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(54) Title: HETEROARYL COMPOUNDS AND PHARMACEUTICAL APPLICATIONS THEREOF

(57) Abstract: The present invention provides herein is a heteroaryl compound or a stereoisomer, a geometric isomer, a tautomer, a racemate, an N-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, as well as a pharmaceutical composition containing the compound disclosed herein. The present invention also provides herein is use of the compound or the pharmaceutical composition thereof disclosed herein in the manufacture of a medicine for treating autoimmune diseases or proliferative diseases.



HETEROARYL COMPOUNDS AND PHARMACEUTICAL APPLICATIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to Chinese Patent Application Serial No. 201410315529.2, filed with the State Intellectual Property Office of China on July 02, 2014; which is hereby incorporated by reference in its entirety and for all purposes as if specifically and fully set forth herein.

FIELD OF THE INVENTION

[0002] The present invention pertains to the field of medicine, specifically relates to a class of heteroaryl compounds and a pharmaceutical composition containing the compound disclosed herein having inhibitory activities for protein kinases. This invention also relates to uses of the compound and pharmaceutical composition containing the compound disclosed herein in medicine.

BACKGROUND OF THE INVENTION

[0003] Protein kinases consisting of a series of structurally related enzymes are responsible for the control of a variety of signal transduction processes within the cell. In general, protein kinases mediate intracellular signaling by affecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor involved in a signaling pathway. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases.

[0004] The Janus kinases (JAK) are a family of tyrosine kinases consisting of JAK1, JAK2, JAK3 and TYK2. The JAKs play a critical role in cytokine signaling. JAK1, JAK2 and TYK2 can inhibit the expression of various genes, but JAK3 plays a role just in granulocyte. Typically, cytokine receptors exist in a form of heterodimer. Therefore, generally not one kind of JAK kinase reacts with cytokine receptor.

[0005] Each of the JAKs is preferentially associated with the intracytoplasmic portion of

discrete cytokine receptors (Annu. Rev. Immunol. 16 (1998), pp. 293-322, herein incorporated by reference). The JAKs are activated following ligand binding and initiate signaling by phosphorylating cytokine receptors that, per se, are devoid of intrinsic kinase activity. This phosphorylation creates docking sites on the receptors for other molecules known as STAT proteins (signal transducers and activators of transcription) and the phosphorylated JAKs bind various STAT proteins. STAT proteins, or STATs, are DNA binding proteins activated by phosphorylation of tyrosine residues, and have function both as signaling molecules and transcription factors and ultimately bind to specific DNA sequences present in the promoters of cytokine-responsive genes (Leonard et al, (2000), J. Allergy Clin. Immunol. 105: 877-888, herein incorporated by reference).

[0006] Genetic and biochemical studies have shown that JAK1 play a role by effecting on IFN α , IFN γ , IL-2, IL-6, and other cytokines receptors, JAK1 knockout mice die due to defects in LIF receptor signaling. Characterization of tissues derived from JAK1 knockout mice demonstrated critical roles for this kinase in the IFN, IL-10, IL-2/IL-4, and IL-6 pathways.

[0007] Biochemical and genetic studies have shown an association between JAK2 and single-chain, IL-3 and interferon γ cytokine receptor families. Consistent with this, JAK2 knockout mice die of anemia. Kinase activating mutations in JAK2 are associated with myeloproliferative disorders in humans, which include polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia and chronic myelomonocytic leukemia.

[0008] JAK3 is associated exclusively with the γ cytokine receptor chain, which is present in the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine receptor complexes. JAK3 is critical for lymphoid cell development and proliferation and mutations in JAK3 result in severe immunodeficiency. XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function. Based on its role in regulating lymphocytes, JAK3 and JAK3-mediated pathways have been targeted for immunosuppressive indications. JAK3 has been implicated in the mediation of many abnormal immune responses such as allergies, asthma, autoimmune diseases such as transplant rejection,

rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis as well as solid and hematologic malignancies such as leukemias and lymphomas.

[0009] JAK3 inhibitors are useful therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

[0010] Non-hematