-(trifluoromethylsulfonyl)benzene (400 mg, 1.32 mmol, 79.5% yield) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.88 (d,  $J$ =2.0 Hz, 1H), 7.86 (d,  $J$ =8.4 Hz 1H), 7.71 (dd,  $J$ =2.4, 8.4 Hz, 1H), 2.55 (s, 3H).

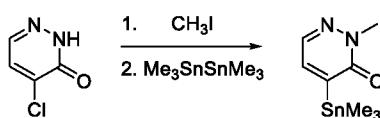
**[000327]** A mixture of 1-bromo-2-methyl-4-(trifluoromethylsulfonyl)benzene (100 mg, 330  $\mu\text{mol}$ , 1.00 *equiv*), bis(pinacolato)diboron (168 mg, 660  $\mu\text{mol}$ , 2.00 *equiv*), potassium acetate (97.1 mg, 990  $\mu\text{mol}$ , 3.00 *equiv*) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (24.1 mg, 33.0  $\mu\text{mol}$ , 0.10 *equiv*) in dioxane (2.00 mL) was purged with nitrogen and then stirred at 90 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to afford 4,4,5,5-tetramethyl-2-[2-methyl-4-(trifluoromethylsulfonyl)phenyl]-1,3,2-dioxaborolane (200 mg, crude) as a black solid that was used into the next step without further purification.

#### INTERMEDIATE D-33



**[000328]** To a solution of diisopropylamine (243 mg, 2.40 mmol, 339  $\mu\text{L}$ , 1.30 *equiv*) in THF (4.00 mL) was added dropwise *n*-BuLi (2.50 M, 961  $\mu\text{L}$ , 1.30 *equiv*) at -78 °C and then the reaction was stirred at -78 °C for 30 mins. 1-cyclopropylpyrazole (200 mg, 1.85 mmol, 1.00 *equiv*) was added and the reaction was stirred at -78°C for 1 h. Tributyl(chloro)stannane (602 mg, 1.85 mmol, 498  $\mu\text{L}$ , 1.00 *equiv*) was added drop-wise and the reaction was stirred at -78 °C for another 30 min. The reaction mixture was partitioned between ethyl acetate (5.00 mL) and saturated ammonium chloride (5.00 mL). The organic phase was separated, washed with brine (5.00 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give tributyl-(2-cyclopropylpyrazol-3-yl)stannane (1.00 g, crude) as a colorless oil which used for the next step without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.51 (d,  $J$ =1.6 Hz, 1H), 6.32 (d,  $J$ =1.6 Hz, 1H), 3.54 - 3.49 (m, 1H), 1.61 - 1.50 (m, 6H), 1.37 - 1.31 (m, 6H), 1.21 - 1.13 (m, 6H), 0.97 - 0.89 (m, 13H).

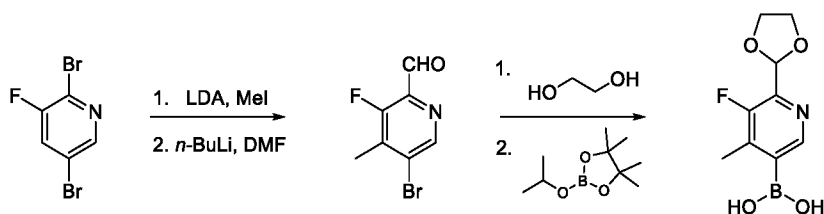
#### INTERMEDIATE D-34



**[000329]** To a solution of 4-chloropyridazin-3-ol (300 mg, 2.30 mmol, 1.00 *equiv*) and methyl iodide (3.26 g, 23.0 mmol, 1.43 mL, 10.0 *equiv*) in dioxane (6.00 mL) was added silver oxide (533 mg, 2.30 mmol, 1.00 *equiv*). The mixture was stirred at 60 °C for 5 h. The mixture was filtered and concentrated in vacuo to provide a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether / ethyl acetate = 1/1) to afford 4-chloro-2-methyl-pyridazin-3-one (110 mg, 761 μmol, 33.1% yield) as a yellow solid. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 7.87 (d, *J*=4.4 Hz, 1H), 7.78 (d, *J*=4.4 Hz, 1H), 3.72 (s, 3H).

**[000330]** To a solution of 4-chloro-2-methyl-pyridazin-3-one (110 mg, 761 μmol, 1.00 *equiv*) and hexamethylditin (998 mg, 3.04 mmol, 631 μL, 4.00 *equiv*) in dioxane (2.00 mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (87.93 mg, 76.09 μmol, 0.10 *equiv*) under nitrogen. The mixture was stirred at 110 °C for 2 h and was subsequently filtered and concentrated in vacuo. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether / ethyl acetate = 1/1) to afford 2-methyl-4-trimethylstannyl-pyridazin-3-one (130 mg, 476 μmol, 62.6% yield) as a white solid. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD) δ = 7.79 (d, *J*=3.6 Hz, 1H), 7.51 (d, *J*=3.6 Hz, 1H), 3.73 (s, 3H), 0.32 (s, 9H).

### INTERMEDIATE D-35



**[000331]** To a solution of 2,5-dibromo-3-fluoro-pyridine (0.50 g, 1.96 mmol, 1.00 *equiv*) in THF (10.0 mL) was added *n*-BuLi (2.50 M, 1.18 mL, 1.50 *equiv*) dropwise at -65 °C. The mixture was stirred at -65 °C for 0.5 h followed by the addition of *N*-isopropylpropan-2-amine (397 mg, 3.92 mmol, 554 μL, 2.00 *equiv*) one portion and stirring at this temperature for an additional 30 min. To this mixture was added methyl iodide (334 mg, 2.35 mmol, 147 μL, 1.20 *equiv*) and the mixture was allowed to stir at -65 °C for 1 h. The reaction mixture was quenched by the addition of satd aq NH<sub>4</sub>Cl (10.0 mL) and the resulting mixture was extracted with ethyl acetate (20.0 mL × 3). The combined organic phase was washed with brine (30.0 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude residue. The residue was purified by prep-HPLC (acidic conditions) to afford 2,5-dibromo-3-fluoro-4-methyl-pyridine (300 mg, 1.12 mmol, 56.9% yield) as a yellow solid. LCMS [M+1]: 269.7.

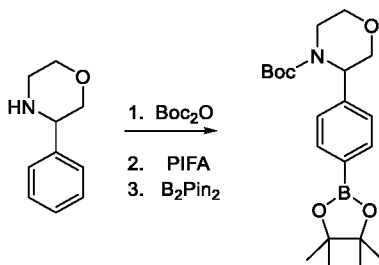
**[000332]** To a solution of 2,5-dibromo-3-fluoro-4-methyl-pyridine (0.80 g, 2.97 mmol, 1.00 *equiv*) in THF (10.0 mL) was added *n*-BuLi (2.5 M, 1.19 mL, 1.00 *equiv*) at -65 °C and the resultant mixture was stirred for 0.5 h followed by the dropwise addition of DMF (326 mg, 4.46 mmol, 343 μL, 1.50 *equiv*). After an additional 30 min of stirring at -65 °C the reaction mixture was quenched with satd aq NH<sub>4</sub>Cl (5.00 mL) and the resulting mixture was extracted with ethyl acetate (30.0 mL × 2). The combined organic phase was washed with brine (30.0 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/0 to 100/1) to afford 5-bromo-3-fluoro-4-methyl-pyridine-2-carbaldehyde (300 mg, 1.38 mmol, 46.3% yield) as a yellow solid.

[000333] <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 10.20 (d, *J*=0.8 Hz, 1H), 8.69 (s, 1H), 2.48 (d, *J*=2.4 Hz, 3H).

[000334] To a solution of 5-bromo-3-fluoro-4-methyl-pyridine-2-carbaldehyde (300 mg, 1.38 mmol, 1.00 equiv) in Tol. (10.0 mL) was added TsOH·H<sub>2</sub>O (26.2 mg, 138 μmol, 0.10 equiv) and ethylene glycol (171 mg, 2.75 mmol, 14 μL, 2.00 equiv). The mixture was stirred at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure to provide a crude residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/0 to 100/1) to afford 5-bromo-2-(1,3-dioxolan-2-yl)-3-fluoro-4-methyl-pyridine (250 mg, 954 μmol, 69.3% yield) as a colorless oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ = 8.49 (s, 1H), 6.13 (s, 1H), 4.32 - 4.20 (m, 2H), 4.14 - 4.04 (m, 2H), 2.39 (d, *J*=2.4 Hz, 3H).

[000335] To a solution of 5-bromo-2-(1,3-dioxolan-2-yl)-3-fluoro-4-methyl-pyridine (450 mg, 1.72 mmol, 1.00 equiv) in Et<sub>2</sub>O (10.0 mL) was added dropwise *n*-BuLi (2.5 M, 756 μL, 1.10 equiv) at -70 °C. The mixture was stirred for 0.5 h at -70 °C and subsequently 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (639 mg, 3.43 mmol, 701 μL, 2.00 equiv) was added. The mixture was stirred at -70 °C for 1 h and was quenched with satd aq NH<sub>4</sub>Cl (10 mL). The mixture was extracted with DCM (30 mL × 3) and the combined organic phase was washed with brine (50.0 mL × 2), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude solid. The crude material was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to afford [6-(1,3-dioxolan-2-yl)-5-fluoro-4-methyl-3-pyridyl]boronic acid (220 mg, 940 μmol, 54.8% yield, 97.0% purity) as a light yellow oil. LCMS [M+1]: 228.0.

#### INTERMEDIATE D-36



[000336] To a solution of 3-phenylmorpholine (500 mg, 3.06 mmol, 1.00 equiv) in tetrahydrofuran (5.00 mL) was added triethylamine (512 μL, 3.68 mmol, 1.20 equiv) and di-*tert*-butyl dicarbonate (669 mg, 3.06 mmol, 704 μL, 1.00 *eq.*). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to give a residue (1.30 g, crude) that was used in the next step directly.

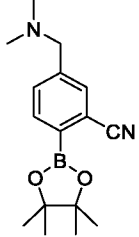
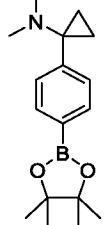
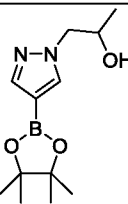
[000337] To a solution of *tert*-butyl 3-phenylmorpholine-4-carboxylate (580 mg, 2.20 mmol, 1.00 equiv) in dichloromethane (6.00 mL) was added phenyl-λ<sup>3</sup>-iodanediyl bis(2,2,2-trifluoroacetate) (1.04 g, 2.42 mmol, 1.10 equiv) and iodine (559 mg, 2.20 mmol, 444 μL, 1.00 equiv). The reaction mixture was stirred at 20 °C for 2 h. The mixture was diluted with sodium bicarbonate solution (20.0 mL) and extracted with dichloromethane (10.0 mL × 3). The combined organic layer was washed with saturated sodium thiosulfate solution (20.0 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate=1/0 to 10/1) to afford *tert*-butyl 3-(4-iodophenyl)morpholine-4-carboxylate (260 mg, 668 μmol, 30.3% yield) as a white oil. <sup>1</sup>H NMR

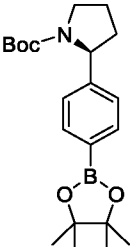
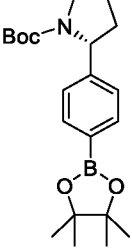
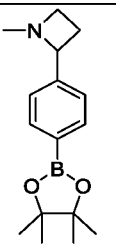
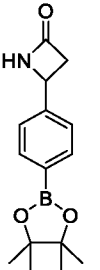
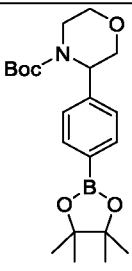
(400MHz, DMSO- $d_6$ )  $\delta$  = 7.73 (br d,  $J$ =8.4 Hz, 2H), 7.16 (br d,  $J$ =8.0 Hz, 2H), 4.92 (br s, 1H), 4.20 (br d,  $J$ =12.0 Hz, 1H), 3.84 - 3.78 (m, 1H), 3.76 - 3.65 (m, 2H), 3.50 - 3.40 (m, 1H), 3.04 - 2.93 (m, 1H), 1.39 (s, 9H).

[000338] A mixture of *tert*-butyl 3-(4-iodophenyl)morpholine-4-carboxylate (260 mg, 668  $\mu$ mol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (254 mg, 1.00 mmol, 1.50 equiv), potassium acetate (131 mg, 1.34 mmol, 2.00 equiv) and Pd(dppf)Cl<sub>2</sub> (48.9 mg, 66.8  $\mu$ mol, 0.10 equiv) in dioxane (2.00 mL) was purged with and subsequently stirred at 100 °C for 2 h under a nitrogen atmosphere. The mixture was filtered and concentrated at reduced pressure to give a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate=1/0 to 10/1) to afford *tert*-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]morpholine-4-carboxylate (100 mg, 257  $\mu$ mol, 38.5% yield) as white oil. <sup>1</sup>H NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 7.67 (d,  $J$ =8.0 Hz, 2H), 7.37 (d,  $J$ =7.6 Hz, 2H), 4.98 (br s, 1H), 4.29 - 4.23 (m, 1H), 3.86 - 3.66 (m, 3H), 3.51 - 3.42 (m, 1H), 3.07 - 2.96 (m, 1H), 1.41 - 1.38 (m, 9H), 1.30 (s, 12H).

### INTERMEDIATES D-37 – D-38

#### Characterization of Intermediates D36 – D38

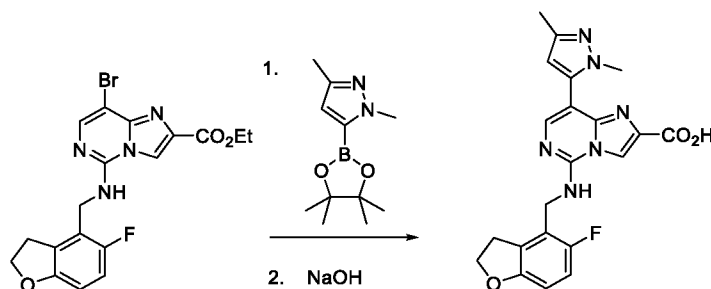
| Int. # | Structure                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                    |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| D-37   |  <p>5-((dimethylamino)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile</p>      | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) $\delta$ = 10.03 (s, 1H), 8.41 (s, 1H), 8.16 - 8.10 (m, 2H).                                                                                                          |
| D-38   |  <p>N,N-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropan-1-amine</p> | <sup>1</sup> H NMR (400MHz, DMSO- $d_6$ ) $\delta$ = 7.64 (d, $J$ =8.4 Hz, 2H), 7.27 (d, $J$ =7.6 Hz, 2H), 3.92 (s, 2H), 2.11 (s, 6H), 1.29 (s, 12H), 0.88 - 0.79 (m, 2H), 0.76 - 0.67 (m, 2H).<br>LCMS [M+1]: 288.2. |
| D-39   |  <p>1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol</p>            | <sup>1</sup> H NMR (400MHz, methanol- $d_4$ ) $\delta$ = 7.84 (s, 1H), 7.68 (s, 1H), 4.16 - 4.04 (m, 3H), 1.31 (s, 12H), 1.16 - 1.12 (m, 3H).<br>LCMS [M+1]: 253.3.                                                   |

| Int. # | Structure                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                     |
|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| D-40   |  <p><i>tert</i>-butyl (S)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate</p> | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ = 7.74 (br d, <i>J</i> =7.6 Hz, 2H), 7.17 (br d, <i>J</i> =7.6 Hz, 2H), 4.79 (br s, 1H), 3.63 (br s, 2H), 2.31 (br s, 1H), 1.94 - 1.73 (m, 3H), 1.35 (s, 12H), 1.19 (s, 9H).                                         |
| D-41   |  <p><i>tert</i>-butyl (R)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate</p> | LCMS [M-55]: 318.2.                                                                                                                                                                                                                                                    |
| D-42   |  <p>1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine</p>                             | LCMS [M+1]: 274.1.                                                                                                                                                                                                                                                     |
| D-43   |  <p>4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidin-2-one</p>                                | LCMS [M+1]: 274.1.                                                                                                                                                                                                                                                     |
| D-44   |  <p><i>tert</i>-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine-4-carboxylate</p>    | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 7.67 (d, <i>J</i> =8.0 Hz, 2H), 7.37 (d, <i>J</i> =7.6 Hz, 2H), 4.98 (br s, 1H), 4.29 - 4.23 (m, 1H), 3.86 - 3.66 (m, 3H), 3.51 - 3.42 (m, 1H), 3.07 - 2.96 (m, 1H), 1.41 - 1.38 (m, 9H), 1.30 (s, 12H). |

[000339] The following Examples are intended to illustrate further certain embodiments of the disclosure and are not intended to limit the scope of the disclosure.

## EXAMPLE 1

## 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid

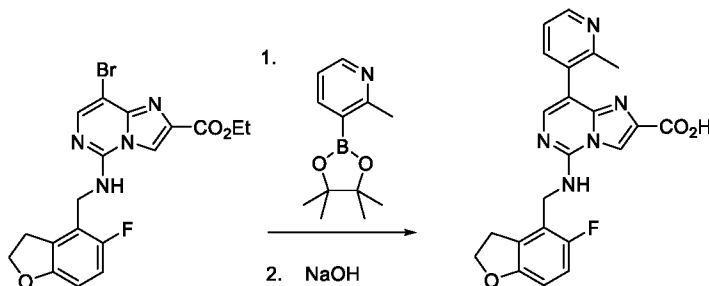


[000340] A mixture of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (0.100 g, 230  $\mu\text{mol}$ , 1.00 equiv), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (81.6 mg, 368  $\mu\text{mol}$ , 1.60 equiv), sodium bicarbonate (77.2 mg, 919  $\mu\text{mol}$ , 4.00 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (16.8 mg, 23.0  $\mu\text{mol}$ , 0.100 equiv) in dioxane (2.10 mL) and water (0.700 mL) was purged with nitrogen three times. Subsequently, the mixture was stirred at 105  $^{\circ}\text{C}$  for 1 h under a nitrogen atmosphere. The reaction mixture was filtered and concentrated *in vacuo*. The crude material was purified by prep-TLC ( $\text{SiO}_2$ , PE: EA = 2:3) to afford ethyl 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (60.0 mg, 47.9 % yield, 82.6 % purity) as an orange solid. LC-MS:  $[\text{M}+1]$  450.9.

[000341] To a solution of ethyl 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (55.0 mg, 101  $\mu\text{mol}$ , 1.00 equiv) in methanol (2.00 mL) was added aq sodium hydroxide (1.00 M, 303  $\mu\text{L}$ , 3.00 equiv). The resultant mixture was stirred at 60  $^{\circ}\text{C}$  for 0.5 h. The mixture was filtered and the majority of the methanol was removed *in vacuo*. The residue was adjusted to pH 4 with 2.00 M aq hydrochloric acid and the precipitate was filtered and dried under vacuum. The crude product was rinsed with methanol (2.00 mL) and dried under vacuum to afford 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (19.7 mg, 44.2% yield, 95.5% purity) as a yellow solid. LC-MS:  $[\text{M}+1]$  423.0.  $^1\text{H}$  NMR (400MHz, MeOD)  $\delta$  = 8.63 (s, 1H), 7.80 (s, 1H), 6.92 - 6.82 (m, 1H), 6.65 (dd,  $J$ =4.0, 8.8 Hz, 1H), 6.27 (s, 1H), 4.83 (s, 2H), 4.59 (t,  $J$ =8.8 Hz, 2H), 3.75 (s, 3H), 3.39 (t,  $J$ =8.8 Hz, 2H), 2.28 (s, 3H).

## EXAMPLE 2

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid

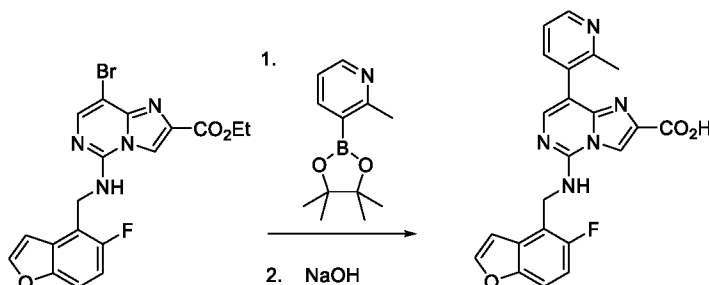


[000342] To a solution of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (50.0 mg, 115  $\mu$ mol, 1.00 equiv), 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (37.8 mg, 172  $\mu$ mol, 1.50 equiv) in dioxane (3.00 mL) was added water (1.00 mL) followed by Pd(dppf)Cl<sub>2</sub> (8.41 mg, 11.5  $\mu$ mol, 0.100 equiv) and sodium bicarbonate (29.0 mg, 345  $\mu$ mol, 3.00 equiv). The reaction mixture was stirred at 105 °C for 1 h under nitrogen. The mixture was cooled to 25 °C and filtered. The filtrate was concentrated *in vacuo* to provide a residue. The crude material was purified by prep-TLC (dichloromethane/methanol = 10/1) to afford ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (40.0 mg, 75.0% yield, 96.4% purity) as a brown solid.

[000343] To a solution of ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (40.0 mg, 86.2  $\mu$ mol, 1.00 equiv) in methanol (4.00 mL) and water (1.00 mL) was added sodium hydroxide (10.3 mg, 258  $\mu$ mol, 3.00 equiv). The reaction mixture was stirred at 55 °C for 20 min. The mixture was concentrated *in vacuo* to remove the majority of the methanol and the pH was adjusted to ~6 with aq hydrochloric acid (1.00 M, 0.500 mL). The resultant suspension was filtered and the filter cake was dried under vacuum to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (18.1 mg, 48.0% yield, 95.7% purity) as a white solid. LCMS: [M+1] 420.2. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.74 (dd, *J*=1.2, 6.0 Hz, 1H), 8.68 (s, 1H), 8.50 (dd, *J*=1.2, 7.6 Hz, 1H), 7.93 (dd, *J*=6.4, 8.0 Hz, 1H), 7.88 (s, 1H), 6.91 - 6.83 (m, 1H), 6.66 (dd, *J*=4.0, 8.8 Hz, 1H), 4.86 (s, 2H), 4.60 (t, *J*=8.8 Hz, 2H), 3.43 (t, *J*=8.8 Hz, 2H), 2.68 (s, 3H).

## EXAMPLE 3

## 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid

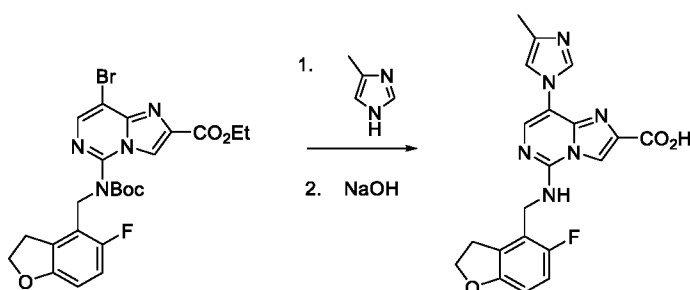


[000344] A mixture of ethyl 8-bromo-5-(((5-fluorobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (120 mg, 274  $\mu$ mol, 1.00 equiv), 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (120 mg, 548  $\mu$ mol, 2.00 equiv), sodium bicarbonate (69.0 mg, 822  $\mu$ mol, 32.0  $\mu$ L, 3.00 equiv) and Pd(dppf)Cl<sub>2</sub> (22.4 mg, 27.4  $\mu$ mol, 0.100 equiv) in dioxane (3.00 mL) and water (0.600 mL) was purged with nitrogen and stirred at 105 °C for 1 h under a nitrogen atmosphere. The mixture was concentrated at reduced pressure to give a residue. The crude material was purified by prep-TLC (DCM / Methyl alcohol = 20 / 1) to afford ethyl 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (100 mg, 78.9% yield, 96.3% purity) as a brown solid. LCMS [M+1]: 446.2.

[000345] To a solution of ethyl 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (100 mg, 216  $\mu$ mol, 1.00 equiv) in methyl alcohol (4.00 mL) and water (1.00 mL) was added sodium hydroxide (17.3 mg, 432  $\mu$ mol, 2.00 equiv). The resultant mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated at reduced pressure, water (2 mL) was added, and the pH was adjusted to 5 with aq hydrochloric acid (1.00 M). The precipitate was filtered to provide the crude material (80 mg) as a brown solid. The crude material was purified by prep-HPLC (column: Phenomenex Synergi C18 150×25×10  $\mu$ m; mobile phase: [water (0.1 %TFA) - ACN]; B%: 12% - 42%, 10 min) to afford 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (10.0 mg, 99.7 % purity) as a gray solid. LCMS [M+1]: 418.1. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.74 (dd, *J*=1.6, 5.6 Hz, 1H), 8.64 (s, 1H), 8.56 (dd, *J*=1.6, 8.0 Hz, 1H), 7.97 (dd, *J*=6.0, 7.6 Hz, 1H), 7.89 (s, 1H), 7.82 (d, *J*=2.4 Hz, 1H), 7.47 (dd, *J*=3.6, 8.8 Hz, 1H), 7.15 - 7.08 (m, 2H), 5.13 (s, 2H), 2.67 (s, 3H).

#### EXAMPLE 4

##### 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid



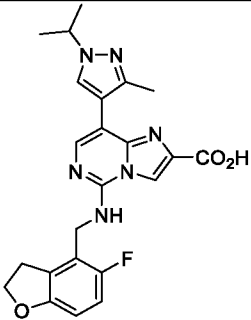
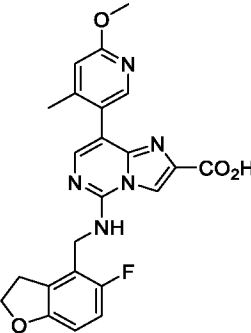
[000346] A mixture of 4-methyl-1H-imidazole (102 mg, 1.24 mmol, 4.40 equiv), ethyl 8-bromo-5-[[tert-butoxycarbonyl-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl]amino]imidazo[1,2-c]pyrimidine-2-carboxylate (160 mg, 282  $\mu$ mol, 1.00 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (25.9 mg, 28.2  $\mu$ mol, 0.10 equiv), ditert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (27.2 mg, 56.5  $\mu$ mol, 0.20 equiv) and potassium phosphate (155 mg, 734  $\mu$ mol, 2.60 equiv) in dioxane (5.00 mL) was purged with nitrogen. The resultant mixture was stirred at 120 °C for 2 h under a nitrogen atmosphere. The mixture was diluted with ethyl acetate (3 mL) and extracted with ethyl acetate (2.00 mL × 3). The combined organic layers were washed with brine (2.00 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated

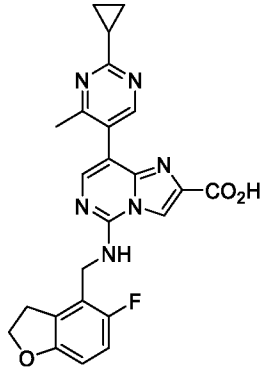
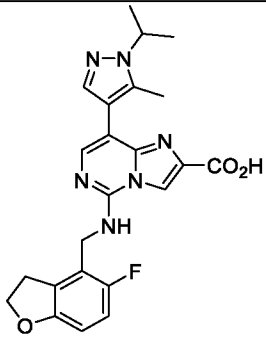
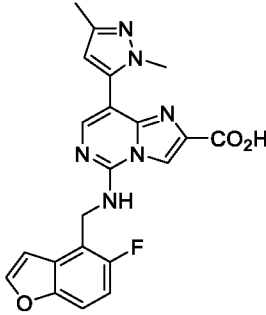
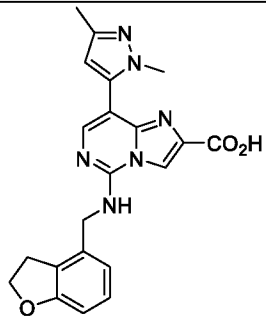
under reduced pressure to afford ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (120 mg, crude) as a yellow oil.

[000347] A mixture of ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (120 mg, 275  $\mu$ mol, 1.00 equiv), sodium hydroxide (33.0 mg, 825  $\mu$ mol, 3.00 equiv) in methyl alcohol (3.00 mL) and water (1.00 mL) was purged with nitrogen. The mixture was stirred at 60 °C for 1 h. The residue was diluted with ethyl acetate (3.00 mL) and extracted with ethyl acetate (2.00 mL  $\times$  3). The combined organic layers were washed with brine (2.00 mL  $\times$  3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide a residue. The crude material was purified by prep-HPLC (basic conditions) to give 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (37.1 mg, 90.0  $\mu$ mol, 32.7 % yield, 99.1% purity) as a bluish solid. LC-MS [M+1]: 409.3.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 8.68 (s, 1H), 8.54 (br s, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.47 (s, 1H), 6.97 - 6.88 (m, 1H), 6.68 (dd,  $J$ =3.6, 8.8 Hz, 1H), 4.70 (br s, 2H), 4.53 (t,  $J$ =8.8 Hz, 2H), 3.31 (br d,  $J$ =8.8 Hz, 2H), 2.18 (s, 3H).

[000348] EXAMPLES 5 -10 were prepared following the procedure set forth in Example 4 and using the general reactions schemes and intermediates described herein.

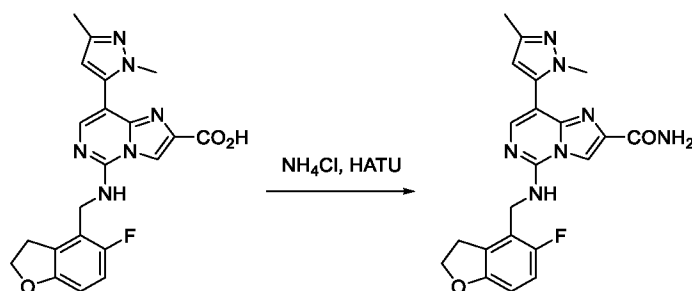
TABLE 1  
Characterization of EXAMPLES 5-10

| Ex. # | Structure                                                                                                                                                                                                                            | $^1\text{H}$ NMR                                                                                                                                                                                                                                                                                                      |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5     |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p> | $^1\text{H}$ NMR (400MHz, $\text{CD}_3\text{OD}$ ) $\delta$ = 8.56 (s, 1H), 8.19 (s, 1H), 7.79 (s, 1H), 6.85 (t, $J$ =9.6 Hz, 1H), 6.63 (dd, $J$ =4.0, 8.8 Hz, 1H), 4.80 (s, 2H), 4.57 (t, $J$ =8.8 Hz, 2H), 4.53 - 4.46 (m, 1H), 3.38 - 3.34 (m, 2H), 2.37 (s, 3H), 1.54 (d, $J$ =6.8 Hz, 6H).<br>LCMS [M+1]: 451.3. |
| 6     |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-methoxy-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p>       | $^1\text{H}$ NMR (400MHz, DMSO- $d_6$ ) $\delta$ = 8.78 (s, 1H), 8.43 (br s, 1H), 8.03 (s, 1H), 7.63 (s, 1H), 6.97 - 6.91 (m, 1H), 6.80 (s, 1H), 6.70 (dd, $J$ =4.0, 8.8 Hz, 1H), 4.70 (br d, $J$ =4.4 Hz, 2H), 4.55 (t, $J$ =8.8 Hz, 2H), 3.87 (s, 3H), 3.33 - 3.29 (m, 2H), 2.15 (s, 3H).<br>LC-MS [M+1]: 450.1.    |

| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                 |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7     |  <p>8-(2-cyclopropyl-4-methylpyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p>  | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.52 - 8.28 (m, 2H), 7.57 (s, 1H), 6.93 (br t, <i>J</i> =9.6 Hz, 1H), 6.73 - 6.63 (m, 1H), 4.72 (br s, 2H), 4.52 (br d, <i>J</i> =8.8 Hz, 2H), 3.30 - 3.24 (m, 2H), 2.34 (s, 3H), 2.25 - 2.17 (m, 1H), 1.17 - 0.91 (m, 4H).<br>LC-MS [M+1]: 461.4.                           |
| 8     |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.71 (s, 1H), 7.92 (s, 1H), 7.67 (s, 1H), 6.90 - 6.82 (m, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.84 (br s, 2H), 4.68 - 4.62 (m, 1H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.39 (t, <i>J</i> =8.4 Hz, 2H), 2.28 (s, 3H), 1.52 (d, <i>J</i> =6.4 Hz, 6H).<br>LCMS [M+1]: 451.3. |
| 9     |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluorobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p>                    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.79 (s, 1H), 8.71 (t, <i>J</i> =4.8 Hz, 1H), 8.06 (d, <i>J</i> =2.0 Hz, 1H), 7.77 (s, 1H), 7.61 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 7.25 - 7.18 (m, 2H), 6.23 (s, 1H), 5.01 (d, <i>J</i> =4.8 Hz, 2H), 3.69 (s, 3H), 2.19 (s, 3H).<br>LCMS: [M+1] 421.2.                       |
| 10    |  <p>5-(((2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid</p>                 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.17 (br s, 1H), 7.65 (s, 1H), 7.11 - 7.03 (m, 1H), 6.89 (d, <i>J</i> =7.6 Hz, 1H), 6.66 (d, <i>J</i> =8.0 Hz, 1H), 6.25 (br s, 1H), 4.78 (s, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.77 (br s, 3H), 3.29 - 3.26 (m, 2H), 2.25 (s, 3H).<br>LC-MS [M+1] 405.2.                   |

## EXAMPLE 11

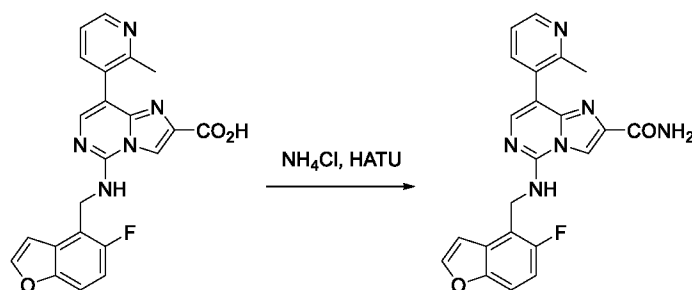
## 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide



[000349] To a solution of 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (24.9 mg, 52.7  $\mu\text{mol}$ , 1.00 equiv) in DMF (1 mL) was added ammonium chloride (8.45 mg, 158  $\mu\text{mol}$ , 3.00 equiv), DIPEA (47.7 mg, 369  $\mu\text{mol}$ , 64.2  $\mu\text{L}$ , 7.00 equiv) and HATU (40.1 mg, 105  $\mu\text{mol}$ , 2.00 equiv). The resultant mixture was stirred at 25  $^{\circ}\text{C}$  for 1 h. The mixture was diluted with water (10.0 mL) and filtered. The precipitate was washed with methanol (1.00 mL) and dried at reduced pressure to provide 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide (12.3 mg, 53.8% yield, 97.5% purity) as a gray solid. LC-MS:  $[\text{M}+1]$  422.1.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 8.64 (s, 1H), 8.51 (br s, 1H), 7.74 (s, 1H), 7.62 (br s, 1H), 7.45 (br s, 1H), 6.93 (t,  $J=9.6$  Hz, 1H), 6.69 (dd,  $J=4.0, 8.8$  Hz, 1H), 6.25 (s, 1H), 4.71 (br d,  $J=4.4$  Hz, 2H), 4.54 (br t,  $J=8.8$  Hz, 2H), 3.72 (s, 3H), 3.31 - 3.27 (m, 2H), 2.18 (s, 3H).

## EXAMPLE 12

## 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide



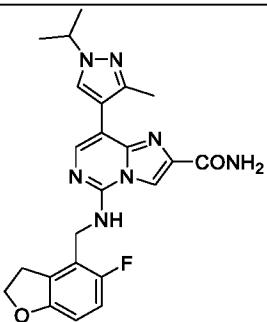
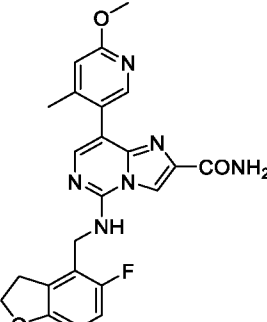
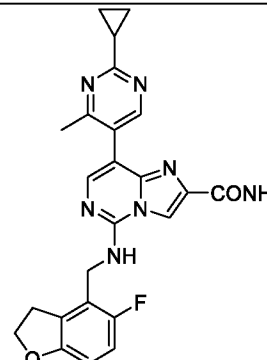
[000350] A mixture of 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (80.0 mg, 192  $\mu\text{mol}$ , 1.00 equiv), DIEA (74.3 mg, 575  $\mu\text{mol}$ , 100  $\mu\text{L}$ , 3.00 equiv) and ammonium chloride (30.8 mg, 575  $\mu\text{mol}$ , 3 equiv) in DMF (3.00 mL) was cooled to 0  $^{\circ}\text{C}$ . To this mixture was added HATU (109 mg, 287  $\mu\text{mol}$ , 1.50 equiv) and the mixture was stirred at 25  $^{\circ}\text{C}$  for 1 h. The solution was diluted with water (10.0 mL), filtered, the filter cake was dried to afford 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (61.0 mg, 74.0 % yield, 96.8 % purity) as a white solid. LCMS  $[\text{M}+1]$ : 417.2.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 8.64 (s, 1H), 8.59 (t,  $J=5.2$  Hz, 1H), 8.48 (dd,  $J=1.6, 4.8$  Hz, 1H), 8.06 (d,  $J=2.0$  Hz, 1H), 7.72 (dd,  $J=1.6, 7.6$  Hz, 1H), 7.65 (s, 1H), 7.59 (dd,  $J=3.6, 9.0$  Hz, 1H), 7.50

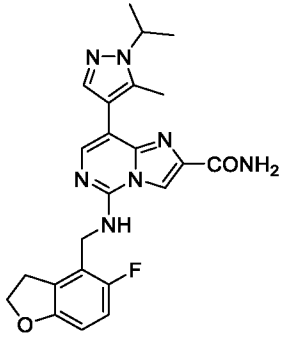
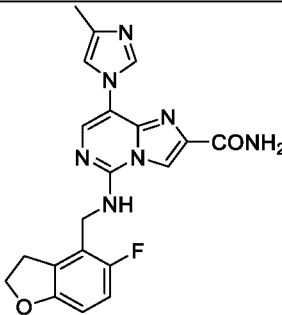
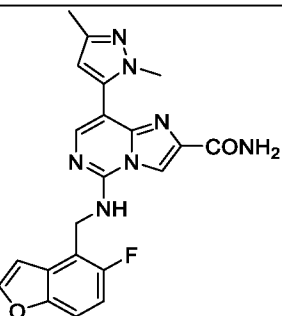
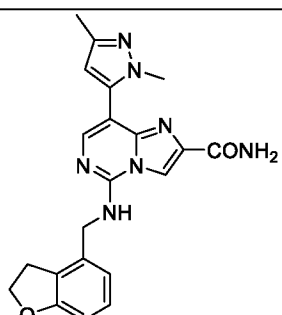
(br s, 1H), 7.39 (br s, 1H), 7.29 (dd,  $J=5.2, 7.6$  Hz, 1H), 7.25-7.18(m, 2 H), 5.00 (d,  $J=5.2$  Hz, 2H), 2.39 (s, 3H).

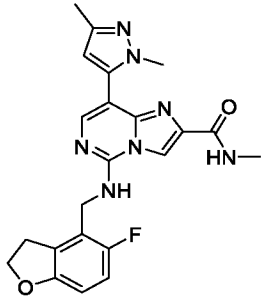
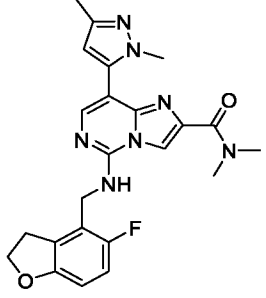
[000351] EXAMPLES 13 -21 were prepared following the procedure set forth in Example 12 and using the general reactions schemes and intermediates described herein.

TABLE 2

Characterization of EXAMPLES 13-21

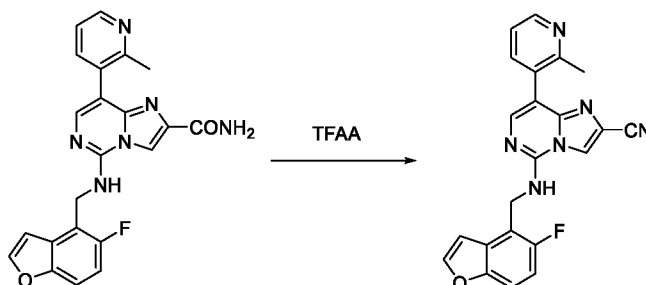
| Ex. # | Structure                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                         |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carboxamide</p>   | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.58 (s, 1H), 8.54 (s, 1H), 8.18 (t, $J=5.2$ Hz, 1H), 7.82 (br s, 1H), 7.79 (s, 1H), 7.51 (br s, 1H), 6.96 - 6.89 (m, 1H), 6.68 (dd, $J=4.0, 8.4$ Hz, 1H), 4.69 (d, $J=4.8$ Hz, 1H), , 4.57 - 4.47 (m, 3H), 3.30 - 3.25 (m, 2H), 2.36 (s, 3H), 1.44 (d, $J=6.8$ Hz, 6H).<br>LCMS [M+1]: 450.3.                |
| 14    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-methoxy-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide</p>        | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.64 (s, 1H), 8.39 (br t, $J=4.4$ Hz, 1H), 8.06 (s, 1H), 7.62 (s, 1H), 7.50(s, 1H), 7.41(s, 1H), 6.95 (br t, $J=9.6$ Hz, 1H), 6.80 (s, 1H), 6.71 (dd, $J=4.0, 8.4$ Hz, 1H), 4.72 (br d, $J=4.8$ Hz, 2H), 4.56 (br t, $J=8.8$ Hz, 2H), 3.88 (s, 3H), 3.34 - 3.28 (m, 2H), 2.19 (s, 3H).<br>LC-MS [M+1]: 449.1. |
| 15    |  <p>8-(2-cyclopropyl-4-methylpyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.65 (s, 1H), 8.54 - 8.43 (m, 2H), 7.71 (s, 1H), 7.57 (br s, 1H), 7.40 (br s, 1H), 6.94 (t, $J=9.2$ Hz, 1H), 6.70 (dd, $J=4.0, 8.4$ Hz, 1H), 4.72 (br d, $J=4.8$ Hz, 2H), 4.55 (t, $J=8.8$ Hz, 2H), 3.32 - 3.29 (m, 2H), 2.36 (s, 3H), 2.26 - 2.17 (m, 1H), 1.14 - 0.98 (m, 4H)<br>LC-MS [M+1]: 460.4.        |

| Ex. # | Structure                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                          |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carboxamide</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.41 (s, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 6.85 (br t, <i>J</i> =9.2 Hz, 1H), 6.68 - 6.58 (m, 1H), 4.80 (s, 2H), 4.68 - 4.55 (m, 1H), 4.56 (br t, <i>J</i> =8.8 Hz, 2H), 3.38 - 3.35 (m, 2H), 2.35 (s, 3H), 1.51 (br d, <i>J</i> =6.4 Hz, 6H)<br>LCMS [M+1]: 450.4.                                                                      |
| 17    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carboxamide</p>            | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ = 8.11 (s, 1H), 7.93 (s, 1H), 6.67 - 6.61 (m, 1H), 6.59 - 6.54 (m, 1H), 5.08 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 4.47 (q, <i>J</i> =7.2 Hz, 2H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H), 1.43 (t, <i>J</i> =7.2 Hz, 3H), 1.36 (s, 9H)<br>LC-MS [M+3]: 537.2.                                                                              |
| 18    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluorobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxamide</p>                   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.76 - 8.56 (m, 2H), 8.06 (br s, 1H), 7.75 (br s, 1H), 7.67 - 7.55 (m, 2H), 7.47 (br s, 1H), 7.28 - 7.16 (m, 2H), 6.25 (br s, 1H), 5.01 (br s, 2H), 3.72 (br s, 3H), 2.19 (br s, 3H).<br>LCMS: [M+1] 420.2.                                                                                                                   |
| 19    |  <p>5-(((2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carboxamide</p>                | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.64 (br s, 2H), 7.71 (br s, 1H), 7.63 (br s, 1H), 7.46 (br s, 1H), 7.10 - 7.01 (m, 1H), 6.85 (br d, <i>J</i> =7.6 Hz, 1H), 6.68 (br d, <i>J</i> =8.0 Hz, 1H), 6.24 (br s, 1H), 4.70 (br s, 2H), 4.54 (br t, <i>J</i> =8.4 Hz, 2H), 3.72 (br s, 3H), 3.26 (br d, <i>J</i> =9.2 Hz, 2H), 2.18 (br s, 3H)<br>LC-MS [M+1] 404.3. |

| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                    |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-N-methylimidazo[1,2-c]pyrimidine-2-carboxamide</p>     | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=8.66 (br s, 1 H), 8.51 (br s, 1 H), 8.22 (br s, 1 H), 7.74 (br s, 1 H), 6.94 (br t, <i>J</i> =8.8 Hz, 1 H), 6.71 (br s, 1 H), 6.24 (br s, 1 H), 4.72 (br s, 2 H), 4.55 (br t, <i>J</i> =7.6 Hz, 2 H), 3.71 (s, 3 H), 3.28 - 3.31 (m, 2 H), 2.78 (s, 3 H), 2.19 (s, 3 H).<br>LCMS [M+1]: 436.4.                           |
| 21    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-N,N-dimethylimidazo[1,2-c]pyrimidine-2-carboxamide</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=8.59 (s, 1 H), 8.51 (br s, 1 H), 7.76 (s, 1 H), 6.94 (t, <i>J</i> =9.2 Hz, 1 H), 6.70 (dd, <i>J</i> =8.4, 3.6 Hz, 1 H), 6.23 (s, 1 H), 4.73 (d, <i>J</i> =2.4 Hz 2 H), 4.55 (br t, <i>J</i> =8.8 Hz, 2 H), 3.72 (s, 3 H), 3.37 (br s, 3 H), 3.26 - 3.31 (m, 2 H), 2.99 (br s, 3 H), 2.18 (s, 3 H).<br>LCMS [M+1]: 450.4. |

## EXAMPLE 22

## 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile

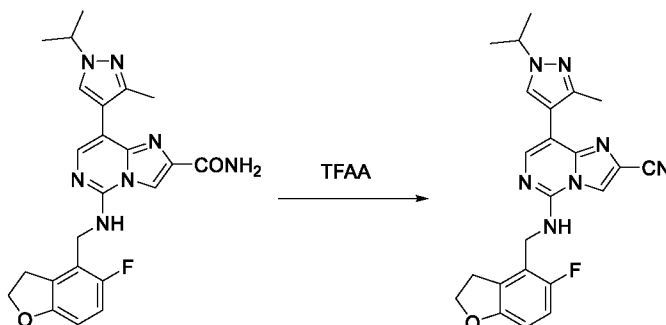


[000352] To a solution of 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (45.0 mg, 108 μmol, 1.00 equiv), TEA (219 mg, 2.16 mmol, 301 μL, 20.0 equiv) in THF (1.50 mL) was added TFAA (136 mg, 648 μmol, 90.2 μL, 6.00 equiv) at 0 °C. The mixture was subsequently stirred at 25 °C for 1 h. The reaction mixture was diluted with ethyl acetate (10.0 mL) and washed with water (10.0 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure to give a residue. The crude material was purified by prep-HPLC (column: Phenomenex Synergi C18 150×25×10 μm; mobile phase: [A = water (0.1 % TFA) – B = acetonitrile]; B%: 18% - 48%, 12 min) to afford 5-(((5-fluorobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (13.0 mg, 29.9% yield, 99.1% purity) as an off-white solid. LCMS [M+1]: 399.3. <sup>1</sup>H NMR (400MHz, METHANOL-*d*<sub>4</sub>) δ

= 8.75 (dd,  $J=1.6, 6.0$  Hz, 1H), 8.65 (s, 1H), 8.54 (dd,  $J=1.6, 7.6$  Hz, 1H), 8.0 - 7.95 (m, 2H), 7.83 (d,  $J=2.0$  Hz, 1H), 7.53 - 7.44 (m, 1H), 7.18 - 7.11 (m, 2H), 5.15 (d,  $J=0.4$  Hz, 2H), 2.68 (s, 3H).

## EXAMPLE 23

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



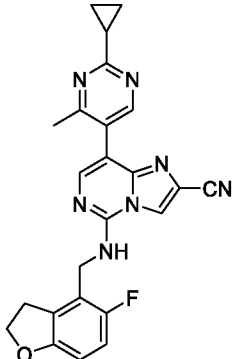
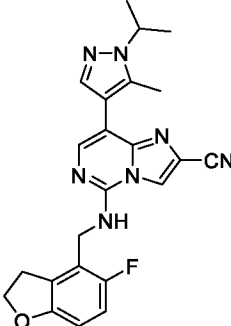
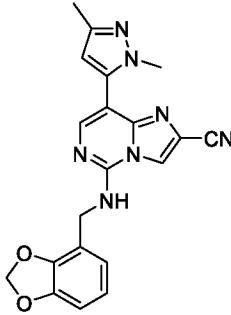
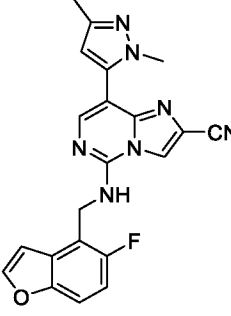
[000353] To a solution of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (49.0 mg, 106  $\mu$ mol, 1.00 equiv) and TEA (215 mg, 2.12 mmol, 296  $\mu$ L, 20.0 equiv) in THF (1.00 mL) was added TFAA (134 mg, 637  $\mu$ mol, 88.7  $\mu$ L, 6.00 equiv) at 0 °C. The mixture was subsequently stirred at 25 °C for 1 h. The reaction mixture was diluted with ethyl acetate (10.0 mL), the pH was adjusted to ~7 with TFA, and the organic layer was washed with brine (5.00 mL  $\times$  3). Concentration *in vacuo* provided the crude material. The crude residue was triturated with methyl alcohol (2.00 mL) and filtered to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (43.0 mg, 92.7% yield, 98.8% purity) as a white solid. LCMS [M+1]: 432.3.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 8.90 (s, 1H), 8.32 (br s, 1H), 8.16 (s, 1H), 7.84 (s, 1H), 6.94 (t,  $J=9.2$  Hz, 1H), 6.70 (dd,  $J=3.6, 8.4$  Hz, 1H), 4.70 (br s, 2H), 4.58 - 4.44 (m, 3H), 3.30 - 3.24 (m, 2H), 2.30 (s, 3H), 1.43 (d,  $J=6.8$  Hz, 6H).

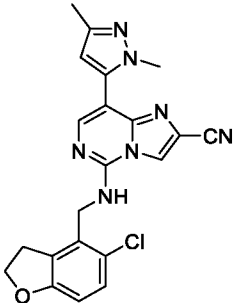
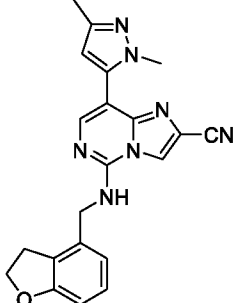
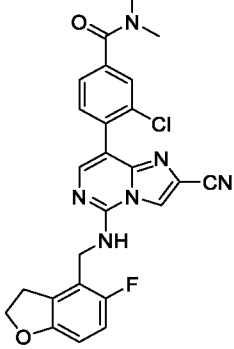
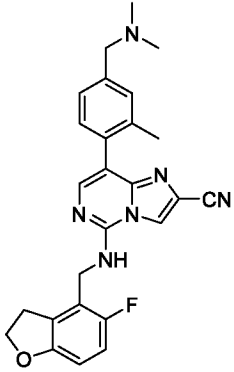
[000354] EXAMPLES 24 -85 were prepared following the procedure set forth in Example 23 and using the general reactions schemes and intermediates described herein.

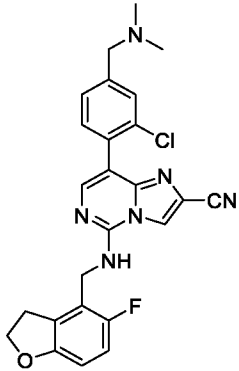
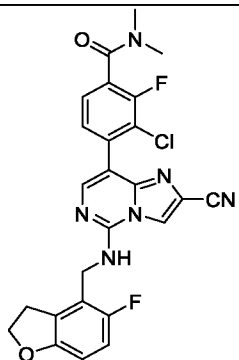
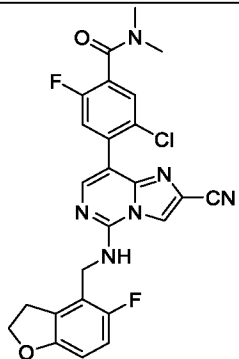
TABLE 3

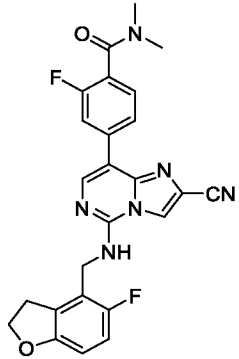
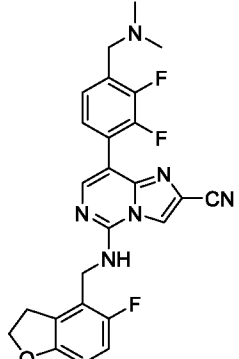
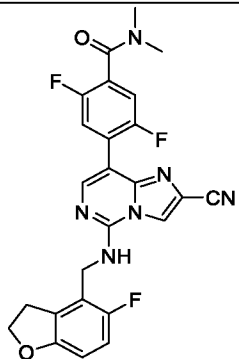
Characterization of EXAMPLES 24-85

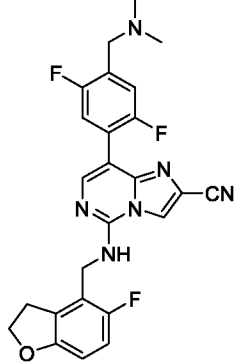
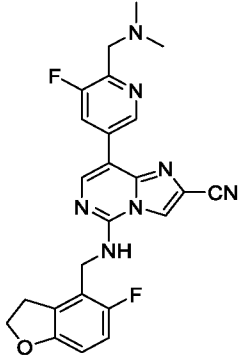
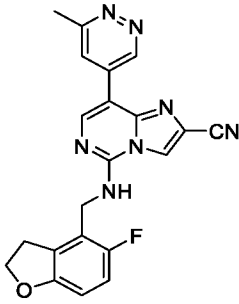
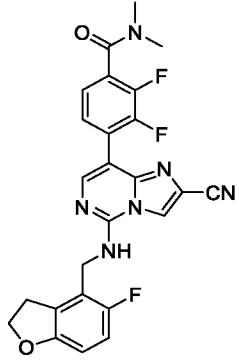
| Ex. # | Structure                                                                                                                               | $^1\text{H}$ NMR                                                                                                                                                                                                                                                                                   |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24    | <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-methoxy-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | $^1\text{H}$ NMR (400MHz, $\text{CD}_3\text{OD}$ ) $\delta$ = 8.63 (s, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 6.91 - 6.85 (m, 1H), 6.81 (s, 1H), 6.67 (dd, $J=4.0, 8.4$ Hz, 1H), 4.84 (s, 2H), 4.60 (t, $J=8.8$ Hz, 2H), 3.96 (s, 3H), 3.41 (br t, $J=8.8$ Hz, 2H), 2.20 (s, 3H).<br>LC-MS [M+1]: 431.3. |

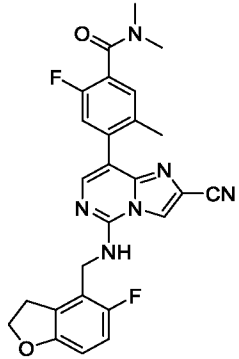
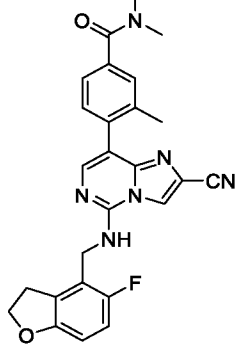
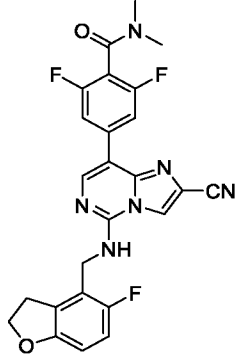
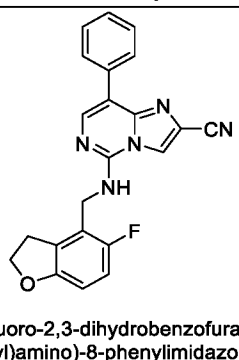
| Ex. # | Structure                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                         |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25    |  <p>8-(2-cyclopropyl-4-methylpyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>  | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.93 (s, 1H), 8.61 (br s, 1H), 8.48 (s, 1H), 7.83 (s, 1H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =4.0 Hz, 2H), 4.56 (t, <i>J</i> =8.8Hz, 2H), 3.33 (br t, <i>J</i> =8.8 Hz, 2H), 2.32 (s, 3H), 2.26 - 2.18 (m, 1H), 1.15 - 1.00 (m, 4H).<br>LC-MS [M+1]: 442.4. |
| 26    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.59 (s, 1H), 7.75 (s, 1H), 7.75 (s, 1H), 6.89 - 6.82 (m, 1H), 6.64 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.80 (s, 2H), 4.72 - 4.63 (m, 1H), 4.57 (t, <i>J</i> =8.8 Hz, 2H), 3.39 - 3.34 (m, 2H), 2.34 (s, 3H), 1.52 (d, <i>J</i> =6.8 Hz, 6H).<br>LCMS [M+1]: 432.4.                                                       |
| 27    |  <p>5-((benzo[d][1,3]dioxol-4-yl)methyl)amino)-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.92 (s, 1H), 8.82 (br t, <i>J</i> =5.2 Hz, 1H), 7.84 (s, 1H), 6.94 - 6.80 (m, 3H), 6.24 (s, 1H), 6.05 (s, 2H), 4.75 (d, <i>J</i> =4.8 Hz, 2H), 3.74 - 3.72 (m, 3H), 2.19 (s, 3H).<br>LCMS: [M+1] 388.2.                                                                                                             |
| 28    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluorobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                    | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.61 (s, 1H), 7.90 (s, 1H), 7.84 (d, <i>J</i> =2.0 Hz, 1H), 7.50 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 7.18 - 7.11 (m, 2H), 6.28 (s, 1H), 5.14 (s, 2H), 3.74 (s, 3H), 2.30 (s, 3H).<br>LCMS: [M+1] 402.2.                                                                                                                   |

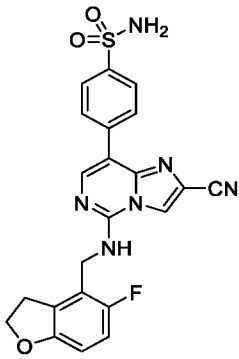
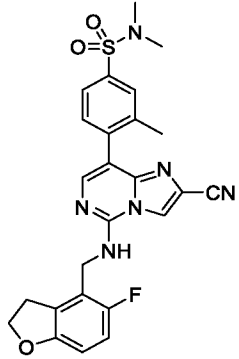
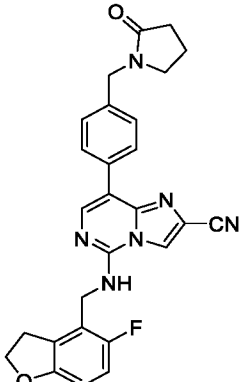
| Ex. # | Structure                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29    |  <p>5-(((5-chloro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>               | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ = 8.67 (s, 1H), 7.91 (s, 1H), 7.19 (d, <i>J</i> =8.4 Hz, 1H), 6.72 (d, <i>J</i> =8.4 Hz, 1H), 6.33 (s, 1H), 4.89 (s, 2H), 4.62 (t, <i>J</i> =8.8 Hz, 2H), 3.77 (s, 3H), 3.44 (t, <i>J</i> =8.8 Hz, 2H), 2.32 (s, 3H).<br>LCMS: [M+1] 420.2.                                                                                                                                                                         |
| 30    |  <p>5-(((2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                        | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.60 (s, 1H), 7.86 (s, 1H), 7.11 - 7.04 (m, 1H), 6.89 (d, <i>J</i> =7.6 Hz, 1H), 6.67 (d, <i>J</i> =8.0 Hz, 1H), 6.32 (s, 1H), 4.79 (s, 2H), 4.57 (t, <i>J</i> =8.8 Hz, 2H), 3.76 (s, 3H), 3.30 - 3.25 (m, 2H), 2.30 (s, 3H).<br>LC-MS [M+3] 386.0.                                                                                                                                                                |
| 31    |  <p>3-chloro-4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,N-dimethylbenzamide</p>              | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.62 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.58 (d, <i>J</i> =8.0 Hz 1H), 7.46 (d, <i>J</i> =8.0 Hz, 1H), 6.86 (t, <i>J</i> =9.2 Hz, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.39 (t, <i>J</i> =8.8 Hz, 2H), 3.13(s, 3H), 3.08(s, 3H).<br>LCMS [M + 1]: 491.2.                                                                                                     |
| 32    |  <p>8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.89 (br s, 1H), 8.94 (d, <i>J</i> =2.0 Hz, 1H), 8.55 (br s, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.43 - 7.35 (m, 2H), 6.96 (t, <i>J</i> =9.6 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (br d, <i>J</i> =4.4 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.30 (br d, <i>J</i> =4.4 Hz, 2H), 3.33 (br t, <i>J</i> =8.8 Hz, 2H), 2.78 (br d, <i>J</i> =4.0 Hz, 6H), 2.20 (s, 3H).<br>LCMS [M+1]: 457.2. |

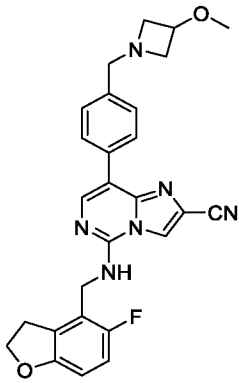
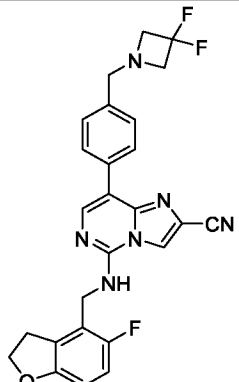
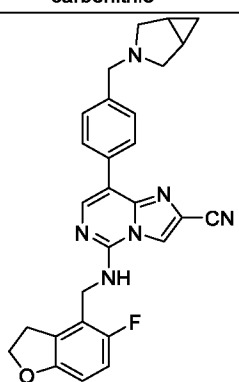
| Ex. # | Structure                                                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                           |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 33    |  <p>8-(2-chloro-4-((dimethylamino)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>      | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 7.84 (s, 1H), 7.74 (d, <i>J</i> =1.6 Hz, 1H), 7.66 - 7.59 (d, <i>J</i> =8.0 Hz, 1H), 7.53 (dd, <i>J</i> =1.6, 7.6 Hz, 1H), 6.85 (t, <i>J</i> =9.6 Hz, 1H), 6.66 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.84 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 4.39 (s, 2H), 3.38 (t, <i>J</i> =8.4 Hz, 2H), 2.93 (s, 6H).<br>LCMS [ <i>M</i> + 1]: 477.3. |
| 34    |  <p>3-chloro-4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2-fluoro-<i>N,N</i>-dimethylbenzamide</p>  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.68 (br s, 1H), 7.90 (s, 1H), 7.51 - 7.43 (m, 2H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.33 (t, <i>J</i> =8.8 Hz, 2H), 3.04 (s, 3H), 2.92 (s, 3H).<br>LCMS [ <i>M</i> +1]: 509.3.                                          |
| 35    |  <p>5-chloro-4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2-fluoro-<i>N,N</i>-dimethylbenzamide</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 7.88 (s, 1H), 7.59 (d, <i>J</i> =6.0 Hz, 1H), 7.43 (d, <i>J</i> =9.6 Hz, 1H), 6.86 (t, <i>J</i> =9.2 Hz, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (s, 2H), 4.59 - 4.56 (m, 2H), 3.38 (t, <i>J</i> =8.8 Hz, 2H), 3.14 (s, 3H), 3.05 (s, 3H).<br>LCMS [ <i>M</i> +1]: 509.3.                                                          |

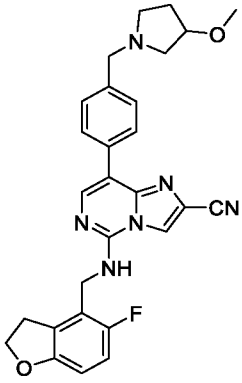
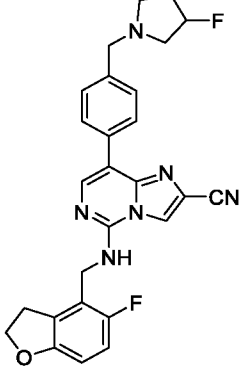
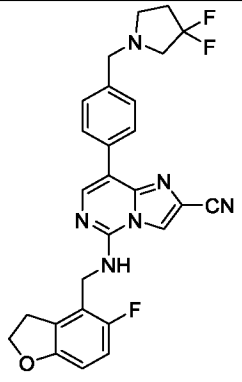
| Ex. # | Structure                                                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 36    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2-fluoro-N,N-dimethylbenzamide</p>                   | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.96 (s, 1H), 8.67 (br s, 1H), 8.29 (s, 1H), 8.04 - 7.96 (m, 2H), 7.47 (br t, <i>J</i> =7.6 Hz, 1H), 6.95 (br t, <i>J</i> =9.2 Hz, 1H), 6.71 (br dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.75 (br d, <i>J</i> =4.0 Hz, 2H), 4.55 (br t, <i>J</i> =8.4 Hz, 2H), 3.38 - 3.24 (m, 2H), 3.03 (s, 3H), 2.90 (s, 3H).<br>LCMS [M+1]: 475.1.                                         |
| 37    |  <p>8-(4-((dimethylamino)methyl)-2,3-difluorophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.98 (br s, 1H), 8.96 (s, 1H), 8.76 (br d, <i>J</i> =4.4 Hz, 1H), 8.01 (s, 1H), 7.71 (br t, <i>J</i> =7.2 Hz, 1H), 7.50 (br t, <i>J</i> =7.2 Hz, 1H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.75 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.45 (s, 2H), 3.33 - 3.29 (m, 2H), 2.84 (s, 6H).<br>LCMS [M+1]: 479.1. |
| 38    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2,5-difluoro-N,N-dimethylbenzamide</p>             | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 8.06 (s, 1H), 7.74 (br dd, <i>J</i> =5.6, 10.0 Hz, 1H), 7.32 (br dd, <i>J</i> =6.0, 10.0 Hz, 1H), 6.88 (br t, <i>J</i> =8.8 Hz, 1H), 6.72 - 6.63 (m, 1H), 4.86 (s, 2H), 4.60 (br t, <i>J</i> =8.8 Hz, 2H), 3.42 - 3.38 (m, 2H), 3.16 (s, 3H), 3.06 (s, 3H).<br>LCMS [M+1]: 493.2.                                                                         |

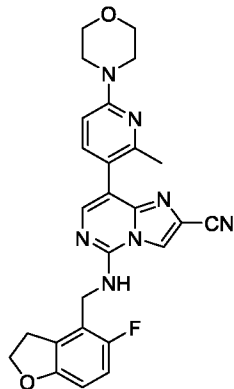
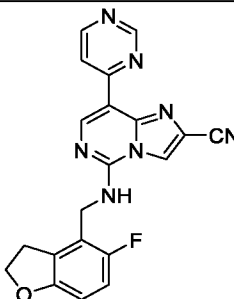
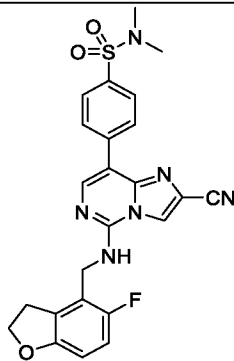
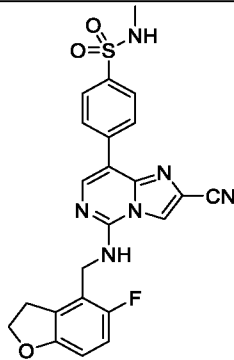
| Ex. # | Structure                                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 39    |  <p>8-((dimethylamino)methyl)-2,5-difluorophenyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>        | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.66 (s, 1H), 8.06 (d, <i>J</i> =1.6 Hz, 1H), 7.81 (dd, <i>J</i> =6.0, 10.4 Hz, 1H), 7.51 (dd, <i>J</i> =6.0, 10.0 Hz, 1H), 6.92 - 6.84 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.86 (s, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 4.48 (s, 2H), 3.40 (t, <i>J</i> =8.8 Hz, 2H), 2.98 (s, 6H).<br>LCMS [M+1]: 479.3.                                            |
| 40    |  <p>8-(6-((dimethylamino)methyl)-5-fluoropyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 9.16 (t, <i>J</i> =1.2 Hz, 1H), 8.67 (s, 1H), 8.42 (dd, <i>J</i> =1.4, 10.8 Hz, 1H), 8.28 (s, 1H), 6.93 - 6.84 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.87 - 4.86 (m, 2H), 4.66 (d, <i>J</i> =1.6 Hz, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 3.41 (t, <i>J</i> =8.8 Hz, 2H), 3.05 (s, 6H). LCMS [M+1]: 462.4.                                               |
| 41    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-methylpyridazin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                        | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.81 (d, <i>J</i> =2.0 Hz, 1H), 8.99 (s, 2H), 8.62 (s, 1H), 8.39 (d, <i>J</i> =1.6 Hz, 1H), 6.95 (t, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.77 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H), 2.70 (s, 3H).<br>LCMS [M+1]: 402.2.                                                |
| 42    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2,3-difluoro-<i>N,N</i>-dimethylbenzamide</p>        | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.97 (s, 1H), 8.76 (br t, <i>J</i> =5.2 Hz, 1H), 8.01 (s, 1H), 7.65 (t, <i>J</i> =6.4 Hz, 1H), 7.31 (t, <i>J</i> =6.4 Hz, 1H), 6.95 (t, <i>J</i> =9.6 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.32 (t, <i>J</i> =8.8 Hz, 2H), 3.03 (s, 3H), 2.93 (s, 3H).<br>LC-MS [M+1]: 493.3. |

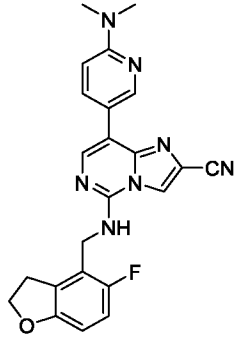
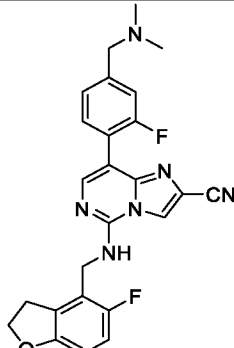
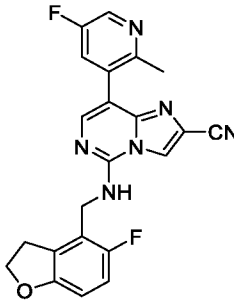
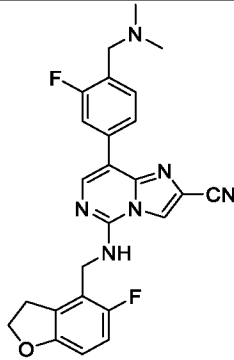
| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 43    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2-fluoro-N,N,5-trimethylbenzamide</p>    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.93 (s, 1H), 8.55 (br t, <i>J</i> =4.8 Hz, 1H), 7.79 (s, 1H), 7.32 (d, <i>J</i> =7.2 Hz, 1H), 7.25 (d, <i>J</i> =10.4 Hz, 1H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (br d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.33 (br t, <i>J</i> =8.4 Hz, 2H), 3.02 (s, 3H), 2.92 (s, 3H), 2.16 (s, 3H).<br>LCMS [M+1]: 489.4. |
| 44    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,N,3-trimethylbenzamide</p>            | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.92 (s, 1H), 8.51 (t, <i>J</i> =4.8 Hz, 1H), 7.75 (s, 1H), 7.37 - 7.33 (m, 2H), 7.30 - 7.26 (m, 1H), 6.99 - 6.93 (m, 1H), 6.72 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.72 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.33 (br t, <i>J</i> =8.8 Hz, 2H), 2.99 (br d, <i>J</i> =7.2 Hz, 6H), 2.19 (s, 3H).<br>LCMS [M+1]: 471.2.                                  |
| 45    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-2,6-difluoro-N,N-dimethylbenzamide</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.97 (s, 1H), 8.80 (t, <i>J</i> =4.8 Hz, 1H), 8.41 (s, 1H), 8.01 (d, <i>J</i> =9.2 Hz, 2H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.75 (d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.34 - 3.30 (m, 2H), 3.05 (s, 3H), 2.93 (s, 3H).<br>LCMS [M+1]: 493.3.                                                                    |
| 46    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-phenylimidazo[1,2-c]pyrimidine-2-carbonitrile</p>                            | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.94 (s, 1H), 8.50 (br s, 1H), 8.09 (s, 1H), 7.96 (br d, <i>J</i> =7.6 Hz, 2H), 7.46 (br t, <i>J</i> =7.6 Hz, 2H), 7.40 - 7.29 (m, 1H), 6.95 (br t, <i>J</i> =9.6 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (s, 2H), 4.54 (br t, <i>J</i> =8.8 Hz, 2H), 3.33 (br s, 2H).<br>LC-MS [M+1]: 386.0.                                                                   |

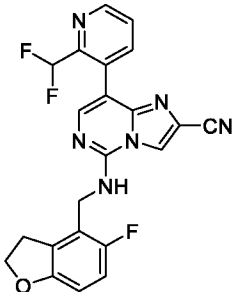
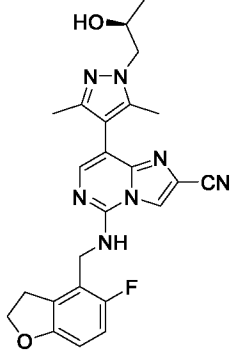
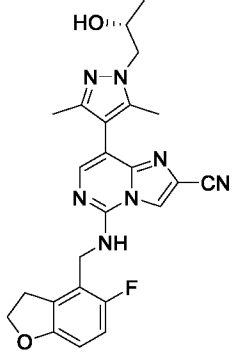
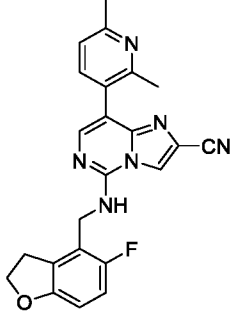
| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 47    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)benzenesulfonamide</p>                           | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.96 (s, 1H), 8.65 (t, <i>J</i> =4.8 Hz, 1H), 8.24 (s, 1H), 8.20 (d, <i>J</i> =8.8 Hz, 2H), 7.90 (d, <i>J</i> =8.4 Hz, 2H), 7.38 (s, 2H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.76 (br d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.36 - 3.33 (m, 2H).<br>LCMS [M+1]: 465.2.                                          |
| 48    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-<i>N,N</i>,3-trimethylbenzenesulfonamide</p>   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.57 (t, <i>J</i> =4.0 Hz 1H), 7.81 (s, 1H), 7.71 (s, 1H), 7.66 - 7.61 (m, 1H), 7.61 - 7.55 (m, 1H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =4.4 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.33 (t, <i>J</i> =8.8 Hz, 2H), 2.69 (s, 6H), 2.29 (s, 3H).<br>LCMS [M + 1]: 507.1.                        |
| 49    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((2-oxopyrrolidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.50 (t, <i>J</i> =4.8 Hz, 1H), 8.09 (s, 1H), 7.94 (d, <i>J</i> =8.4 Hz, 2H), 7.32 (d, <i>J</i> =8.0 Hz, 2H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.42 (s, 2H), 3.33 - 3.27 (m, 4H), 2.37 - 2.27 (m, 2H), 2.03 - 1.90 (m, 2H).<br>LC-MS [M+1]: 483.0. |

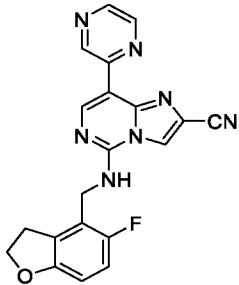
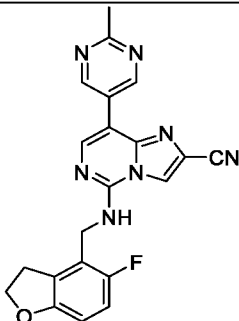
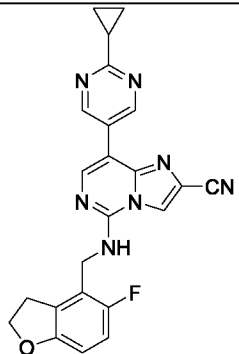
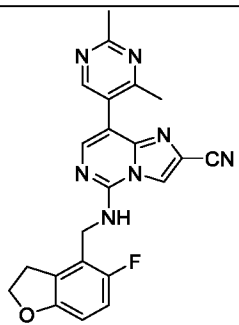
| Ex. # | Structure                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 50    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((3-methoxyazetidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>          | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 10.47 (s, 0.5H), 9.89 (s, 0.5H), 8.95 (s, 1H), 8.59 (br t, <i>J</i> =5.2 Hz, 1H), 8.16 (s, 1H), 8.07 (d, <i>J</i> =8.4 Hz, 2H), 7.62 - 7.53 (m, 2H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =5.2 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.42 (br s, 2H), 4.35 - 4.22 (m, 3H), 4.01 (br.s, 2H), 3.32 - 3.28 (m, 2H), 3.26 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 485.4. |
| 51    |  <p>8-(4-((3,3-difluoroazetidin-1-yl)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>      | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.62 (s, 1H), 8.05 (s, 1H), 8.00 (d, <i>J</i> =8.0 Hz, 2H), 7.57 (d, <i>J</i> =8.0 Hz, 2H), 6.89 - 6.82 (m, 1H), 6.65 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.83 (s, 2H), 4.63 - 4.54 (m, 6H), 4.45 (s, 2H), 3.37 (t, <i>J</i> =8.8 Hz, 2H). LCMS [ <i>M</i> +1]: 491.3.                                                                                                                                                       |
| 52    |  <p>8-(4-((3-azabicyclo[3.1.0]hexan-3-yl)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, methanol-d <sub>4</sub> ) δ = 8.63 (s, 1H), 8.06 (s, 1H), 8.01 (d, <i>J</i> =8.4 Hz, 2H), 7.59 (d, <i>J</i> =8.0 Hz, 2H), 6.86 (t, <i>J</i> =8.8 Hz, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 4.42 (s, 2H), 3.55 (s, 3H), 3.37 (t, <i>J</i> =8.8 Hz, 2H), 3.34-3.33 (m, 1H), 1.89 (dd, <i>J</i> =3.6, 8.0 Hz, 2H), 0.91 - 0.79 (m, 1H), 0.73 - 0.64 (m, 1H).<br>LCMS [ <i>M</i> +1]: 481.4.       |

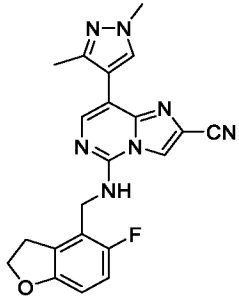
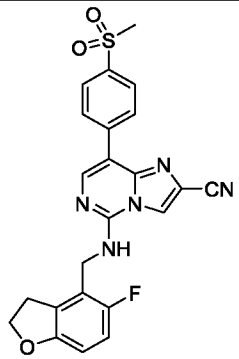
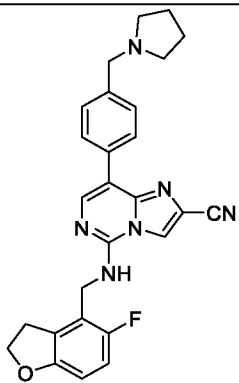
| Ex. # | Structure                                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 53    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((3-methoxypyrrolidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>      | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.62 (s, 1H), 8.05 (d, <i>J</i> =2.0 Hz, 1H), 8.01(d, <i>J</i> =7.6 Hz, 2H), (d, <i>J</i> =8.0 Hz, 2H), 6.85 (t, <i>J</i> =9.2 Hz, 1H), 6.64 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.82 - 4.79 (m, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 4.51 - 4.38 (m, 2H), 4.20 (br.s, 1H), 3.74 - 3.50 (m, 2H), 3.40 - 3.32 (m, 7H), 2.50 - 2.04 (m, 2H).<br>LCMS [M + 1]: 499.1.                                                                                  |
| 54    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((3-fluoropyrrolidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>      | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 10.52 (s, 0.5H), 10.16 (s, 0.3H), 8.95 (s, 1H), 8.60 (t, <i>J</i> =5.2 Hz, 1H), 8.18 (s, 1H), 8.09 (br d, <i>J</i> =8.0 Hz, 2H), 7.70 - 7.58 (m, 2H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.63 - 5.33 (m, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.51 - 4.39 (m, 2H), 3.50 - 3.37 (m, 5H), 3.32(t, <i>J</i> =8.8 Hz, 2H), 2.25 - 2.05 (m, 1H).<br>LCMS [M + 1]: 487.2. |
| 55    |  <p>8-(4-((3,3-difluoropyrrolidin-1-yl)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.95 (s, 1H), 8.50 (t, <i>J</i> =5.2 Hz, 1H), 8.10 (s, 1H), 7.94 (d, <i>J</i> =8.0 Hz, 2H), 7.40 (d, <i>J</i> =8.0 Hz, 2H), 6.99 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 3.67 (s, 2H), 3.35 - 3.32 (m, 2H), 2.89 (t, <i>J</i> =13.2 Hz, 2H), 2.73 (t, <i>J</i> =6.8 Hz, 2H), 2.32 - 2.21 (m, 2H).<br>LCMS [M+1]: 505.2.                                  |

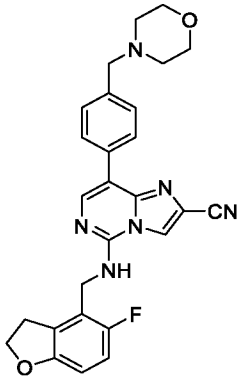
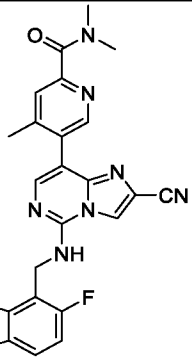
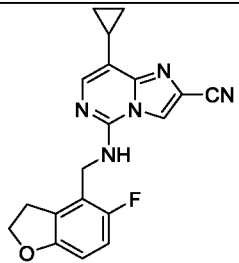
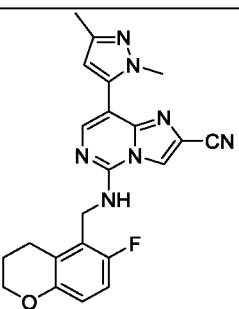
| Ex. # | Structure                                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 56    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-6-morpholinopyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>    | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.91 (s, 1H), 8.47 (br s, 1H), 7.72 (s, 1H), 7.61 (br d, <i>J</i> =8.4 Hz, 1H), 6.99 - 6.91 (m, 1H), 6.87 (br d, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.77 - 3.67 (m, 4H), 3.59 - 3.51 (m, 4H), 3.32 (t, <i>J</i> =8.4 Hz, 2H), 2.28 (s, 3H).<br>LCMS [M+1]: 496.4.    |
| 57    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyrimidin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                      | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.17 (d, <i>J</i> =0.8 Hz, 1H), 8.98 (s, 2H), 8.95 (s, 1H), 8.86 (d, <i>J</i> =5.6 Hz, 1H), 8.75 (dd, <i>J</i> =1.2, 5.2 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.79 (s, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.36 - 3.28 (m, 2H).<br>LCMS [M + 1]: 388.3.                                                                           |
| 58    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-<i>N,N</i>-dimethylbenzenesulfonamide</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.97 (s, 1H), 8.69 (t, <i>J</i> =4.8 Hz, 1H), 8.31 (d, <i>J</i> =9.2 Hz, 2H), 8.29 (s, 1H), 7.84 (d, <i>J</i> =8.8 Hz, 2H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.35 - 3.34 (m, 2H), 2.66 (s, 6H).<br>LCMS [M+1]: 493.3.                                        |
| 59    |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-<i>N</i>-methylbenzenesulfonamide</p>     | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.97 (s, 1H), 8.67 (t, <i>J</i> =4.8 Hz, 1H), 8.26 (s, 1H), 8.24 (d, <i>J</i> =8.4 Hz, 2H), 7.86 (d, <i>J</i> =8.4 Hz, 2H), 7.50 - 7.46 (m, 1H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.35 - 3.34 (m, 2H), 2.46 (d, <i>J</i> =4.8 Hz, 3H).<br>LCMS [M+1]: 479.2. |

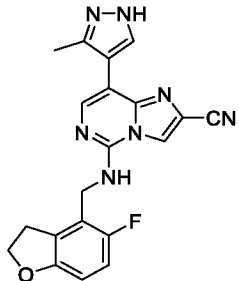
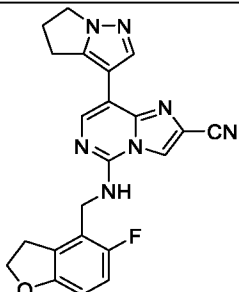
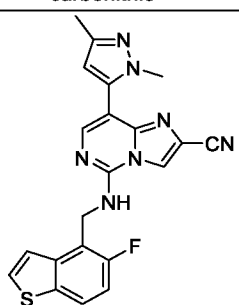
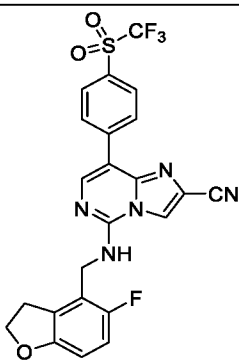
| Ex. # | Structure                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                              |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 60    |  <p>8-(6-(dimethylamino)pyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>              | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.95 (s, 1H), 8.83 (s, 1H), 8.60 (br s, 1H), 8.41 (br d, <i>J</i> =7.6 Hz, 1H), 8.22 (s, 1H), 7.14 (br s, 1H), 6.99 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.31 (br t, <i>J</i> =8.8 Hz, 2H), 3.19 (s, 6H).<br>LCMS [ <i>M</i> + 1]: 430.0.        |
| 61    |  <p>8-(4-((dimethylamino)methyl)-2-fluorophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.73 (br s, 1H), 8.97 (s, 1H), 8.79 - 8.67 (m, 1H), 8.32 (s, 1H), 8.15 - 7.99 (m, 2H), 7.67 (t, <i>J</i> =7.6 Hz, 1H), 7.01 - 6.91 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.39 (br s, 2H), 3.30 (m, 2H), 2.81 (br s, 6H).<br>LC-MS [ <i>M</i> +1]: 461.2. |
| 62    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-fluoro-2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>            | <sup>1</sup> H NMR (400 MHz, methanol- <i>d</i> <sub>4</sub> ) δ = 8.65 (s, 1H), 8.51 (d, <i>J</i> =2.8 Hz, 1H), 7.86 (s, 1H), 7.79 (dd, <i>J</i> =2.8, 8.8 Hz, 1H), 6.88 (t, <i>J</i> =8.8 Hz, 1H), 6.67 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.80 - 4.74 (m, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 3.41 (t, <i>J</i> =8.8 Hz, 2H), 2.47 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 419.3.                   |
| 63    |  <p>8-(4-((dimethylamino)methyl)-3-fluorophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> - <i>d</i> ) δ = 8.05 (s, 1H), 8.01 (s, 1H), 7.92 (t, <i>J</i> =7.6 Hz, 1H), 7.33 (d, <i>J</i> =9.2 Hz, 2H), 6.84 (t, <i>J</i> =9.2 Hz, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 6.03 (br s, 1H), 4.85 (br s, 2H), 4.64 (t, <i>J</i> =8.8 Hz, 2H), 4.20 (s, 2H), 3.43 (t, <i>J</i> =8.8 Hz, 2H), 2.84 (s, 6H).<br>LC-MS [ <i>M</i> +1]: 461.    |

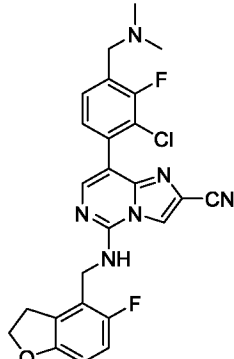
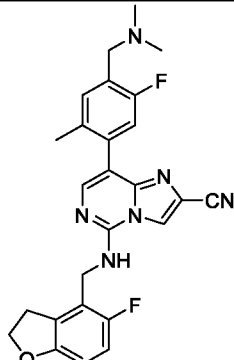
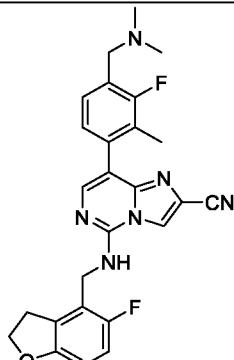
| Ex. # | Structure                                                                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 64    |  <p>8-(2-(difluoromethyl)pyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                       | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.77 (dd, <i>J</i> =1.6, 4.8 Hz, 1H), 8.62 (br s, 1H), 7.97 (d, <i>J</i> =8.0 Hz, 1H), 7.76 (s, 1H), 7.68 (dd, <i>J</i> =4.8, 8.0 Hz, 1H), 7.0, 6.86, 6.72 (m, 1H), 6.99 - 6.92 (m, 1H), 6.73 - 6.69 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =4.4 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.38 - 3.32 (m, 2H).<br>LCMS [ <i>M</i> + 1]: 437.1. |
| 65    |  <p>(<i>S</i>)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxypropyl)-3,5-dimethyl-1<i>H</i>-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, methanol- <i>d</i> <sub>4</sub> ) δ = 8.63 (s, 1H), 7.73 (s, 1H), 6.91 - 6.85 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (s, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 4.23 - 4.15 (m, 1H), 4.13 - 4.02 (m, 2H), 3.41 (t, <i>J</i> =8.8 Hz, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 1.28 (d, <i>J</i> =6.4 Hz, 3H).<br>LCMS [ <i>M</i> + 1]: 462.1.                                                              |
| 66    |  <p>(<i>R</i>)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxypropyl)-3,5-dimethyl-1<i>H</i>-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, methanol- <i>d</i> <sub>4</sub> ) δ = 8.51 (s, 1H), 7.59 (s, 1H), 6.76 (t, <i>J</i> =9.2 Hz, 1H), 6.55 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.71 (s, 2H), 4.48 (t, <i>J</i> =8.8 Hz, 2H), 4.14 - 4.04 (m, 1H), 4.00 - 3.88 (m, 2H), 3.29 (t, <i>J</i> =8.8 Hz, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.16 (d, <i>J</i> =6.4 Hz, 3H).<br>LCMS [ <i>M</i> + 1]: 462.2.                                                   |
| 67    |  <p>8-(2,6-dimethylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                           | <sup>1</sup> H NMR (400 MHz, methanol- <i>d</i> <sub>4</sub> ) δ = 8.66 (s, 1H), 8.38 (d, <i>J</i> =8.0 Hz, 1H), 7.91 (s, 1H), 7.78 (d, <i>J</i> =8.0 Hz, 1H), 6.86 (t, <i>J</i> =8.8 Hz, 1H), 6.65 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.84 (br s, 2H), 4.58 (t, <i>J</i> =8.4 Hz, 2H), 3.40 (t, <i>J</i> =8.8 Hz, 2H), 2.82 (s, 3H), 2.64 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 415.3.                                                         |

| Ex. # | Structure                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                             |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 68    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyrazin-2-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                 | <sup>1</sup> H NMR (400 MHz, methanol- <i>d</i> <sub>4</sub> ) δ = 9.85 (d, <i>J</i> =1.2 Hz, 1H), 8.77 (s, 1H), 8.68 - 8.65 (m, 1H), 8.63 (s, 1H), 8.50 (d, <i>J</i> =2.4 Hz, 1H), 6.86 (t, <i>J</i> =8.8 Hz, 1H), 6.65 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.86 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.38 (t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [ <i>M</i> + 1]: 388.2.        |
| 69    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyrimidin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>       | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ = 9.18 (s, 2H), 8.01 (s, 1H), 7.95 (s, 1H), 6.87 (t, <i>J</i> =9.2 Hz, 1H), 6.69 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.64 (s, 1H), 4.86 (br d, <i>J</i> =4.0 Hz, 2H), 4.65 (br t, <i>J</i> =8.4 Hz, 2H), 3.43 (br t, <i>J</i> =8.4 Hz, 2H), 2.81 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 402.1.                                       |
| 70    |  <p>8-(2-cyclopropylpyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.21 (s, 2H), 9.04 (s, 1H), 8.83 (s, 1H), 8.24 (s, 1H), 6.94 (t, <i>J</i> =8.8 Hz, 1H), 6.69 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.74 (br d, <i>J</i> =4.0 Hz, 2H), 4.53 (br t, <i>J</i> =8.8 Hz, 2H), 3.31 (br t, <i>J</i> =8.4 Hz, 2H), 2.30 - 2.21 (m, 1H), 1.10 - 1.05 (m, 4H).<br>LCMS [ <i>M</i> + 1]: 428.2. |
| 71    |  <p>8-(2,4-dimethylpyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.60 (t, <i>J</i> =4.8 Hz, 1H), 8.54 (s, 1H), 7.84 (s, 1H), 7.00 - 6.90 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.36 - 3.32 (m, 2H), 2.63 (s, 3H), 2.34 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 416.1.                            |

| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 72    |  <p>8-(1,3-dimethyl-1H-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>      | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.90 (s, 1H), 8.32 (br t, <i>J</i> =5.2 Hz, 1H), 8.16 (s, 1H), 7.85 (s, 1H), 6.95 (t, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.84 (s, 3H), 3.31 - 3.26 (m, 2H), 2.30 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 404.3.                                                                                                                               |
| 73    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(methylsulfonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>          | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.03 (s, 1H), 8.79 (t, <i>J</i> =5.2 Hz, 1H), 8.39 - 8.32 (m, 3H), 8.07 (d, <i>J</i> =8.8 Hz, 2H), 7.02 (t, <i>J</i> =8.8 Hz, 1H), 6.78 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.82 (d, <i>J</i> =4.8 Hz, 2H), 4.62 (t, <i>J</i> =8.8 Hz, 2H), 3.38 - 3.35 (m, 2H), 3.32 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 464.2.                                                                                                                       |
| 74    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(pyrrolidin-1-ylmethyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.83 (br s, 1H), 8.96 (s, 1H), 8.61 (t, <i>J</i> =5.6 Hz, 1H), 8.18 (s, 1H), 8.10 (d, <i>J</i> =8.4 Hz, 2H), 7.61 (d, <i>J</i> =8.4 Hz, 2H), 6.99 - 6.92 (m, 1H), 6.72 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.75 (br d, <i>J</i> =4.4 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.41 (br d, <i>J</i> =5.2 Hz, 2H), 3.43 - 3.39 (m, 4H), 3.19 - 3.09 (m, 2H), 2.12 - 2.01 (m, 2H), 1.93 - 1.82 (m, 2H).<br>LCMS [ <i>M</i> + 1]: 469.2. |

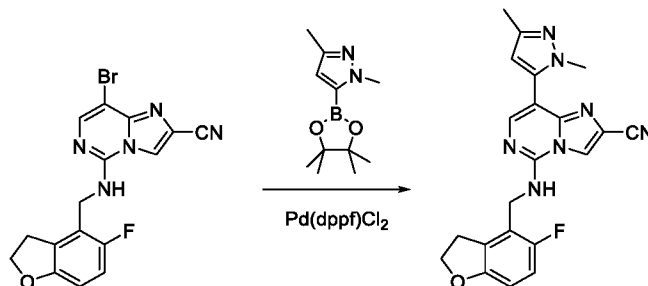
| Ex. # | Structure                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 75    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(morpholinomethyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.89 (br s, 1H), 8.96 (s, 1H), 8.62 (br s, 1H), 8.18 (s, 1H), 8.11 (br d, <i>J</i> =7.2 Hz, 2H), 7.60 (br d, <i>J</i> =7.2 Hz, 2H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.75 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.41 (br s, 2H), 3.99 (br d, <i>J</i> =11.2 Hz, 2H), 3.64 (br t, <i>J</i> =11.2 Hz, 2H), 3.35 - 3.30 (m, 4H), 3.22 - 3.08 (m, 2H).<br>LCMS [M+1]: 485.4. |
| 76    |  <p>5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,N,4-trimethylpicolinamide</p>  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.59 (s, 1H), 8.45 (s, 1H), 7.85 (s, 1H), 7.53 (s, 1H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =2.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.38 - 3.33 (m, 2H), 3.03 (s, 3H), 3.01 (s, 3H), 2.25 (s, 3H).<br>LCMS [M + 1]: 472.2.                                                                                                                              |
| 77    |  <p>8-cyclopropyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.83 (s, 1H), 8.18 (br s, 1H), 7.51 (s, 1H), 6.93 (t, <i>J</i> =8.8 Hz, 1H), 6.69 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.64 (s, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 3.27 (t, <i>J</i> =8.8 Hz, 2H), 2.08-2.03 (m, 1H), 0.92 - 0.84 (m, 4H).<br>LCMS [M + 1]: 350.2.                                                                                                                                                                   |
| 78    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((6-fluorochroman-5-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>            | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.96 (s, 1H), 8.66 (t, <i>J</i> =5.2 Hz, 1H), 7.82 (s, 1H), 7.09 - 6.99 (m, 1H), 6.91 (d, <i>J</i> =7.2 Hz, 1H), 6.70 (d, <i>J</i> =7.6 Hz, 1H), 6.23 (s, 1H), 4.69 (d, <i>J</i> =5.2 Hz, 2H), 4.16 - 4.05 (m, 2H), 3.68 (s, 3H), 2.77 (t, <i>J</i> =6.4 Hz, 2H), 2.18 (s, 3H), 2.03 - 1.89 (m, 2H).<br>LC-MS [M+1]: 400.3.                                                                                                        |

| Ex. # | Structure                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                   |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 79    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(3-methyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                  | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.90 (s, 1H), 8.33 (t, <i>J</i> =5.2 Hz, 1H), 7.98 (s, 1H), 7.82 (s, 1H), 7.00 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.30 (br t, <i>J</i> =8.8 Hz, 2H), 2.35 (s, 3H).<br>LCMS [M+1]: 390.3.                                    |
| 80    |  <p>8-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.89 (s, 1H), 8.30 (br s, 1H), 8.12 (s, 1H), 7.88 (s, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.70 (s, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 4.12 (t, <i>J</i> =7.2 Hz, 2H), 3.28 - 3.23 (m, 2H), 3.12 (t, <i>J</i> =6.8 Hz, 2H), 2.65 - 2.56 (m, 2H).<br>LCMS [M+1]: 416.1. |
| 81    |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluorobenzo[b]thiophen-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                   | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.60 (s, 1H), 7.96 - 7.89 (m, 2H), 7.75 (d, <i>J</i> =5.6 Hz, 1H), 7.71 (dd, <i>J</i> =0.8, 5.6 Hz, 1H), 7.24 (t, <i>J</i> =9.6 Hz, 1H), 6.33 (s, 1H), 5.25 (d, <i>J</i> =1.2 Hz, 2H), 3.77 (s, 3H), 2.32 (s, 3H).<br>LCMS [M+1]: 418.2.                                                                         |
| 82    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((trifluoromethyl)sulfonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.02 (s, 1H), 8.91 (t, <i>J</i> =5.2 Hz, 1H), 8.54 (d, <i>J</i> =8.8 Hz, 2H), 8.44 (s, 1H), 8.20 (d, <i>J</i> =8.8 Hz, 2H), 6.99 - 6.92 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.78 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.30 - 3.27 (m, 2H).<br>LC-MS [M+1]: 518.3.             |

| Ex. # | Structure                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 83    |  <p>8-(2-chloro-4-((dimethylamino)methyl)-3-fluorophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.64 (s, 1H), 7.87 (s, 1H), 7.61 - 7.55 (t, <i>J</i> =7.2 Hz, 1H), 7.48 (d, <i>J</i> =8.4 Hz, 1H), 6.87 (t, <i>J</i> =9.6 Hz, 1H), 6.66 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.84 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 4.52 (s, 2H), 3.39 (t, <i>J</i> =8.8 Hz, 2H), 2.97 (s, 6H).<br>LCMS [M + 1]: 495.3.                                                                                                 |
| 84    |  <p>8-(4-((dimethylamino)methyl)-5-fluoro-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.82 (br s, 1H), 8.94 (s, 1H), 8.60 (br t, <i>J</i> =4.4 Hz, 1H), 7.78 (s, 1H), 7.53 (d, <i>J</i> =7.6 Hz, 1H), 7.33 (d, <i>J</i> =10.8 Hz, 1H), 7.01 - 6.91 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.37 (br s, 2H), 3.33 (t, <i>J</i> =8.8 Hz, 2H), 2.83 (s, 6H), 2.18 (s, 3H). LCMS [M+1]: 475.4.                      |
| 85    |  <p>8-(4-((dimethylamino)methyl)-3-fluoro-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.80 (br s, 1H), 8.94 (s, 1H), 8.59 (t, <i>J</i> =4.8 Hz, 1H), 7.76 (s, 1H), 7.47 (t, <i>J</i> =7.6 Hz, 1H), 7.30 (d, <i>J</i> =8.0 Hz, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.40 (br s, 2H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H), 2.82 (s, 6H), 2.11 (d, <i>J</i> =2.0 Hz, 3H).<br>LC-MS [M+1]: 475.3. |

## EXAMPLE 86

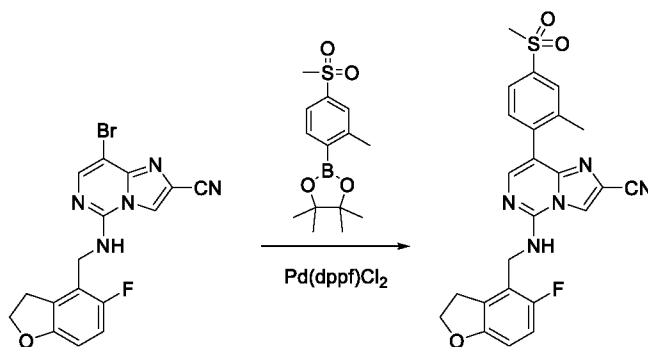
## 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000355] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (90.0 mg, 231  $\mu$ mol, 1.00 equiv), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (103 mg, 463  $\mu$ mol, 2.00 equiv), Pd(dppf)Cl<sub>2</sub> (16.9 mg, 23.1  $\mu$ mol, 0.100 equiv), sodium bicarbonate (58.4 mg, 695  $\mu$ mol, 27.0  $\mu$ L, 3 equiv) in dioxane (6.00 mL) and water (3.00 mL) was purged with nitrogen. The resultant mixture was stirred at 100 °C for 2 h under an atmosphere of nitrogen. Water (8.00 mL) was added and the mixture was extracted with ethyl acetate (8.00 mL  $\times$  3). The combined organic layer was concentrated *in vacuo* to give a residue. The crude material was purified by Prep-HPLC (column: Phenomenex Synergi C18 150\*25\*10  $\mu$ m; mobile phase: [water(0.1%TFA)-ACN];B%: 33%-63%,13min) to 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (51.0 mg, 120  $\mu$ mol, 52.0% yield, 95.4% purity) as a white solid. LC-MS: [M+1] 404. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.92 (s, 1H), 8.64 (br t, *J* = 4.8 Hz, 1H), 7.86 (s, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd, *J* = 4.0, 8.8 Hz, 1H), 6.23 (s, 1H), 4.72 (br d, *J* = 4.4 Hz, 2H), 4.55 (t, *J* = 8.8 Hz, 2H), 3.67 (s, 3H), 3.31 (t, *J* = 8.8 Hz, 2H), 2.18 (s, 3H).

## EXAMPLE 87

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-4-(methylsulfonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile



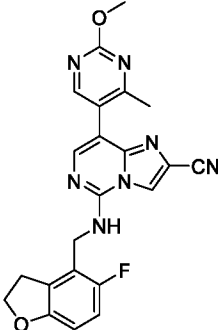
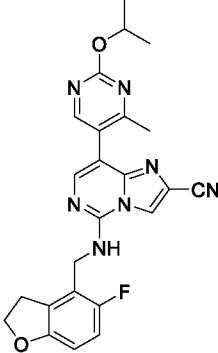
[000356] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (90.0 mg, 231  $\mu$ mol, 1.00 equiv), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (103 mg, 463  $\mu$ mol, 2.00 equiv), Pd(dppf)Cl<sub>2</sub> (16.9 mg, 23.1  $\mu$ mol, 0.100 equiv), sodium bicarbonate (58.4 mg, 695  $\mu$ mol, 27.0  $\mu$ L, 3 equiv) in dioxane (6.00 mL) and water (3.00 mL) was purged with nitrogen. The resultant mixture was stirred at 100 °C for 2 h under an atmosphere of nitrogen. Water (8.00 mL) was added and the mixture was extracted with ethyl acetate (8.00 mL  $\times$  3).

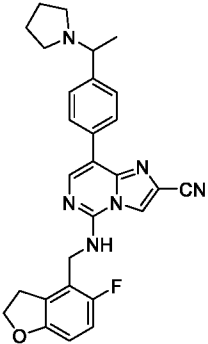
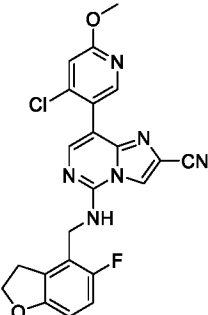
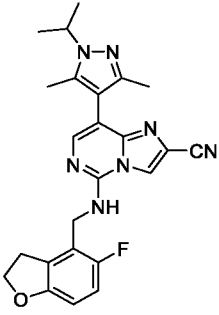
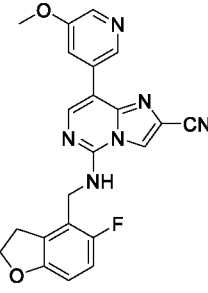
The combined organic layer was concentrated *in vacuo* to give a residue. The crude material was purified by Prep-HPLC (column: Phenomenex Synergi C18 150\*25\*10  $\mu\text{m}$ ; mobile phase: [water(0.1%TFA)-ACN];B%: 33%-63%,13min) to 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (51.0 mg, 120  $\mu\text{mol}$ , 52.0% yield, 95.4% purity) as a white solid. LC-MS: [M+1] 404.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 8.92 (s, 1H), 8.64 (br t,  $J$  = 4.8 Hz, 1H), 7.86 (s, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd,  $J$  = 4.0, 8.8 Hz, 1H), 6.23 (s, 1H), 4.72 (br d,  $J$  = 4.4 Hz, 2H), 4.55 (t,  $J$  = 8.8 Hz, 2H), 3.67 (s, 3H), 3.31 (t,  $J$  = 8.8 Hz, 2H), 2.18 (s, 3H).

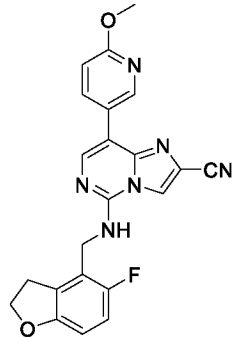
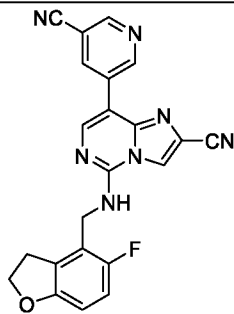
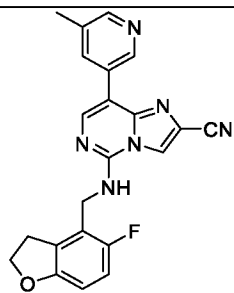
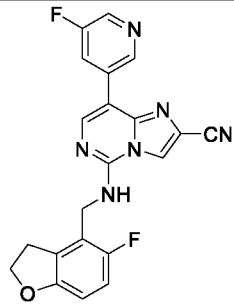
[000357] EXAMPLES 88 -136 were prepared following the procedure set forth in Example 87 and using the general reactions schemes and intermediates described herein.

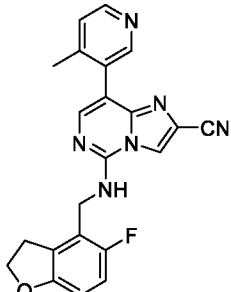
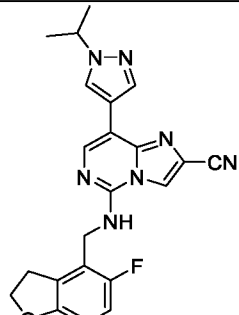
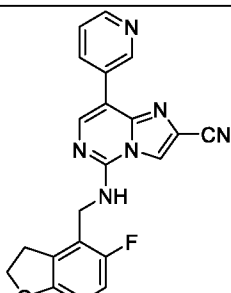
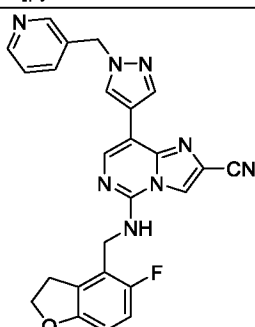
TABLE 4

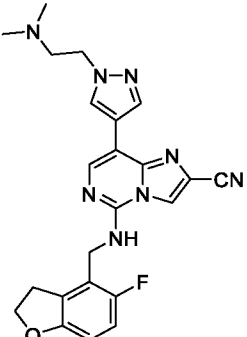
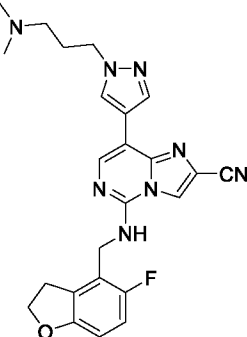
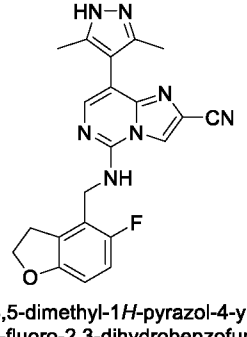
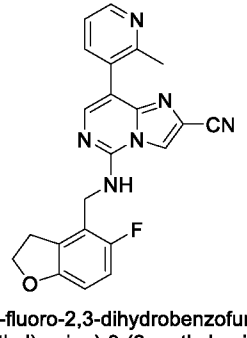
Characterization of EXAMPLES 88-136

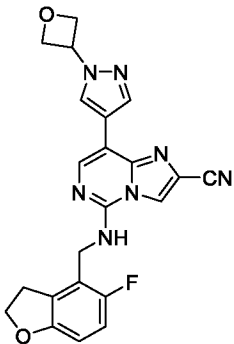
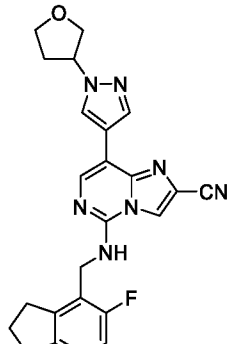
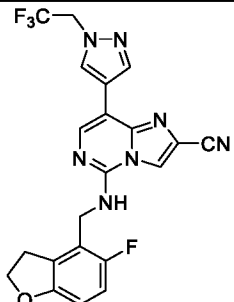
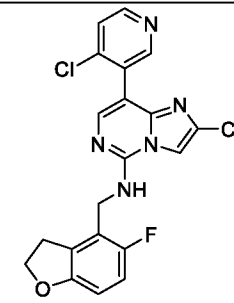
| Ex. # | Structure                                                                                                                                                                                                                        | $^1\text{H}$ NMR                                                                                                                                                                                                                                                                                                                                      |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 88    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methoxy-4-methylpyrimidin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | $^1\text{H}$ NMR (400MHz, $\text{CDCl}_3$ ) $\delta$ = 8.45 (s, 1H), 8.00 (s, 1H), 7.74 (s, 1H), 6.86 (t, $J$ =9.2 Hz, 1H), 6.69 (dd, $J$ =4.0, 8.8 Hz, 1H), 5.76 (br s, 1H), 4.84 (s, 2H), 4.65 (t, $J$ =8.8 Hz, 2H), 4.09 (s, 4H), 3.43 (t, $J$ =8.8 Hz, 2H), 2.46 (s, 3H).<br>LCMS: [M+1] 432.2.                                                   |
| 89    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-isopropoxy-4-methylpyrimidin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | $^1\text{H}$ NMR (400MHz, DMSO- $d_6$ ) $\delta$ = 8.93 (s, 1H), 8.57 (br t, $J$ =5.2 Hz, 1H), 8.43 (s, 1H), 7.82 (s, 1H), 6.96 (t, $J$ =9.2 Hz, 1H), 6.72 (dd, $J$ =4.0, 8.8 Hz, 1H), 5.29 - 5.23 (m, 1H), 4.73 (d, $J$ =4.8 Hz, 2H), 4.56 (t, $J$ =8.8 Hz, 2H), 3.38 - 3.35 (m, 2H), 2.30 (s, 3H), 1.35 (d, $J$ =6.4 Hz, 6H).<br>LCMS: [M+1] 460.4. |

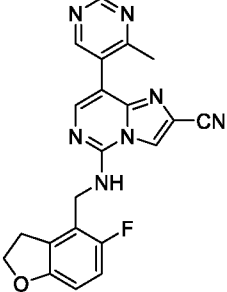
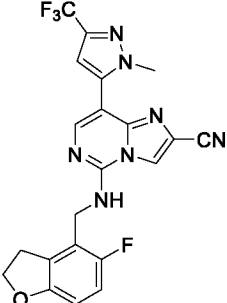
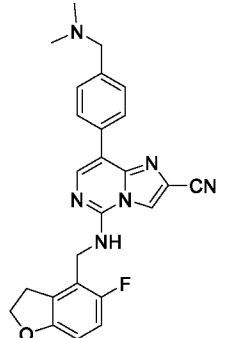
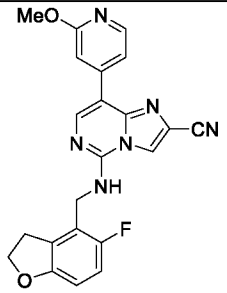
| Ex. # | Structure                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 90    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(1-(pyrrolidin-1-yl)ethyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>         | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ = 8.65 (s, 1H), 8.07 (s, 1H), 8.03 (d, <i>J</i> =8.4 Hz, 2H), 7.60 (d, <i>J</i> =8.4 Hz, 2H), 6.91 - 6.84 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.84 (s, 3H), 4.60 (t, <i>J</i> =8.4 Hz, 2H), 4.45 (q, <i>J</i> =6.8 Hz, 1H), 3.83 (m, 1H), 3.39 (t, <i>J</i> =8.8 Hz, 2H), 3.20 - 3.02 (m, 2H), 2.28 - 1.91 (m, 5H), 1.80 (d, <i>J</i> =6.8 Hz, 3H).<br>LCMS: [M+1] 483.4. |
| 91    |  <p>8-(4-chloro-6-methoxypyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>             | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ = 8.17 (s, 1H), 7.83 (s, 1H), 7.74 (s, 1H), 6.87 (s, 1H), 6.79 (t, <i>J</i> =9.6 Hz, 1H), 6.62 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.43 (br s, 1H), 4.76 (s, 2H), 4.57 (t, <i>J</i> =8.8 Hz, 2H), 3.91 (s, 3H), 3.36 (t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [M+1]: 451.                                                                                                                          |
| 92    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-3,5-dimethyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.88 (s, 1H), 8.34 (br t, <i>J</i> =4.8 Hz, 1H), 7.63 (s, 1H), 6.95 (t, <i>J</i> =9.6 Hz, 1H), 6.71 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.70 (br d, <i>J</i> =4.4 Hz, 2H), 4.61 - 4.36 (m, 3H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H), 2.13 (s, 3H), 2.05 (s, 3H), 1.39 (d, <i>J</i> =6.8 Hz, 6H).<br>LC-MS [M+1]:446.                                                                        |
| 93    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-methoxypyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.96 (s, 1H), 8.81 (d, <i>J</i> =1.6 Hz, 1H), 8.66 (br s, 1H), 8.29 (d, <i>J</i> =2.8 Hz, 1H), 8.27 (s, 1H), 7.98 - 7.96 (m, 1H), 7.01 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.75 (br s, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 3.90 (s, 3H), 3.30 - 3.28 (m, 2H).<br>LCMS: [M+1] 417.3.                                                                                 |

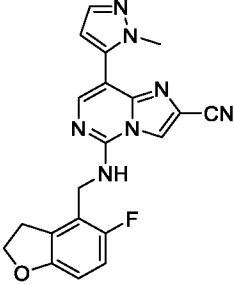
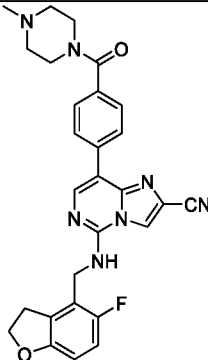
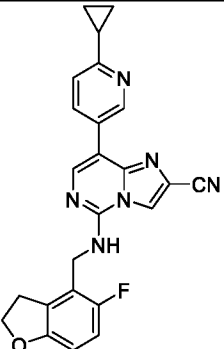
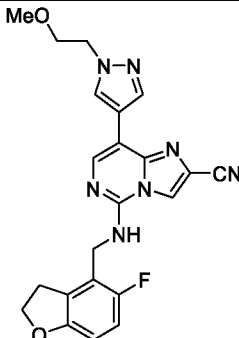
| Ex. # | Structure                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                            |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 94    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-methoxypyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>  | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.93 (s, 1H), 8.74 (d, <i>J</i> =2.4 Hz, 1H), 8.53 (br s, 1H), 8.29 (dd, <i>J</i> =2.4, 8.8 Hz, 1H), 8.11 (s, 1H), 7.01 - 6.89 (m, 2H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.90 (s, 3H), 3.31 - 3.28 (m, 2H).<br>LCMS: [M+1] 417.3.                                 |
| 95    |  <p>8-(5-cyanopyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.52 (d, <i>J</i> =2.4 Hz, 1H), 9.00 - 8.97 (m, 2H), 8.90 (t, <i>J</i> =2.0 Hz, 1H), 8.81 (t, <i>J</i> =4.8 Hz, 1H), 8.39 (s, 1H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.31 (br s, 2H).<br>LCMS: [M+1] 412.3.         |
| 96    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.42 (s, 1H), 9.26 - 9.16 (m, 2H), 8.99 (s, 1H), 8.72 (s, 1H), 8.48 (s, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.76 (br d, <i>J</i> =4.4 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.34 (br t, <i>J</i> =8.8 Hz, 2H), 2.54 (s, 3H).<br>LCMS: [M+1] 401.1.                            |
| 97    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-fluoropyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.13 (s, 1H), 9.04 (s, 1H), 8.86 (br t, <i>J</i> =4.8 Hz, 1H), 8.56 (d, <i>J</i> =2.4 Hz, 1H), 8.43 - 8.30 (m, 2H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.75 (br d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H).<br>LCMS: [M + 1] 405.1. |

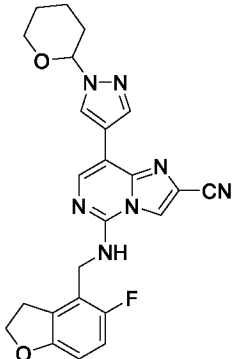
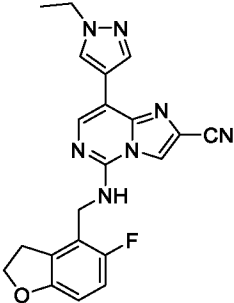
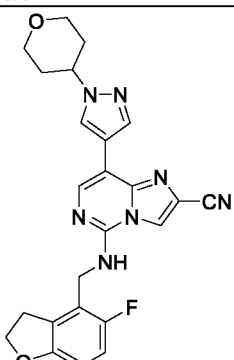
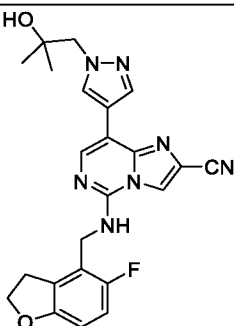
| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 98    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                     | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.11 (s, 1H), 9.02 (br s, 1H), 8.86 (s, 1H), 8.81 (d, <i>J</i> =5.6 Hz, 1H), 8.02 (d, <i>J</i> =6.0 Hz, 1H), 7.96 (s, 1H), 6.95 (t, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.74 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.35 (br t, <i>J</i> =8.4 Hz, 2H), 2.48 (br s, 3H).<br>LCMS: [M+1] 401.1.                                                               |
| 99    |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-isopropyl-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>              | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.41 (s, 1H), 8.39 - 8.35 (m, 1H), 8.17 (s, 1H), 8.11 (s, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.70 (br d, <i>J</i> =3.6 Hz, 2H), 4.64 - 4.57 (m, 1H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.30 (br t, <i>J</i> =8.8 Hz, 2H), 1.46 (d, <i>J</i> =6.4 Hz, 6H).<br>LCMS: [M+1] 418.3.                                                                         |
| 100   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                           | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 9.40 (d, <i>J</i> =1.6 Hz, 1H), 9.11 (s, 1H), 9.02 (br t, <i>J</i> =4.8 Hz, 1H), 8.87 (br d, <i>J</i> =8.0 Hz, 1H), 8.72 (d, <i>J</i> =5.2 Hz, 1H), 8.39 (s, 1H), 7.87 (dd, <i>J</i> =5.6, 8.0 Hz, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.76 (br d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.4 Hz, 2H), 3.33 (br t, <i>J</i> =8.8 Hz, 2H).<br>LCMS: [M + 1] 387.3. |
| 101   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.92 (s, 1H), 8.69 - 8.60 (m, 3H), 8.39 (br t, <i>J</i> =5.2 Hz, 1H), 8.21 (s, 1H), 8.18 (s, 1H), 7.91 (br d, <i>J</i> =8.0 Hz, 1H), 7.63 - 7.54 (m, 1H), 6.99 - 6.88 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.55 (s, 2H), 4.71 (br d, <i>J</i> =4.4 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.29 (t, <i>J</i> =8.8 Hz, 2H).<br>LCMS: [M+1] 467.3.                                                 |

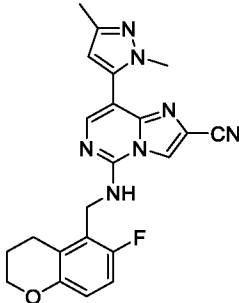
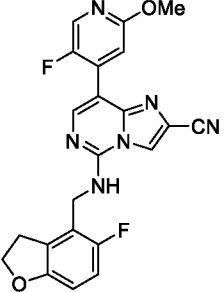
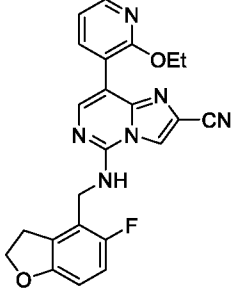
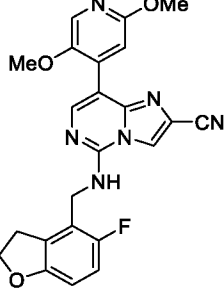
| Ex. # | Structure                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 102   |  <p>8-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.92 (s, 1H), 8.43 (s, 1H), 8.38 (t, <i>J</i> =4.8 Hz, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.70 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.29 (t, <i>J</i> =6.4 Hz, 2H), 3.32 - 3.27 (m, 2H), 2.72 (br t, <i>J</i> =6.0 Hz, 2H), 2.21 (s, 6H).<br>LCMS: [M+1] 447.3.             |
| 103   |  <p>8-(1-(3-(dimethylamino)propyl)-1H-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.92 (s, 1H), 8.48 (s, 1H), 8.40 (t, <i>J</i> =5.2 Hz, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.29 (t, <i>J</i> =6.8 Hz, 2H), 3.30 - 3.27 (m, 2H), 3.08 (br s, 2H), 2.79 (s, 6H), 2.23 - 2.15 (m, 2H)<br>LCMS: [M+1] 461.                        |
| 104   |  <p>8-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>               | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 12.34 (br s, 1H), 8.95 (s, 1H), 8.45 (br s, 1H), 7.64 (s, 1H), 6.95 (t, <i>J</i> =9.6 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.70 (br s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.31 (br s, 2H), 2.31 - 1.94 (m, 6H).<br>LCMS: [M+1] 404.                                                                                                                       |
| 105   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                       | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.93 (s, 1H), 8.56 - 8.51 (m, 1H), 8.50 (dd, <i>J</i> =1.6, 4.8 Hz, 1H), 7.79 (s, 1H), 7.70 (dd, <i>J</i> =1.6, 7.6 Hz, 1H), 7.31 (dd, <i>J</i> =4.8, 7.6 Hz, 1H), 6.96 (t, <i>J</i> =9.6 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.73 (br d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.33 - 3.32 (m, 2H), 2.37 (s, 3H).<br>LC-MS: [M+1] 400.9. |

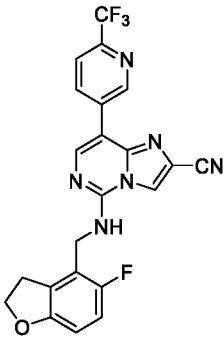
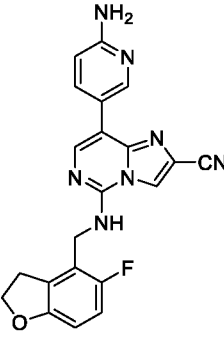
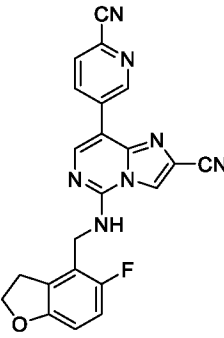
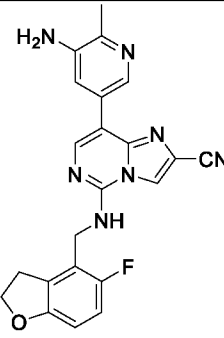
| Ex. # | Structure                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 106   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>            | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.88 (s, 1H), 8.53 (s, 1H), 8.43 (br s, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 6.94 (t, <i>J</i> =9.6 Hz, 1H), 6.69 (dd, <i>J</i> =3.7, 8.8 Hz, 1H), 5.72 (quin, <i>J</i> =7.2 Hz, 1H), 4.94 (d, <i>J</i> =7.2 Hz, 4H), 4.70 (s, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.31 - 3.26 (m, 2H).<br>LCMS: [M+1] 432.                                                           |
| 107   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.46 (s, 1H), 8.38 (br t, <i>J</i> =5.2 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.18 - 5.10 (m, 1H), 4.70 (br d, <i>J</i> =4.4 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.04 - 3.96 (m, 2H), 3.94 - 3.81 (m, 2H), 3.32 - 3.26 (m, 2H), 2.45 - 2.35 (m, 2H).<br>LCMS: [M+1] 446.3. |
| 108   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.61 (s, 1H), 8.43 (t, <i>J</i> =5.2 Hz, 1H), 8.25 (s, 2H), 6.94 (t, <i>J</i> =8.8 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.29 - 5.22 (m, 2H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 3.31 - 3.27 (m, 2H).<br>LCMS: [M + 1] 458.2.                                                                                  |
| 109   |  <p>8-(4-chloropyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                     | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.94 (s, 1H), 8.66 (s, 2H), 8.59 (d, <i>J</i> =5.6 Hz, 1H), 7.91 (s, 1H), 7.71 (d, <i>J</i> =5.6 Hz, 1H), 6.96 (t, <i>J</i> =9.6 Hz, 1H), 6.72 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.74 (br s, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.35 (br s, 2H).<br>LCMS [M+1]: 421/423.                                                                                          |

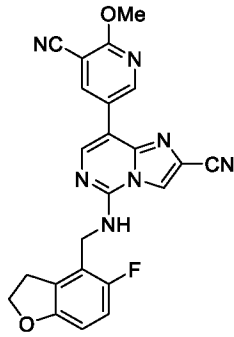
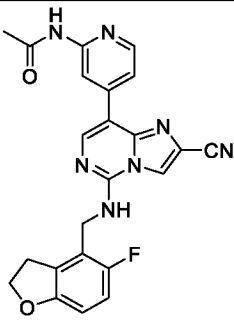
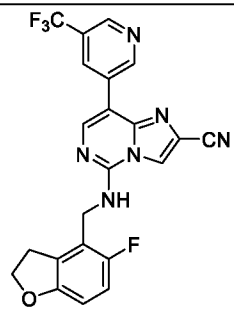
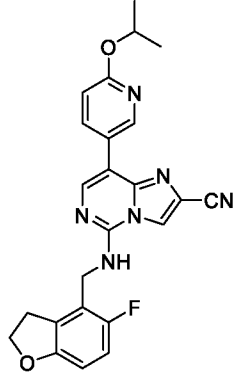
| Ex. # | Structure                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 110   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methylpyrimidin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                       | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 9.25 (s, 1H), 8.93 (s, 1H), 8.66 (s, 1H), 7.93 (s, 1H), 6.89 - 6.82 (m, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.85 (br s, 2H), 4.59 (t, <i>J</i> =8.4 Hz, 2H), 3.41 (t, <i>J</i> =8.8 Hz, 2H), 2.60 (s, 3H).<br>LCMS: [M+1]: 402.1.                                                                                                                             |
| 111   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.96 (s, 1H), 8.79 (br t, <i>J</i> =5.2 Hz, 1H), 8.00 (s, 1H), 7.00 - 6.93 (m, 2H), 6.72 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.75 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.87 (s, 3H), 3.30 - 3.29 (m, 2H).<br>LCMS [M+1]: 458.                                                                                                           |
| 112   |  <p>8-(4-((dimethylamino)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>            | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ= 8.96 (s, 1H), 8.55 (t, <i>J</i> = 4.4 Hz, 1H), 8.10 (s, 1H), 7.93 (d, <i>J</i> = 8.0 Hz, 2H), 7.39 (d, <i>J</i> = 8.4 Hz, 2H), 6.95 (t, <i>J</i> = 9.2 Hz, 1H), 6.71 (dd, <i>J</i> = 8.8, 4.0 Hz, 1H), 4.73 (d, <i>J</i> = 4.8 Hz, 2H), 4.55 (t, <i>J</i> = 8.8 Hz, 2H), 3.47 (s, 1H), 3.33 - 3.28 (m, 4H), 2.20 (s, 6H).<br>LCMS [M + 1]: 443.1.          |
| 113   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methoxypyridin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                      | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ = 8.25 (d, <i>J</i> = 5.6 Hz, 1H), 8.10 (s, 1H), 7.91 (s, 1H), 7.45 (dd, <i>J</i> = 5.2, 1.2 Hz, 1H), 7.40 (s, 1H), 6.85 (t, <i>J</i> = 9.2 Hz, 1H), 6.68 (dd, <i>J</i> = 8.4, 4.0 Hz, 1H), 5.56 (t, <i>J</i> = 5.6 Hz, 1H), 4.84 (d, <i>J</i> = 5.6 Hz, 2H), 4.64 (t, <i>J</i> = 8.4 Hz, 2H), 3.99 (s, 3H), 3.42 (t, <i>J</i> = 8.8 Hz, 2H).<br>LCMS [M + 1]: 417.0. |

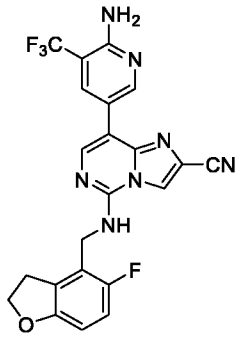
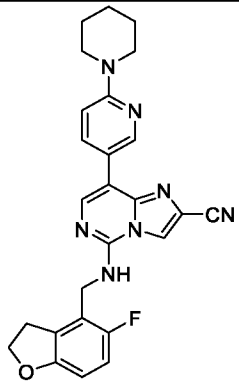
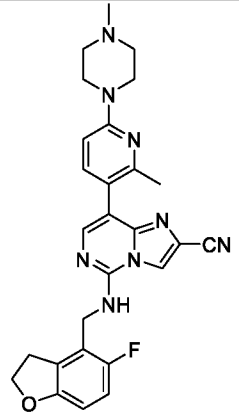
| Ex. # | Structure                                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 114   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.62 (s, 1H), 7.88 (s, 1H), 7.55 (s, 1H), 6.85 (br t, <i>J</i> =8.8 Hz, 1H), 6.69 - 6.60 (m, 1H), 6.47 (s, 1H), 4.58 (br t, <i>J</i> =8.8 Hz, 2H), 3.81 (s, 3H), 3.40 - 3.35 (m, 2H).<br>LCMS [ <i>M</i> + 1]: 390.2.                                                                                                                                                                             |
| 115   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(4-methylpiperazine-1-carbonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.65 (s, 1H), 8.08 (s, 1H), 8.04 (d, <i>J</i> =8.4 Hz, 2H), 7.61 (d, <i>J</i> =8.0 Hz, 2H), 6.91 - 6.83 (m, 1H), 6.66 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.84 (s, 2H), 4.59 (t, <i>J</i> =8.8 Hz, 2H), 3.67 - 3.34 (m, 8H), 3.28 - 3.16 (m, 2H), 2.99 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 512.4.                                                                                                      |
| 116   |  <p>8-(6-cyclopropylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>             | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ = 8.82 (d, <i>J</i> = 2.0 Hz, 1H), 8.18 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.25 (d, <i>J</i> = 8.4 Hz, 1H), 6.82 - 6.90 (m, 1H), 6.69 (dd, <i>J</i> = 8.8, 4.0 Hz, 1H), 5.47 (t, <i>J</i> = 6.0 Hz, 1H), 4.83 (d, <i>J</i> = 5.2 Hz, 2H), 4.65 (t, <i>J</i> = 8.4 Hz, 2H), 3.43 (t, <i>J</i> = 8.8 Hz, 2H), 2.10 (m, 1H), 1.06 (m, 4H).<br>LCMS [ <i>M</i> + 1]: 427.1. |
| 117   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>    | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ ppm 8.93 (s, 1H), 8.43 - 8.38 (m, 2H), 8.17 (s, 1H), 8.11 (s, 1H), 6.97 - 6.89 (m, 1H), 6.69 (dd, <i>J</i> =8.4, 4.0 Hz, 1H), 4.70 (d, <i>J</i> =5.2 Hz, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 4.33 (t, <i>J</i> =5.26 Hz, 2H), 3.71 (t, <i>J</i> =5.2 Hz, 2H), 3.29 (t, <i>J</i> =8.8 Hz, 2H), 3.23 (s, 3H).<br>LCMS [ <i>M</i> + 1]: 434.0.                                             |

| Ex. # | Structure                                                                                                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 118   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ ppm = 8.50 (s, 1 H), 7.98 (s, 1 H), 7.92 (br s, 1 H), 7.77 (s, 1 H), 6.82 - 6.74 (m, 1 H), 6.61 (dd, <i>J</i> =8.8, 4.0 Hz, 1 H), 5.41 (dd, <i>J</i> =9.6, 2.4 Hz, 1 H), 4.71 (s, 2 H), 4.57 (t, <i>J</i> =8.8 Hz, 2 H), 4.12 - 3.98 (m, 1 H), 3.78 - 3.61 (m, 1 H), 3.35 (t, <i>J</i> =8.8 Hz, 2 H), 2.25 - 1.88 (m, 3 H), 1.77 - 1.47 (m, 3 H).<br>LCMS [M+1]: 460.4.      |
| 119   |  <p>8-(1-ethyl-1H-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                        | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.91 (s, 1H), 8.42 (s, 1H), 8.36 (t, <i>J</i> =5.2 Hz, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 6.98 - 6.92 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.70 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.24 - 4.19 (m, 2H), 3.30 (t, <i>J</i> =8.8 Hz, 2H), 1.41 (t, <i>J</i> =7.6 Hz, 3H).<br>LCMS [M + 1]: 404.2.                                   |
| 120   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.91 (s, 1 H), 8.46 (s, 1 H), 8.37 (t, <i>J</i> =4.8 Hz, 1 H), 8.18 (s, 1 H), 8.14 (s, 1 H), 6.92 - 6.98 (m, 1 H), 6.70 (dd, <i>J</i> =8.4, 3.6 Hz, 1 H), 4.73 - 5.66 (m, 1 H), 4.71 (d, <i>J</i> =5.2 Hz, 2 H), 4.48 - 4.57 (m, 3 H), 4.02-3.94 (m, 2 H), 3.46 - 3.69 (m, 2 H), 3.30 (t, <i>J</i> =8.8 Hz, 2 H), 1.96 - 2.04 (m, 4 H).<br>LCMS: [M + 1]: 460.3. |
| 121   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.90 (s, 1H), 8.43 (s, 1H), 8.35 (br s, 1H), 8.19 (s, 1H), 8.09 (s, 1H), 6.98 - 6.90 (m, 1H), 6.69 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (s, 1H), 4.70 (br s, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 4.08 (s, 2H), 3.31 - 3.26 (m, 2H), 1.08 (s, 6H).<br>LCMS [M + 1]: 448.2.                                                                                       |

| Ex. # | Structure                                                                                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 122   |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-((6-fluorochroman-5-yl)methyl)aminoimidazo[1,2-c]pyrimidine-2-carbonitrile</p>                    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.96 (s, 1H), 8.66 (t, <i>J</i> =5.2 Hz, 1H), 7.82 (s, 1H), 7.09 - 6.99 (m, 1H), 6.91 (d, <i>J</i> =7.2 Hz, 1H), 6.70 (d, <i>J</i> =7.6 Hz, 1H), 6.23 (s, 1H), 4.69 (d, <i>J</i> =5.2 Hz, 2H), 4.16 - 4.05 (m, 2H), 3.68 (s, 3H), 2.77 (t, <i>J</i> =6.4 Hz, 2H), 2.18 (s, 3H), 2.03 - 1.89 (m, 2H).<br>LC-MS: [M+1] 400.3.                                                                                                      |
| 123   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-fluoro-2-methoxypyridin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.94 (s, 1H), 8.80 (br s, 1H), 8.24 (d, <i>J</i> =2.4 Hz, 1H), 8.11 (d, <i>J</i> =0.8 Hz, 1H), 7.38 (d, <i>J</i> =5.2 Hz, 1H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (s, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.88 (s, 3H), 3.29 - 3.20 (m, 2H).<br>LCMS [M + 1]: 435.4.                                                                                                                    |
| 124   |  <p>8-(2-ethoxypyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>         | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.52 (t, <i>J</i> =4.8 Hz, 1H), 8.17 (dd, <i>J</i> =2.0, 5.2 Hz, 1H), 8.04 (dd, <i>J</i> =2.0, 7.6 Hz, 1H), 8.02 (s, 1H), 7.09 (dd, <i>J</i> =4.8, 7.2 Hz, 1H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.37 - 4.32 (m, 2H), 3.32 (t, <i>J</i> =8.8 Hz, 2H), 1.24 (t, <i>J</i> =7.2 Hz, 3H).<br>LCMS [M + 1]: 431.4. |
| 125   |  <p>8-(2,5-dimethoxypyridin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>    | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.63 (t, <i>J</i> =4.8 Hz, 1H), 8.03 (s, 1H), 7.99 (s, 1H), 7.15 (s, 1H), 6.98 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.32 - 3.27 (m, 2H).<br>LCMS [M + 1]: 447.3.                                                                                                                                      |

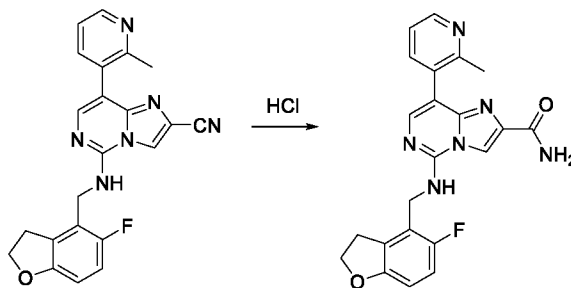
| Ex. # | Structure                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 126   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-(trifluoromethyl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.35 (d, <i>J</i> =1.6 Hz, 1H), 8.96 (s, 1H), 8.80 (br s, 1H), 8.75 (dd, <i>J</i> =2.0, 8.8 Hz, 1H), 8.39 (s, 1H), 8.00 (d, <i>J</i> =8.0 Hz, 1H), 6.95 (t, <i>J</i> =8.8 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.76 (s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.37 - 3.32 (m, 2H).<br>LCMS [ <i>M</i> + 1]: 455.3.                                                                |
| 127   |  <p>8-(6-aminopyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>             | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=8.97 (s, 1 H), 8.72 (d, <i>J</i> =2.0 Hz, 1 H), 8.68 (br t, <i>J</i> =4.0 Hz, 1 H), 8.49 (dd, <i>J</i> =1.6, 9.2 Hz, 1 H), 8.21 (s, 1 H), 7.98 (br s, 2 H), 7.04 (d, <i>J</i> =9.2 Hz, 1 H), 6.99 - 6.89 (m, 1 H), 6.71 (dd, <i>J</i> =8.8, 4.0 Hz, 1 H), 4.74 (d, <i>J</i> =4.8 Hz, 2 H), 4.55 (t, <i>J</i> =8.4 Hz, 2 H), 3.31 (t, <i>J</i> =8.8 Hz, 2 H).<br>LCMS [ <i>M</i> +1]: 402.3. |
| 128   |  <p>8-(6-cyanopyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>           | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=9.42 (d, <i>J</i> =1.6 Hz, 1 H), 8.98 (s, 1 H), 8.86 (br s, 1 H), 8.76 (dd, <i>J</i> = 8.4, 2.4 Hz, 1 H), 8.46 (s, 1 H), 8.14 (d, <i>J</i> =8.4 Hz, 1 H), 6.89 - 7.06 (m, 1 H), 6.72 (dd, <i>J</i> =8.4, 3.6 Hz, 1 H), 4.77 (br d, <i>J</i> =4.0 Hz, 2 H), 4.55 (t, <i>J</i> =8.8 Hz, 2 H), 3.32 - 3.30 (m, 2 H).<br>LCMS [ <i>M</i> +1]: 412.3.                                            |
| 129   |  <p>8-(5-amino-6-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=8.99 (s, 1 H), 8.83 (t, <i>J</i> =4.4 Hz, 1 H), 8.44 (s, 1 H), 8.27 (s, 1 H), 8.22 (s, 1 H), 6.96 (t, <i>J</i> =8.8 Hz, 1 H), 6.72 (dd, <i>J</i> =8.8, 4.0 Hz, 1 H), 6.35 (br s, 2 H), 4.76 (br d, <i>J</i> =4.8 Hz, 2 H), 4.56 (t, <i>J</i> =8.8 Hz, 2 H), 3.32 (br t, <i>J</i> =8.8 Hz, 2 H), 2.48 (br s, 3 H).<br>LCMS [ <i>M</i> +1]: 416.3.                                            |

| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 130   |  <p>8-(5-cyano-6-methoxypyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ=9.11 (d, <i>J</i> =2.4 Hz, 1 H), 8.98 (s, 1 H), 8.82 (d, <i>J</i> =2.8 Hz, 1 H), 8.72 (br s, 1 H), 8.24 (s, 1 H), 6.95 (t, <i>J</i> =9.2 Hz, 1 H), 6.71 (dd, <i>J</i> =8.0, 3.6 Hz, 1 H), 4.74 (s, 2 H), 4.55 (t, <i>J</i> =8.8 Hz, 2 H), 4.06 (s, 3 H), 3.30 - 3.29 (m, 2 H).<br>LCMS [M+1]: 442.3.                                                                                                            |
| 131   |  <p>N-(4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)pyridin-2-yl)acetamide</p>             | <sup>1</sup> H NMR (400MHz, DMSO) δ = 10.95 (s, 1H), 8.98 (s, 1H), 8.88 (br s, 1H), 8.70 (s, 1H), 8.37 - 8.33 (m, 2H), 7.83 (br d, <i>J</i> =5.6 Hz, 1H), 6.99 - 6.93 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.77 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 3.32 (t, <i>J</i> =8.8 Hz, 2H), 2.17 (s, 3H).<br>LCMS [M + 1]: 444.2.                                                                                                                |
| 132   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-(trifluoromethyl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.51 (s, 1H), 8.98 (s, 1H), 8.95 (s, 1H), 8.85 (s, 1H), 8.79 (br t, <i>J</i> =4.8 Hz, 1H), 8.43 (s, 1H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.76 (br d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.33 (br t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [M + 1]: 455.3.                                                                                                   |
| 133   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-isopropoxypyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>        | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1 H), 8.72 (d, <i>J</i> =2.4 Hz, 1 H), 8.53 (t, <i>J</i> =4.8 Hz, 1 H), 8.27 (dd, <i>J</i> =8.8, 2.4 Hz, 1 H), 8.10 (s, 1 H), 6.92 - 6.99 (m, 1 H), 6.86 (d, <i>J</i> =8.8 Hz, 1 H), 6.71 (dd, <i>J</i> =8.8, 4.0 Hz, 1 H), 5.30 (m, 1 H), 4.73 (d, <i>J</i> =4.8 Hz, 2 H), 4.55 (t, <i>J</i> =8.8 Hz, 2 H), 3.31 (t, <i>J</i> =8.4 Hz, 2 H), 1.33 (d, <i>J</i> =6.0 Hz, 6 H).<br>LCMS [M+1]: 445.3. |

| Ex. # | Structure                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 134   |  <p>8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>           | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1 H), 8.78 (d, <i>J</i> =1.6 Hz, 1 H), 8.52 (t, <i>J</i> =4.8 Hz, 1 H), 8.41 (d, <i>J</i> =2.0 Hz, 1 H), 8.14 (s, 1 H), 6.91 - 6.98 (m, 1 H), 6.71 (m, 3 H), 4.72 (d, <i>J</i> =4.8 Hz, 2 H), 4.55 (t, <i>J</i> =8.8 Hz, 2 H), 3.32 (t, <i>J</i> =8.8 Hz, 2 H).<br>LCMS: [M + 1]: 470.3.                                                                                       |
| 135   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-(piperidin-1-yl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.95 (s, 1H), 8.80 (d, <i>J</i> =1.6 Hz, 1H), 8.62 (br s, 1H), 8.40 (br d, <i>J</i> =9.6 Hz, 1H), 8.22 (s, 1H), 7.30 (br d, <i>J</i> =9.2 Hz, 1H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 1H), 3.66 (br s, 4H), 3.31 (br t, <i>J</i> =8.8 Hz, 2H), 1.65 (br s, 6H).<br>LCMS [M + 1]: 470.4. |
| 136   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.62 (s, 1H), δ = 7.74 (s, 1H), 7.71 (d, <i>J</i> =8.8 Hz, 1H), 6.97 (d, <i>J</i> =8.8 Hz, 1H), 6.86 (t, <i>J</i> =8.8 Hz, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.81 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.57 - 3.34 (m, 7H), 2.99 (s, 3H), 2.35 (s, 3H).<br>LCMS: [M+1]: 499.4.                                                                                                        |

## EXAMPLE 137

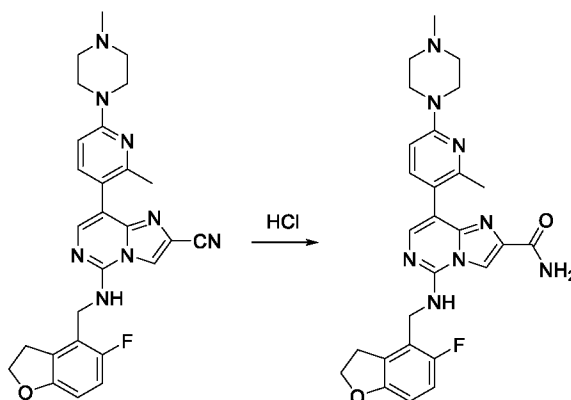
## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide



[000358] A mixture of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (38.0 mg, 92.5  $\mu\text{mol}$ , 1.00 equiv) in conc. hydrochloric acid (1.00 mL) was stirred at 26 °C for 4 h. The reaction mixture was adjusted to pH 7 with satd aq sodium bicarbonate aqueous solution at which time a precipitate formed. The precipitate was filtered and dried at reduced pressure. The crude product was washed with methanol (2.00 mL) and filtered to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (24.0 mg, 60.4 % yield, 97.4 % purity) as an off-white solid. LC-MS:  $[M+1]$  419.1.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 8.65 (s, 1H), 8.48 (m, 1H), 8.42 (br t,  $J$ =4.8 Hz, 1H), 7.72 (m, 1H), 7.65 (s, 1H), 7.50 (br s, 1H), 7.40 (br s, 1H), 7.30 (dd,  $J$ =4.8, 7.6 Hz, 1H), 6.94 (t,  $J$ =9.6 Hz, 1H), 6.70 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.72 (br d,  $J$ =4.4 Hz, 2H), 4.55 (t,  $J$ =8.8 Hz, 2H), 3.33 - 3.29 (m, 2H), 2.40 (s, 3H).

## EXAMPLE 138

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide

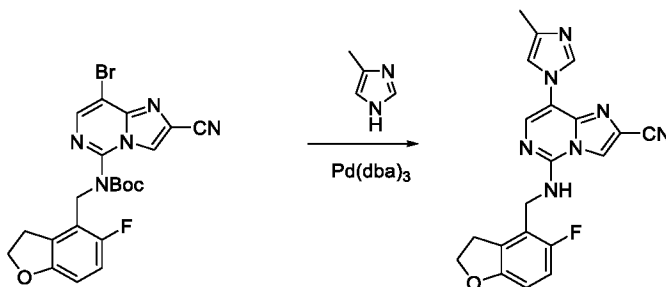


[000359] 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (25.0 mg, 49.8  $\mu\text{mol}$ , 1.00 equiv) in HCl (0.500 mL) was stirred at 25 °C for 0.5 h. The pH was adjusted to 8 with saturated aqueous  $\text{NaHCO}_3$  and filtered. The precipitate was triturated with MeOH (2.00 mL) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (6.00 mg, 11.2  $\mu\text{mol}$ , 22.4% yield, 96.0% purity) as a brown solid. LCMS  $[M+1]$ : 517.5.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 8.62 (s, 1H), 8.30 (br s, 1H), 7.56 (s,

1H), 7.51 - 7.45 (m, 2H), 7.39 (br s, 1H), 6.94 (br t,  $J=9.2$  Hz, 1H), 6.75 - 6.67 (m, 2H), 4.71 (br d,  $J=4.4$  Hz, 2H), 4.55 (br t,  $J=8.4$  Hz, 2H), 3.53 (br s, 4H), 3.32 - 3.25 (m, 6H), 2.25 (s, 6H).

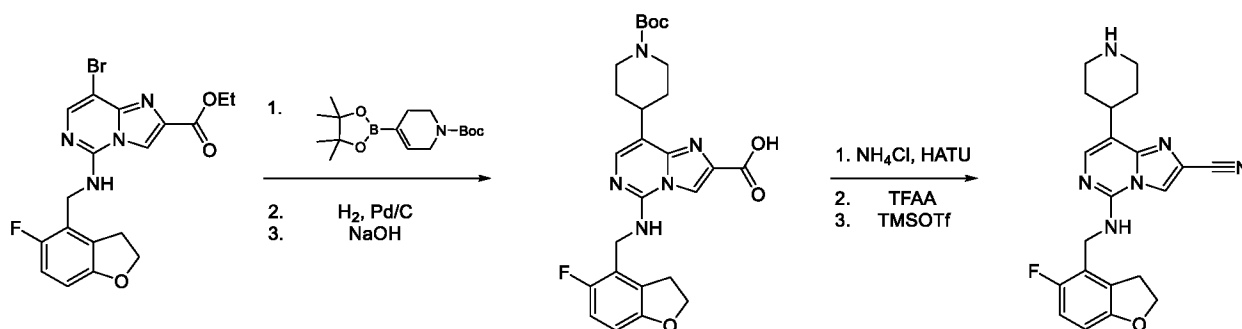
## EXAMPLE 139

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000360] A mixture of tert-butyl (8-bromo-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (70.0 mg, 139  $\mu$ mol, 1.00 equiv), 4-methyl-1H-imidazole (50.2 mg, 612  $\mu$ mol, 4.40 equiv),  $\text{Pd}_2(\text{dba})_3$  (12.7 mg, 13.9  $\mu$ mol, 0.100 equiv), ditert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl] phosphane (13.4 mg, 27.8  $\mu$ mol, 0.20 eq.) and potassium phosphate (76.7 mg, 362  $\mu$ mol, 2.60 equiv) in dioxane (0.50 mL) was purged with nitrogen. The mixture was stirred at 120 °C for 12 h under an atmosphere of nitrogen. The mixture was filtered and concentrated *in vacuo* to provide the crude residue. The residue was triturated with methanol (2.00 mL) and filtered to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (9.89 mg, 24.8  $\mu$ mol, 17.8% yield, 97.6% purity) as a yellow solid. LC-MS  $[M+1]$ : 390.4.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 8.97 (s, 1H), 8.63 (br t,  $J=4.8$  Hz, 1H), 8.13 - 8.06 (m, 2H), 7.42 (s, 1H), 6.95 (t,  $J=9.2$  Hz, 1H), 6.71 (dd,  $J=4.0, 8.8$  Hz, 1H), 4.71 (br d,  $J=4.8$  Hz, 2H), 4.55 (t,  $J=8.8$  Hz, 2H), 3.31 - 3.23 (m, 2H), 2.18 (s, 3H).

## EXAMPLE 140



[000361] A mixture of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (0.20 g, 460  $\mu$ mol, 1.00 equiv), *tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (227 mg, 735  $\mu$ mol, 1.60 equiv),  $\text{NaHCO}_3$  (116 mg, 1.38 mmol, 3.00 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (33.6 mg, 46.0  $\mu$ mol, 0.100 equiv) in dioxane (2.10 mL) and water (0.700 mL) was purged with nitrogen. The mixture was stirred at 105 °C for 1 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by prep-TLC ( $\text{SiO}_2$ ,  $\text{DCM}/\text{MeOH}$ , 20/1) to provide ethyl 8-(1-(tert-butoxycarbonyl)-

1,2,3,6-tetrahydropyridin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (230 mg, 89.8% yield, 96.4% purity) as a yellow oil. LC-MS [M+1]: 538.3.

**[000362]** A mixture of ethyl 8-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (220 mg, 395  $\mu$ mol, 1.00 equiv) and Pd/C 10 w. % (100 mg) in methanol (5.00 mL) was stirred at 25 °C for 12 h under an atmosphere of hydrogen gas (15.0 psi). The reaction mixture was filtered and concentrated *in vacuo* to provide ethyl 8-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (230 mg) as a yellow oil. LC-MS[M+1]: 540.2.

**[000363]** To a solution of ethyl 8-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (260 mg, 476  $\mu$ mol, 1.00 equiv) in methanol (5.00 mL) was added aq sodium hydroxide (1.00 M, 1.43 mL, 3.00 equiv). The mixture was stirred at 25 °C for 3 h and subsequently concentrated *in vacuo*. The mixture was adjusted to pH=6 with acetic acid and the resultant precipitate was filtered. The solid was dried at reduced pressure to provide 8-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (230 mg, 450  $\mu$ mol, 94.5% yield) as a light yellow solid. LC-MS [M+1]: 512.3.

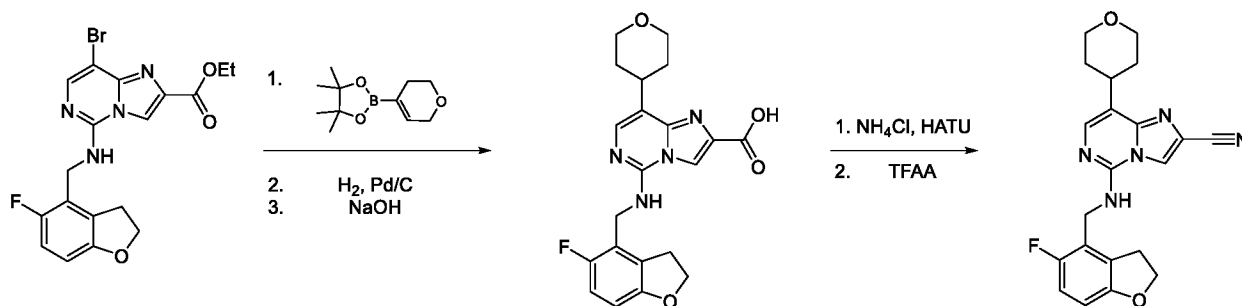
**[000364]** To a solution of 8-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylic acid (0.220 g, 430  $\mu$ mol, 1.00 equiv) in DMF (3.00 mL) was added ammonium chloride (184 mg, 3.44 mmol, 8.00 equiv), DIEA (1.00 g, 7.74 mmol, 1.35 mL, 18.0 equiv) and HATU (327 mg, 860  $\mu$ mol, 2.00 equiv). The mixture was stirred at 25 °C for 1 h and subsequently diluted with water 10.0 mL. The formed precipitate was filtered and dried at reduced pressure to provide *tert*-butyl 4-(2-carbamoyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)piperidine-1-carboxylate (210 mg, 95.6% yield) as a white solid. LC-MS: [M+1] 511.2.

**[000365]** To a solution of *tert*-butyl 4-(2-carbamoyl-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)piperidine-1-carboxylate (150 mg, 294  $\mu$ mol, 1.00 equiv) in THF (3.00 mL) was added triethylamine (595 mg, 5.88 mmol, 818  $\mu$ L, 20.0 equiv) followed by TFAA (370 mg, 1.76 mmol, 245  $\mu$ L, 6.00 equiv) at 0 °C. The mixture was stirred at 25 °C for 1 h and subsequently diluted with DCM 30 mL. The organic layer was washed with brine (20 mL  $\times$  2) and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resultant residue was purified by prep-TLC (SiO<sub>2</sub>, PE/EA, 1/1) to afford *tert*-butyl 4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)piperidine-1-carboxylate (130 mg, 263  $\mu$ mol, 89.4% yield, 99.5% purity) as a yellow solid. LC-MS: [M+Na<sup>+</sup>] 515.3.

**[000366]** To a solution of *tert*-butyl 4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)piperidine-1-carboxylate (100 mg, 202  $\mu$ mol, 1.00 equiv) in DCM (3.00 mL) was added 2,6-lutidine (173 mg, 1.62 mmol, 188  $\mu$ L, 8.00 equiv) followed by TMSOTf (112 mg, 505  $\mu$ mol, 91.3  $\mu$ L, 2.50 equiv) at 0 °C. The mixture was stirred at 25 °C for 48 h and

subsequently diluted with DCM (10 mL) and water (10 mL). The resultant mixture was filtered and the precipitate was dried at reduced pressure. The crude material was triturated with hot methanol (2 mL) and filtered. The solid was dried at reduced pressure to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(piperidin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (44.4 mg, 111  $\mu$ mol, 55.1% yield, 98.5% purity) as an off-white solid. LC-MS: [M+1] 393.3.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 8.94 (s, 1H), 8.44 (br s, 1H), 7.60 (br s, 1H), 6.93 (br t,  $J$ =9.6 Hz, 1H), 6.69 (br d,  $J$ =4.8 Hz, 1H), 4.65 (br s, 2H), 4.54 (br t,  $J$ =8.0 Hz, 2H), 3.21 - 3.06 (m, 4H), 2.99 (br s, 3H), 2.01 (br s, 4H).

## EXAMPLE 141



**[000367]** To a solution of ethyl 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (100 mg, 230  $\mu$ mol, 1.00 equiv), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (48.3 mg, 230  $\mu$ mol, 1.00 equiv) and cesium carbonate (150 mg, 460  $\mu$ mol, 2.00 equiv) in dioxane (1.00 mL) and water (0.300 mL) was added Pd(dppf)Cl<sub>2</sub> (16.8 mg, 23.0  $\mu$ mol, 0.100 equiv). The vessel was purged with nitrogen, stirred at 105 °C for 1 h and subsequently concentrated *in vacuo* to provide a residue. The residue was purified by Prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 1/1) to afford ethyl 8-(3,6-dihydro-2H-pyran-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (81.0 mg, 77.7% yield, 96.6% purity) as a white solid. LCMS [M+1]: 439.2.

**[000368]** To a solution of ethyl 8-(3,6-dihydro-2H-pyran-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carboxylate (70.0 mg, 160  $\mu$ mol, 1.00 equiv) in methanol (5.00 mL) and THF (5.00 mL) was added palladium on carbon 10 w. % (172 mg, 0.1 equiv) at 25 °C. The mixture was purged with hydrogen and allowed to stir for 1 h at 25 °C under an atmosphere of hydrogen gas (15.0 psi). The mixture was filtered and concentrated under reduced pressure to provide a residue. The residue was rinsed with 5 mL petroleum ether/ethyl acetate (2/1) to afford ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (50.0 mg, 64.6 yield, 90.9% purity) as a white solid.

**[000369]** To a solution of ethyl 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylate (50.0 mg, 103  $\mu$ mol, 1.00 equiv) in THF (6.0 mL) and water (3.0 mL) was added sodium hydroxide (4.13 mg, 103  $\mu$ mol, 1.00 equiv). The mixture was stirred at 25 °C for 1 h and subsequently concentrated *in vacuo* to remove the majority of the THF. The aqueous solution was adjusted to pH = 6 with aq hydrochloric acid (1.0 M, 0.5 mL) and the resultant precipitate was filtered. The solid was triturated with 3 mL petroleum ether/ethyl acetate (2:1) and dried at reduced pressure to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-

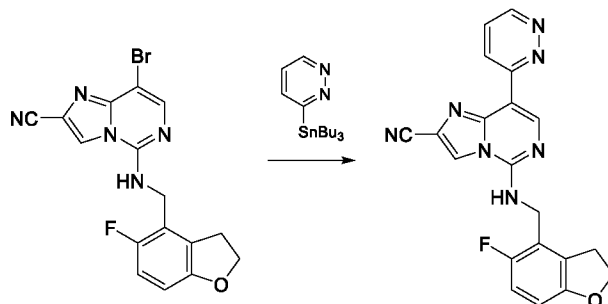
pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (41.0 mg, 95.0% yield, 98.6% purity) as a white solid. LCMS [M+1]: 413.2. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.08 (s, 1H), 7.50 (s, 1H), 6.85 (t, *J*=9.2 Hz, 1H), 6.64 (dd, *J*=4.0, 8.8 Hz, 1H), 4.76 (s, 2H), 4.56 (t, *J*=8.8 Hz, 2H), 4.06 (dd, *J*=3.2, 11.2 Hz, 2H), 3.73 - 3.64 (m, 2H), 3.44 - 3.37 (m, 1H), 3.32 - 3.28 (m, 2H), 2.00 (dd, *J*=2.0, 12.8 Hz, 2H), 1.91 - 1.77 (m, 2H).

**[000370]** A mixture of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxylic acid (34.0 mg, 81.3  $\mu$ mol, 1.00 equiv), HATU (46.4 mg, 122  $\mu$ mol, 1.50 equiv), DIEA (84.1 mg, 650  $\mu$ mol, 113  $\mu$ L, 8.00 equiv) and ammonium chloride (13.0 mg, 244  $\mu$ mol, 3.00 equiv) in DMF (2.00 mL) was purged with nitrogen. The mixture was stirred at 30 °C for 1 h and was subsequently concentrated *in vacuo* to provide the crude solid. The solid was rinsed with water (1.00 mL), filtered and dried at reduced pressure. The solid was triturated with 2 mL petroleum ether/ethyl acetate (2:1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (20.0 mg, 46.6  $\mu$ mol, 57.3% yield, 95.8% purity) as a white solid. LCMS [M+1]: 412.17. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.54 (s, 1H), 8.11 (br t, *J*=4.8 Hz, 1H), 7.57 (br s, 1H), 7.52 (s, 1H), 7.47 (br s, 1H), 6.92 (t, *J*=9.2 Hz, 1H), 6.68 (dd, *J*=3.6, 8.8 Hz, 1H), 4.65 (br d, *J*=4.8 Hz, 2H), 4.53 (t, *J*=8.8 Hz, 2H), 3.97 (br d, *J*=10.8 Hz, 2H), 3.53 - 3.40 (m, 3H), 3.30 - 3.24 (m, 2H), 3.18 - 3.10 (m, 1H), 1.93 - 1.82 (m, 4H).

**[000371]** To a mixture of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-c]pyrimidine-2-carboxamide (28.0 mg, 68.1  $\mu$ mol, 1 equiv), triethylamine (138 mg, 1.36 mmol, 189  $\mu$ L, 20.0 equiv) in THF (4.00 mL) was added TFAA (42.9 mg, 204  $\mu$ mol, 28.4  $\mu$ L, 3.00 equiv) at 0 °C. The resultant mixture was stirred at 0 - 30 °C for 1 h and was subsequently filtered and concentrated to provide the crude residue. The residue was purified by prep-HPLC (column: Gemini 150 $\times$ 25 5  $\mu$ ; mobile phase: [water (0.04 %NH<sub>3</sub>H<sub>2</sub>O) - ACN]; B %: 35.0 % - 65.0 %, 10 min) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyridazin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (26.0 mg, 63.1  $\mu$ mol, 92.7% yield, 95.5% purity) as a yellow solid. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.84 (s, 1H), 8.24 (br s, 1H), 7.63 (s, 1H), 6.93 (t, *J*=9.6 Hz, 1H), 6.69 (dd, *J*=3.6, 8.4 Hz, 1H), 4.65 (br d, *J*=3.2 Hz, 2H), 4.54 (br t, *J*=8.8 Hz, 2H), 4.01 - 3.90 (m, 2H), 3.53 - 3.42 (m, 1H), 3.29 - 3.27 (m, 3H), 3.16 - 3.05 (m, 1H), 1.94 - 1.74 (m, 4H). LCMS: [M+1] 394.1.

#### EXAMPLE 142

#### 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyridazin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile

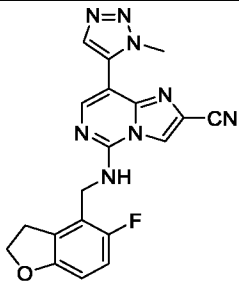
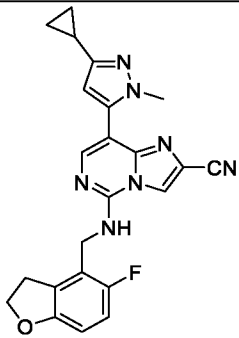


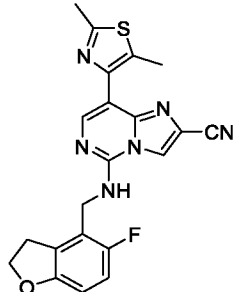
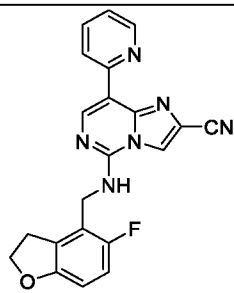
[000372] A mixture of tributyl(pyridazin-3-yl)stannane (90.7 mg, 246  $\mu$ mol, 1.20 eq.), 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (80.0 mg, 205  $\mu$ mol, 1.00 eq.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (23.7 mg, 20.5  $\mu$ mol, 0.10 eq.) in toluene (1.00 mL) was purged with nitrogen and was subsequently stirred at 110 °C for 2 h. The reaction mixture was cooled to rt and quenched with sat aq potassium fluoride (2.00 mL). The mixture was extracted with ethyl acetate (2.00 mL  $\times$  3) and the combined organic layer was washed with brine (2.00 mL  $\times$  2), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC and lyophilized to provide title compound 5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]-8-pyridazin-3-yl-imidazo[1,2-c]pyrimidine-2-carbonitrile (6.84 mg, 8.51% yield, 98.6% purity) as a yellow solid. LCMS [M+1]: 388.3. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>)  $\delta$  = 9.95 (dd, *J*=0.8, 2.0 Hz, 1H), 9.26 (dd, *J*=0.8, 5.6 Hz, 1H), 8.99 (s, 1H), 8.95 (br t, *J*=5.2 Hz, 1H), 8.62 (s, 1H), 8.46 (dd, *J*=2.4, 5.6 Hz, 1H), 7.01 - 6.91 (m, 1H), 6.72 (dd, *J*=4.0, 8.8 Hz, 1H), 4.78 (d, *J*=5.2 Hz, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.32 - 3.28 (m, 2H).

[000373] EXAMPLES 143 -146 were prepared following the procedure set forth in Example 142 and using the general reactions schemes and intermediates described herein.

TABLE 5

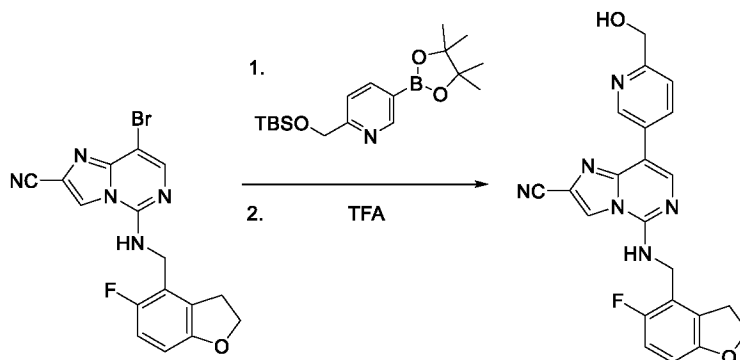
Characterization of EXAMPLES 143-146

| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 143   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-1H-1,2,3-triazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>         | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.81 (br s, 2H), 7.93 (s, 1H), 7.90 (s, 1H), 6.93 (br t, <i>J</i> =9.2 Hz, 1H), 6.68 (dd, <i>J</i> =4.0, 9.2 Hz, 1H), 4.71 (br s, 2H), 4.53 (br t, <i>J</i> =8.8 Hz, 2H), 4.02 (s, 3H).<br>LCMS [M + 1]: 391.0.                                                                                                                                         |
| 144   |  <p>8-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.93 (s, 1H), 8.64 (br t, <i>J</i> =4.8 Hz, 1H), 7.85 (s, 1H), 6.96 (t, <i>J</i> =9.2 Hz, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 6.17 (s, 1H), 4.73 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.66 (s, 3H), 3.32 (t, <i>J</i> =8.8 Hz, 2H), 1.94 - 1.81 (m, 1H), 0.95 - 0.81 (m, 2H), 0.75 - 0.62 (m, 2H).<br>LCMS [M + 1]: 430.1. |

| Ex. # | Structure                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                     |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 145   |  <p>8-((2,5-dimethylthiazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.61 (s, 1H), 7.88 (s, 1H), 6.85 (t, <i>J</i> =9.6 Hz, 1H), 6.64 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.82 (s, 2H), 4.57 (t, <i>J</i> =8.8 Hz, 2H), 3.37 (br t, <i>J</i> =8.8 Hz, 2H), 2.68 (s, 3H), 2.37 (s, 3H).<br>LC-MS [M+1]: 421.1.                                                                                              |
| 146   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(pyridin-2-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>              | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.99 (s, 1H), 8.83 (t, <i>J</i> =4.8 Hz 1H), 8.77 (s, 1H), 8.74 - 8.65 (m, 2H), 8.02 (br t, <i>J</i> =7.6 Hz, 1H), 7.45 - 7.41 (m, 1H), 6.99 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.77 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 3.32 (t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [M+1]: 387.3. |

## EXAMPLE 147

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-(hydroxymethyl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



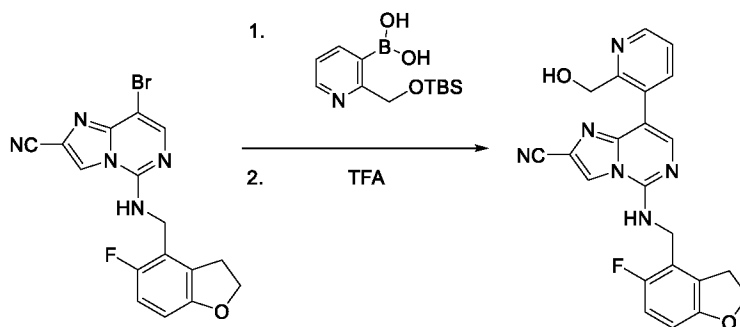
[000374] A solution of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 252 μmol, 1.00 eq.), *tert*-butyl-dimethyl-[(5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl)methoxy)silane] (200 mg, 458 μmol, 1.82 eq.), sodium bicarbonate (65.0 mg, 774 μmol, 3.10 eq.) and Pd(dppf)Cl<sub>2</sub> (19 mg, 26 μmol, 0.1 eq.) in dioxane (1.70 mL) and water (0.30 mL) was flushed with nitrogen. The mixture was stirred at 95 °C for 1 h. The mixture was cooled to rt, filtered, and concentrated to provide the crude material. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/MeOH = 20/1) to afford 8-[6-[[*tert*-butyl(dimethyl)silyl]-oxymethyl]-3-pyridyl]-5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]imidazo[1,2-c]pyrimidine-2-carbonitrile (140 mg, 224 μmol, 89.1% yield, 85.0% purity) as a yellow oil. LCMS [M + 1]: 531.2. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 9.05 (d, *J*=2.0 Hz, 1H), 8.95 (s, 1H), 8.59 (t, *J*=5.2 Hz, 1H), 8.41 (dd, *J*=2.0, 8.0 Hz, 1H), 8.20 (s,

1H), 7.53 (d,  $J=8.4$  Hz, 1H), 7.01 - 6.89 (m, 1H), 6.71 (dd,  $J=4.0, 8.4$  Hz, 1H), 4.80 (s, 2H), 4.74 (br d,  $J=4.4$  Hz, 2H), 4.54 (t,  $J=8.8$  Hz, 2H), 3.34 - 3.29 (m, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

**[000375]** A solution of 8-[6-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-pyridyl]-5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]imidazo[1,2-*c*]pyrimidine-2-carbonitrile (90.0 mg, 144  $\mu$ mol, 1.00 eq.) in dichloromethane (1.00 mL) and TFA (2.00 mL) was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , dichloromethane/methanol = 10/1) to provide the crude product. The solid was triturated with methanol (7.00 mL) and collected by filtration to afford title compound 5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]-8-[6-(hydroxymethyl)-3-pyridyl]imidazo[1,2-*c*]pyrimidine-2-carbonitrile (45.0 mg, 106  $\mu$ mol, 73.5% yield, 98.0% purity) as an off-white solid. LCMS [ $M + 1$ ]: 417.0.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO-d}_6$ )  $\delta$  = 9.04 (s, 1H), 8.94 (s, 1H), 8.59 (t,  $J=4.8$  Hz, 1H), 8.37 (dd,  $J=2.0, 8.0$  Hz, 1H), 8.18 (s, 1H), 7.56 (d,  $J=8.0$  Hz, 1H), 6.95 (t,  $J=9.2$  Hz, 1H), 6.71 (dd,  $J=4.0, 8.8$  Hz, 1H), 5.44 (t,  $J=6.0$  Hz, 1H), 4.74 (br d,  $J=4.8$  Hz, 2H), 4.61 (d,  $J=5.6$  Hz, 2H), 4.55 (t,  $J=8.8$  Hz, 2H), , 3.29 - 3.33 (m, 2H).

#### EXAMPLE 148

##### 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-(hydroxymethyl)pyridin-3-yl)imidazo[1,2-*c*]pyrimidine-2-carbonitrile



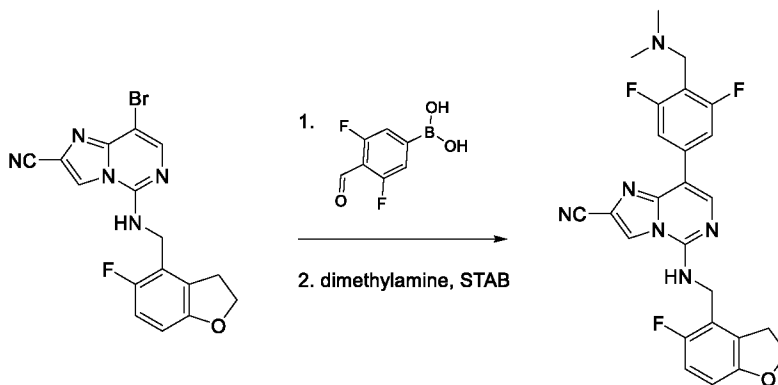
**[000376]** A solution of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (30.0 mg, 75.0  $\mu$ mol, 1.00 eq.), [2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-pyridyl]boronic acid (20.0 mg, 74.9  $\mu$ mol, 0.10 eq.), sodium bicarbonate (18.9 mg, 225  $\mu$ mol, 3.00 eq.) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (5.50 mg, 7.50  $\mu$ mol, 0.10 eq.) in dioxane (1.00 mL) and water (0.20 mL) was purged with nitrogen and stirred at 95  $^\circ\text{C}$  for 1 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 8-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (30.0 mg, 41.8  $\mu$ mol, 55.8% yield, 74.0% purity) as a white solid.

**[000377]** A mixture of 8-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (15.0 mg, 20.9  $\mu$ mol, 1.00 eq.) and trifluoroacetic acid (1.11 mL, 15.0 mmol, 717 eq.) in dichloromethane (1.00 mL) was stirred at rt for 1 h. The mixture was filtered and concentrated under reduced pressure to provide the crude residue. The residue was purified by prep-HPLC to afford title compound 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-(hydroxymethyl)pyridin-3-yl)imidazo[1,2-*c*]pyrimidine-2-

carbonitrile (3.05 mg, 7.05  $\mu$ mol, 33.7% yield, 96.3% purity) as a yellow oil. LC-MS [M+1]: 417.3.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 8.95 (s, 1H), 8.65 (d,  $J$ =4.0 Hz, 1H), 8.61 (br s, 1H), 8.00 (br d,  $J$ =7.6 Hz, 1H), 7.89 (s, 1H), 7.60 - 7.54 (m, 1H), 7.00 - 6.92 (m, 1H), 6.72 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.74 (d,  $J$ =4.4 Hz, 2H), 4.59 - 4.52 (m, 4H), 3.34 - 3.32 (m, 2H).

#### EXAMPLE 149

#### 8-(4-((dimethylamino)methyl)-3,5-difluorophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



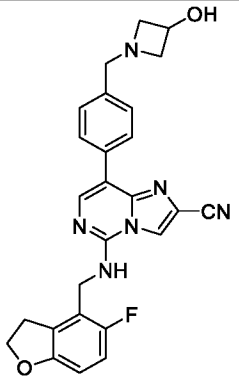
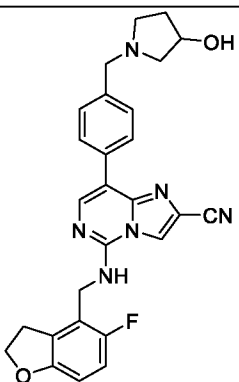
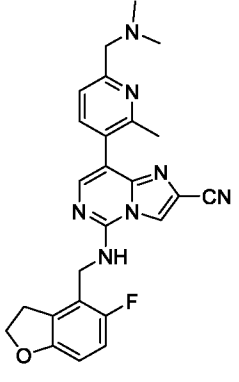
[000378] To a solution of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (50.0 mg, 129  $\mu$ mol, 1.00 eq.), (3,5-difluoro-4-formyl-phenyl)boronic acid (28.7 mg, 155  $\mu$ mol, 1.20 eq.) in dioxane (1.00 mL) and water (0.20 mL) was added Pd(dppf)Cl<sub>2</sub> (9.42 mg, 12.9  $\mu$ mol, 0.10 eq.) and sodium bicarbonate (21.6 mg, 257  $\mu$ mol, 2.00 eq.) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 1 h and subsequently concentrated in vacuo to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to give 8-(3,5-difluoro-4-formylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 66.8  $\mu$ mol, 51.8% yield) as a white solid.

[000379] To a solution of 8-(3,5-difluoro-4-formylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 66.8  $\mu$ mol, 1.00 eq.), *N*-methylmethanamine (2M in THF, 67.6  $\mu$ L, 133  $\mu$ mol, 2.00 eq.) in methanol (2.00 mL) was added sodium triacetoxyborohydride (28.3 mg, 134  $\mu$ mol, 2.00 eq.). The mixture was stirred at 40 °C for 30 min. The mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (TFA condition) to give 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-(hydroxymethyl)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (11.0 mg, 17.8  $\mu$ mol, 26.7% yield, 96.0% purity, TFA salt) as a white solid. LCMS [M+1]: 479.4.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 9.96 (br s, 1H), 8.99 (s, 1H), 8.85 (t,  $J$ =4.8 Hz, 1H), 8.44 (s, 1H), 8.08 (d,  $J$ =9.6 Hz, 2H), 7.00 - 6.92 (m, 1H), 6.72 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.76 (d,  $J$ =4.8 Hz, 2H), 4.56 (t,  $J$ =8.4 Hz, 2H), 4.40 (br s, 2H), 3.33 - 3.29 (m, 2H), 2.84 (s, 6H).

[000380] EXAMPLES 150 -152 were prepared following the procedure set forth in Example 149 and using the general reactions schemes and intermediates described herein.

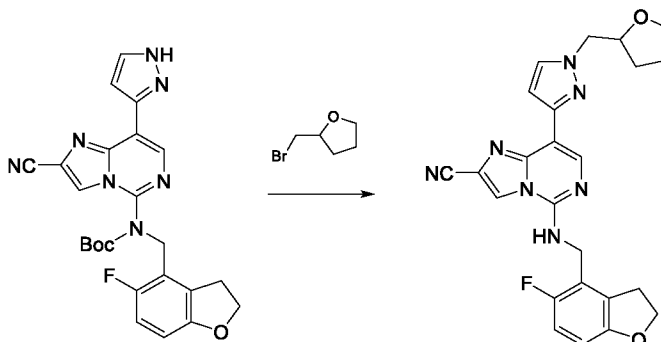
TABLE 6

Characterization of EXAMPLES 150-152

| Ex. # | Structure                                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 150   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(((3-hydroxyazetidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>        | <sup>1</sup> H NMR (400MHz, methanol-d <sub>4</sub> ) δ = 8.62 (s, 1H), 8.05 (s, 1H), 8.01 (d, <i>J</i> =8.4 Hz, 2H), 7.55 (d, <i>J</i> =8.0 Hz, 2H), 6.86 (t, <i>J</i> =9.2, 1H), 6.65 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.83 - 4.83 (m, 2H), 4.58 (t, <i>J</i> =8.4 Hz, 2H), 4.44 (br s, 2H), 4.35 (br dd, <i>J</i> =6.4 Hz, 11.2 Hz, 2H), 3.99 (br dd, <i>J</i> =5.6, 11.6 Hz, 2H), 3.37 (t, <i>J</i> =8.4 Hz, 2H), 3.36 - 3.34 (m, 1H).<br>LCMS [M+1]: 471.4.                                                                |
| 151   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(((3-hydroxypyrrolidin-1-yl)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 10.33 - 9.90 (m, 1H), 8.96 (s, 1H), 8.60 (br t, <i>J</i> =4.8 Hz, 1H), 8.18 (s, 1H), 8.09 (br d, <i>J</i> =8.0 Hz, 2H), 7.62 (br d, <i>J</i> =8.4 Hz, 2H), 7.01 - 6.92 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 5.58 - 5.39 (m, 1H), 4.75 (br d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 4.51 - 4.26 (m, 3H), 3.60 - 3.45 (m, 1H), 3.38 - 3.34 (m, 2H), 3.29 - 2.99 (m, 3H), 2.08 - 1.93 (m, 1H), 1.90 - 1.75 (m, 1H).<br>LCMS [M+1]: 485.4. |
| 152   |  <p>8-(6-((dimethylamino)methyl)-2-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.66 (s, 1H), 7.86 - 7.76 (m, 2H), 7.41 (d, <i>J</i> =7.6 Hz, 1H), 6.91 - 6.84 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.85 (s, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 4.51 (s, 2H), 3.41 (t, <i>J</i> =8.8 Hz, 2H), 3.01 (s, 6H), 2.49 (s, 3H).<br>LC-MS [M+1]: 458.1.                                                                                                                                                                                                |

## EXAMPLE 153

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000381] To a solution of *tert*-butyl (2-cyano-8-(1H-pyrazol-3-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 57.4  $\mu$ mol, 1.00 eq.) in DMF (1.00 mL) was added sodium hydride (4.59 mg, 115  $\mu$ mol, 60.0% purity, 2.00 eq.) at 0 °C. The mixture was stirred at 0 °C for 30 min prior to the dropwise addition of 2-(bromomethyl)tetrahydrofuran (11.5 mg, 69.7  $\mu$ mol, 1.21 eq.). The mixture was allowed to stir for 3 h and was quenched with water (10.0 mL) and extracted with ethyl acetate (20.0 mL  $\times$  2). The combined organic layer was washed with water (20.0 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give title compound 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (12.2 mg, 26.5  $\mu$ mol, 46.2% yield, 99.8% purity) as a white solid. LCMS [M + 1]: 460.3. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>)  $\delta$  = 8.92 (s, 1H), 8.48 (t, *J*=5.2 Hz, 1H), 8.30 (s, 1H), 7.77 (d, *J*=2.4 Hz, 1H), 7.06 (d, *J*=2.4 Hz, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd, *J*=3.6, 8.4 Hz, 1H), 4.73 (d, *J*=4.8 Hz, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 4.24 - 4.18 (m, 3H), 3.80 - 3.72 (m, 1H), 3.68 - 3.60 (m, 1H), 3.30 (t, *J*=8.4 Hz, 2H), 2.01 - 1.88 (m, 1H), 1.84 - 1.70 (m, 2H), 1.69 - 1.57 (m, 1H).

[000382] EXAMPLE 154 was prepared following the procedure set forth in Example 153 and using the general reactions schemes and intermediates described herein.

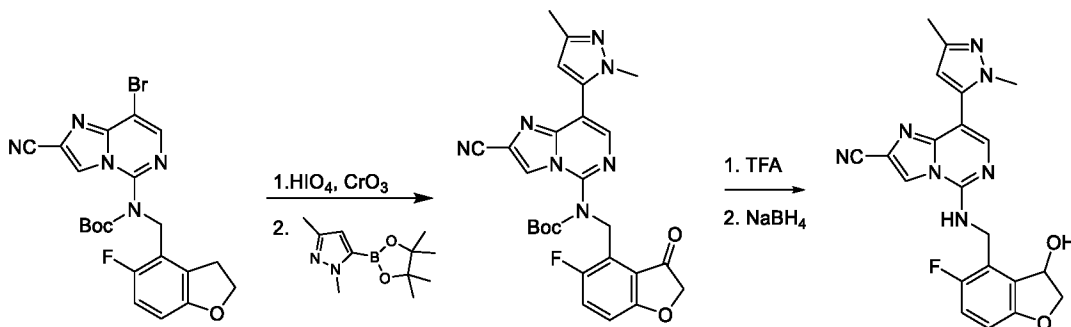
TABLE 7

Characterization of EXAMPLE 154

| Ex. # | Structure                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 154   | <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) $\delta$ = 8.91 (s, 1H), 8.47 (t, <i>J</i> =5.2 Hz, 1H), 8.29 (s, 1H), 7.84 (d, <i>J</i> =2.0 Hz, 1H), 7.05 (d, <i>J</i> =2.4 Hz, 1H), 6.99 - 6.89 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.16 (d, <i>J</i> =7.6 Hz, 2H), 3.80 - 3.75 (m, 1H), 3.70 - 3.60 (m, 2H), 3.54 - 3.49 (m, 1H), 3.29 (t, <i>J</i> =8.8 Hz, 2H), 2.83 - 2.71 (m, 1H), 1.99 - 1.86 (m, 1H), 1.68 - 1.57 (m, 1H).<br>LCMS [M+1]: 460.3. |

## EXAMPLE 155

## 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-3-hydroxy-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000383] To a solution of *tert*-butyl (8-bromo-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (200 mg, 410  $\mu$ mol, 1.00 eq.) in acetonitrile (4.50 mL) was added periodic acid (345 mg, 1.52 mmol, 345  $\mu$ L, 3.70 eq.) and chromium trioxide (90.1 mg, 901  $\mu$ mol, 2.20 eq.). The mixture was stirred at 15 °C for 3 h. The reaction mixture was filtered through a plug of Celite. The filtrate was diluted with water (3.00 mL) and extracted with ethyl acetate (5.00 mL  $\times$  3). The combined organic phase was washed with aqueous sodium sulfite solution (2.00 mL), brine (2.00 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to provide the crude material. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 10/1 to 5/1) to give *tert*-butyl (8-bromo-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (114 mg, 227  $\mu$ mol, 18.5% yield) as a colorless oil. LCMS [M+1]: 503.8.

[000384] <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>-d)  $\delta$  = 8.09 (s, 1H), 7.70 (s, 1H), 7.24 (t, *J*=9.4 Hz, 1H), 6.99 (dd, *J*=3.6, 9.2 Hz, 1H), 5.34 (s, 2H), 4.47 (s, 2H), 1.34 (s, 9H).

[0100] A mixture of *tert*-butyl (8-bromo-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (114 mg, 227  $\mu$ mol, 1.00 eq.), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (101 mg, 454  $\mu$ mol, 2.00 eq.), Pd(dppf)Cl<sub>2</sub> (16.6 mg, 22.7  $\mu$ mol, 0.10 eq.) and sodium bicarbonate (38.1 mg, 454  $\mu$ mol, 2.00 eq.) in dioxane (1.50 mL) and water (0.30 mL) was purged with nitrogen and subsequently stirred at 95 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 3:1) to afford *tert*-butyl (2-cyano-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (40.0 mg, 77.3  $\mu$ mol, 34.1% yield) as a yellow oil. LCMS [M+1]: 518.4.

[000385] To a solution of *tert*-butyl (2-cyano-8-(1,3-dimethyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (40.0 mg, 77.3  $\mu$ mol, 1.00 eq.) in dichloromethane (0.30 mL) was added trifluoroacetic acid (154 mg, 1.35 mmol, 0.10 mL, 17.5 eq.). The mixture was stirred at 15 °C for 30 min and was subsequently concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2.00 mL) and washed with saturated sodium bicarbonate (1.00 mL) and brine (1.00 mL). The organic phase was dried, filtered and concentrated to give 8-(1,3-dimethyl-1H-

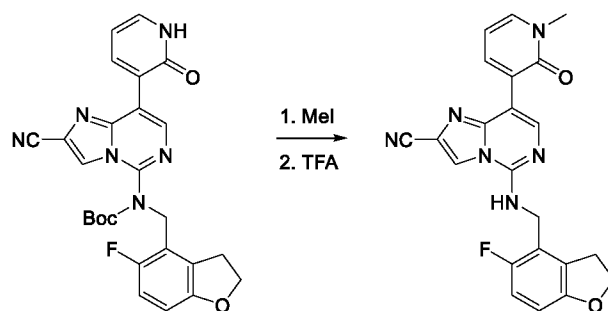
pyrazol-5-yl)-5-(((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 71.9  $\mu$ mol, 93.0% yield) as a brown solid. LCMS [M+1]: 418.1.

[000386] To a solution of 8-(2,5-dimethylpyrazol-3-yl)-5-[(5-fluoro-3-oxo-benzofuran-4-yl)methylamino]imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 71.9  $\mu$ mol, 1.00 eq.) in methanol (0.50 mL) was added sodium borohydride (5.44 mg, 144  $\mu$ mol, 2.00 eq.) at 0 °C. The mixture was stirred at 0 °C for 1 h prior to being quenched with water (0.10 mL). The mixture was purified by prep-HPLC to give title compound 8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluoro-3-hydroxy-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (6.52 mg, 15.5  $\mu$ mol, 21.6% yield, 99.7% purity) as an off-white solid. LCMS [M+1]: 420.2.

[000387] <sup>1</sup>H NMR (400MHz, MeOD-d<sub>4</sub>)  $\delta$  = 8.59 (br s, 1H), 7.80 (s, 1H), 7.12 - 6.97 (m, 1H), 6.78 (dd,  $J$ =3.6, 8.8 Hz, 1H), 6.25 (s, 1H), 5.68 (br d,  $J$ =6.0 Hz, 1H), 5.05 (br d,  $J$ =14.6 Hz, 1H), 4.56 (br dd,  $J$ =6.0, 10.4 Hz, 2H), 4.44 (br d,  $J$ =10.4 Hz, 1H), 3.71 (s, 3H), 2.27 (s, 3H).

#### EXAMPLE 156

##### 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000388] To a solution of tert-butyl (2-cyano-8-(2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (45.0 mg, 89.6  $\mu$ mol, 1.00 eq.) in DMF (0.50 mL) was added potassium carbonate (24.8 mg, 179  $\mu$ mol, 2.00 eq.) at 0 °C. The mixture was stirred at 0 °C for 30 min prior to the dropwise addition of methyl iodide (15.3 mg, 107  $\mu$ mol, 6.69  $\mu$ L, 1.20 eq.). The mixture was stirred at 0 °C for 1 hour followed by being quenched with saturated ammonium chloride (1.50 mL). The mixture was extracted with ethyl acetate (2.00 mL  $\times$  3) and the combined organic phase was washed with brine (2.00 mL  $\times$  2), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give tert-butyl (2-cyano-8-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 62.2% yield, 96.0% purity) as a yellow solid. LCMS [M+1]: 517.4.

[000389] To a solution of tert-butyl (2-cyano-8-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 55.8  $\mu$ mol, 1.00 eq.) in dichloromethane (1.00 mL) was added trifluoroacetic acid (380 mg, 3.33 mmol, 247  $\mu$ L, 59.8 eq.). The mixture was stirred at 25 °C for 1 h prior to being filtered and concentrated under reduced pressure to provide the crude residue. The crude material was purified by prep-HPLC to give title compound 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (16.8 mg, 71.3% yield, 98.5% purity) as a white solid.

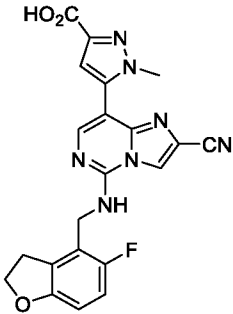
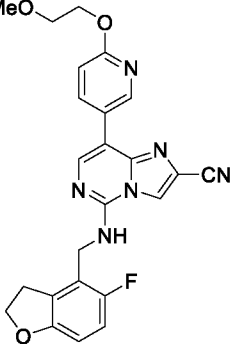
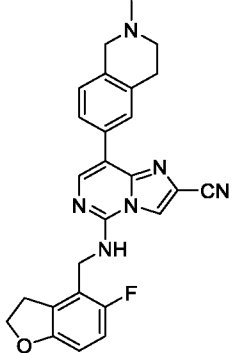
LCMS [M+1]: 417.3. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 8.90 (s, 1H), 8.58 (s, 1H), 8.49 (t, *J*=5.2 Hz, 1H), 8.31 (dd, *J*=2.0, 7.2 Hz, 1H), 7.75 (dd, *J*=2.0, 6.4 Hz, 1H), 6.99 - 6.91 (m, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 6.40 (t, *J*=6.8 Hz, 1H), 4.73 (d, *J*=5.2 Hz, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.53 (s, 3H), 3.33 - 3.28 (m, 2H).

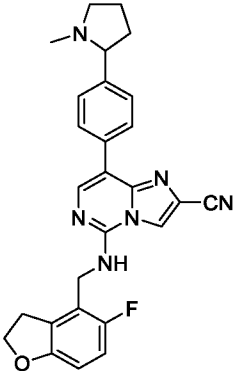
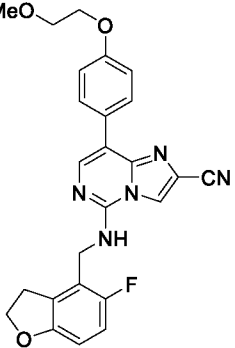
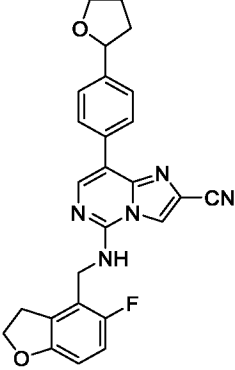
## EXAMPLES 157 - 184

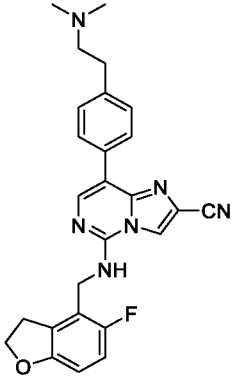
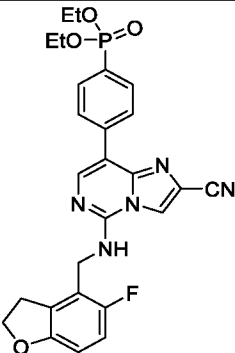
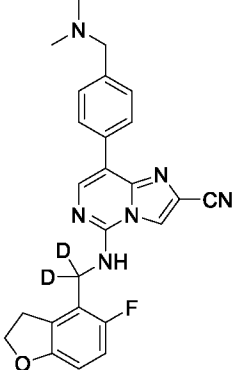
[000390] EXAMPLES 157 -184 were prepared following the procedure set forth in EXAMPLE 87 and using the general reactions schemes and intermediates described herein.

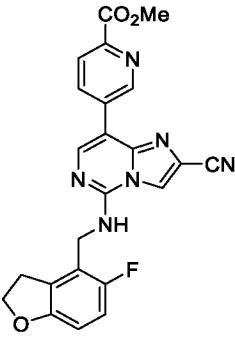
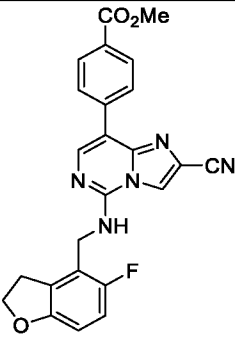
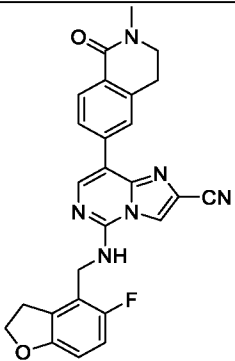
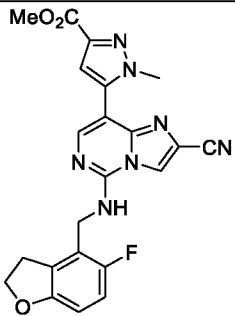
TABLE 8

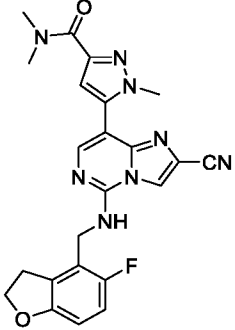
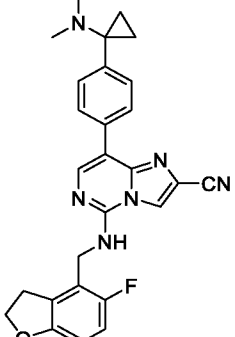
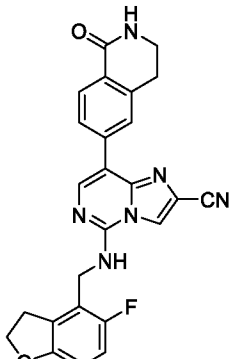
Characterization of EXAMPLES 157 - 184

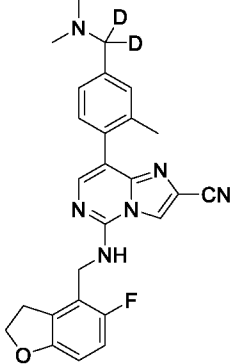
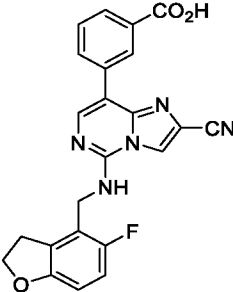
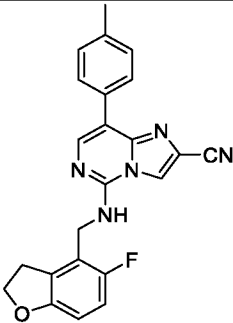
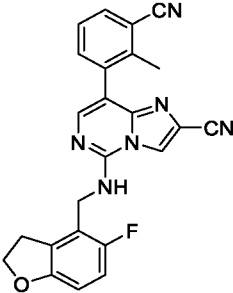
| Ex. # | Structure                                                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 157   |  <p>5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-1-methyl-1H-pyrazole-3-carboxylic acid</p>           | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 7.91 (s, 1H), 6.94 - 6.83 (m, 1H), 6.67 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 6.48 (s, 1H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 3.80 (s, 3H), 3.56 (s, 2H), 3.40 (br t, <i>J</i> =8.8 Hz, 2H), 2.33 (s, 6H).<br>LCMS [M+1]: 447.2.                                                                                                                                                |
| 158   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(6-(2-methoxyethoxy)pyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>             | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.99 (s, 1H), 8.73 (d, <i>J</i> =2.4 Hz, 1H), 8.61 (br t, <i>J</i> =4.8 Hz, 1H), 8.31 (dd, <i>J</i> =2.4, 8.8 Hz, 1H), 8.11 (s, 1H), 6.99 - 6.91 (m, 2H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.47 - 4.40 (m, 2H), 3.73 - 3.65 (m, 2H), 3.36 - 3.27 (m, 5H).<br>LC-MS [M+1]: 461.2.                     |
| 159   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.50 - 8.40 (m, 1H), 8.05 (s, 1H), 7.76 - 7.66 (m, 2H), 7.14 (d, <i>J</i> =8.8 Hz, 1H), 7.04 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (br d, <i>J</i> =4. Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.53 (s, 2H), 3.29 (br s, 2H), 2.89 (br t, <i>J</i> =5.6 Hz, 2H), 2.63 (br t, <i>J</i> =5.6 Hz, 2H), 2.37 (s, 3H).<br>LC-MS [M+1]: 455.1. |

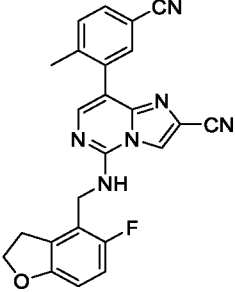
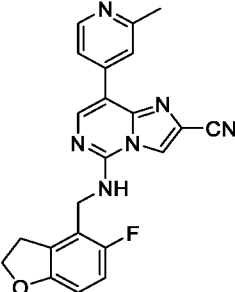
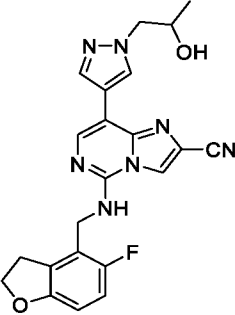
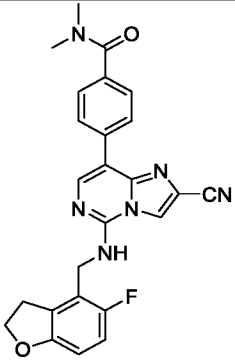
| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 160   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(1-methylpyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.93 (s, 1H), 8.48 (br s, 1H), 8.07 (s, 1H), 7.89 (br d, <i>J</i> =8.4 Hz, 2H), 7.41 (br d, <i>J</i> =8.0 Hz, 2H), 6.98 - 6.93 (m, 1H), 6.71 (br dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =4.4 Hz, 2H), 4.55 (br t, <i>J</i> =8.8 Hz, 2H), 3.18 - 3.12 (m, 2H), 3.08 - 2.96 (m, 2H), 2.30 - 2.24 (m, 1H), 2.17 - 2.08 (m, 3H), 1.86 - 1.76 (m, 2H), 1.68 - 1.55 (m, 2H).<br>LC-MS [M+1]: 469.4.          |
| 161   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(2-methoxyethoxy)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>        | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.94 (s, 1H), 8.52 - 8.42 (m, 1H), 8.03 (s, 1H), 7.94 - 7.87 (m, 2H), 7.07 - 7.01 (m, 2H), 6.97 - 6.91 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.72 (br d, <i>J</i> =4.0 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.16 - 4.11 (m, 2H), 3.72 - 3.66 (m, 2H), 3.33 (s, 3H), 3.33 - 3.28 (m, 2H).<br>LC-MS [M+1]: 460.0.                                                                                         |
| 162   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(tetrahydrofuran-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.93 (s, 1H), 8.50 (br s, 1H), 8.08 (s, 1H), 7.92 (d, <i>J</i> =8.0 Hz, 2H), 7.40 (d, <i>J</i> =8.0 Hz, 2H), 6.95 (t, <i>J</i> =9.6 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.85 (t, <i>J</i> =7.2 Hz, 1H), 4.74 (s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.09 - 3.95 (m, 1H), 3.90 - 3.76 (m, 1H), 3.31 - 3.26 (m, 2H), 2.36 - 2.26 (m, 1H), 2.01 - 1.90 (m, 2H), 1.77 - 1.64 (m, 1H).<br>LCMS [M+1]: 456.2. |

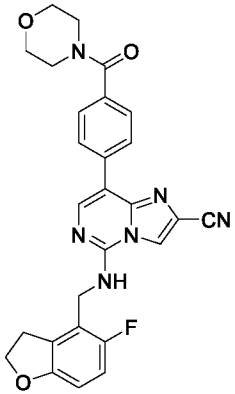
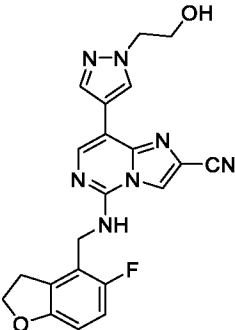
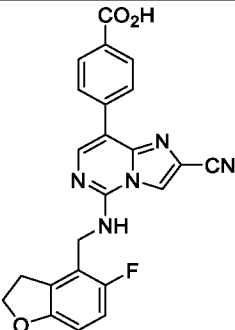
| Ex. # | Structure                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 163   |  <p>8-(4-(2-(dimethylamino)ethyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                  | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.59 (s, 1H), 7.96 (s, 1H), 7.79 (d, <i>J</i> =8.4 Hz, 2H), 7.33 (d, <i>J</i> =8.0 Hz, 2H), 6.90 - 6.82 (m, 1H), 6.64 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.81 (s, 2H), 4.57 (br t, <i>J</i> =8.8 Hz, 2H), 3.36 (s, 2H), 2.92 - 2.82 (m, 2H), 2.70 - 2.61 (m, 2H), 2.36 (s, 6H).<br>LCMS [M+1]: 457.2.                                                           |
| 164   |  <p>diethyl (4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)phenyl)phosphonate</p>                          | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.95 (s, 1H), 8.64 (br s, 1H), 8.22 (s, 1H), 8.17 (dd, <i>J</i> =4.0, 8.4 Hz, 2H), 7.79 (dd, <i>J</i> =8.4, 12.8 Hz, 2H), 6.98 - 6.90 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.75 (br d, <i>J</i> =3.6 Hz, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 4.09 - 3.96 (m, 4H), 3.29 (br s, 2H), 1.25 (t, <i>J</i> =6.8 Hz, 6H).<br>LCMS [M+1]: 522.0. |
| 165   |  <p>8-(4-(((dimethylamino)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)-d<sub>2</sub>)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.77 - 8.66 (m, 1H), 8.04 (d, <i>J</i> =13.6 Hz, 1H), 7.59 - 7.42 (m, 3H), 6.88 (t, <i>J</i> =9.6 Hz, 1H), 6.68 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.68 - 4.54 (m, 2H), 4.45 - 4.33 (m, 2H), 3.52 - 3.36 (m, 2H), 2.96 - 2.88 (m, 6H), 2.32 - 2.24 (m, 3H).<br>LCMS [M+1]: 459.2.                                                                               |

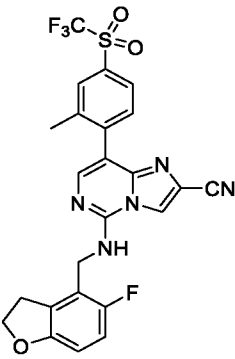
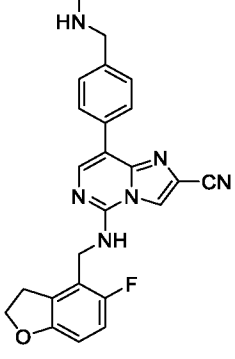
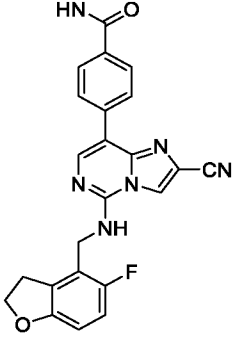
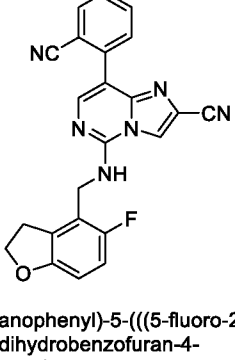
| Ex. # | Structure                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 166   |  <p>methyl 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)picolinate</p>                                       | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.32 (d, <i>J</i> =2.0 Hz, 1H), 8.97 (s, 1H), 8.78 (t, <i>J</i> =5.2 Hz, 1H), 8.66 (dd, <i>J</i> =2.4, 8.0 Hz, 1H), 8.38 (s, 1H), 8.15 (d, <i>J</i> =8.4 Hz, 1H), 6.99 - 6.90 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.90 (s, 3H), 3.29 - 3.29 (m, 2H).<br>LC-MS [M+1]: 445.2. |
| 167   |  <p>methyl 4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)benzoate</p>                                         | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.97 (s, 1H), 8.68 (br t, <i>J</i> =4.8 Hz, 1H), 8.26 (s, 1H), 8.19 (d, <i>J</i> =8.8 Hz, 2H), 8.07 - 7.99 (m, 2H), 6.97 - 6.91 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.75 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.87 (s, 3H), 3.37 - 3.35 (m, 2H).<br>LC-MS [M+1]: 443.9.                                               |
| 168   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.98 (s, 1H), 8.65 (t, <i>J</i> =5.2 Hz, 1H), 8.18 (s, 1H), 7.99 - 7.95 (m, 1H), 7.94 - 7.90 (m, 2H), 6.98 - 6.90 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.58 (t, <i>J</i> =6.8 Hz, 2H), 3.32 (br t, <i>J</i> =8.8 Hz, 2H), 3.12 - 2.97 (m, 5H).<br>LCMS [M+1]: 469.3.         |
| 169   |  <p>methyl 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-1-methyl-1H-pyrazole-3-carboxylate</p>            | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 7.93 (s, 1H), 6.97 (s, 1H), 6.90 - 6.81 (m, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.39 (t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [M + 1]: 448.2.                                                                                                                           |

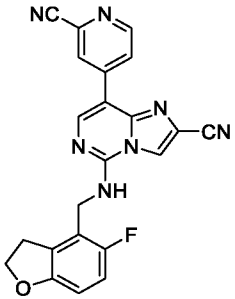
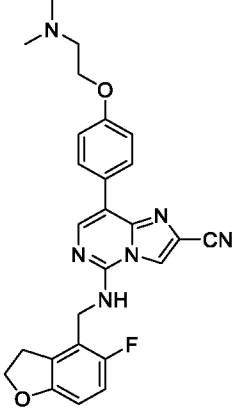
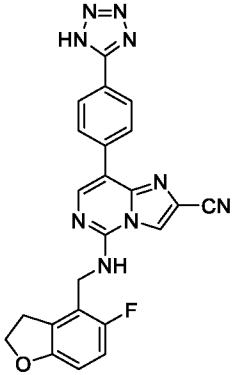
| Ex. # | Structure                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 170   |  <p>5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,N,1-trimethyl-1H-pyrazole-3-carboxamide</p>     | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.98 (s, 1H), 8.76 (t, <i>J</i> =4.8 Hz, 1H), 7.95 (s, 1H), 6.99 - 6.91 (m, 1H), 6.74 (s, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8Hz, 2H), 3.82 (s, 3H), 3.36 - 3.28 (m, 5H), 2.99 (s, 3H).<br>LC-MS [M+1]: 461.3.                                                                |
| 171   |  <p>8-(4-(1-(dimethylamino)cyclopropyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.60 (s, 1H), 8.00 (s, 1H), 7.86 (d, <i>J</i> =8.4 Hz, 2H), 7.45 (d, <i>J</i> =8.4 Hz, 2H), 6.90 - 6.82 (m, 1H), 6.65 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (br s, 2H), 4.58 (t, <i>J</i> =8.8 Hz, 2H), 3.37 (t, <i>J</i> =8.4 Hz, 2H), 2.29 (s, 6H), 1.02 - 0.98 (m, 2H), 0.92 - 0.88 (m, 2H).<br>LCMS [M+1]: 469.4.                                |
| 172   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.64 (s, 1H), 8.13 (s, 1H), 8.04 (d, <i>J</i> =8.4 Hz, 1H), 7.93 (s, 1H), 7.89 (d, <i>J</i> =8.0 Hz, 1H), 6.88 (t, <i>J</i> =8.8 Hz, 1H), 6.67 (dd, <i>J</i> =4.4, 8.4 Hz, 1H), 4.83 - 4.82 (m, 2H), 4.60 (t, <i>J</i> =8.8 Hz, 2H), 3.58 (t, <i>J</i> =6.8 Hz, 2H), 3.39 - 3.37 (m, 2H), 3.10 (br t, <i>J</i> =6.8 Hz, 2H).<br>LCMS [M + 1]: 455.2. |

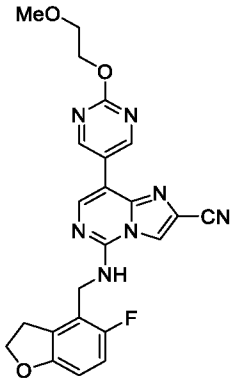
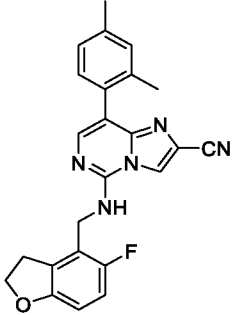
| Ex. # | Structure                                                                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                             |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 173   |  <p>8-(4-((dimethylamino)methyl-<i>d</i><sub>2</sub>)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.87 (br s, 1H), 8.94 (s, 1H), 8.54 (br t, <i>J</i> =4.8 Hz, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.42 - 7.36 (m, 2H), 6.99 - 6.90 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.4 Hz, 1H), 4.72 (br d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.33 - 3.29 (m, 2H), 2.78 (s, 6H), 2.20 (s, 3H).<br>LCMS [M+1]: 459.3.                          |
| 174   |  <p>3-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)benzoic acid</p>                                                     | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 13.03 (s, 1H), 8.95 (s, 1H), 8.63 - 8.53 (m, 2H), 8.19 - 8.15 (m, 2H), 7.93 (d, <i>J</i> =8.0 Hz, 1H), 7.59 (t, <i>J</i> =8.0 Hz, 1H), 6.95 (t, <i>J</i> =9.6 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.34 - 3.37 (m, 2H).<br>LCMS [M + 1]: 430.2.                        |
| 175   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(<i>p</i>-tolyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                              | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.92 (s, 1H), 8.45 (t, <i>J</i> =5.2 Hz, 1H), 8.06 (s, 1H), 7.86 (d, <i>J</i> =8.0 Hz, 2H), 7.27 (d, <i>J</i> =8.0 Hz, 2H), 6.98 - 6.91 (m, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.73 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.31 (t, <i>J</i> =8.8 Hz, 2H), 2.35 (s, 3H).<br>LC-MS [M+1]: 400.0.                      |
| 176   |  <p>8-(3-cyano-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                      | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.56 (t, <i>J</i> =4.8 Hz, 1H), 7.86 (dd, <i>J</i> =1.2, 7.6 Hz, 1H), 7.78 (s, 1H), 7.66 (dd, <i>J</i> =0.8, 7.6 Hz, 1H), 7.51 - 7.46 (m, 1H), 6.99 - 6.94 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.50 - 3.48 (m, 2H), 2.35 (s, 3H).<br>LCMS [M+1]: 425.0. |

| Ex. # | Structure                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 177   |  <p>8-(5-cyano-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.99 (s, 1H), 8.63 (t, <i>J</i> =5.2 Hz, 1H), 7.88 - 7.84 (m, 2H), 7.82 (d, <i>J</i> =1.6 Hz, 1H), 7.61 (d, <i>J</i> =8.0 Hz, 1H), 7.05 - 6.99 (m, 1H), 6.78 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.79 (d, <i>J</i> =4.8 Hz, 2H), 4.62 (t, <i>J</i> =8.8 Hz, 2H), 3.47 - 3.45 (m, 2H), 2.31 (s, 3H).<br>LC-MS [M+1]: 425.0.                                                               |
| 178   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methylpyridin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.99 - 8.92 (m, 2H), 8.78 (d, <i>J</i> =5.2 Hz, 1H), 8.73 (s, 1H), 8.59 (s, 1H), 8.56 (dd, <i>J</i> =1.6, 5.2 Hz, 1H), 6.95 (t, <i>J</i> =9.2 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.77 (br d, <i>J</i> =4.0 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.28 - 3.21 (m, 2H).<br>LCMS [M+1]: 411.9.                                                                            |
| 179   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.90 (s, 1H), 8.41 (s, 1H), 8.35 (t, <i>J</i> =5.2 Hz, 1H), 8.18 (s, 1H), 8.11 (s, 1H), 6.98 - 6.90 (m, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.89 (br s, 1H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.08 (dd, <i>J</i> =3.2, 5.2 Hz, 2H), 4.04 - 3.96 (m, 1H), 3.29 (t, <i>J</i> =8.8 Hz, 2H), 1.06 (d, <i>J</i> =6.0 Hz, 3H).<br>LCMS [M+1] : 434.3. |
| 180   |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,N-dimethylbenzamide</p>                  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz): δ = 8.95 (s, 1H), 8.55 (t, <i>J</i> = 5.2 Hz, 1H), 8.18 (s, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 2H), 7.49 (d, <i>J</i> = 8.4 Hz, 2H), 6.91-6.98 (m, 1H), 6.71 (dd, <i>J</i> = 8.8, 4.0 Hz, 1H), 4.74 (d, <i>J</i> = 4.8 Hz, 2H), 4.55 (t, <i>J</i> = 8.8 Hz, 2H), 3.31 - 3.27 (m, 2H), 2.99 (br s, 6H).<br>LC-MS [M+1]: 456.7.                                                              |

| Ex. # | Structure                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                              |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 181   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(morpholine-4-carbonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>     | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.94 (s, 1H), 8.56 (t, <i>J</i> =5.2 Hz, 1H), 8.17 (s, 1H), 8.07 (d, <i>J</i> =8.4 Hz, 2H), 7.50 (d, <i>J</i> =8.4 Hz, 2H), 6.94 (t, <i>J</i> =9.6 Hz, 1H), 6.70 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 3.62 (br s, 5H), 3.55 - 3.33 (m, 5H).<br>LC-MS [M+1]: 499.1.            |
| 182   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.91 (s, 1H), 8.42 (s, 1H), 8.35 (t, <i>J</i> =5.2 Hz, 1H), 8.18 (s, 1H), 8.11 (s, 1H), 6.99 - 6.90 (m, 1H), 6.70 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.71 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.22 (t, <i>J</i> =5.6 Hz, 2H), 3.77 (t, <i>J</i> =5.6 Hz, 2H), 3.29 (t, <i>J</i> =8.4 Hz, 2H).<br>LC-MS [M+1]: 420.3. |
| 183   |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)benzoic acid</p>                          | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ = 8.98 (s, 1H), 8.22 (s, 1H), 8.11 (d, <i>J</i> =8.0 Hz, 2H), 8.00 (d, <i>J</i> =8.0 Hz, 2H), 6.96 (t, <i>J</i> =8.8 Hz, 1H), 6.71 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.76 (s, 2H), 4.55 (t, <i>J</i> =8.4 Hz, 2H), 3.28 - 3.25 (m, 2H).<br>LC-MS [M+1]: 430.3.                                                                               |

| Ex. # | Structure                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 184   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-4-((trifluoromethyl)sulfonyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.95 (s, 1H), 8.67 (br t, <i>J</i> =4.8 Hz, 1H), 8.11 (s, 1H), 8.03 (d, <i>J</i> =8.0 Hz, 1H), 7.90 (s, 1H), 7.82 (d, <i>J</i> =8.0 Hz, 1H), 7.02 - 6.88 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (d, <i>J</i> =4.4 Hz, 2H), 4.56 (t, <i>J</i> =8.8 Hz, 2H), 3.34 (t, <i>J</i> =8.8 Hz, 2H), 2.37 (s, 3H).<br>LC-MS [M+1]: 532.0.                                                |
| 185   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-((methylamino)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>               | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.95 (s, 1H), 8.77 (s, 2H), 8.60 (t, <i>J</i> = 5.1 Hz, 1H), 8.16 (s, 1H), 8.11 – 8.01 (m, 2H), 7.59 – 7.49 (m, 2H), 6.94 (dd, <i>J</i> = 10.3, 8.7 Hz, 1H), 6.70 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 4.73 (d, <i>J</i> = 4.9 Hz, 2H), 4.54 (t, <i>J</i> = 8.7 Hz, 2H), 4.17 (s, 2H), 3.29 (s, 1H), 2.59 (d, <i>J</i> = 4.8 Hz, 3H).<br>LCMS [M+1]: 429.3.                                     |
| 186   |  <p>4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N-methylbenzamide</p>                             | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.96 (s, 1H), 8.59 (t, <i>J</i> = 5.2 Hz, 1H), 8.45 (d, <i>J</i> = 4.7 Hz, 1H), 8.21 (s, 1H), 8.14 – 8.05 (m, 2H), 7.92 (d, <i>J</i> = 8.5 Hz, 2H), 6.95 (dd, <i>J</i> = 10.3, 8.7 Hz, 1H), 6.71 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 4.75 (d, <i>J</i> = 4.9 Hz, 2H), 4.55 (t, <i>J</i> = 8.7 Hz, 2H), 3.31 (d, <i>J</i> = 8.8 Hz, 2H), 2.82 (d, <i>J</i> = 4.5 Hz, 3H).<br>LCMS [M+1]: 443.0. |
| 187   |  <p>8-(2-cyanophenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                              | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (s, 1H), 8.71 (t, <i>J</i> = 5.1 Hz, 1H), 7.99 (d, <i>J</i> = 14.2 Hz, 2H), 7.86 – 7.75 (m, 2H), 7.62 (ddd, <i>J</i> = 7.8, 6.2, 2.6 Hz, 1H), 7.03 – 6.91 (m, 1H), 6.73 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 4.76 (d, <i>J</i> = 4.8 Hz, 2H), 4.56 (t, <i>J</i> = 8.7 Hz, 2H), 3.33 (d, <i>J</i> = 8.7 Hz, 2H).<br>LCMS [M+1]: 411.0.                                                      |

| Ex. # | Structure                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 188   |  <p>8-(2-cyanopyridin-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (d, <i>J</i> = 8.6 Hz, 2H), 8.77 (dd, <i>J</i> = 20.1, 3.6 Hz, 2H), 8.65 – 8.51 (m, 2H), 6.96 (t, <i>J</i> = 9.4 Hz, 1H), 6.72 (dd, <i>J</i> = 8.7, 3.9 Hz, 1H), 4.78 (d, <i>J</i> = 4.6 Hz, 2H), 4.56 (t, <i>J</i> = 8.7 Hz, 2H), 3.12 (m, 2H).<br>LCMS [M+1]: 411.9.                                                                        |
| 189   |  <p>8-(4-(2-(dimethylamino)ethoxy)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.80 (bs, 1H), 8.44 (bs, 1H), 7.98 (s, 1H), 7.89 (d, <i>J</i> = 8.7 Hz, 2H), 7.02 (d, <i>J</i> = 8.4 Hz, 2H), 6.92 (t, <i>J</i> = 9.4 Hz, 1H), 6.67 (d, <i>J</i> = 8.3 Hz, 1H), 4.69 (s, 2H), 4.53 (t, <i>J</i> = 8.7 Hz, 2H), 4.09 (t, <i>J</i> = 5.8 Hz, 2H), 3.29 (m, 2H), 2.65 (t, <i>J</i> = 5.8 Hz, 3H), 2.23 (s, 6H).<br>LCMS [M+1]: 473.1. |
| 190   |  <p>8-(4-(1H-tetrazol-5-yl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>       | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.00 (s, 1H), 8.70 (t, <i>J</i> = 5.1 Hz, 1H), 8.28 (t, <i>J</i> = 4.3 Hz, 2H), 8.14 (d, <i>J</i> = 8.3 Hz, 2H), 7.02 – 6.87 (m, 1H), 6.71 (dd, <i>J</i> = 8.7, 3.9 Hz, 1H), 4.76 (d, <i>J</i> = 4.9 Hz, 2H), 4.56 (t, <i>J</i> = 8.7 Hz, 2H), 3.54 – 3.50 (m, 2H).<br>LCMS [M+1]: 453.9.                                                          |

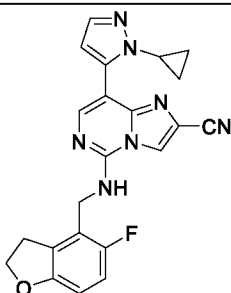
| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                     |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 191   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-(2-methoxyethoxy)pyrimidin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.17 (s, 2H), 8.96 (s, 1H), 8.66 (s, 1H), 8.22 (s, 1H), 6.95 (dd, <i>J</i> = 10.3, 8.7 Hz, 1H), 6.71 (dd, <i>J</i> = 8.7, 3.9 Hz, 1H), 4.74 (d, <i>J</i> = 4.9 Hz, 2H), 4.55 (t, <i>J</i> = 8.7 Hz, 2H), 4.51 – 4.45 (m, 2H), 3.74 – 3.67 (m, 2H), 3.38 – 3.28 (m, 5H).<br>LCMS [M+1]: 462.0.                                             |
| 192   |  <p>8-(2,4-dimethylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>               | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (d, <i>J</i> = 3.5 Hz, 1H), 8.49 (s, 1H), 7.65 (s, 1H), 7.18 – 7.12 (m, 2H), 7.06 (dd, <i>J</i> = 7.7, 1.9 Hz, 1H), 6.95 (dd, <i>J</i> = 10.3, 8.6 Hz, 1H), 6.71 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 4.72 (d, <i>J</i> = 3.6 Hz, 2H), 4.55 (t, <i>J</i> = 8.7 Hz, 2H), 3.31 (m, 2H), 2.33 (s, 3H), 2.12 (s, 3H).<br>LCMS [M+1]: 414.1. |

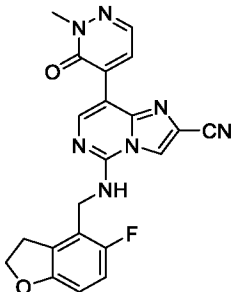
## EXAMPLES 193 and 194

[000391] EXAMPLES 193 and 194 were prepared following the procedure set forth in EXAMPLE 142 and using the general reactions schemes and intermediates described herein.

TABLE 9

Characterization of EXAMPLES 193 and 194

| Ex. # | Structure                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                 |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 193   |  <p>8-(1-cyclopropyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, <i>d</i> -DMSO) δ = 8.95 (s, 1H), 8.66 (br s, 1H), 8.02 (s, 1H), 7.47 (d, <i>J</i> = 1.6 Hz, 1H), 7.05 – 6.89 (m, 1H), 6.72 (dd, <i>J</i> = 4.0, 8.8 Hz, 1H), 6.53 (d, <i>J</i> = 1.6 Hz, 1H), 4.75 (s, 2H), 4.55 (t, <i>J</i> = 8.8 Hz, 2H), 3.74 – 3.68 (m, 1H), 3.32 – 3.28 (m, 2H), 0.98 – 0.91 (m, 2H), 0.86 – 0.78 (m, 2H).<br>LCMS [M+1]: 416. |

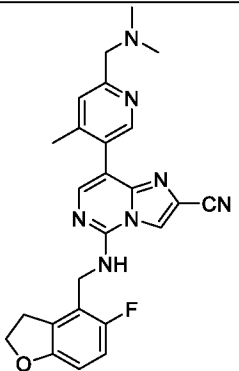
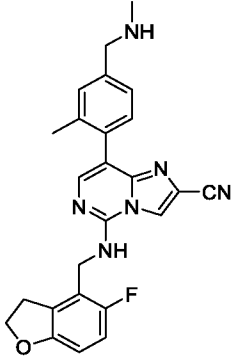
| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                             |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 194   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.18 (s, 1H), 8.94 (s, 1H), 8.82 (t, <i>J</i> =4.8 Hz, 1H), 8.60 (d, <i>J</i> =4.4 Hz, 1H), 8.04 (d, <i>J</i> =4.8 Hz, 1H), 6.98 - 6.91 (m, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.76 (d, <i>J</i> =4.8 Hz, 2H), 4.54 (t, <i>J</i> =8.4 Hz, 2H), 3.76 (s, 3H), 3.30 - 3.27 (m, 2H).<br>LC-MS [M+1]: 418.2. |

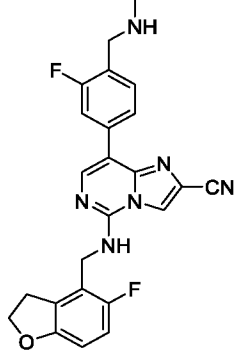
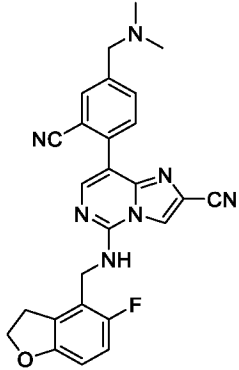
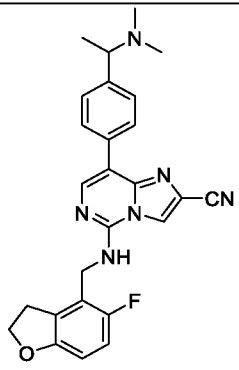
## EXAMPLES 195 -202

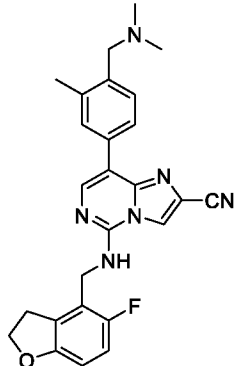
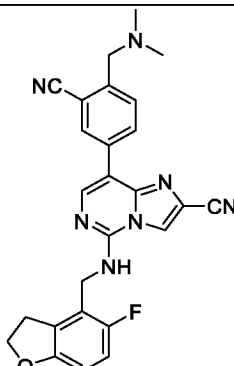
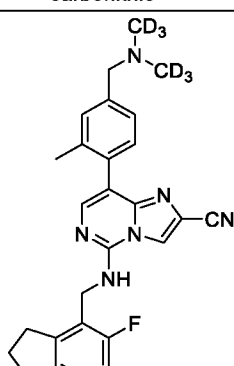
[000392] EXAMPLES 195 -202 were prepared following the procedure set forth in EXAMPLE 149 and using the general reactions schemes and intermediates described herein.

TABLE 10

Characterization of EXAMPLES 195 - 202

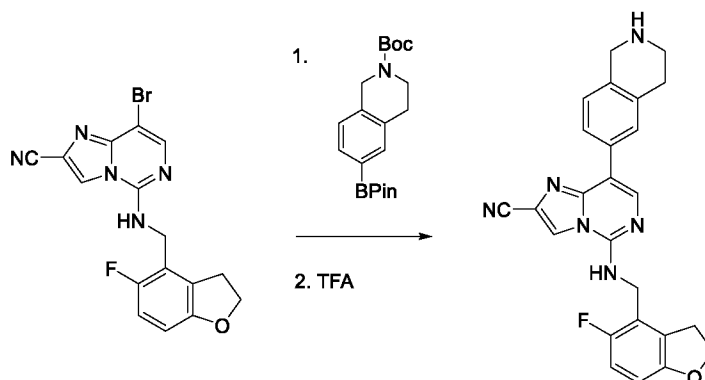
| Ex. # | Structure                                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 195   |  <p>8-(6-((dimethylamino)methyl)-4-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.03 (s, 1H), 8.64 (br s, 1H), 8.44 (s, 1H), 7.89 (s, 1H), 7.49 (s, 1H), 7.10 - 7.02 (m, 1H), 6.82 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.83 (br s, 2H), 4.66 (t, <i>J</i> =8.8 Hz, 2H), 3.63 (s, 2H), 2.34 (s, 6H), 2.31 (s, 3H).<br>LCMS [M+1]: 458.3.                                                                                                                                                      |
| 196   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-4-((methylamino)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>        | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.33 - 9.12 (m, 2H), 9.06 (s, 1H), 8.76 - 8.51 (m, 1H), 7.71 - 7.62 (m, 1H), 7.46 (s, 1H), 7.42 - 7.35 (m, 2H), 6.94 (t, <i>J</i> =9.6 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.8 Hz, 1H), 4.72 (br d, <i>J</i> =4.4 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.12 (br t, <i>J</i> =5.6 Hz, 2H), 3.34 (br t, <i>J</i> =8.4 Hz, 2H), 2.57 (t, <i>J</i> =5.2 Hz, 3H), 2.23 - 2.16 (m, 3H).<br>LCMS [M+1]: 443.0. |

| Ex. # | Structure                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 197   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(3-fluoro-4-((methylamino)methyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.26 (br s, 2H), 9.12 (s, 1H), 9.01 - 8.89 (m, 1H), 8.28 (s, 1H), 8.04 (br d, <i>J</i> =12.0 Hz, 1H), 7.97 (d, <i>J</i> =8.0 Hz, 1H), 7.71 (t, <i>J</i> =8.4 Hz, 1H), 6.94 (t, <i>J</i> =9.6 Hz, 1H), 6.69 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =4.4 Hz, 2H), 4.54 (t, <i>J</i> =8.8 Hz, 2H), 4.20 (br t, <i>J</i> =5.2 Hz, 2H), 3.32 (br t, <i>J</i> =8.4 Hz, 2H), 2.60 (t, <i>J</i> =5.2 Hz, 3H).<br>LCMS [M+1]: 447.0. |
| 198   |  <p>8-(2-cyano-4-((dimethylamino)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.96 (s, 1H), 8.69 (br s, 1H), 7.99 (s, 1H), 7.83 (s, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 6.99 - 6.92 (m, 1H), 6.72 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.75 (d, <i>J</i> =3.6 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.50 (s, 2H), 3.35 (br s, 2H), 2.20 (s, 6H).<br>LCMS [M+1]: 468.2.                                                                                                                                         |
| 199   |  <p>8-(4-(1-(dimethylamino)ethyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>       | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.68 - 8.61 (m, 1H), 8.07 - 8.01 (m, 2H), 7.99 (d, <i>J</i> =8.4 Hz, 1H), 7.69 (d, <i>J</i> =8.0 Hz, 1H), 7.62 (d, <i>J</i> =8.4 Hz, 1H), 6.92 - 6.80 (m, 1H), 6.70 - 6.61 (m, 1H), 4.88 (br s, 2H), 4.64 - 4.52 (m, 3H), 3.42 - 3.34 (m, 2H), 2.95 - 2.89 (m, 3H), 2.80 - 2.74 (m, 3H), 1.84 - 1.75 (m, 3H).<br>LCMS [M+1]: 457.0.                                                                                                                  |

| Ex. # | Structure                                                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                    |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 200   |  <p>8-(((dimethylamino)methyl)-3-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                             | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.50 (br s, 1H), 8.06 (s, 1H), 7.76 - 7.72 (m, 2H), 7.29 (d, <i>J</i> =8.0 Hz, 1H), 7.00 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.73 (s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.38 - 3.36 (m, 2H), 2.38 (s, 3H), 2.18 (s, 6H).<br>LCMS [M+1]: 457.3.                                       |
| 201   |  <p>8-(3-cyano-4-((dimethylamino)methyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                           | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.96 (s, 2H), 8.65 (s, 2H), 8.44 (d, <i>J</i> = 1.9 Hz, 1H), 8.38 - 8.23 (m, 3H), 7.65 (d, <i>J</i> = 8.2 Hz, 2H), 7.02 - 6.88 (m, 2H), 6.71 (dd, <i>J</i> = 8.6, 3.9 Hz, 2H), 4.75 (d, <i>J</i> = 5.0 Hz, 3H), 4.56 (t, <i>J</i> = 8.7 Hz, 3H), 3.59 (s, 2H), 3.32 - 3.30 (m, 2 H), 2.22 (s, 6H).<br>LCMS [M+1]: 468.0. |
| 202   |  <p>8-(4-((bis(methyl-<i>d</i><sub>3</sub>)amino)methyl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.91 (s, 1H), 8.44 (s, 1H), 7.70 (s, 1H), 7.31 - 7.14 (m, 3H), 6.96 (dd, <i>J</i> = 10.3, 8.6 Hz, 1H), 6.72 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 4.78 - 4.66 (m, 2H), 4.56 (t, <i>J</i> = 8.7 Hz, 2H), 3.40 (m, 2H), 3.31 (m, 2H), 2.15 (s, 3H).<br>LCMS [M+1]: 463.4.                                                      |

## EXAMPLE 203

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,2,3,4-tetrahydroisoquinolin-6-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000393] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (70.0 mg, 180  $\mu$ mol, 1.00 equiv), *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (97.2 mg, 270  $\mu$ mol, 1.50 equiv), sodium bicarbonate (30.3 mg, 361  $\mu$ mol, 14.0  $\mu$ L, 2.00 equiv), Pd(dppf)Cl<sub>2</sub> (13.2 mg, 18.0  $\mu$ mol, 0.10 equiv) in dioxane (1.00 mL) and water (0.30 mL) was purged with nitrogen and then stirred at 100 °C for 2 h. The reaction was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 2/1) to afford *tert*-butyl 6-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (67.0 mg, 124  $\mu$ mol, 68.7% yield) as a yellow solid.

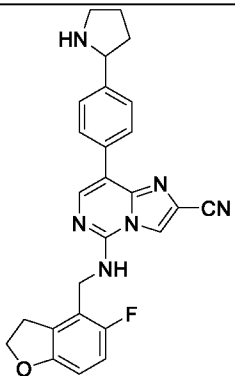
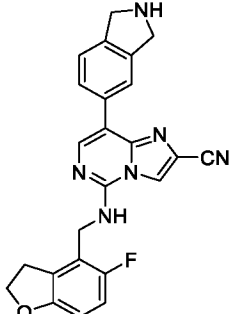
[000394] <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.61 (s, 1H), 7.98 (s, 1H), 7.69 (s, 1H), 7.67 (br d, *J*=8.0 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 1H), 6.87 (t, *J*=9.2 Hz, 1H), 6.66 (dd, *J*=4.0, 8.8 Hz, 1H), 4.83 (br s, 2H), 4.63 - 4.58 (m, 4H), 3.70 (br t, *J*=6.0 Hz, 2H), 3.38 (br t, *J*=8.8 Hz, 2H), 2.94 (br t, *J*=6.0 Hz, 2H), 1.53 (s, 9H).

[000395] To a solution of *tert*-butyl 6-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (50.0 mg, 92.5  $\mu$ mol, 1.00 equiv) in dichloromethane (1.00 mL) was added trifluoroacetic acid (10.6 mg, 92.5  $\mu$ mol, 6.85  $\mu$ L, 1.00 equiv), the mixture was stirred at room temperature for 0.5 h. The mixture was filtered and concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (hydrochloric acid conditions) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1,2,3,4-tetrahydroisoquinolin-6-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile hydrochloride salt (12.4 mg, 25.7  $\mu$ mol, 27.8% yield, 98.6% purity) as a yellow solid. LC-MS [*M*+1]: 441.1. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.43 (br s, 2H), 9.08 (s, 1H), 8.77 (br s, 1H), 8.10 (s, 1H), 7.86 (br d, *J*=8.4 Hz, 1H), 7.84 (br s, 1H), 7.31 (br d, *J*=7.6 Hz, 1H), 6.94 (br t, *J*=9.6 Hz, 1H), 6.70 (br dd, *J*=3.6, 8.4 Hz, 1H), 4.73 (br d, *J*=4.4 Hz, 2H), 4.54 (br t, *J*=8.8 Hz, 2H), 4.30 (br s, 2H), 3.30 - 3.27 (m, 2H), 3.26 - 3.19 (m, 2H), 3.09 (br d, *J*=5.2 Hz, 2H).

[000396] EXAMPLE 204 was prepared following the procedure set forth in EXAMPLE 193 and using the general reactions schemes and intermediates described herein.

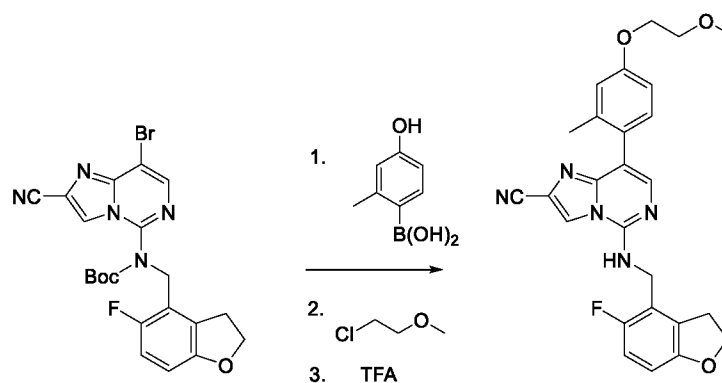
TABLE 11

Characterization of EXAMPLE 194

| Ex. # | Structure                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 204   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.47 (br s, 1H), 8.07 (s, 1H), 7.88 (d, <i>J</i> =8.0 Hz, 2H), 7.45 (d, <i>J</i> =8.4 Hz, 2H), 6.99 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br d, <i>J</i> =4.0 Hz, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 4.08 (t, <i>J</i> =7.6 Hz, 1H), 3.10 - 3.01 (m, 2H), 2.95 - 2.85 (m, 2H), 2.21 - 2.07 (m, 1H), 1.85 - 1.73 (m, 2H), 1.62 - 1.43 (m, 1H).<br>LC-MS [M+1]: 455.3. |
| 205   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(isoindolin-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>          | <sup>1</sup> H NMR (400 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 7.83 (s, 1H), 7.78 - 7.69 (m, 1H), 7.42 (d, <i>J</i> = 7.9 Hz, 1H), 6.93 - 6.80 (m, 1H), 6.66 (dd, <i>J</i> = 8.7, 3.9 Hz, 1H), 4.59 (t, <i>J</i> = 8.7 Hz, 2H), 4.34 (bs, 4H), 3.38 (t, <i>J</i> = 8.7 Hz, 2H).<br>LCMS [M+1]: 427.2.                                                                                                                                                                  |

## EXAMPLE 206

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(2-methoxyethoxy)-2-methylphenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000397] To a solution of (4-hydroxy-2-methyl-phenyl)boronic acid (30.5 mg, 201 μmol, 1.40 equiv), *tert*-butyl (8-bromo-2-cyanoimidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (70.0 mg, 143 μmol, 1.00 equiv) in dioxane (1.00 mL) and water (0.20 mL) were added Pd(dppf)Cl<sub>2</sub> (10.5 mg, 14.3 μmol, 0.10 equiv) and sodium bicarbonate (24.1 mg, 286 μmol, 2.00 equiv) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 2 h and subsequently was

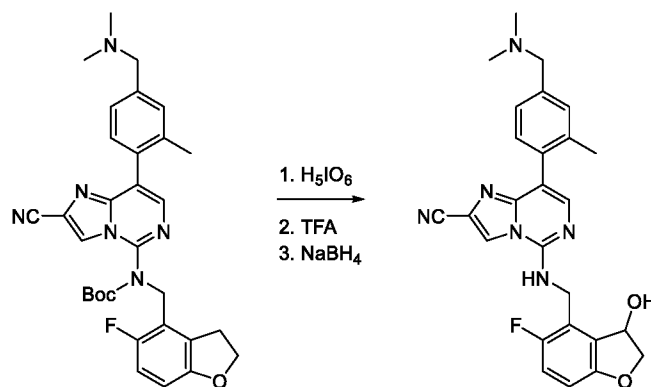
concentrated in vacuo to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to afford *tert*-butyl (2-cyano-8-(4-hydroxy-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (70.0 mg, 136 μmol, 94.7% yield) as a yellow solid. LCMS [M+1]: 516.1. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 9.64 (s, 1H), 8.71 (s, 1H), 7.99 (s, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 6.82 - 6.74 (m, 2H), 6.72 (dd, *J*=2.4, 8.4 Hz, 1H), 6.62 (dd, *J*=4.0, 8.8 Hz, 1H), 5.04 (s, 2H), 4.54 (t, *J*=8.8 Hz, 2H), 3.30 - 3.26 (m, 2H), 2.02 (s, 3H), 1.34 (s, 9H).

**[000398]** To a solution *tert*-butyl (2-cyano-8-(4-hydroxy-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (70.0 mg, 135 μmol, 1.00 equiv), 1-chloro-2-methoxy-ethane (51.4 mg, 543 μmol, 49.4 μL, 4.00 equiv) in acetonitrile (1.00 mL) was added potassium carbonate (37.5 mg, 272 μmol, 2.00 equiv). The mixture was stirred at 85 °C for 12 h. The mixture was concentrated in vacuo to afford *tert*-butyl (2-cyano-8-(4-(2-methoxyethoxy)-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, crude) as a gray solid. LCMS [M+1]: 574.6.

**[000399]** To a solution of *tert*-butyl (2-cyano-8-(4-(2-methoxyethoxy)-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (25.0 mg, 43.6 μmol, 1.00 equiv) in dichloromethane (1.00 mL) was added trifluoroacetic acid (0.30 mL). The mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (neutral conditions) to afford 5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]-8-[4-(2-methoxyethoxy)-2-methyl-phenyl]imidazo[1,2-*c*]pyrimidine-2-carbonitrile (6.50 mg, 13.7 μmol, 31.5% yield, 99.9% purity) as a gray solid. LCMS [M+1]: 474.4. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ = 8.89 (s, 1H), 8.39 (br s, 1H), 7.65 (s, 1H), 7.18 (d, *J*=8.4 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.90 (d, *J*=2.4 Hz, 1H), 6.83 (dd, *J*=2.8, 8.4 Hz, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 4.71 (br d, *J*=3.6 Hz, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 4.18 - 4.10 (m, 2H), 3.70 - 3.66 (m, 2H), 2.12 (s, 3H).

#### EXAMPLE 207

**8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-3-hydroxy-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile**



**[000400]** A mixture of *tert*-butyl (2-cyano-8-(4-((dimethylamino)methyl)-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (200 mg, 359 μmol, 1.00 equiv), chromium trioxide (53.9 mg, 539 μmol, 20.0 μL, 1.50 equiv) and periodic acid (221 mg, 970 μmol, 221 μL, 2.70 equiv) in acetonitrile (1.00 mL) was stirred at room temperature for 2 h. The mixture

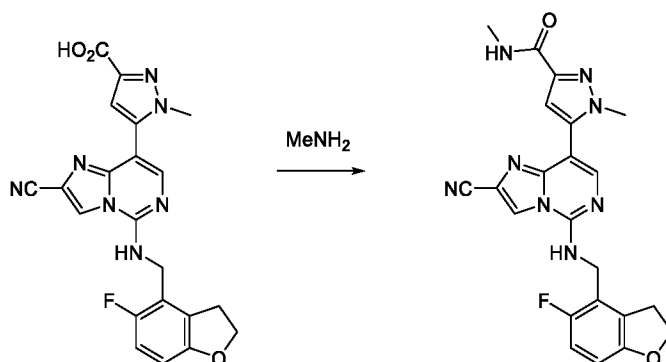
was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (trifluoroacetic acid conditions) to afford *tert*-butyl (2-cyano-8-(4-((dimethylamino)methyl)-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 48.9  $\mu$ mol, 13.6% yield, 93.0% purity) as a white solid. LCMS [*M*+1]: 571.3.

[000401] A mixture of *tert*-butyl (2-cyano-8-(4-((dimethylamino)methyl)-2-methylphenyl)imidazo[1,2-*c*]pyrimidin-5-yl)((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 52.6  $\mu$ mol, 1.00 equiv) and trifluoroacetic acid (1.54 g, 13.5 mmol, 1.00 mL, 257 equiv) in dichloromethane (3.00 mL) was stirred at room temperature for 1 h. The mixture was filtered and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (trifluoroacetic acid conditions) to afford 8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (20.0 mg, 31.0  $\mu$ mol, 59.0 % yield, 90.6% purity, trifluoroacetic acid salt) as a purple solid. LC-MS [*M*+1]: 471.1. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.64 (br s, 1H), 8.85 (s, 1H), 8.33 (t, *J*=4.4 Hz, 1H), 7.72 (s, 1H), 7.65 (t, *J*=9.2 Hz, 1H), 7.48 - 7.38 (m, 3H), 7.34 (dd, *J*=3.2, 8.8 Hz, 1H), 5.05 (d, *J*=4.4 Hz, 2H), 4.91 (s, 2H), 4.30 (br s, 2H), 2.79 (br s, 6H), 2.21 (s, 3H).

[000402] A mixture of 8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-3-oxo-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (10.0 mg, 21.3  $\mu$ mol, 1.00 equiv) and sodium borohydride (1.61 mg, 42.5  $\mu$ mol, 2.00 equiv) in methyl alcohol (1.00 mL) was stirred at 0 °C for 2.5 h. The mixture was concentrated under reduced pressure to give a residue. The mixture was purified by prep-HPLC (neutral conditions) to afford 8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-3-hydroxy-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidine-2-carbonitrile (3.69 mg, 7.80  $\mu$ mol, 36.7% yield, 99.9% purity) as an off-white solid. LC-MS [*M*+1]:473.4.

### EXAMPLE 208

5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidin-8-yl)-*N*,1-dimethyl-1*H*-pyrazole-3-carboxamide

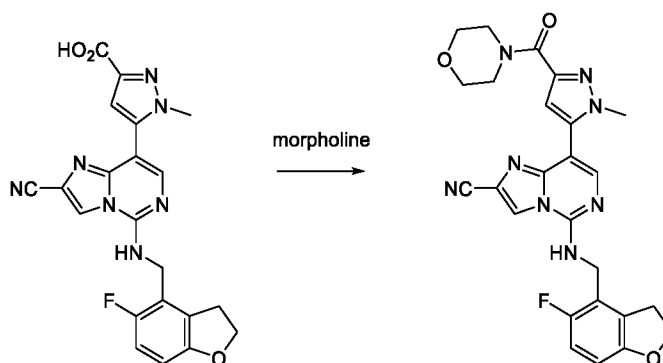


[000403] To a solution of 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-*c*]pyrimidin-8-yl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (150 mg, 346  $\mu$ mol, 1.00 equiv), DIEA (135 mg, 1.04 mmol, 182  $\mu$ L, 3.02 equiv) and methylamine (2 M in THF, 519.16  $\mu$ L, 3.00 equiv) in DMF (1.50 mL) was added HATU (200 mg, 526  $\mu$ mol, 1.52 equiv). The

mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (5.00 mL) and filtered to afford the crude product. The crude product was triturated with methanol (5.00 mL) and collected by filtration to provide 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,1-dimethyl-1H-pyrazole-3-carboxamide (130 mg, 256  $\mu$ mol, 74.0% yield, 88.0% purity) as a yellow solid. A portion (40 mg) of the material was purified by prep-HPLC (neutral conditions) to give 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-N,1-dimethyl-1H-pyrazole-3-carboxamide (8.4 mg, 17.5  $\mu$ mol, 22.2% yield, 93.0% purity) as a white solid. LCMS [M+1]: 447.2.  $^1\text{H}$  NMR (400MHz, DMSO-*d*6)  $\delta$  = 8.92 (s, 1H), 8.12 (d, *J*=4.8 Hz, 1H), 7.94 (s, 1H), 6.95 (t, *J*=9.6 Hz, 1H), 6.81 (s, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 4.73 (s, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.83 (s, 3H), 3.30 - 3.32 (m, 2H), 2.76 (d, *J*=4.8 Hz, 3H).

### EXAMPLE 209

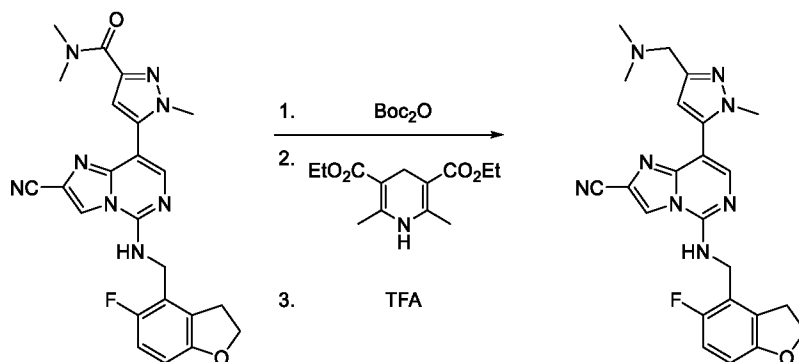
**5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-(morpholine-4-carbonyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile**



**[000404]** To a solution of 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-1-methyl-1H-pyrazole-3-carboxylic acid (50.0 mg, 115  $\mu$ mol, 1.00 equiv) and morpholine (20.00 mg, 229  $\mu$ mol, 20.2  $\mu$ L, 1.99 equiv) in DMF (1.00 mL) was added HATU (83.0 mg, 173  $\mu$ mol, 1.50 equiv) and DIEA (45.0 mg, 348  $\mu$ mol, 60.7  $\mu$ L, 3.02 equiv). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (15.0 mL) and extracted with dichloromethane (10.0 mL  $\times$  3). The combined organic layer was washed with water (20.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral conditions) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-(morpholine-4-carbonyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (6.10 mg, 11.6  $\mu$ mol, 10.0% yield, 95.3% purity) as a white solid. LCMS [M+1]: 503.2.  $^1\text{H}$  NMR (400MHz, DMSO-*d*6)  $\delta$  = 8.92 (s, 1H), 7.94 (s, 1H), 6.95 (t, *J*=9.6 Hz, 1H), 6.77 (s, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 4.73 (s, 2H), 4.55 (t, *J*= 8.8 Hz, 2H), 4.02 (s, 2H), 3.81 (s, 3H), 3.63 (s, 6H), 3.32 - 3.30 (m, 2H).

## EXAMPLE 210

## 8-(3-(((dimethylamino)methyl)-1-methyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000405] To a solution of 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-*N,N*,1-trimethyl-1H-pyrazole-3-carboxamide (100 mg, 217  $\mu\text{mol}$ , 1.00 equiv) in THF (1.00 mL) was added di-*tert*-butyl dicarbonate (56.9 mg, 261  $\mu\text{mol}$ , 59.9  $\mu\text{L}$ , 1.20 equiv) and DMAP (2.65 mg, 21.7  $\mu\text{mol}$ , 0.10 equiv). The mixture was stirred at 60 °C for 4 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 3/1 to 1/1) to afford *tert*-butyl (2-cyano-8-(3-(dimethylcarbamoyl)-1-methyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (80.0 mg, 143  $\mu\text{mol}$ , 65.7% yield) as an off-white solid. LCMS [ $\text{M}+1$ ]: 561.6.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.07 (s, 1H), 7.84 (s, 1H), 7.00 (s, 1H), 6.74 - 6.65 (m, 1H), 6.64 - 6.56 (m, 1H), 5.14 (s, 2H), 4.60 (t,  $J$ =8.8 Hz, 2H), 3.95 (s, 3H), 3.42 (s, 3H), 3.34 (br t,  $J$ =8.8 Hz, 2H), 3.14 (s, 3H), 1.43 (s, 9H).

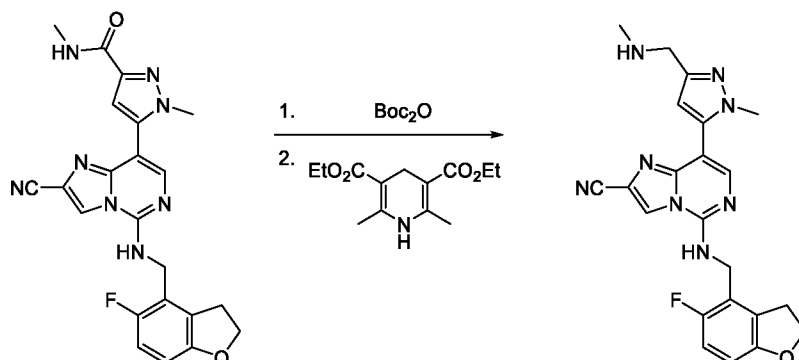
[000406] To a flame dried RBF charged with *tert*-butyl (2-cyano-8-(3-(dimethylcarbamoyl)-1-methyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 53.5  $\mu\text{mol}$ , 1.00 equiv) was added dichloromethane (1.00 mL) followed by trifluoromethanesulfonic anhydride (30.2 mg, 107  $\mu\text{mol}$ , 17.7  $\mu\text{L}$ , 2.00 equiv). The resultant solution was stirred at room temperature under an atmosphere of nitrogen for 30 min followed by the addition diethyl 2,6-dimethyl-1,4-dihydropyridine -3,5-dicarboxylate (54.2 mg, 214  $\mu\text{mol}$ , 4.00 equiv). The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , dichloromethane/methanol = 10/1) to afford *tert*-butyl (2-cyano-8-(3-(((dimethylamino)methyl)-1-methyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg) as a light yellow solid. LCMS [ $\text{M}+1$ ]: 547.3.

[000407] A mixture of *tert*-butyl (2-cyano-8-(3-(((dimethylamino)methyl)-1-methyl-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (30.0 mg, 54.9  $\mu\text{mol}$ , 1.00 equiv) in trifluoroacetic acid (0.30 mL) and dichloromethane (1.00 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (neutral conditions) to afford 8-(3-(((dimethylamino)methyl)-1-methyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (2.50 mg,

5.46  $\mu\text{mol}$ , 9.96% yield, 97.6% purity) as a yellow solid. LCMS  $[M+1]$ : 447.2.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.63 (s, 1H), 7.91 (s, 1H), 6.94 - 6.83 (m, 1H), 6.67 (dd,  $J=4.0, 8.8$  Hz, 1H), 6.48 (s, 1H), 4.60 (t,  $J=8.8$  Hz, 2H), 3.80 (s, 3H), 3.56 (s, 2H), 3.40 (br t,  $J=8.8$  Hz, 2H), 2.33 (s, 6H).

## EXAMPLE 211

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-((methylamino)methyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



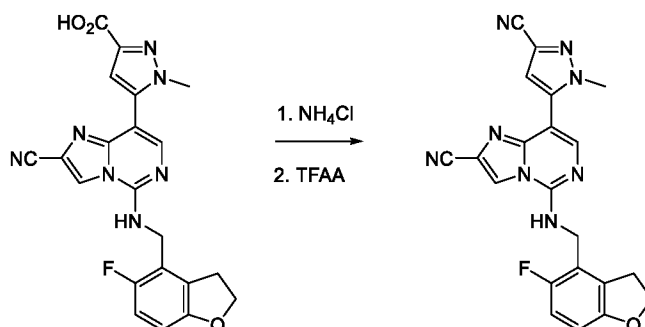
**[000408]** To a solution of 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-*N*,1-dimethyl-1H-pyrazole-3-carboxamide (80.0 mg, 157  $\mu\text{mol}$ , 1.00 equiv) in THF (1.50 mL) was added di-*tert*-butyl dicarbonate (41.3 mg, 189  $\mu\text{mol}$ , 1.20 equiv) and DMAP (2.06 mg, 16.9  $\mu\text{mol}$ , 0.10 equiv). The mixture was stirred at 60 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ( $\text{SiO}_2$ , petroleum ether/ethyl acetate=3/1 to 1/1) to afford *tert*-butyl (2-cyano-8-(1-methyl-3-(methylcarbamoyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (50.0 mg, 91.5  $\mu\text{mol}$ , 58.0% yield) as a yellow solid. LCMS  $[M+1]$ : 547.2.

**[000409]** To a flame-dried 10 mL round-bottom flask was added *tert*-butyl (2-cyano-8-(1-methyl-3-(methylcarbamoyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (25.0 mg, 45.7  $\mu\text{mol}$ , 1.00 equiv) followed by dichloromethane (1.80 mL) and 2-fluoropyridine (9.80 mg, 101  $\mu\text{mol}$ , 8.67  $\mu\text{L}$ , 2.21 equiv). The solution was then cooled to -78 °C and stirred for 10 min. To this solution was added dropwise  $\text{TiF}_4$  (27.1 mg, 96.1  $\mu\text{mol}$ , 15.9  $\mu\text{L}$ , 2.10 equiv) and the reaction was stirred for an additional 10 min. The solution was warmed at 0 °C and the reaction was stirred for 10 min. To this solution was added dropwise  $\text{Et}_3\text{SiH}$  (11.7 mg, 101  $\mu\text{mol}$ , 16.07  $\mu\text{L}$ , 2.20 equiv) and the reaction was stirred for 10 min. The solution was allowed to warm to room temperature and was stirred for 5 h. To the mixture was added diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (34.8 mg, 137.2  $\mu\text{mol}$ , 3.00 equiv) and the yellow suspension was stirred for 12 h at room temperature. The reaction mixture was concentrated to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , dichloromethane/methanol = 10/1) to give partially pure material. This material was purified by prep-HPLC (HCl conditions) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-((methylamino)methyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile hydrochloride salt (2.50 mg, 5.75  $\mu\text{mol}$ , 12.6% yield, 99.4% purity) as an off-white solid. LCMS  $[M+1]$ : 433.2.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.65 (s, 1H), 7.90 (s, 1H), 6.91 - 6.81 (m, 1H),

6.65 (dd,  $J=4.0, 8.8$  Hz, 1H), 6.58 (s, 1H), 4.63 - 4.54 (m, 2H), 4.26 - 4.19 (m, 2H), 3.82 (s, 3H), 3.42 - 3.35 (m, 2H), 3.32 (s, 2H), 2.77 (s, 3H).

## EXAMPLE 212

**8-(3-cyano-1-methyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile**

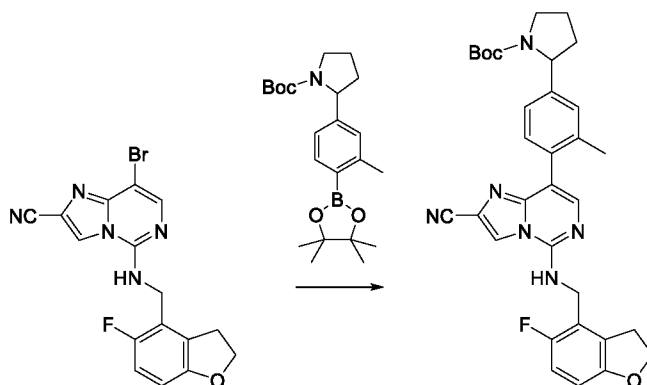


**[000410]** To a solution of 5-[2-cyano-5-[(5-fluoro-2,3-dihydrobenzofuran -4-yl)methylamino]imidazo[1,2-c]pyrimidin-8-yl]-1-methyl-pyrazole-3-carboxylic acid (100 mg, 185  $\mu\text{mol}$ , 1.00 equiv) and ammonium chloride (30.0 mg, 561  $\mu\text{mol}$ , 3.04 equiv) in DMF (2.00 mL) was added HATU (105 mg, 276  $\mu\text{mol}$ , 1.50 equiv) and DIEA (72.0 mg, 557  $\mu\text{mol}$ , 97.0  $\mu\text{L}$ , 3.02 equiv). The mixture was stirred at room temperature for 3 h. The mixture was diluted with water (20.0 mL) at which time a precipitate formed. The solid was filtered and dried under reduced pressure to give the crude product. The crude product was triturated with methanol (10.0 mL) and filtered to afford 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-1-methyl-1H-pyrazole-3-carboxamide (44 mg) as a yellow solid that was used into the next step without further purification. LC-MS  $[M+1]$ : 433.1.

**[000411]** To a mixture of 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-1-methyl-1H-pyrazole-3-carboxamide (44.0 mg, 102  $\mu\text{mol}$ , 1.00 equiv), TEA (206 mg, 2.04 mmol, 283  $\mu\text{L}$ , 20.0 equiv) in anhydrous THF (0.50 mL) was added TFAA (192 mg, 916  $\mu\text{mol}$ , 127  $\mu\text{L}$ , 9.00 equiv) at 0  $^{\circ}\text{C}$  with stirring. The resulting mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was concentrated to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 1/1). The obtained material was purified again by prep-HPLC (hydrochloric acid conditions) to give 8-(3-cyano-1-methyl-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (6.10 mg, 14.6  $\mu\text{mol}$ , 14.4% yield, 99.3% purity) as a white solid. LC-MS  $[M+1]$ : 415.2.  $^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 8.63 (s, 1H), 7.93 (s, 1H), 7.34 (s, 1H), 6.97 (s, 1H), 6.85 (t,  $J=9.6$  Hz, 1H), 6.65 (dd,  $J=3.6, 8.8$  Hz, 1H), 4.76 (s, 2H), 4.58 (t,  $J=8.8$  Hz, 2H), 3.89 (s, 3H), 3.39 (br t,  $J=8.8$  Hz, 2H).

## EXAMPLES 213 and 214

## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000412] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (255 mg, 657  $\mu$ mol, 1.00 equiv), *tert*-butyl 2-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-1-carboxylate (280 mg, 723  $\mu$ mol, 1.10 equiv), Pd(dppf)Cl<sub>2</sub> (48.1 mg, 65.7  $\mu$ mol, 0.10 equiv) and sodium bicarbonate (166 mg, 1.97 mmol, 76.7  $\mu$ L, 3.00 equiv) in dioxane (3.00 mL) and water (0.60 mL) was purged with nitrogen and then stirred at 95 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, petroleum ether/ethyl acetate = 1/1) to afford *tert*-butyl 2-(4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-3-methylphenyl)pyrrolidine-1-carboxylate (160 mg, 38.7% yield, 90.4% purity) as a yellow solid. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.61 (s, 1H), 7.69 (s, 1H), 7.26 (br d, *J*=7.6 Hz, 1H), 7.15 (s, 1H), 7.10 (br d, *J*=7.6 Hz, 1H), 6.92 - 6.84 (m, 1H), 6.70 - 6.62 (m, 1H), 4.82 - 4.75 (m, 1H), 4.62 - 4.56 (m, 4H), 3.65 - 3.60 (m, 2H), 3.39 (t, *J*=8.8 Hz, 2H), 2.40 (br s, 1H), 2.20 (s, 3H), 2.0 - 1.80 (m, 3H), 1.49 (br s, 3H), 1.31 - 1.23 (m, 6H).

[000413] Chiral SFC separation of *tert*-butyl 2-(4-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)-3-methylphenyl)pyrrolidine-1-carboxylate provided enantiomerically pure intermediates **A** and **B**.

[000414] To a solution of **A** or **B** (60.0 mg, 105  $\mu$ mol, 1.00 equiv) was added TFA (2.31 g, 20.3 mmol, 1.50 mL, 192 equiv). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/methanol = 10/1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methyl-4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile.

[000415] EXAMPLE 213: (18.06 mg, 34.6 % yield, 94.6 % purity), LCMS [M+1]: 469.1, (Amycoat 50×4.6mm I.D., 3  $\mu$ m; 30% MeOH (0.05% DEA) in CO<sub>2</sub>; 3 mL/min; *t<sub>r</sub>* = 1.32 min).

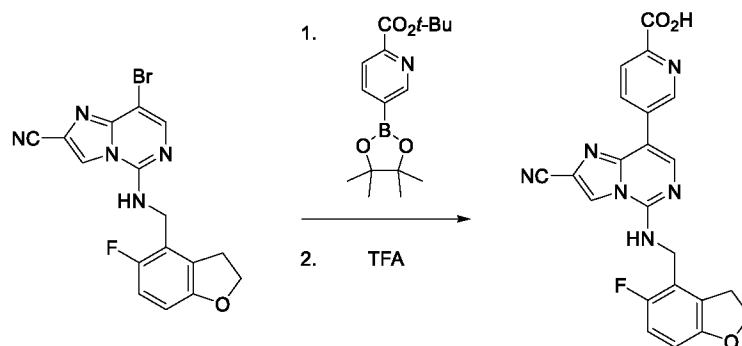
[000416] <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.60 (s, 1H), 7.68 (s, 1H), 7.35 (s, 1H), 7.28 (s, 2H), 6.85 (t, *J*=9.2 Hz, 1H), 6.64 (dd, *J*=4.0, 8.8 Hz, 1H), 4.81 (s, 2H), 4.57 (t, *J*=8.8 Hz, 2H), 4.20 (dd, *J*=7.2, 8.8 Hz, 1H), 3.40 - 3.35 (m, 2H), 3.29 - 3.24 (m, 1H), 3.11 - 3.03 (m, 1H), 2.37 - 2.26 (m, 1H), 2.19 (s, 3H), 2.09 - 1.95 (m, 2H), 1.94 - 1.82 (m, 1H).

[000417] EXAMPLE 214: (18.1 mg, 35.7  $\mu$ mol, 33.8% yield, 92.4% purity), LCMS [M+1]: 469.1, (Amycoat 50 $\times$ 4.6mm I.D., 3  $\mu$ m; 30% MeOH (0.05% DEA) in CO<sub>2</sub>; 3 mL/min;  $t_r$  = 3.22 min).

[000418] <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.61 (s, 1H), 7.69 (s, 1H), 7.38 (s, 1H), 7.32 (d,  $J$ =0.8 Hz, 2H), 6.89 - 6.82 (m, 1H), 6.64 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.81 (s, 2H), 4.58 (t,  $J$ =8.8 Hz, 2H), 4.42 - 4.36 (m, 1H), 3.40 - 3.35 (m, 2H), 3.27 - 3.20 (m, 1H), 2.45 - 2.35 (m, 1H), 2.21 (s, 3H), 2.19 - 2.12 (m, 1H), 2.11 - 1.98 (m, 2H).

### EXAMPLE 215

#### 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)picolinic acid

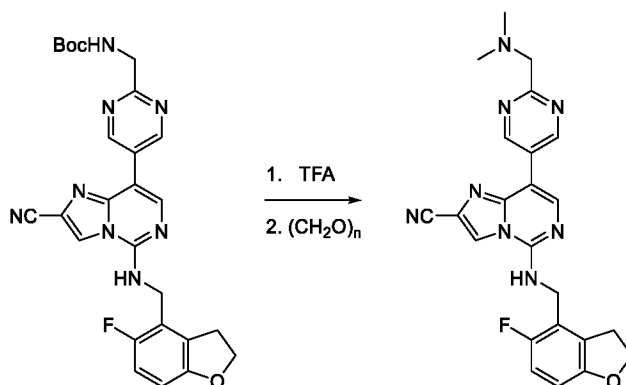


[000419] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (39.0 mg, 100  $\mu$ mol, 1.00 equiv), *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate (73.6 mg, 121  $\mu$ mol, 1.20 equiv), sodium bicarbonate (25.3 mg, 301  $\mu$ mol, 3.00 equiv) and Pd(dppf)Cl<sub>2</sub> (7.35 mg, 10.1  $\mu$ mol, 0.10 equiv) in dioxane (1.00 mL) and water (0.20 mL) was purged with nitrogen and stirred at 95 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/methyl alcohol = 10/1) to afford *tert*-butyl 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)picolinate (50.0 mg, 60.0  $\mu$ mol, 59.8% yield, 58.4% purity) as a yellow solid. LC-MS [M+1]: 487.4. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.30 (d,  $J$ =1.6 Hz, 1H), 8.97 (s, 1H), 8.77 (t,  $J$ =5.2 Hz, 1H), 8.63 (dd,  $J$ =2.4, 8.0 Hz, 1H), 8.68 - 8.59 (m, 1H), 8.36 (s, 1H), 8.09 (d,  $J$ =8.0 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.71 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.77 (br d,  $J$ =4.4 Hz, 2H), 4.55 (br t,  $J$ =8.8 Hz, 2H), 3.31 - 3.29 (m, 2H), 1.59 (s, 9H).

[000420] A mixture of *tert*-butyl 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)picolinate (50.0 mg, 103  $\mu$ mol, 1.00 equiv) and trifluoroacetic acid (3.85 g, 33.8 mmol, 2.50 mL, 329 equiv) in dichloromethane (0.50 mL) was stirred at 25 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic conditions) to afford 5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)picolinic acid (6.73 mg, 15.4  $\mu$ mol, 15.0% yield, 98.4% purity) as a yellow solid. LC-MS [M+1]: 431.3. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.25 (br s, 1H), 8.98 (s, 1H), 8.48 (br d,  $J$ =9.6 Hz, 1H), 8.27 (br s, 1H), 8.05 (br d,  $J$ =8.4 Hz, 1H), 7.01 - 6.92 (m, 1H), 6.71 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.77 (s, 2H), 4.55 (t,  $J$ =8.8 Hz, 2H), 3.26 - 3.24 (m, 2H).

## EXAMPLE 216

## 8-(2-((dimethylamino)methyl)pyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile

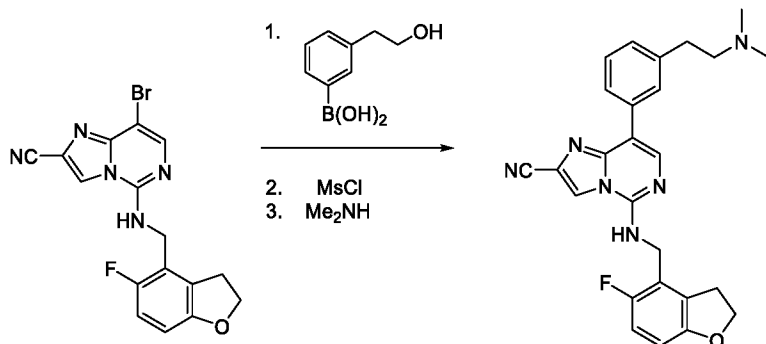


**[000421]** To a solution of *tert*-butyl ((5-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)pyrimidin-2-yl)methyl)carbamate (90.0 mg, 156  $\mu$ mol, 1.00 equiv) in DCM (2.00 mL) was added TFA (890 mg, 7.81 mmol, 578  $\mu$ L, 50.0 equiv). The mixture was stirred at room temperature for 1 h prior to concentration under reduced pressure. The residue was diluted with saturated sodium bicarbonate aqueous solution and subsequently filtered to provide 8-[2-(aminomethyl)pyrimidin-5-yl]-5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]imidazo[1,2-c]pyrimidine-2-carbonitrile (75.0 mg, 147  $\mu$ mol, 93.9% yield, 81.4% purity) as a purple solid. LCMS [M+1]: 417.0.

**[000422]** To a solution of 8-[2-(aminomethyl)pyrimidin-5-yl]-5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]imidazo[1,2-c]pyrimidine-2-carbonitrile (65.0 mg, 127  $\mu$ mol, 1 equiv) in MeOH (0.60 mL) was added paraformaldehyde (11.5 mg, 381  $\mu$ mol, 10.5  $\mu$ L, 3.00 equiv) and CH<sub>3</sub>COOH (1 drop). The mixture was stirred at 60 °C for 1 h and then cooled to room temperature. To the resultant mixture was added NaBH<sub>3</sub>CN (24.0 mg, 381  $\mu$ mol, 3.00 equiv). After 1 h, the mixture was filtered and concentrated in vacuo to provide a residue. The residue was purified by prep-HPLC (basic conditions) to afford 8-(2-((dimethylamino)methyl)pyrimidin-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (2.16 mg, 4.19  $\mu$ mol, 3.3% yield, 86.3% purity) as a yellow gum. LCMS [M+1]: 445.1. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.36 (s, 2H), 8.97 (s, 1H), 8.75 (br s, 1H), 8.32 (s, 1H), 6.96 (t, *J*=8.8 Hz, 1H), 6.71 (dd, *J*=4.0, 8.8 Hz, 1H), 4.76 (br s, 2H), 4.55 (t, *J*=8.8 Hz, 2H), 3.70 (s, 2H), 3.31 - 3.28 (m, 2H), 2.28 (s, 6H).

## EXAMPLE 217

## 8-(3-(2-(dimethylamino)ethyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



**[000423]** A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (50.0 mg, 129  $\mu\text{mol}$ , 1.00 equiv), [3-(2-hydroxyethyl)phenyl]boronic acid (32.1 mg, 193  $\mu\text{mol}$ , 1.50 equiv), sodium bicarbonate (32.5 mg, 386  $\mu\text{mol}$ , 3.00 equiv) and  $\text{Pd(dppf)Cl}_2$  (9.42 mg, 12.9  $\mu\text{mol}$ , 0.10 equiv) in dioxane (2.00 mL) and water (0.40 mL) was purged with nitrogen and subsequently allowed to stir at 100 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol=10/1) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(3-(2-hydroxyethyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (38.0 mg, 87.6  $\mu\text{mol}$ , 68.0% yield, 99.0% purity) as a yellow solid. LC-MS  $[M+1]$ : 430.2.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.97 (s, 1H), 7.90 (s, 1H), 7.74 (br s, 2H), 7.44 (t,  $J$ =8.0 Hz, 1H), 7.30 - 7.28 (m, 1H), 6.87 (t,  $J$ =9.6 Hz, 1H), 6.69 (dd,  $J$ =4.0, 8.4 Hz, 1H), 5.43 (s, 1H), 4.84 (d,  $J$ =5.6 Hz, 2H), 4.65 (t,  $J$ =8.8 Hz, 2H), 3.94 (t,  $J$ =6.4 Hz, 2H), 3.44 (t,  $J$ =8.8 Hz, 2H), 2.97 (t,  $J$ =6.4 Hz, 2H).

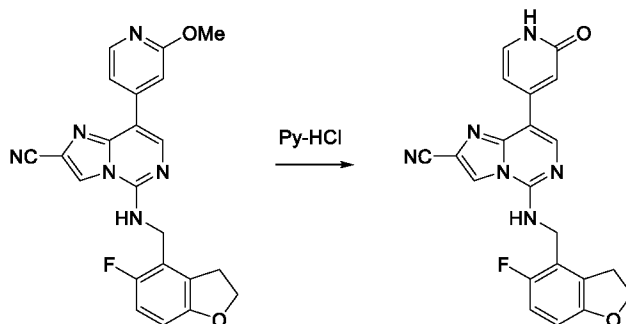
**[000424]** A mixture of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(3-(2-hydroxyethyl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (30.0 mg, 69.9  $\mu\text{mol}$ , 1.00 equiv), mesyl chloride (16.0 mg, 140  $\mu\text{mol}$ , 10.8  $\mu\text{L}$ , 2.00 equiv) and triethylamine (28.3 mg, 279  $\mu\text{mol}$ , 38.9  $\mu\text{L}$ , 4.00 equiv) in dichloromethane (1.00 mL) was stirred at 0 °C for h. The mixture was concentrated under reduced pressure to afford 3-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)phenethyl methanesulfonate (20.0 mg, 39.4  $\mu\text{mol}$ ) as a yellow oil that was used in the following step without purification. LC-MS  $[M+1]$ : 508.3.

**[000425]** A mixture of 3-(2-cyano-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidin-8-yl)phenethyl methanesulfonate (20.0 mg, 39.4  $\mu\text{mol}$ , 1.00 equiv), dimethylamine (1.00 M in THF, 394  $\mu\text{L}$ , 10.0 equiv) and diisopropylethylamine (15.3 mg, 118  $\mu\text{mol}$ , 20.6  $\mu\text{L}$ , 3.00 equiv) in dimethyl formamide (0.50 mL) was stirred at room temperature for 2 h prior to concentration in vacuo. The residue was purified by prep-HPLC (basic conditions) to afford 8-(3-(2-(dimethylamino)ethyl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (5.94 mg, 12.9  $\mu\text{mol}$ , 32.8% yield, 99.2% purity) as a white solid. LC-MS  $[M+1]$ : 457.1.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 8.93 (s, 1H), 8.49 (t,  $J$ =5.6 Hz, 1H), 8.07 (s, 1H), 7.82 - 7.76 (m, 2H), 7.36 (t,  $J$ =7.6 Hz, 1H), 7.22 (d,  $J$ =8.0 Hz, 1H), 6.98 - 6.91 (m, 1H), 6.70 (dd,  $J$ =4.0, 8.8

Hz, 1H), 4.73 (d,  $J=4.4$  Hz, 2H), 4.55 (t,  $J=8.8$  Hz, 2H), 3.35 - 3.33 (m, 2H), 3.28 (br s, 2H), 2.78 (br t,  $J=7.6$  Hz, 2H), 2.22 (br s, 6H).

## EXAMPLE 218

5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-methoxy-4-pyridyl)imidazo[1,2-c]pyrimidine-2-carbonitrile

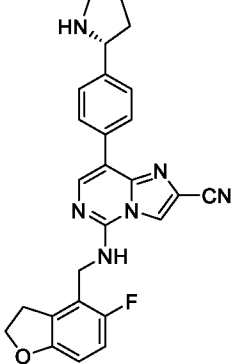
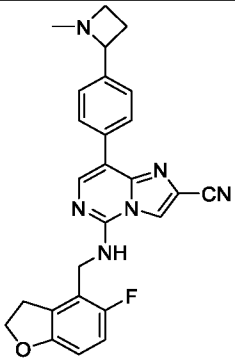
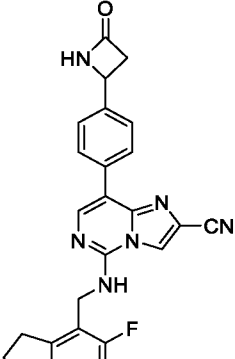


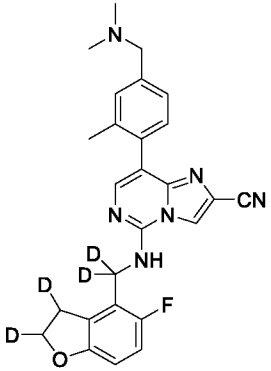
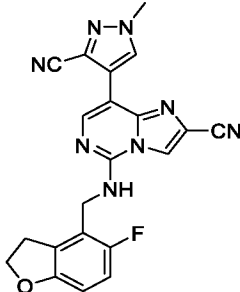
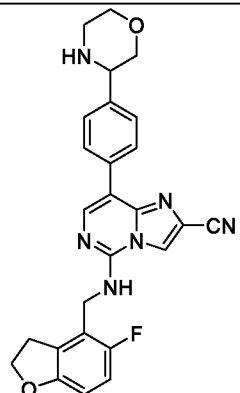
[000426] A mixture of 5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methylamino]-8-(2-methoxy-4-pyridyl)imidazo[1,2-c]pyrimidine-2-carbonitrile (55.0 mg, 125  $\mu$ mol, 1.00 equiv) and pyridine hydrochloride (71.5 mg, 619  $\mu$ mol, 4.93 equiv) was heated at 130 °C for 0.5 h. The reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate (10.0 mL  $\times$  2). The combined organic layer was concentrated under reduced pressure to give a residue. The residue was triturated with methanol and filtered to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (14.2 mg, 33.9  $\mu$ mol, 27.0% yield, 96.1% purity) as an off-white solid. LCMS [ $M + 1$ ]: 403.1.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 11.47 (s, 1H), 8.94 (s, 1H), 8.76 (s, 1H), 8.30 (s, 1H), 7.39 (d,  $J=6.8$  Hz, 1H), 7.25 (d,  $J=1.6$  Hz, 1H), 6.95 (t,  $J=9.6$  Hz, 1H), 6.83 (dd,  $J=1.6, 7.2$  Hz, 1H), 6.70 (dd,  $J=4.0, 8.8$  Hz, 1H), 4.74 (s, 2H), 4.54 (t,  $J=8.8$  Hz, 2H), 3.31 - 3.27 (m, 2H).

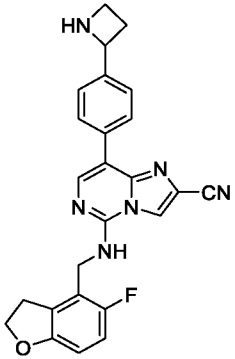
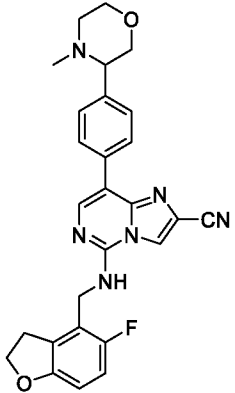
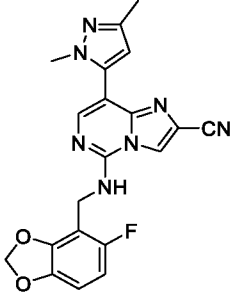
[000427] EXAMPLES 219 -228 were prepared following the procedure set forth in Example 87 and using the general reactions schemes and intermediates described herein.

TABLE 12

| Ex. # | Structure                                                                                                                              | $^1\text{H}$ NMR                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 219   | <p>(S)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | $^1\text{H}$ NMR (400MHz, DMSO- $d_6$ ) $\delta$ = 8.93 (s, 1H), 8.54 (br s, 1H), 8.08 - 8.01 (m, 1H), 7.90 - 7.82 (m, 2H), 7.47 - 7.21 (m, 2H), 6.94 (t, $J=9.2$ Hz, 1H), 6.70 (dd, $J=4.0, 8.8$ Hz, 1H), 4.72 (s, 2H), 4.54 (t, $J=8.8$ Hz, 2H), 4.05 (t, $J=8.0$ Hz, 1H), 3.31 - 3.28 (m, 3H), 3.10 - 2.98 (m, 1H), 2.93 - 2.83 (m, 1H), 2.18 - 2.05 (m, 1H), 1.86 - 1.69 (m, 2H), 1.58 - 1.43 (m, 1H).<br>LCMS [ $M+1$ ]: 455.3. |

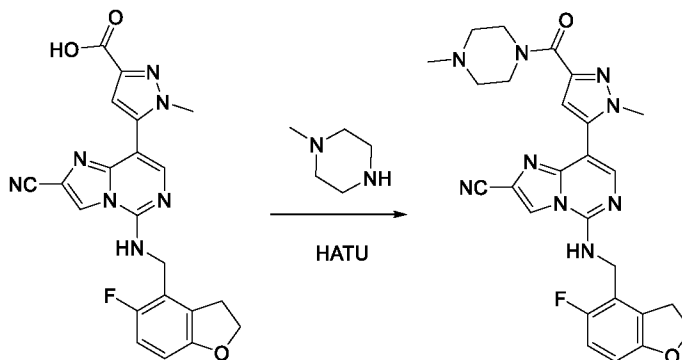
| Ex. # | Structure                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 220   |  <p>(R)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>    | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ ppm 8.62 (s, 1H), 8.02 (s, 1H), 7.90 (d, <i>J</i> =8.4 Hz, 2H), 7.51 (d, <i>J</i> =8.4 Hz, 2H), 6.91 - 6.83 (m, 1H), 6.66 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.84 (s, 2H), 4.59 (t, <i>J</i> =8.8 Hz, 2H), 4.28 (t, <i>J</i> =8.4 Hz, 1H), 3.38 (t, <i>J</i> =8.8 Hz, 2H), 3.31 - 3.27 (m, 1H), 3.16 - 3.08 (m, 1H), 2.42 - 2.30 (m, 1H), 2.16 - 2.00 (m, 2H), 1.99 - 1.86 (m, 1H).<br>LCMS [M+1]: 455.3.                       |
| 221   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(1-methylazetidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (br s, 1H), 8.50 (br s, 1H), 8.07 (s, 1H), 7.91 (d, <i>J</i> =8.0 Hz, 2H), 7.46 (d, <i>J</i> =8.0 Hz, 2H), 6.95 (t, <i>J</i> =10.0 Hz, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (s, 2H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.90 (t, <i>J</i> =8.0 Hz, 1H), 3.31 - 3.30 (m, 2H), 2.86 - 2.76 (m, 1H), 2.53 - 2.52 (m, 1H), 2.32 - 2.26 (m, 1H), 2.25 (s, 3H), 2.03 - 1.92 (m, 1H).<br>LC-MS [M-1]: 453.3. |
| 222   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(4-oxoazetidin-2-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>   | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.51 (br s, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 7.99 (d, <i>J</i> =8.4 Hz, 2H), 7.46 (d, <i>J</i> =8.4 Hz, 2H), 7.01 - 6.92 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.74 (br s, 2H), 4.71 (dd, <i>J</i> =2.4, 5.2 Hz, 1H), 4.55 (t, <i>J</i> =8.8 Hz, 2H), 3.41 - 3.37 (m, 1H), 3.31 - 3.26 (m, 2H), 2.72 (dd, <i>J</i> =1.6, 14.8 Hz, 1H).<br>LCMS [M+1]: 455.2.                                |

| Ex. # | Structure                                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                   |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 223   |  <p>8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)-2,3-d<sub>2</sub>)methyl-d<sub>2</sub>)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.92 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.26 - 7.19 (m, 2H), 7.16(d, <i>J</i> =8.0 Hz, 1H), 7.00 - 6.91 (m, 1H), 6.71 (dd, <i>J</i> =4.0, 8.8 Hz, 1H), 4.53 (d, <i>J</i> =10.0 Hz, 1H), 3.39 (s, 2H), 3.38 - 3.36 (m, 1H), 2.18 (s, 6H), 2.15 (s, 3H).<br>LCMS [M+1]: 461.4.                         |
| 224   |  <p>8-(3-cyano-1-methyl-1<i>H</i>-pyrazol-4-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                  | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (s, 1H), 8.64 - 8.56 (m, 2H), 8.20 (s, 1H), 6.94 (t, <i>J</i> =9.2 Hz, 1H), 6.70 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.73 (br s, 2H), 4.53 (t, <i>J</i> =8.8 Hz, 2H), 4.03 (s, 3H), 3.29 - 3.24 (m, 2H).<br>LCMS [M+1]: 414.9.                                                                       |
| 225   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(morpholin-3-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>                                                | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ = 8.63 (s, 1H), 8.12 - 7.99 (m, 3H), 7.59 (br d, <i>J</i> =8.2 Hz, 2H), 6.87 (br t, <i>J</i> =9.2 Hz, 1H), 6.66 (dd, <i>J</i> =3.6, 8.4 Hz, 1H), 4.85 - 4.83 (m, 2H), 4.65 - 4.53 (m, 3H), 4.24 - 4.11 (m, 2H), 4.04 - 3.84 (m, 2H), 3.52 - 3.43 (m, 2H), 3.38 (br t, <i>J</i> =8.8 Hz, 2H).<br>LCMS [M+1]: 471.3. |

| Ex. # | Structure                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 226   |  <p>8-(4-(azetidin-2-yl)phenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>           | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ = 7.95 (s, 1H), 7.87 (s, 1H), 7.85 – 7.81 (m, 2H), 7.51 – 7.48 (m, 2H), 6.88 – 6.82 (m, 1H), 6.68 (dd, <i>J</i> = 8.7, 4.0 Hz, 1H), 5.48 – 5.40 (m, 1H), 5.03 – 4.98 (m, 1H), 4.85 – 4.79 (m, 2H), 4.67 – 4.60 (m, 2H), 3.81 – 3.73 (m, 1H), 3.46 – 3.39 (m, 3H), 2.65 – 2.56 (m, 1H), 2.47 – 2.35 (m, 1H).<br>LCMS [M-1]: 439.3.                                               |
| 227   |  <p>5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(4-(4-methylmorpholin-3-yl)phenyl)imidazo[1,2-c]pyrimidine-2-carbonitrile</p> | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.94 (s, 1H), 8.50 (br s, 1H), 8.09 (s, 1H), 7.92 (d, <i>J</i> = 8.3 Hz, 2H), 7.44 (d, <i>J</i> = 8.2 Hz, 2H), 6.99 – 6.93 (m, 1H), 6.74 – 6.68 (m, 1H), 4.76 – 4.72 (m, 2H), 4.58 – 4.52 (m, 2H), 3.87 – 3.82 (m, 1H), 3.68 – 3.60 (m, 2H), 3.31 – 3.23 (m, 3H), 3.10 – 3.05 (m, 1H), 2.87 – 2.82 (m, 1H), 2.35 – 2.26 (m, 1H), 2.02 (s, 3H).<br>LCMS [M+1]: 485.5 |
| 228   |  <p>8-(1,3-dimethyl-1H-pyrazol-5-yl)-5-(((5-fluorobenzo[d][1,3]dioxol-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile</p>       | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.81 (s, 1H), 7.81 (s, 1H), 6.91 – 6.85 (m, 1H), 6.72 – 6.65 (m, 1H), 6.21 (s, 1H), 6.06 (s, 2H), 4.71 (s, 2H), 3.67 (s, 3H), 2.18 (s, 3H).<br>LCMS [M+1]: 406.3                                                                                                                                                                                                    |

## EXAMPLE 229

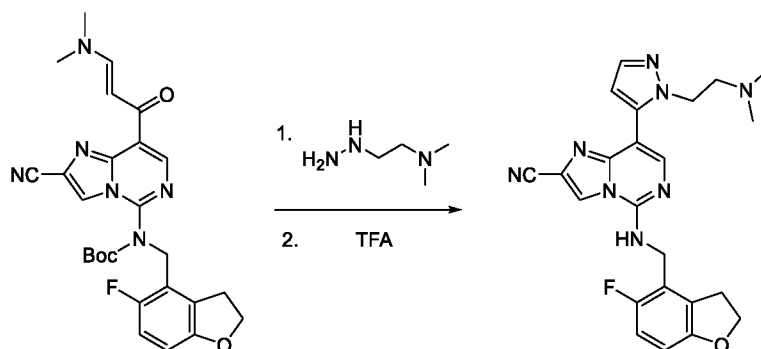
## 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-(4-methylpiperazine-1-carbonyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000428] To a solution of 5-[2-cyano-5-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl]amino]imidazo[1,2-c]pyrimidin-8-yl]-1-methylpyrazole-3-carboxylic acid (40.0 mg, 92.3  $\mu$ mol, 1.00 equiv) and 1-methylpiperazine (20.4  $\mu$ L, 184  $\mu$ mol, 1.99 equiv) in DMF (1.00 mL) was added HATU (66.4 mg, 139  $\mu$ mol, 1.50 equiv) and DIEA (48.5  $\mu$ L, 279  $\mu$ mol, 3.02 equiv). The reaction was stirred at 25 °C for 1 h and was subsequently quenched by the addition of water (30.0 mL) at 25 °C. The aqueous layer was diluted with ethyl acetate (50.0 mL), at which time a white precipitate formed. The solid was filtered off and dried at reduced pressure to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-methyl-3-(4-methylpiperazine-1-carbonyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (24.5 mg, 45.8  $\mu$ mol, 49.6% yield, 96.4% purity) as a white solid. LCMS [M+1]: 516.3. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>)  $\delta$  = 8.95 (s, 1H), 8.73 (t, J=5.2 Hz, 1H), 7.96 (s, 1H), 7.03 - 6.88 (m, 1H), 6.75 (s, 1H), 6.72 (dd, J=4.0, 8.8 Hz, 1H), 4.74 (d, J=4.8 Hz, 2H), 4.56 (t, J=8.8 Hz, 2H), 3.97 (s, 2H), 3.82 (s, 3H), 3.63 (s, 2H), 3.35 - 3.32 (m, 2H), 2.53 - 2.50 (m, 2H), 2.35 - 2.33 (m, 2H), 2.21 (s, 3H).

## EXAMPLE 230

## 8-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



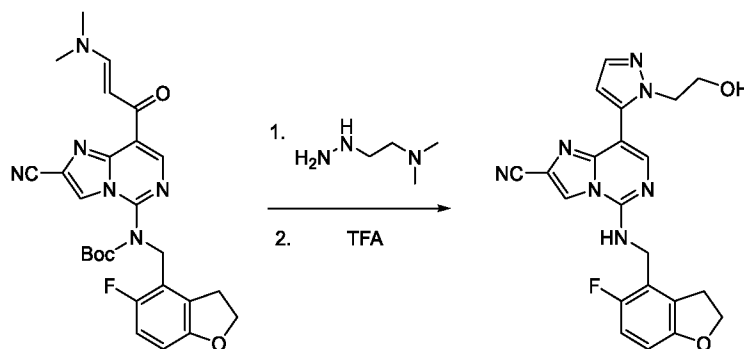
[000429] To a solution of tert-butyl (E)-(2-cyano-8-(3-(dimethylamino)acryloyl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (13.0 mg, 25.0  $\mu$ mol, 1.00 equiv) in ethanol (2.00 mL) was added 2-hydrazino-N,N-dimethyl-ethanamine-HCl (14.0 mg, 99.9  $\mu$ mol, 4.00 equiv), the reaction was stirred at 80 °C for 1 h. The reaction was concentrated under reduced

pressure to give tert-butyl N-[2-cyano-8-[2-[2-(dimethylamino)ethyl]pyrazol-3-yl]imidazo[1,2-c]pyrimidin-5-yl]-N-[(5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl]carbamate (15.0 mg, crude) as brown oil. LCMS: [M+1]: 547.6.

**[000430]** A solution of tert-butyl (2-cyano-8-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (15.0 mg, 27.4  $\mu$ mol, 1.00 equiv) in DCM (0.50 mL) was added TFA (0.50 mL) was stirred at 25 °C for 30 min. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral conditions) and lyophilization to afford 8-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-5-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (11.0 mg, 24.5  $\mu$ mol, 89.2% yield, 99.4% purity) as a white solid. LCMS [M+1]: 447.4. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD)  $\delta$  = 8.62 (s, 1H), 7.89 (s, 1H), 7.60 (d, J=2.0 Hz, 1H), 6.90 - 6.80 (m, 1H), 6.64 (dd, J=4.0, 8.8 Hz, 1H), 6.43 (d, J=2.0 Hz, 1H), 4.83 (s, 2H), 4.58 (t, J=8.4 Hz, 2H), 4.22 - 4.15 (m, 2H), 3.38 (t, J=8.4 Hz, 2H), 2.81 - 2.76 (m, 2H), 2.14 (s, 6H).

### EXAMPLE 231

#### 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile



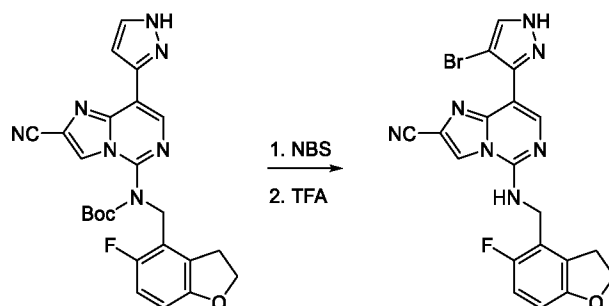
**[000431]** To a solution of tert-butyl (E)-(2-cyano-8-(3-(dimethylamino)acryloyl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (16.0 mg, 31.6  $\mu$ mol, 1.00 equiv) in ethanol (1.00 mL) was added 2-hydrazinoethanol (4.81 mg, 63.2  $\mu$ mol, 4.29  $\mu$ L, 2.00 equiv). The mixture was stirred at 80 °C for 1 h and subsequently concentrated under reduced pressure to provide a residue. The residue was purified by prep-TLC (dichloromethane/methanol = 20/1) to afford tert-butyl (2-cyano-8-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (13.0 mg, 22.3  $\mu$ mol, 70.5% yield, 89.0% purity) as a brown solid.

**[000432]** To a solution of tert-butyl (2-cyano-8-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (13.0 mg, 22.3  $\mu$ mol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.30 mL) and the resultant mixture was stirred at 25 °C for 1 h. The reaction was concentrated under reduced pressure to give a residue that was purified by prep-HPLC (neutral conditions) to afford 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (2.97 mg, 7.02  $\mu$ mol, 31.5% yield, 99.2% purity) as a white solid. LCMS [M+1]: 420.2. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  = 8.64 (s,

1H), 7.95 (s, 1H), 7.64 (d,  $J=2.0$  Hz, 1H), 6.92 - 6.84 (m, 1H), 6.66 (dd,  $J=4.0, 8.8$  Hz, 1H), 6.47 (d,  $J=2.0$  Hz, 1H), 4.84 (s, 2H), 4.63 - 4.56 (m, 2H), 4.22 (t,  $J=5.6$  Hz, 2H), 3.85 (t,  $J=5.6$  Hz, 2H), 3.40 (t,  $J=8.8$  Hz, 2H).

## EXAMPLE 232

**8-(4-bromo-1H-pyrazol-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile**

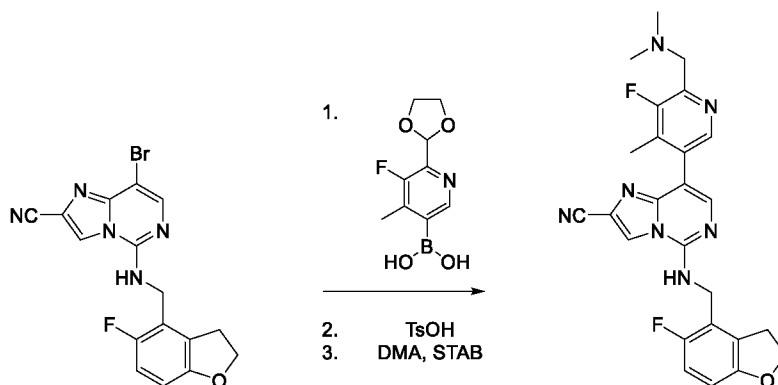


**[000433]** To a solution of *tert*-butyl (2-cyano-8-(1H-pyrazol-3-yl)imidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (95.0 mg, 200  $\mu$ mol, 1.00 equiv) in dry chloroform (1.00 mL) was added portionwise NBS (53.5 mg, 300  $\mu$ mol, 1.50 equiv). The mixture was stirred at 25 °C for 1 h. The reaction mixture was cooled to 0 °C and filtered through a pad of Celite. The filtrate was evaporated to give a residue. The residue was purified by prep-TLC ( $\text{SiO}_2$ , petroleum ether/ethyl acetate = 2/1) to afford *tert*-butyl (8-(4-bromo-1H-pyrazol-3-yl)-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (20.0 mg, 27.4  $\mu$ mol, 13.7% yield, 76% purity) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.23 (s, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 6.72 - 6.64 (m, 1H), 6.59 (dd,  $J=4.0, 8.8$  Hz, 1H), 5.13 (s, 2H), 4.60 (t,  $J=8.8$  Hz, 2H), 3.34 (t,  $J=8.8$  Hz, 2H), 1.41 (s, 9H).

**[000434]** A mixture of *tert*-butyl (8-(4-bromo-1H-pyrazol-3-yl)-2-cyanoimidazo[1,2-c]pyrimidin-5-yl)((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)carbamate (20.0 mg, 36.1  $\mu$ mol, 1.00 equiv) in TFA (0.40 mL) and DCM (2.00 mL) was stirred at 25 °C for 3 h. The reaction mixture was evaporated to give a residue. The residue was triturated with methanol and filtered to afford 8-(4-bromo-1H-pyrazol-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2c]pyrimidine-2-carbonitrile (3.10 mg, 5.98  $\mu$ mol, 16.6% yield, 87.6% purity) as a gray solid. LCMS  $[M + 1]$ : 456.1.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 13.38 (s, 1H), 8.96 (s, 0.5 H), 8.91 (s, 0.5 H), 8.75 (s, 0.5 H), 8.55 (s, 0.5 H), 8.14 - 8.06 (m, 1H), 7.84 (s, 0.5 H), 7.69 (s, 0.5 H), 7.01 - 6.90 (m, 1H), 6.75 - 6.67 (m, 1H), 4.74 (s, 2H), 4.55 (t,  $J=8.8$  Hz, 2H), 3.31 - 3.29 (m, 2H).

## EXAMPLE 233

## 8-(6-(((dimethylamino)methyl)-5-fluoro-4-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile



[000435] A mixture of 8-bromo-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (300 mg, 773  $\mu$ mol, 1.00 equiv), [6-(1,3-dioxolan-2-yl)-5-fluoro-4-methyl-3-pyridyl]boronic acid (217 mg, 927  $\mu$ mol, 1.20 equiv), Pd(dppf)Cl<sub>2</sub> (56.6 mg, 77.3  $\mu$ mol, 0.10 equiv), NaHCO<sub>3</sub> (195 mg, 2.32 mmol, 90.2  $\mu$ L, 3.00 equiv) in dioxane (3.00 mL) and water (1.00 mL) was purged with nitrogen and subsequently stirred at 100 °C for 2 h under an atmosphere of nitrogen. The reaction mixture was filtered and concentrated under reduced pressure to provide the crude residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/methanol = 20/1) to afford 8-(6-(1,3-dioxolan-2-yl)-5-fluoro-4-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (180 mg, 367  $\mu$ mol, 47.5% yield) as a yellow solid. LCMS [M+1]: 491.2.

[000436] To a solution of 8-(6-(1,3-dioxolan-2-yl)-5-fluoro-4-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (100 mg, 204  $\mu$ mol, 1.00 equiv) in acetone (3.00 mL) and water (1.50 mL) was added TsOH-H<sub>2</sub>O (77.6 mg, 408  $\mu$ mol, 2.00 equiv). The mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with DCM 20.0 mL and was neutralized with sodium bicarbonate. The organic phase was separated, dried, and concentrated under reduced pressure to give the crude residue. The residue was purified by prep-TLC (SiO<sub>2</sub>, dichloromethane/methanol = 20/1) to give 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-fluoro-6-formyl-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (60.0 mg, 134  $\mu$ mol, 65.9% yield) as a yellow solid. LCMS [M+1]: 447.2.

[000437] A mixture of 5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)-8-(5-fluoro-6-formyl-4-methylpyridin-3-yl)imidazo[1,2-c]pyrimidine-2-carbonitrile (90.0 mg, 202  $\mu$ mol, 1.00 eq.), *N*-methylmethanamine (2 M, 302  $\mu$ L, 3.00 equiv), AcOH (24.2 mg, 403  $\mu$ mol, 23.1  $\mu$ L, 2.00 equiv) and Ti(Oi-Pr)<sub>4</sub> (115 mg, 403  $\mu$ mol, 119  $\mu$ L, 2.00 equiv) in DCE (2.00 mL) was stirred at 45 °C for 1 h. To this mixture was added NaBH(OAc)<sub>3</sub> (128 mg, 605  $\mu$ mol, 3.00 equiv) was added and the mixture was allowed to stir at 25 °C for 1 h. The reaction was quenched with water (2 mL) and the resultant suspension was filtered. The filtrate was dried and concentrated under reduced pressure to provide the crude residue. The residue was purified by prep-HPLC (acidic conditions) followed by prep-HPLC (basic

conditions) to afford 8-(6-((dimethylamino)methyl)-5-fluoro-4-methylpyridin-3-yl)-5-(((5-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile (10.3 mg, 21.7  $\mu$ mol, 10.7% yield, 100% purity) as a white solid. LCMS [M+1]: 476.5.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  = 8.90 (s, 1H), 8.59 (s, 1H), 8.27 (s, 1H), 7.81 (s, 1H), 7.01 - 6.89 (m, 1H), 6.69 (dd,  $J$ =4.0, 8.8 Hz, 1H), 4.71 (s, 2H), 4.53 (t,  $J$ =8.8 Hz, 2H), 3.58 (d,  $J$ =2.4 Hz, 2H), 3.34 - 3.31 (m, 2H), 2.20 (s, 6H), 2.11 (d,  $J$ =2.4 Hz, 3H).

**[000438]** The compounds of the present disclosure may have one or more chiral center and, if so, are synthesized as stereoisomeric mixtures, isomers of identical constitution that differ in the arrangement of their atoms in space. The compounds may be used as mixtures or the individual components/isomers may be separated using commercially available reagents and conventional methods for isolation of stereoisomers and enantiomers well-known to those skilled in the art, e.g., using CHIRALPAK® (Sigma-Aldrich) or CHIRALCEL® (Diacel Corp) chiral chromatographic HPLC columns according to the manufacturer's instructions, as well as methods described herein, e.g., EXAMPLES 213 and 214. Alternatively, compounds of the present disclosure may be synthesized using optically pure, chiral reagents and intermediates to prepare individual isomers or enantiomers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the disclosure.

**[000439]** Also contemplated within the scope of the disclosure are variants of compounds of the present disclosure in which one or more hydrogen atoms have been replaced with deuterium. As exemplified herein, Intermediates C-11 and D-31 have one or more hydrogen atom replaced with deuterium and were used to generate EXAMPLE 165 and 173, respectively. Intermediates B-7, B-8, and C18 also contain deuteriums substituted as specifies location(s). In addition, EXAMPLE 202 illustrates deuterated compounds of the present disclosure wherein  $R^7$  is deuterated. By substituting one or more hydrogen for deuterium on the Intermediates A – D exemplified herein, deuterated versions of the compounds of the present disclosure can be readily generated using methods well known in the art.

#### EXAMPLE 1

**[000440]** This Example illustrates that exemplary compounds of the present disclosure inhibit PRC2 enzymatic activity.

**[000441]** Ten-point dose-response curves for compounds of the present disclosure were determined using a Hot Spot HMT assay (Reaction Biology Corp; see Horiuchi et al., Assay Drug Dev Technol. (2013) 4: 227-236 doi: 10.1089/adt.2012.480). The assay uses purified human, His-tagged PRC2 complex, including N-terminal His-tagged EZH2 enzyme, N-terminal Flag-tagged embryonic ectoderm development protein (EED), N-terminal His-tagged suppressor of zeste 12 (SUZ12), N-terminal His-tagged AEBP2, and N-terminal His-tagged RbAp48. In this assay, the transfer of the tritiated methyl group from radiolabeled S-adenosyl methionine (SAM) to purified core histone protein by EZH2 is quantitated after filtration to determine the activity of the core PRC2 complex in the presence and absence of compound.

**[000442]** Briefly, compounds of the present disclosure were solubilized in DMSO and a series of 10, three-fold serial dilutions were made for each compound in 15% DMSO. The initial starting

concentration for the serial dilutions of each compound was 1.0  $\mu$ M. Control samples lacking compound, EZH2 enzyme or various reaction components also were prepared and processed in parallel with compound test samples. SAH (S-(5-adenosyl)-L-homocysteine) was used as a positive control for assay validation.

**[000443]** An aliquot of each serial dilution of test compound was added to deep 384 well plate using Acoustic Technology instrument (Echo 550, LabCyte) containing reaction buffer (50 mM Tris-HCl (pH 8.)), 0.01% Brij35, 1 mM EDTA, 1 mM DTT, 1 mM PMSF and 1% DMSO), 10 nM purified PRC2 complex and 0.05 mg/ml core histone H3 in a 5  $\mu$ l volume. The reaction was mixed gently and then pre-incubated for 20 min at 30°C. The enzymatic reaction was initiated by adding 1  $\mu$ M S-Adenosyl-L-[methyl –  $^3$ H]methionine and incubated for 1 hr at 30°C. After 1 hr, the reaction product was detected using a filter binding method and the amount of tritiated H3 core histone was quantitated using a scintillation counter. The IC<sub>50</sub> value for each compound was determined from each 10-point dose-response curve using GraphPad Prism software and the results for exemplary compounds of Formula (I) are shown in Table 13. Key: A = <100 nM; B = >100 nM - <500 nM; and C = >500 nM.

TABLE 13

Inhibition of PRC2-mediated Enzymatic Activity by Exemplary Compounds of Formula (I)

| Example No. | IC <sub>50</sub> | Example No. | IC <sub>50</sub> |
|-------------|------------------|-------------|------------------|
| 1           | A                | 118         | A                |
| 2           | A                | 119         | B                |
| 3           | B                | 120         | C                |
| 4           | A                | 121         | A                |
| 5           | A                | 122         | C                |
| 6           | B                | 123         | A                |
| 7           | A                | 124         | A                |
| 8           | A                | 125         | A                |
| 9           | A                | 126         | B                |
| 10          | A                | 127         | A                |
| 11          | A                | 128         | A                |
| 12          | A                | 129         | A                |
| 13          | A                | 130         | B                |
| 14          | B                | 131         | A                |
| 15          | B                | 132         | C                |
| 16          | A                | 133         | A                |
| 17          | B                | 134         | B                |
| 18          | A                | 135         | A                |
| 19          | A                | 136         | B                |
| 20          | A                | 137         | A                |
| 21          | C                | 138         | A                |
| 22          | B                | 139         | A                |
| 23          | B                | 140         | C                |
| 24          | B                | 141         | C                |
| 25          | B                | 142         | A                |
| 26          | B                | 143         | A                |
| 27          | C                | 144         | A                |
| 28          | A                | 145         | B                |
| 29          | C                | 146         | B                |
| 30          | B                | 147         | B                |
| 31          | A                | 148         | A                |

| Example No. | IC <sub>50</sub> | Example No. | IC <sub>50</sub> |
|-------------|------------------|-------------|------------------|
| 32          | B                | 149         | B                |
| 33          | A                | 150         | A                |
| 34          | A                | 151         | A                |
| 35          | A                | 152         | B                |
| 36          | A                | 153         | B                |
| 37          | A                | 154         | B                |
| 38          | A                | 155         | A                |
| 39          | A                | 156         | B                |
| 40          | A                | 157         | A                |
| 41          | A                | 158         | B                |
| 42          | A                | 159         | B                |
| 43          | A                | 160         | A                |
| 44          | A                | 161         | A                |
| 45          | A                | 162         | A                |
| 46          | A                | 163         | A                |
| 47          | A                | 164         | A                |
| 48          | A                | 165         | A                |
| 49          | A                | 166         | A                |
| 50          | A                | 167         | B                |
| 51          | A                | 168         | A                |
| 52          | A                | 169         | A                |
| 53          | A                | 170         | A                |
| 54          | A                | 171         | A                |
| 55          | A                | 172         | A                |
| 56          | A                | 173         | A                |
| 57          | A                | 174         | A                |
| 58          | A                | 175         | B                |
| 59          | A                | 176         | A                |
| 60          | B                | 177         | B                |
| 61          | A                | 178         | B                |
| 62          | A                | 179         | A                |
| 63          | A                | 180         | A                |
| 64          | A                | 181         | A                |
| 65          | B                | 182         | B                |
| 66          | B                | 183         | A                |
| 67          | A                | 184         | B                |
| 68          | A                | 185         | A                |
| 69          | A                | 186         | A                |
| 70          | A                | 187         | A                |
| 71          | A                | 188         | B                |
| 72          | A                | 189         | B                |
| 73          | A                | 190         | A                |
| 74          | A                | 191         | B                |
| 75          | A                | 192         | C                |
| 76          | A                | 193         | A                |
| 77          | B                | 194         | B                |
| 78          | C                | 195         | A                |
| 79          | A                | 196         | B                |
| 80          | A                | 197         | A                |
| 81          | C                | 198         | A                |
| 82          | B                | 199         | A                |
| 83          | A                | 200         | B                |
| 84          | B                | 201         | A                |
| 85          | A                | 202         | A                |

| Example No. | IC <sub>50</sub> | Example No. | IC <sub>50</sub> |
|-------------|------------------|-------------|------------------|
| 86          | A                | 203         | B                |
| 87          | A                | 204         | B                |
| 88          | A                | 205         | B                |
| 89          | A                | 206         | B                |
| 90          | A                | 207         | A                |
| 91          | B                | 208         | A                |
| 92          | B                | 200         | A                |
| 93          | B                | 210         | A                |
| 94          | A                | 211         | A                |
| 95          | A                | 212         | A                |
| 96          | A                | 213         | A                |
| 97          | A                | 214         | A                |
| 98          | A                | 215         | A                |
| 99          | A                | 216         | A                |
| 100         | A                | 217         | A                |
| 101         | B                | 218         | A                |
| 102         | B                | 219         | A                |
| 103         | B                | 220         | B                |
| 104         | C                | 221         | A                |
| 105         | A                | 222         | A                |
| 106         | B                | 223         | A                |
| 107         | B                | 224         | B                |
| 108         | A                | 225         | A                |
| 109         | A                | 226         | B                |
| 110         | A                | 227         | A                |
| 111         | A                | 228         | B                |
| 112         | A                | 229         | A                |
| 113         | A                | 230         | A                |
| 114         | A                | 231         | B                |
| 115         | A                | 232         | B                |
| 116         | A                | 233         | A                |
| 117         | B                |             |                  |

**EXAMPLE 2**

**[000444]** This Example illustrates that treatment of bone marrow derived CD34<sup>+</sup> cells from two healthy human donors with compound Example 32 (8-(4-((dimethylamino)methyl)-2-methylphenyl)-5-(((5-fluoro-2,3-dihydrobenzofuran-2-yl)methyl)amino)imidazo[1,2-c]pyrimidine-2-carbonitrile) increases fetal hemoglobin levels in the cells.

**[000445]** Cell Culture and differentiation protocol. Human bone marrow derived CD34<sup>+</sup> cells from healthy donors were purchased from StemCell (#70002.2). The CD34<sup>+</sup> cells were differentiated using the STEMdiff™ Erythroid kit (StemCell #100-0074) according to manufacturer's instructions. The CD34<sup>+</sup> cells were differentiated for 14 days, and the differentiation medium consisted of StemSpan™ SFEM II media and 10% of STEMdiff™ Erythroid Supplement E2 (10X). The CD34<sup>+</sup> cells were thawed and plated in a 12-well plate (Corning #3512) at a density of 40,000 cells/well in 1mL of differentiation media. 100 µL of STEMdiff™ Erythroid Supplement E2 (10X) was added to each well on Day 2, 4, 9 and 11 during differentiation. On day 7, cells were passaged and replated at a density of 167,000 cells/well in a 12-well plate. Flow cytometry was performed every 7 days to assess the stages of

differentiation using anti-human CD71 and anti-human glycophorin A (CD235a) antibody (StemCell #60106AZ; #60152FI).

**[000446]** Treatment of differentiated CD34+ cells with compound Example 32 or hydroxyurea (HU). After 14 days of differentiation, cells were plated in a 12-well plate at a density of 150,000 cells/well in 1 mL differentiation media in quadruplets. The next day, cells were treated with vehicle, 7 concentrations of compound Example 32 in concentrations ranging from 15.625 nM to 1  $\mu$ M (1:5-fold serial dilution) and 20  $\mu$ M of HU. 100  $\mu$ L of STEMdiff™ Erythroid Supplement E2 (10X) was added to each well on Day 2 and 4. Cells were treated with vehicle, compound Example 32, or HU for 7 days and were then harvested for RT-qPCR and flow cytometry.

**[000447]** RNA extraction and RT-qPCR analysis. The cell pellets harvested for mRNA analysis were first washed once with PBS and then resuspended in 600  $\mu$ L of RLT lysis buffer (from the Qiagen kit) supplemented with 1% of beta-mercaptoethanol (Sigma-Aldrich #M6250). RNA was extracted by QIAcube (Qiagen #9001292, software v1.0.1) using the RNeasy Mini QIAcube kit (Qiagen #74116) according to manufacturer's instructions. The extracted RNA was then quantified using a NanoDrop™ 8000 Spectrophotometer (ThermoFisher #ND8000-GL, software version 2.3.2). RT qPCR reactions were set up using 3  $\mu$ L of 3 ng of RNA in 7  $\mu$ L of pre-mixed SensiFAST™ SYBR No-ROX One-Step Kit reagents (BIOLINE, Cat# BIO-98005) and RT-qPCR was run on a Bio-Rad CFX384 Real-Time PCR System. HBG1 and HBG2 mRNA levels were normalized to housekeeping gene RPL27 and are plotted relative to mRNA levels in vehicle treated cells.

Primer sequences for RT-qPCR

| Species | Genes | Forward Primers           | Reverse Primers        |
|---------|-------|---------------------------|------------------------|
| Human   | RPL27 | CTGGAATTGACCGCTACC<br>C   | TGGGCATTAGGTGATTGTAGTT |
|         | HBG1  | CATGGACCCAGAGGTTCT<br>TT  | AGGAAGTCAGCACCTTCTTG   |
|         | HBG2  | GAGGAGGACAAGGCTAC<br>TATC | TGGGTCCATGGGTAGACAA    |

**[000448]** Flow Cytometry. The cell pellets harvested for flow cytometry analysis were collected in a V-shaped 96-well polypropylene plate (ThermoFisher #249944). The cells were washed with PBS and resuspended in 100  $\mu$ L of PBS. The cells were first stained with eFluor 450 viability dye (diluted 1:250 in cold PBS; Invitrogen #65-0863-14) for 5 minutes on ice in the dark followed by incubation in Fc receptor blocking solution for 10 minutes (BioLegend #422302). The cells were then washed with FACS buffer (1X PBS, 0.5% BSA, 0.02% NaAzide and 2 mM EDTA) and resuspend in 100  $\mu$ L of FACS buffer. The cells were next stained with fluorochrome conjugated antibodies targeted against cell surface receptors such as anti-human CD235a-FITC (StemCell #60152FI) and/or anti-human CD71-APC (StemCell #60106AZ) for 25 minutes on ice. The cells were washed twice using FACS buffer and then fixed using Fixation buffer from the Fixation/Permeabilization kit (BD biosciences #554714) for 10 minutes on ice. The cells were further washed twice with 1X Permeabilization/Wash buffer and then

incubated in the same buffer for 5 minutes. The permeabilized cells were stained using anti-human Fetal Hemoglobin-APC (ThermoFisher #MHFH05) for 15 minutes on ice in 1X Permeabilization/Wash buffer. Cells were washed twice and resuspended in FACS buffer and then analyzed by flow cytometry. Data was acquired using SONY SA3800 cytometer (software version 2.0.4.13263) and analyzed using FlowJo.

**[000449]** Bone marrow derived CD34+ cells from two healthy human donors (donor A and donor B) were differentiated into erythroid progenitor cells (erythroblasts) expressing Glycophorin A and CD71. Fourteen-day differentiated cells were then treated with vehicle (veh), different concentrations of compound Example 32, or 20  $\mu$ M HU for 7 days and cells were analyzed for increase in fetal hemoglobin levels at both mRNA and protein levels. In vehicle treated cells, around 10-15% of all live cells showed the presence of fetal hemoglobin (% F cells) by flow cytometry (FIG. 1A, FIG. 1B). Treatment with compound Example 32 resulted in a 2.6-2.7-fold increase to around 30-40% of F cells in two independent donors A and B, and this increase in % F cells was dose-dependent (FIG. 1A, FIG. 1B). In comparison, treatment with 20  $\mu$ M HU achieved a 1.9-fold increase in % F cells in Donor A (FIG. 1A) and a 1.3-fold increase in Donor B (Fig. 1B).

**[000450]** HBG1 and HBG2 are the genes that encode the gamma-globin subunit that is unique to fetal hemoglobin. Consistent with treatment-induced increases in the percentage of fetal hemoglobin containing cells, HBG1 and HBG2 mRNA levels also increased in a dose-dependent manner when cells were treated with compound Example 32 (FIG. 2A-2D). Donor A showed a 4-fold increase in HBG1 (FIG. 2A) and a 9-fold increase in HBG2 mRNA levels (FIG. 2B) following treatment with compound Example 32. Donor B showed a 4-fold increase in both HBG1 (FIG. 2C) and HBG2 mRNA levels (FIG. 2D) following treatment with compound Example 32. Treatment of the cells with hydroxyurea (HU) increased HBG2 levels by 2.7-fold (FIG. 2B) but not HBG1 levels in Donor A (FIG. 2A). A modest increase (1.7-fold) with HU treatment was observed for HBG1 mRNA in Donor B (FIG. 2C), but not for HBG2 (FIG. 2D). These data indicate that treatment of CD34-differentiated cells with compound Example 32 increases fetal hemoglobin levels, to a larger extent as observed with HU.

#### **EXAMPLE 3: Preparation of crystalline Form 1 of Example 32**

**[000451]** 150  $\mu$ L of methanol was added to 50 mg of the free base of Example 32 and the resulting slurry was stirred at room temperature for one day. The resulting solids were vacuum filtered and dried under ambient condition overnight to afford Form 1 of Example 32.

#### **EXAMPLE 4A: Preparation of crystalline Form 2 of Example 32**

**[000452]** 400 mg of the free base of Example 32 was dissolved in 1.5 mL of 2-methyltetrahydrofuran at 50 °C, to which was added 1.5 mL n-heptane at about 47 °C, and the resulting mixture was cooled 10 °C. The resulting solids were vacuum filtered and allowed to air dry overnight under ambient conditions to afford Form 2 of Example 32.

#### **EXAMPLE 4B: Preparation of crystalline Form 2 of Example 32**

**[000453]** A quantity of the free base of Example 32 was dissolved in 2-methyltetrahydrofuran (10 volumes) and then distilled to 3 volumes. The temperature of the solution was adjusted to about 25 °C and the resulting slurry was stirred for greater than 30 minutes. To the slurry was added n-heptane (7

volumes) over 2 hours and the resulting mixture was stirred for greater than 4 hours. The resulting solid was filtered, the filter cake was washed with 30% 2-methyltetrahydrofuran/heptane (2 volumes) and dried in a vacuum oven to provide Form 2 of Example 32.

**EXAMPLE 5: X-ray powder diffraction (XRPD) analysis of Form 1 and Form 2 of Example 32**

**[000454]** XRPD analyses of crystalline polymorphic forms of Example 32 were performed using Panalytical X'pert<sup>3</sup> X-ray powder diffractometer. Samples were spread on the middle of a zero-background Si holder. The 2-theta position was calibrated against a Panalytical Si reference standard disc. The parameters used for the analyses are set forth in Table 1.

Table 1

| Parameter                | Reflection Mode                                                                                                                                   |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| X-ray wavelength         | Cu, $\text{K}\alpha$<br>K $\alpha$ 1 (angstroms): 1.540598; K $\alpha$ 2 (angstroms): 1.544426<br>K $\alpha$ 2/K $\alpha$ 1 intensity ratio: 0.50 |
| X-ray tube setting       | 45 kV, 40 mA                                                                                                                                      |
| Divergence slit          | 1/8°                                                                                                                                              |
| Scan mode                | Continuous                                                                                                                                        |
| Scan range (° 2-theta)   | 3° to 40°                                                                                                                                         |
| Scan step time (seconds) | 18.87                                                                                                                                             |
| Step size (° 2-theta)    | 0.0131                                                                                                                                            |
| Test time                | About 4 minutes, 15 seconds                                                                                                                       |

**[000455]** Polymorphic Form 1 of Example 32 was analyzed by XRPD as set forth above and exhibited the peaks set forth in Table 2. The error associated with each °2-theta position was determined to be  $\pm 0.2^\circ$  theta.

Table 2

| Position (°2-theta) | Relative intensity (%) |
|---------------------|------------------------|
| 5.7                 | 23.83                  |
| 8.1                 | 100                    |
| 9.6                 | 32.45                  |
| 9.8                 | 17.88                  |
| 12.9                | 18.43                  |
| 15.2                | 18.62                  |
| 17.7                | 18.68                  |
| 19.7                | 22.92                  |
| 22.0                | 22.15                  |

**[000456]** Polymorphic Form 2 of Example 32 was analyzed by XRPD as set forth above and exhibited the peaks set forth in Table 3. The error associated with each °2-theta position was determined to be  $\pm 0.2^\circ$  theta.

Table 3

| Position (°2-theta) | Relative intensity (%) |
|---------------------|------------------------|
| 5.5                 | 70.17                  |
| 7.7                 | 100                    |
| 8.6                 | 62.56                  |
| 10.6                | 55.03                  |
| 11.0                | 41.46                  |
| 13.7                | 85.08                  |
| 15.4                | 47.42                  |
| 15.9                | 60.49                  |
| 19.2                | 78.68                  |
| 19.9                | 60.93                  |
| 21.0                | 50.16                  |
| 24.1                | 68.95                  |
| 25.3                | 38.36                  |
| 26.3                | 57.53                  |

**EXAMPLE 6: Thermal gravimetric analyses and differential scanning calorimetry analyses of Form 1 and Form 2 of Example 32**

[000457] Thermal gravimetric analysis (TGA) data were collected using TA Discovery TGA 550 TGA from TA Instruments, and differential scanning calorimetry (DSC) analyses were performed using a TA Q2000 DSC from TA Instruments using the parameters set forth in Table 4.

Table 4

| Parameter         | TGA                              | DSC                              |
|-------------------|----------------------------------|----------------------------------|
| Method            | Ramp                             | Ramp                             |
| Sample pan        | Platinum, open                   | Aluminum, crimped                |
| Temperature range | Room temperature to about 380 °C | Room temperature to about 380 °C |
| Heating rate      | 10 °C/minute                     | 10 °C/minute                     |
| Purge gas         | Nitrogen                         | Nitrogen                         |

[000458] A thermal gravimetric analysis (TGA) of a sample of Form 1 of Example 32, when conducted under the conditions set forth in Table 4, exhibited a weight loss of about 1% upon heating the sample from room temperature to about the onset of melting (about 207 °C). A differential scanning calorimetry (DSC) analysis of Form 1 of Example 32, when conducted under the conditions set forth in Table 4, exhibited peaks at between about 170 °C and 172 °C, and between about 207 °C and 208 °C.

[000459] A thermal gravimetric analysis (TGA) of a sample of Form 2 of Example 32, when conducted under the conditions set forth in Table 4, exhibited a weight loss of about 2% upon heating the sample from room temperature to about the onset of melting (about 204 °C). A differential scanning calorimetry (DSC) analysis of Form 2 of Example 32, when conducted under the conditions set forth in Table 4, exhibited a peak between about 203 °C and 204 °C.

**EXAMPLE 7: Preparation of crystalline Form 2 of Example 32**

[000460] A reactor was evacuated and charged with nitrogen to atmospheric pressure. The reactor was then charged with a solution of Example 32 (approximately 2.41 kg as determined by solution assay using HPLC) in 2-methyltetrahydrofuran (2-MeTHF, 36 kg, 15 volumes) and the batch was concentrated to a batch volume of about 5 L (about 2 volumes) via distillation under reduced pressure. The resulting solution was adjusted to about 25 °C and then n-heptane (0.4 kg, 0.2 volumes) was added in portions over a period of about 3 hours. The resulting solution was then seeded with Example 32 Form 2 (9 g, 0.4 wt%), the resulting mixture was stirred for about 1.3 hours, and then additional n-heptane (24 kg, 10 volumes) was added over about 6 hours. The resulting slurry was stirred for about 4.25 hours at 25 °C and then filtered. The reactor was then rinsed with n-heptane (5.8 kg, 2.5 V), and this mixture was rinsed forward to the filter cake, which was deliquored and the solids were dried under reduced pressure at 40 °C and 50 °C for 19 hours to provide 2.48 kg of Form 2 of Example 32.

[000461] While the disclosure has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the disclosure following, in general, the principles of the disclosure and including such departures from the present disclosure as come within known or customary practice within the art to which the disclosure pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

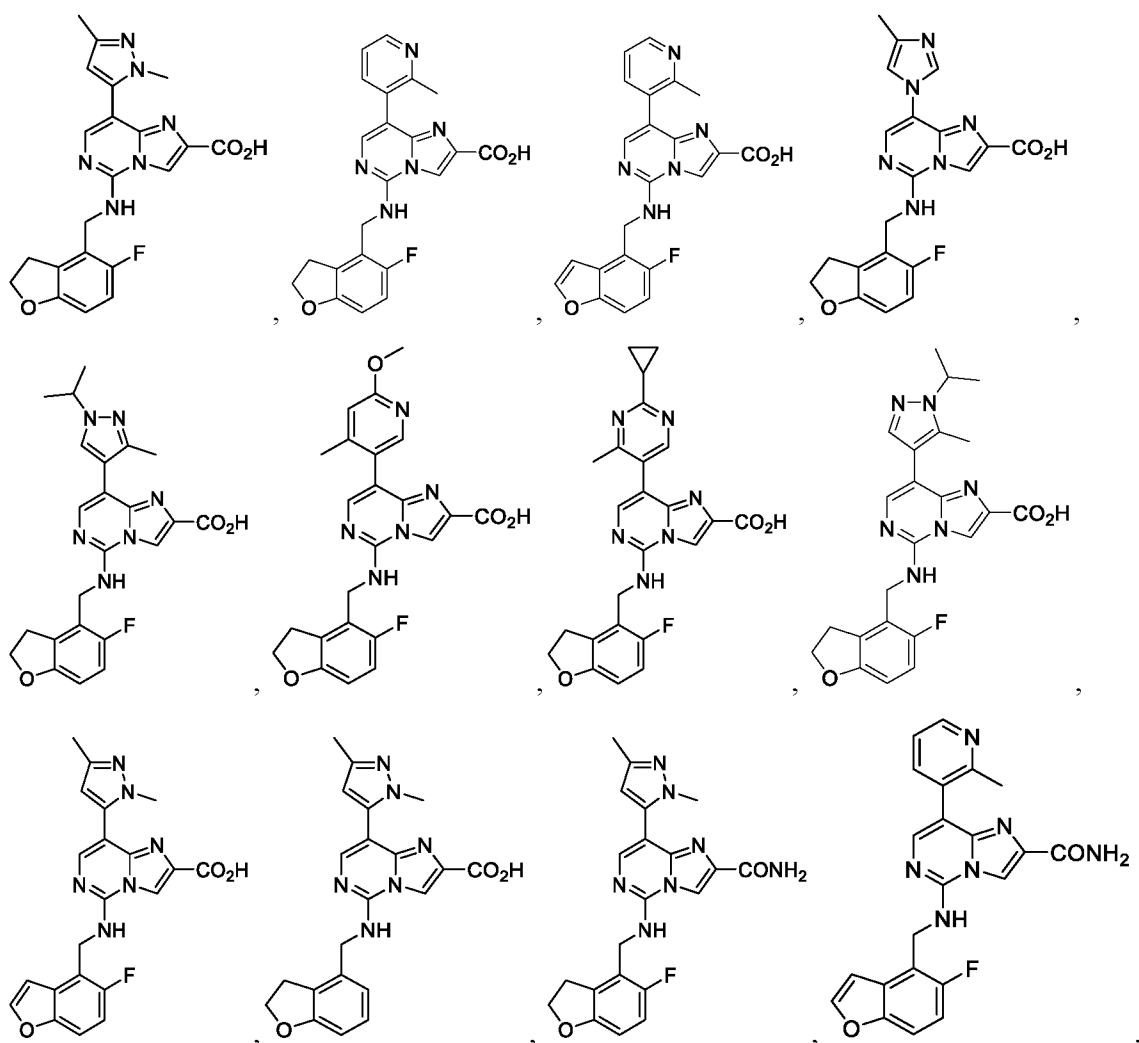
## CLAIMS

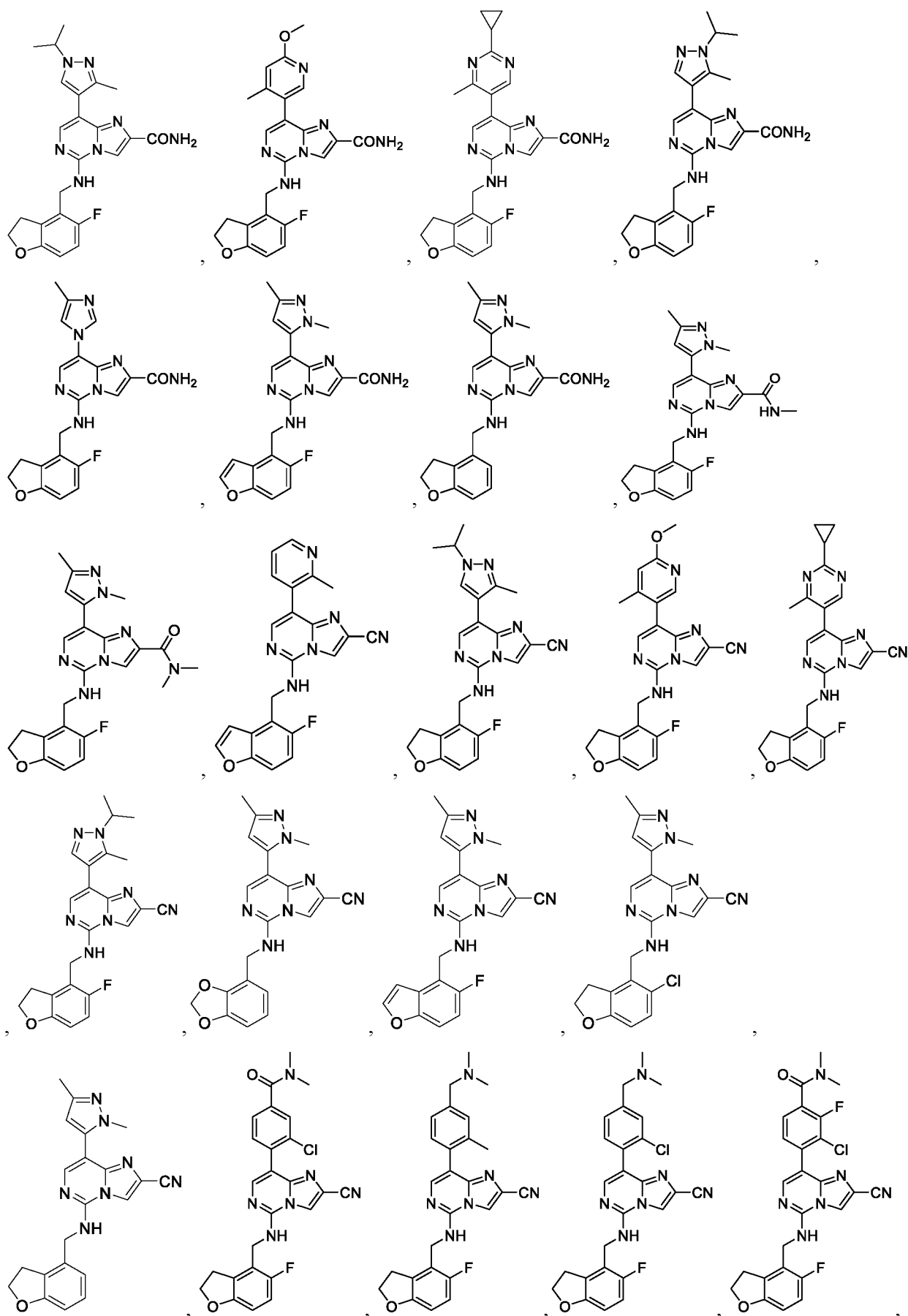
## WE CLAIM:

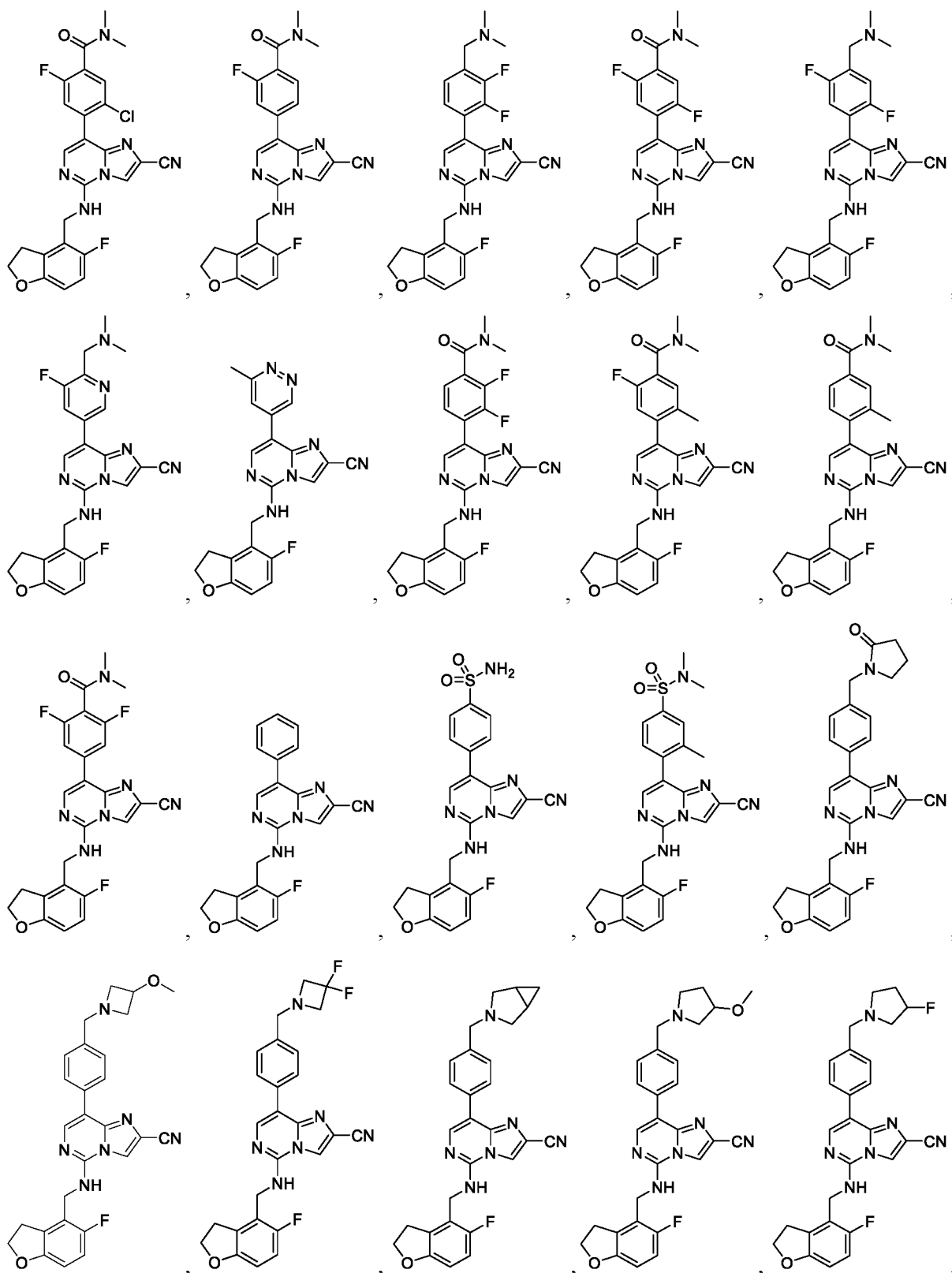
1. A method of treating sickle cell disease in a subject, comprising administering to the subject a therapeutically effective amount of an inhibitor of polycomb repressive complex 2 (PRC2), wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has:

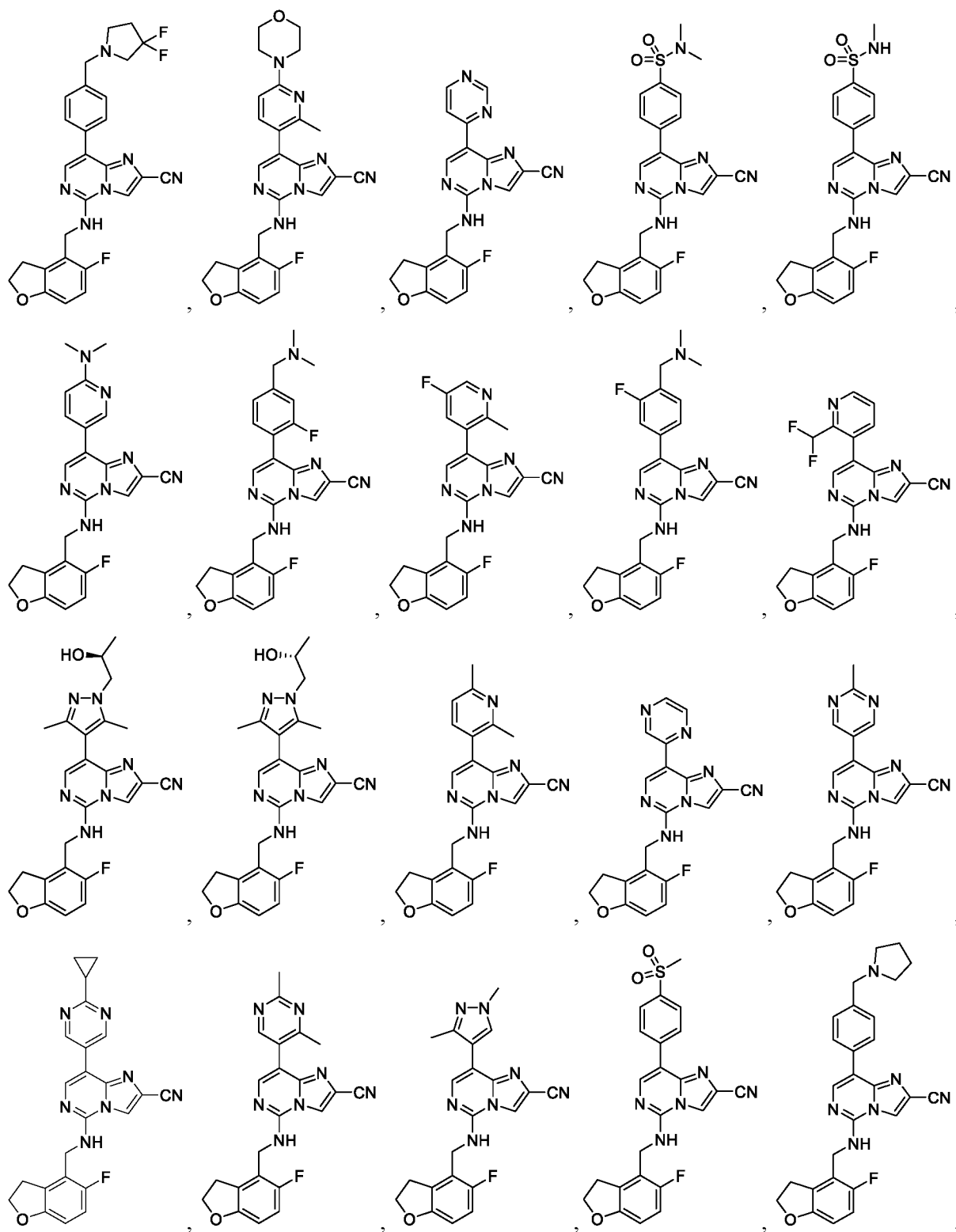
- a. been administered hydroxyurea; and/or
- b. been administered a stable dose of one or more of voxelotor, crizanlizumab, and L-glutamine; and

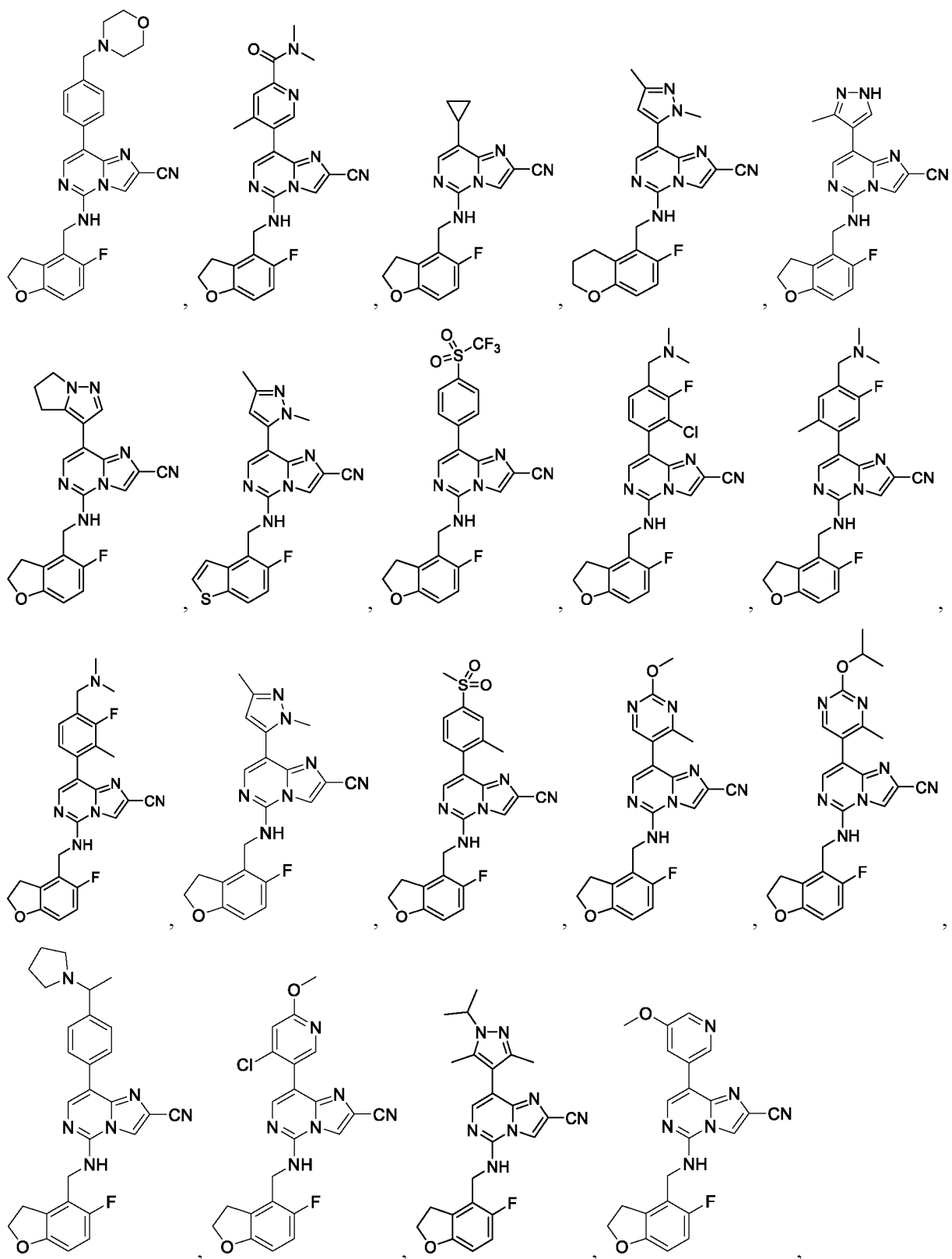
wherein the inhibitor of polycomb repressive complex 2 (PRC2) is a compound selected from the group consisting of:

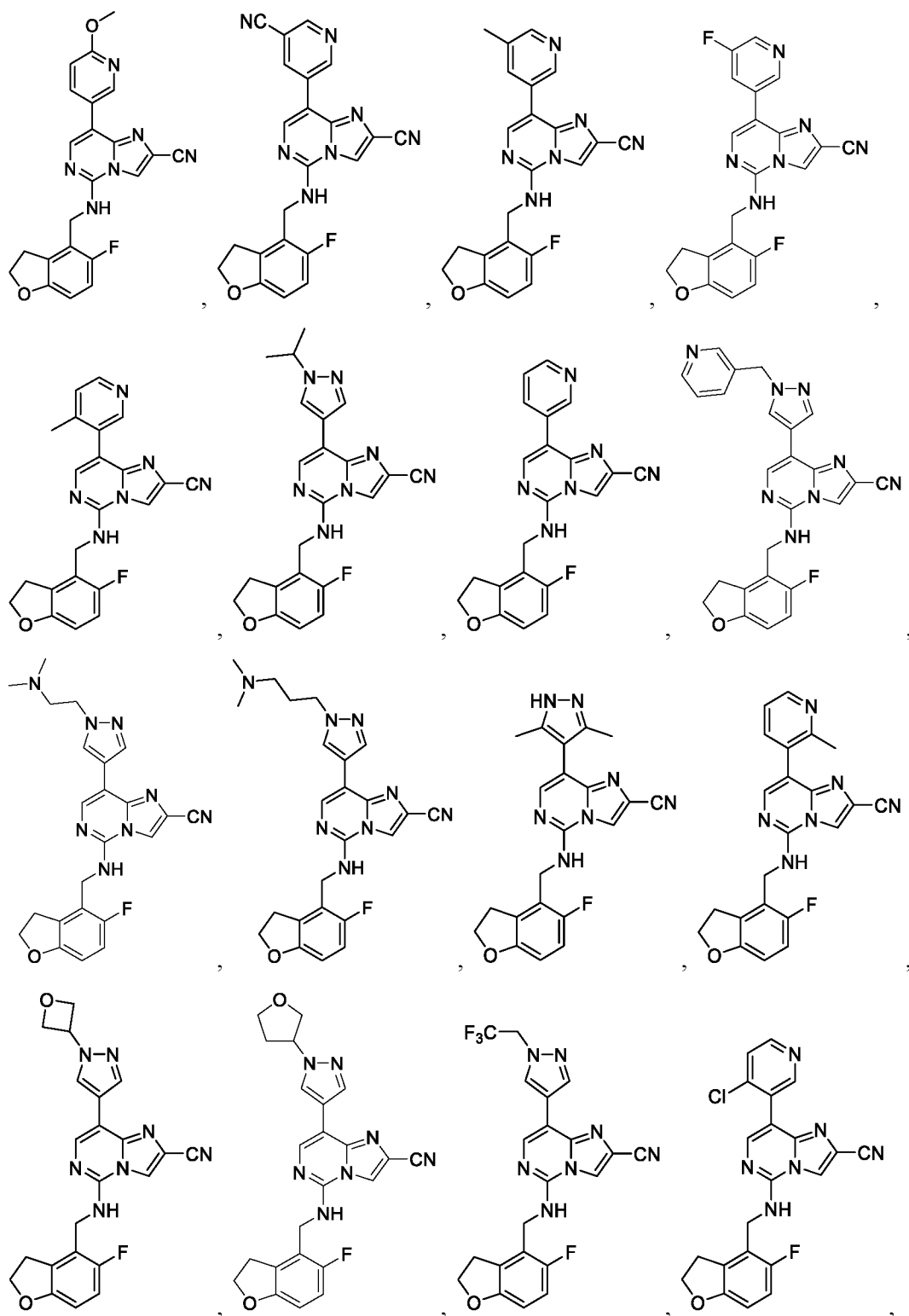


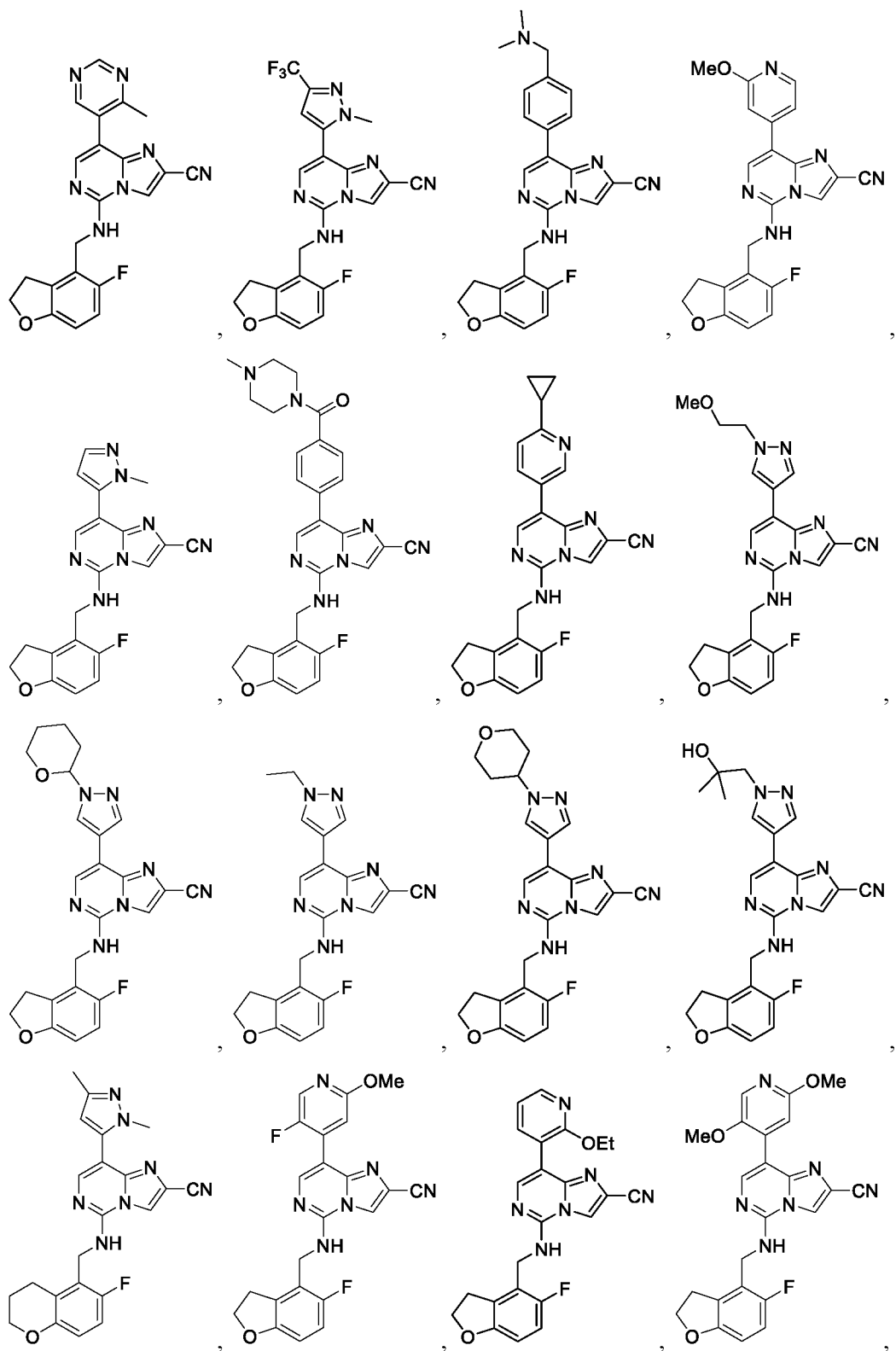


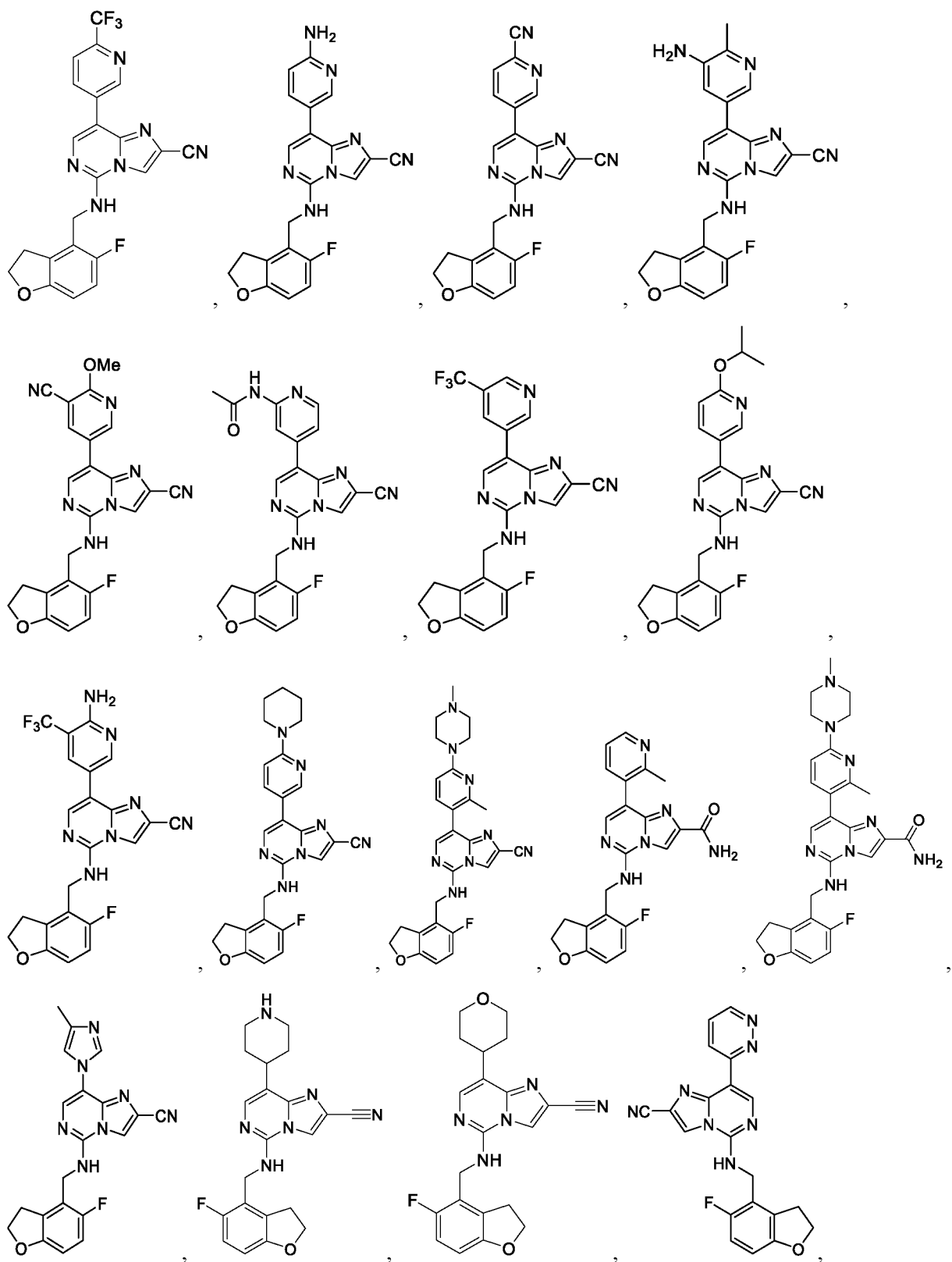


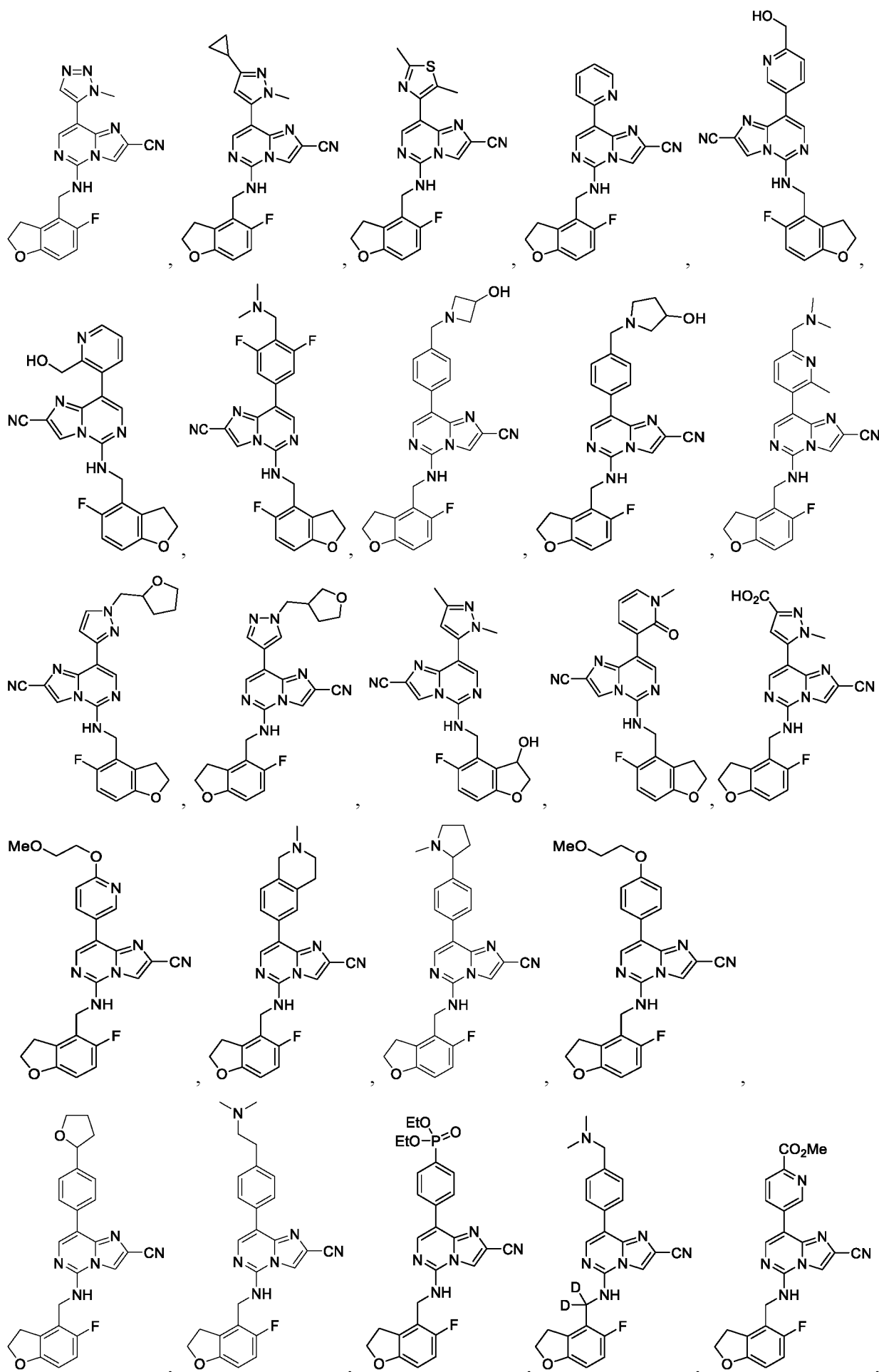


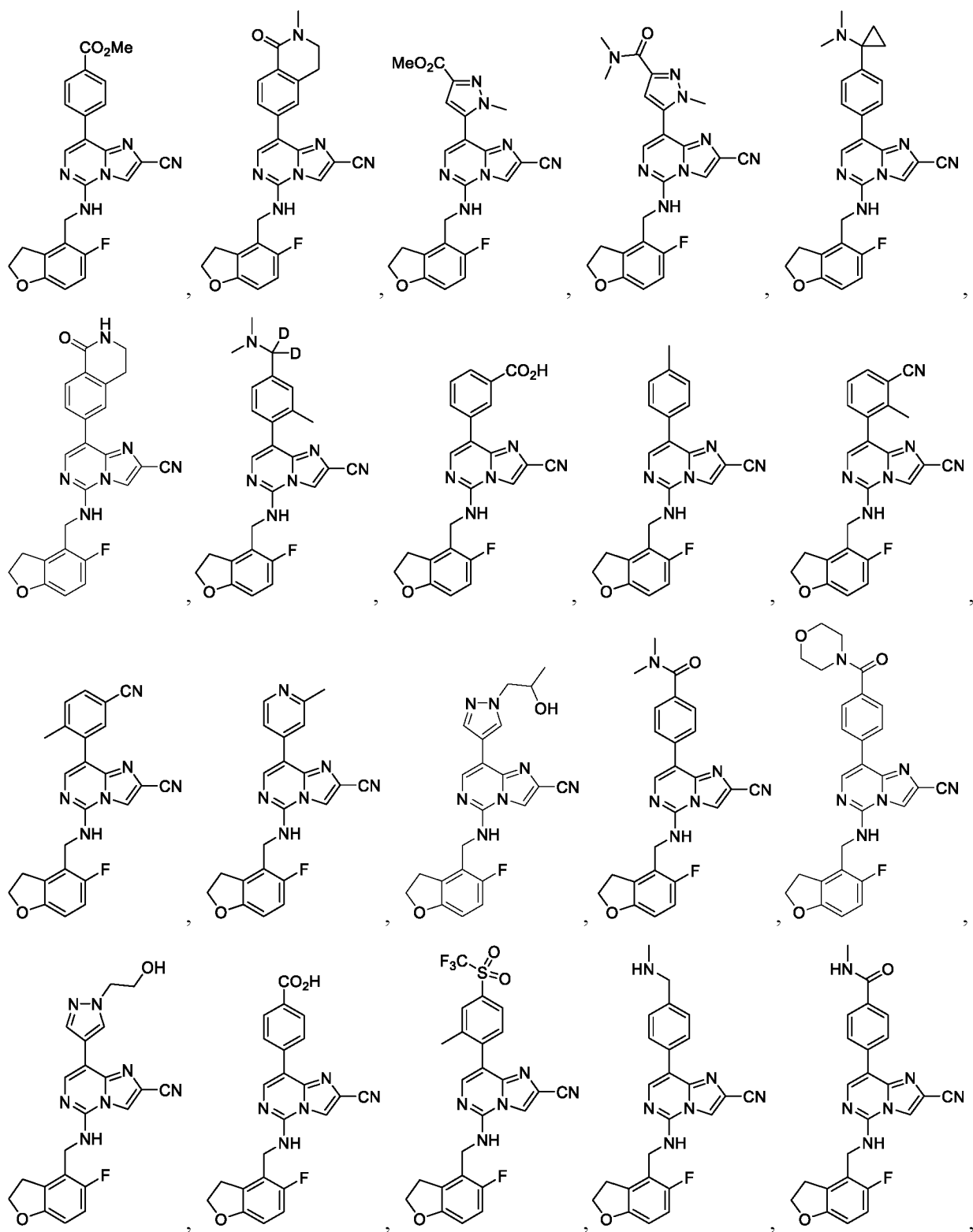


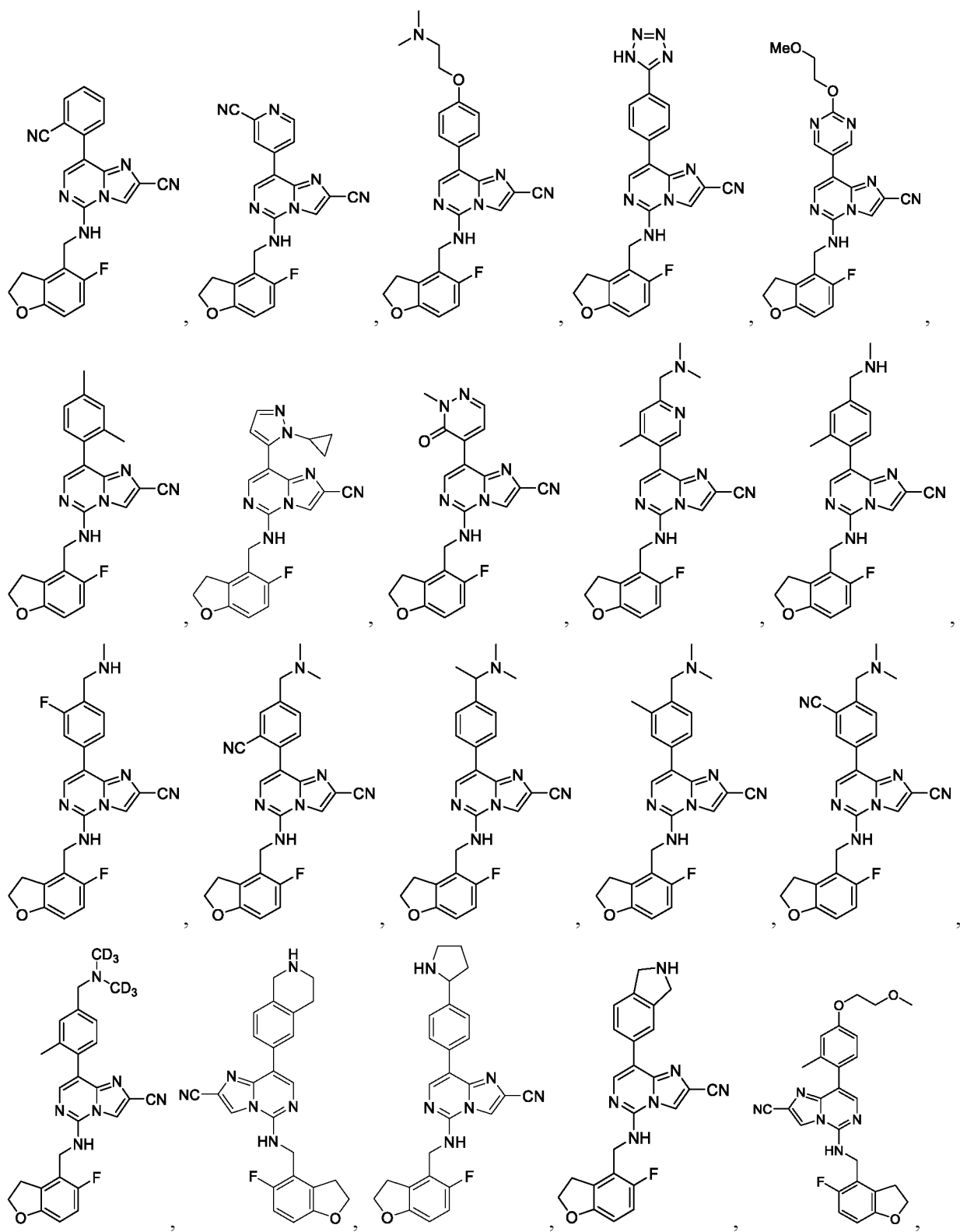


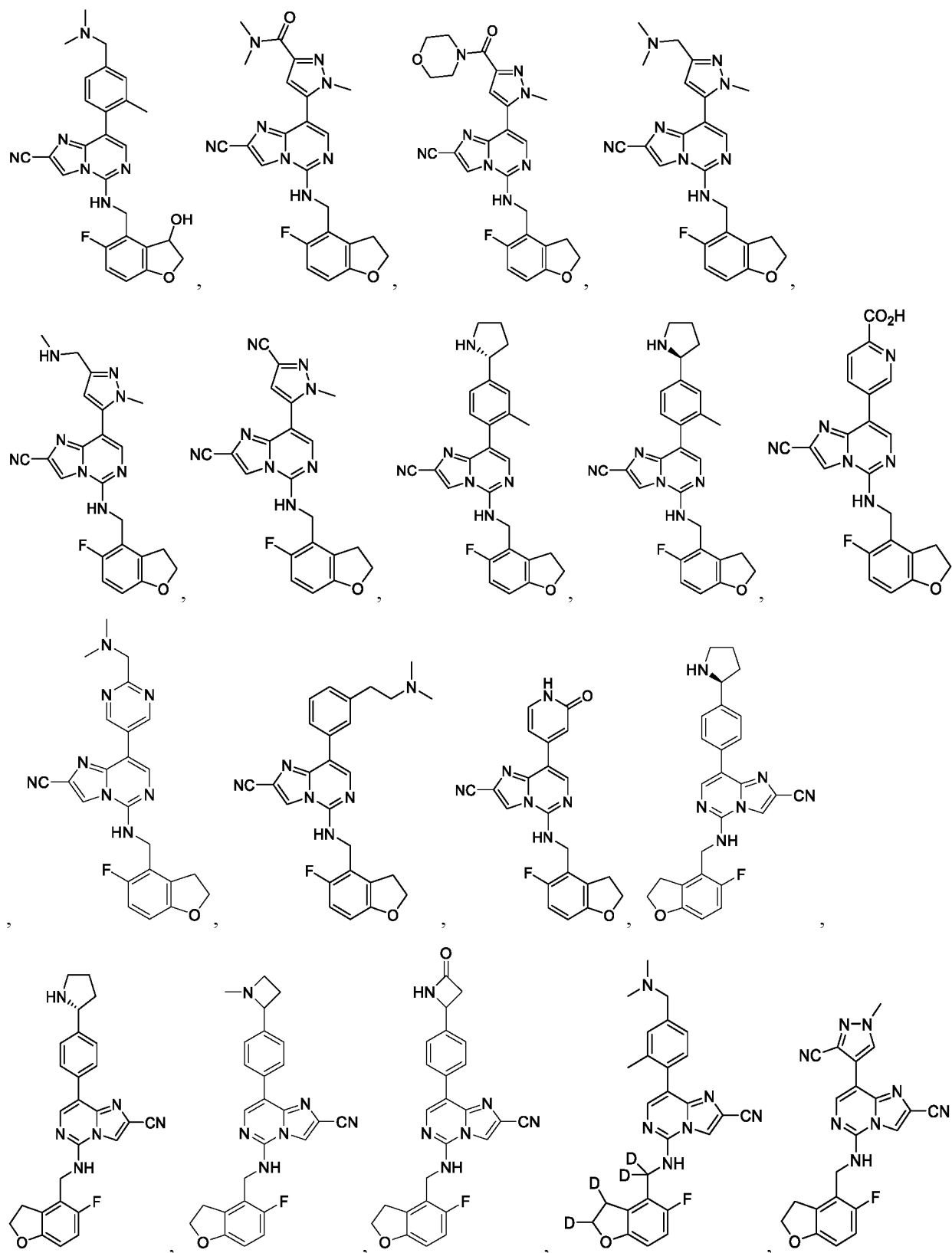


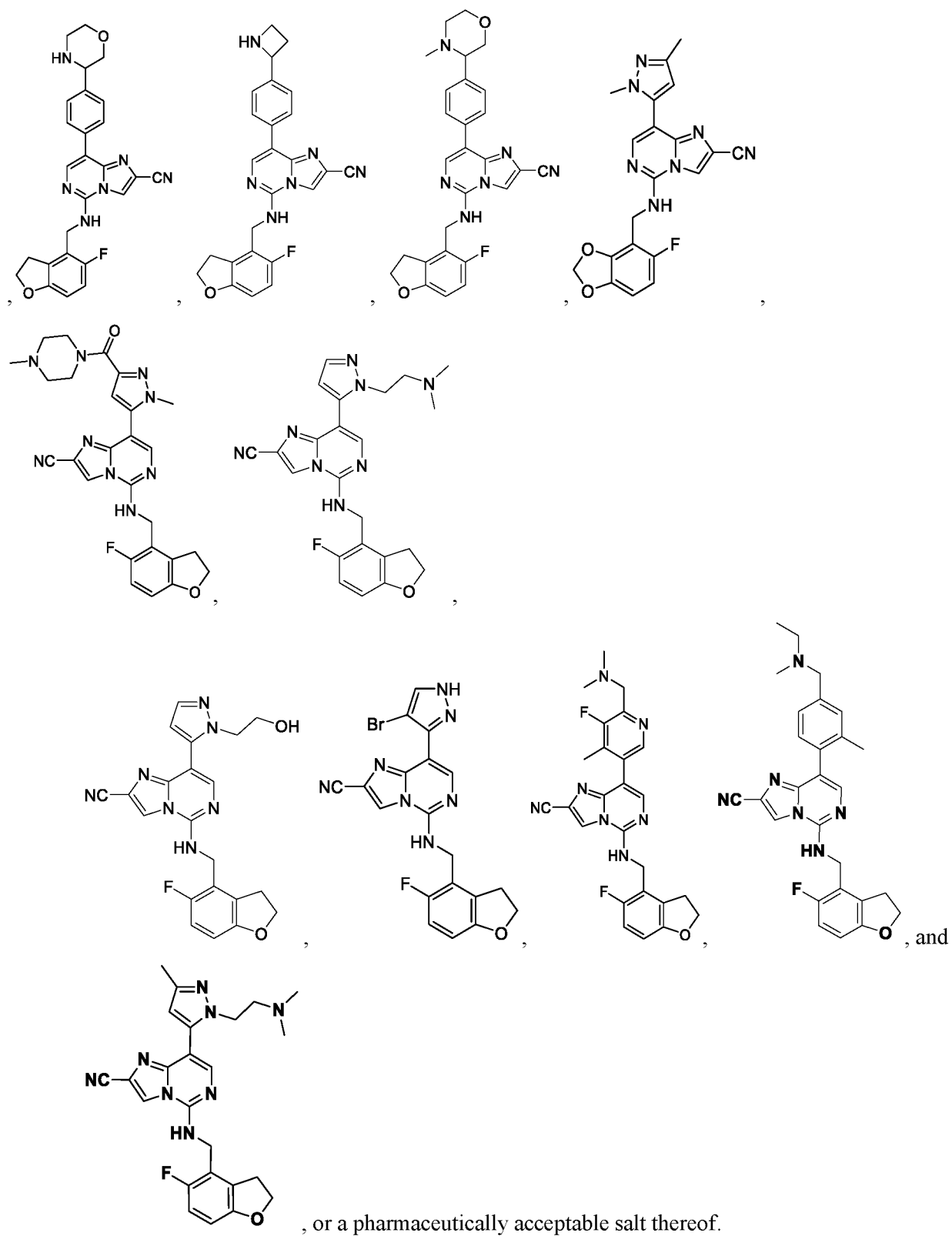




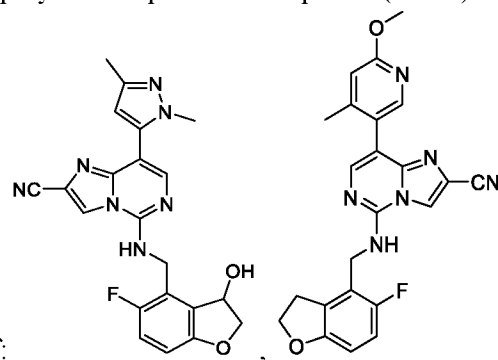




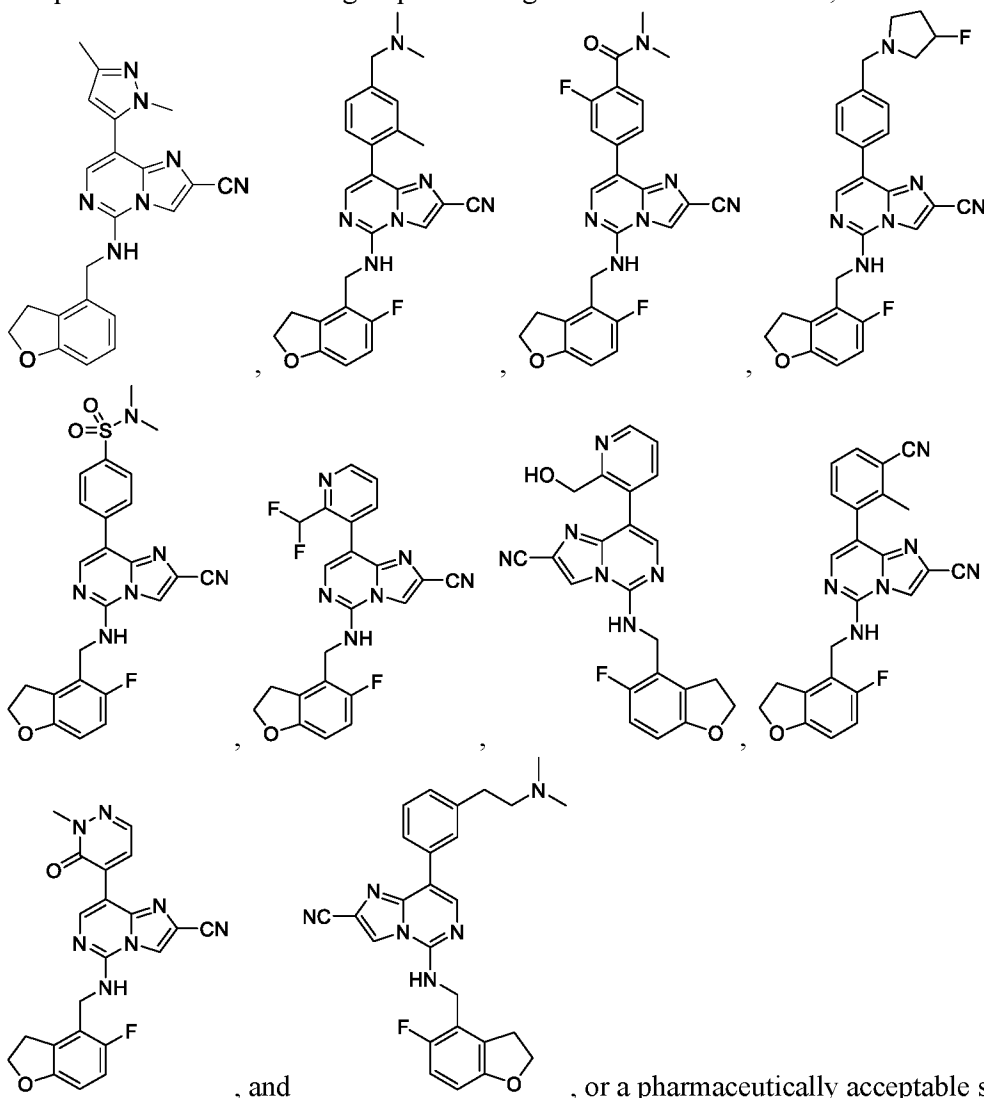




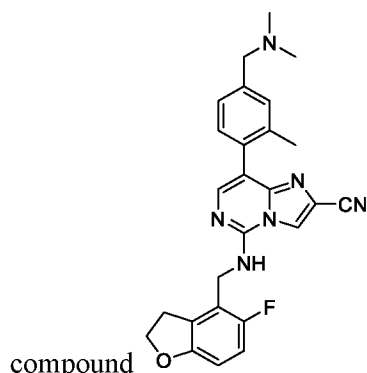
2. The method of claim 1, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is a



compound selected from the group consisting of:



3. The method of claim 1, wherein the inhibitor of polycomb repressive complex 2 (PRC2) is the



compound, or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced:
  - a. one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea; or
  - b. one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.
5. The method of claim 4, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued vaso-occlusive crisis (VOC) events or episodes of acute chest syndrome (ACS) for at least 6 months while being administered hydroxyurea at the maximum tolerated dose; (ii) an inability to tolerate the adverse effects of the continued administration to the subject of hydroxyurea; (iii) unmanageable drug-drug interactions as a result of the continued administration to the subject of hydroxyurea; and (iv) the subject's refusal to continue the further administration of hydroxyurea.
6. The method of claim 4, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (i) continued pain crisis events and other vaso-occlusive crisis (VOC) events while on a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months; (ii) a failure to increase hemoglobin (Hb) by 1 g/dL in a subject receiving voxelotor; (iii) continued vaso-occlusive crisis (VOC) events in a subject receiving crizanlizumab or L-glutamine; (iv) an inability to tolerate the adverse effects of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; (v) unmanageable drug-drug interactions as a result of the continued administration to the subject of voxelotor, crizanlizumab, or L-glutamine; and (vi) the subject's refusal to continue the further administration of voxelotor, crizanlizumab, or L-glutamine.
7. The method of claim 1, wherein the subject has been administered hydroxyurea prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).

8. The method of claim 7, wherein in the 6-month period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of (a) the same or higher number of pain crises or other vaso-occlusive crisis (VOC) events compared to the prior to the 6-month period; (b) episodes of acute chest syndrome (ACS); (c) an inability to tolerate continued administration of hydroxyurea; (d) unmanageable drug-drug interactions with the continued administration of hydroxyurea; and (e) the subject's refusal to continue the further administration of hydroxyurea.
9. The method of claim 1, wherein the subject has been administered one or more of voxelotor, crizanlizumab, and L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).
10. The method of claim 9, wherein the subject has been administered voxelotor prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).
11. The method of claim 9, wherein the subject has been administered crizanlizumab prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).
12. The method of claim 9, wherein the subject has been administered L-glutamine prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2).
13. The method claim 1, wherein prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has further experienced one or more of:
  - a. 4 or more vaso-occlusive crisis (VOC) events over the prior 12-month period;
  - b. 2 or more vaso-occlusive crisis (VOC) events over the prior 6-month period;
  - c. 2 or more vaso-occlusive crisis (VOC) events over the prior 12-month period and at least one of one or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism;
  - d. 2 or more acute chest syndrome (ACS) events, hepatic and splenic sequestration, and priapism over the prior 12-month period;
  - e. pulmonary hypertension; and
  - f. chronic kidney disease.
14. The method of claim 1, wherein the subject is not concurrently administered the inhibitor of polycomb repressive complex 2 (PRC2) and hydroxyurea, voxelotor, crizanlizumab, or L-glutamine.
15. The method of claim 1, wherein in the 60-day period prior to the administration to the subject of the inhibitor of polycomb repressive complex 2 (PRC2) the subject has not been administered one or more of hydroxyurea, voxelotor, crizanlizumab, and L-glutamine.

FIG. 1A

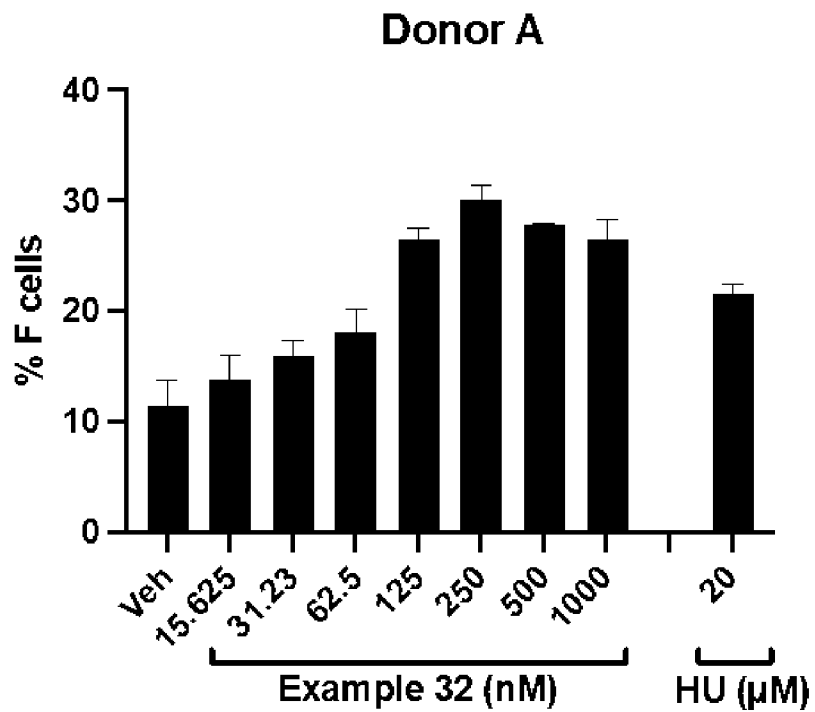


FIG. 1B

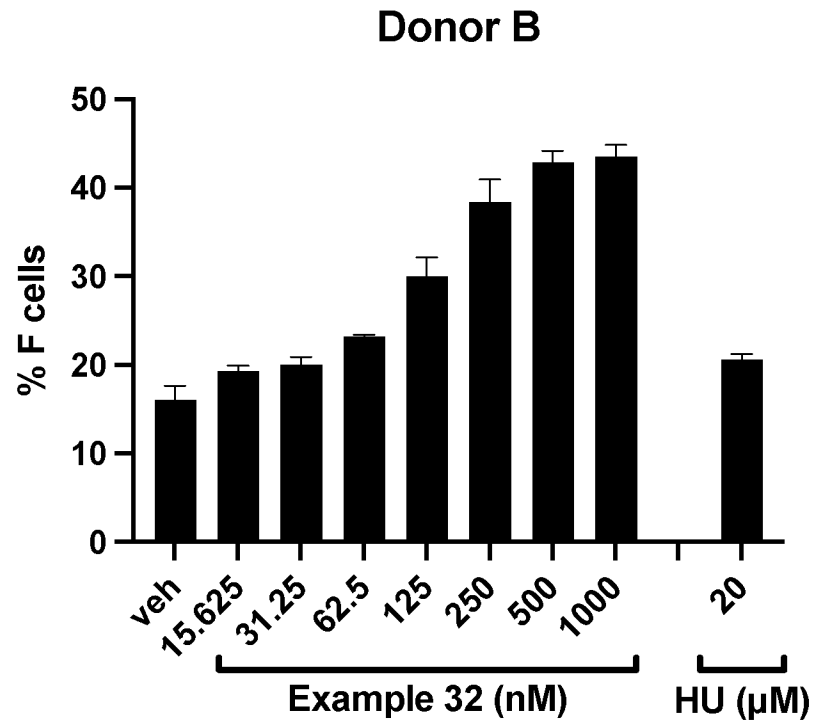


FIG. 2A

## Donor A - HBG1 mRNA

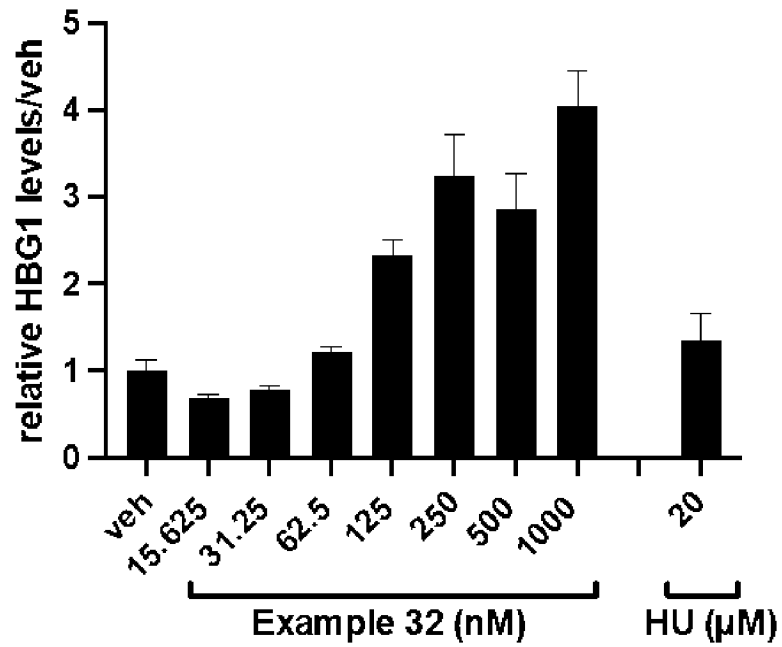


FIG. 2B

## Donor A - HBG2 mRNA

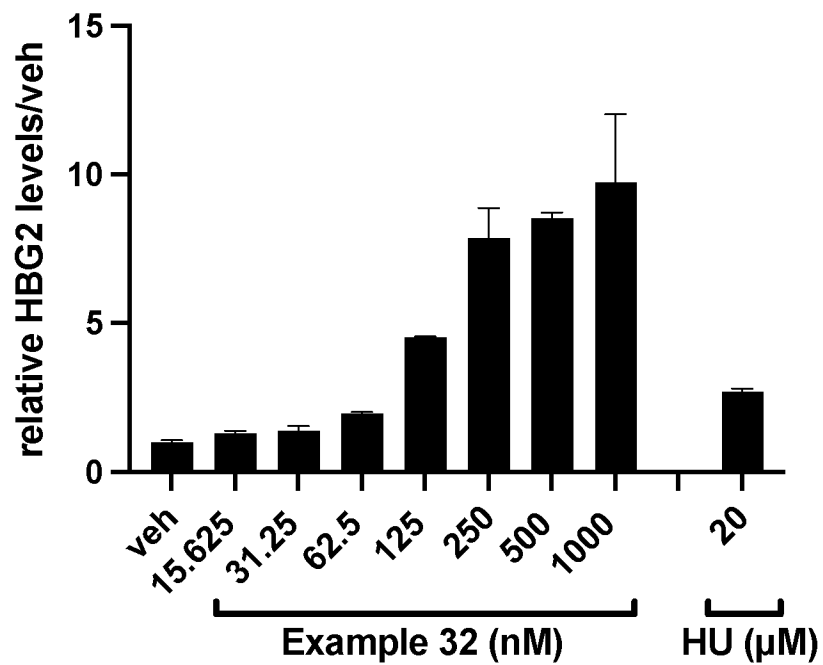


FIG. 2C

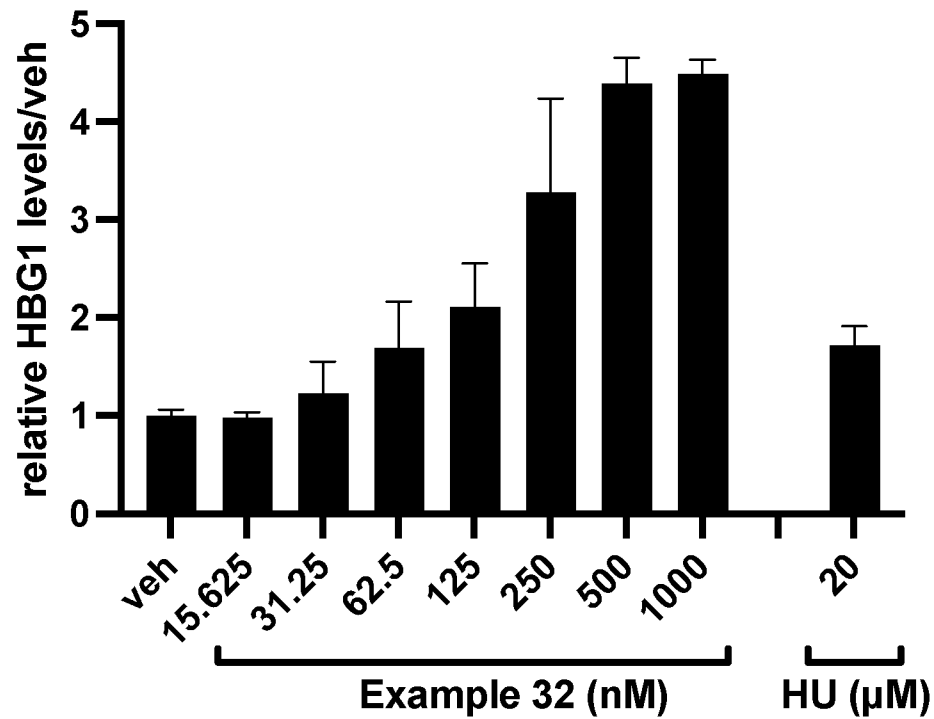
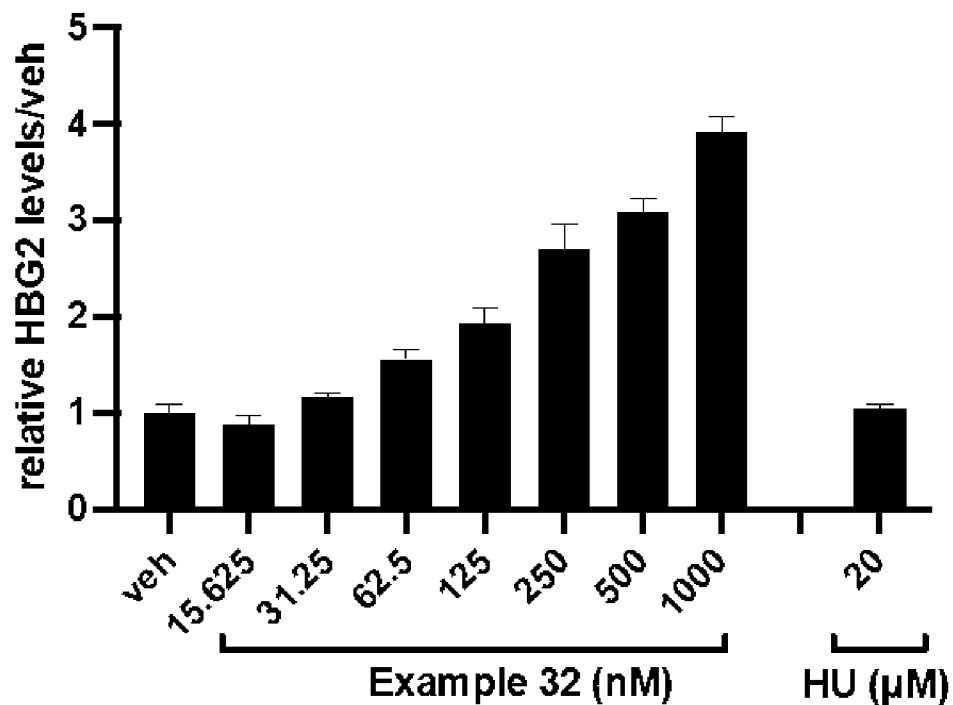
**Donor B - HBG1 mRNA**

FIG. 2D

**Donor B - HBG2 mRNA**

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2024/043672

## A. CLASSIFICATION OF SUBJECT MATTER

**A61K 31/519 (2006.01) A61K 31/17 (2006.01) A61K 31/198 (2006.01) A61K 31/4439 (2006.01) A61K 39/395 (2006.01) A61P 7/00 (2006.01) A61P 7/06 (2006.01)**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**Databases:** REGISTRY, BIOSIS, CAPLUS, EMBASE, MEDLINE, EPOQUE (PATENW). **Keywords:** PCR2, Polycomb Repressive Complex 2, H3K27ME3, EED, Embryonic Ectoderm Development, Sick Cell, Hemoglobin, Anemia, Inhibitor, Blocker, Antagonist, Reduction, Downregulate, and like terms.

Applicant/Inventor search conducted in Australian Preliminary Search Tool (APST), Espacenet, and PubMed.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
|           | Documents are listed in the continuation of Box C                                  |                       |



Further documents are listed in the continuation of Box C



See patent family annex

|                                                                                                                                                                         |                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                |                                                                                                                                                                                                                                                  |
| "A" document defining the general state of the art which is not considered to be of particular relevance                                                                | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
| "D" document cited by the applicant in the international application                                                                                                    | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |
| "E" earlier application or patent but published on or after the international filing date                                                                               | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" document member of the same patent family                                                                                                                                                                                                    |
| "O" document referring to an oral disclosure, use, exhibition or other means                                                                                            |                                                                                                                                                                                                                                                  |
| "P" document published prior to the international filing date but later than the priority date claimed                                                                  |                                                                                                                                                                                                                                                  |

Date of the actual completion of the international search  
15 October 2024

Date of mailing of the international search report  
15 October 2024

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| INTERNATIONAL SEARCH REPORT                           |                                                                                                                                                                                                                                                                                  | International application No. |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                  | PCT/US2024/043672             |
| Category*                                             | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                               | Relevant to claim No.         |
| X                                                     | WO 2023049723 A1 (ORIC PHARMACEUTICALS, INC.) 30 March 2023<br>Title, Abstract, Page 1, Examples (A), Claims (23 and 25)                                                                                                                                                         | 1-15                          |
| X                                                     | WO 2023049724 A1 (ORIC PHARMACEUTICALS, INC.) 30 March 2023<br>Title, Abstract, Page 1, Examples (A and B), Claims                                                                                                                                                               | 1-15                          |
| A                                                     | BRUNO P., ET AL., "P1472 INTERIM RESULTS OF SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS FROM AN ONGOING OPEN-LABEL STUDY INVESTIGATING FTX-6058 IN ADULTS LIVING WITH SICKLE CELL DISEASE", HemaSphere, 2022, 6:S3, 2581<br>Whole Document, Background, Results | 1-15                          |
| A                                                     | STUART B., ET AL., "P1498 INHIBITION OF POLYCOMB REPRESSIVE COMPLEX 2 THROUGH EED INDUCES FETAL HEMOGLOBIN IN HEALTHY AND SICKLE CELL DISEASE MODELS", HemaSphere, 2022, 6:S3, 2628<br>Whole Document                                                                            | 1-15                          |
| A                                                     | BRANDOW A. M. and LIEM R. I, "Advances in the diagnosis and treatment of sickle cell disease", Journal of Hematology & Oncology, 2022, 15:20, 1-13, DOI: 10.1186/s13045-022-01237-z<br>Whole Document                                                                            | 1-15                          |
|                                                       |                                                                                                                                                                                                                                                                                  |                               |

Form PCT/ISA/210 (fifth sheet) (July 2019)

|                                                                                                                                                                                                                                                                       |                         |                                                           |                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------------------------------------------------|-------------------------|
| <b>INTERNATIONAL SEARCH REPORT</b><br>Information on patent family members                                                                                                                                                                                            |                         | International application No.<br><b>PCT/US2024/043672</b> |                         |
| This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information. |                         |                                                           |                         |
| <b>Patent Document/s Cited in Search Report</b>                                                                                                                                                                                                                       |                         | <b>Patent Family Member/s</b>                             |                         |
| <b>Publication Number</b>                                                                                                                                                                                                                                             | <b>Publication Date</b> | <b>Publication Number</b>                                 | <b>Publication Date</b> |
| WO 2023049723 A1                                                                                                                                                                                                                                                      | 30 March 2023           | WO 2023049723 A1                                          | 30 Mar 2023             |
| WO 2023049724 A1                                                                                                                                                                                                                                                      | 30 March 2023           | WO 2023049724 A1                                          | 30 Mar 2023             |
|                                                                                                                                                                                                                                                                       |                         | EP 4404932 A1                                             | 31 Jul 2024             |
| <b>End of Annex</b>                                                                                                                                                                                                                                                   |                         |                                                           |                         |
| <div>Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.<br/>Form PCT/ISA/210 (Family Annex)(July 2019)</div>                                                                                   |                         |                                                           |                         |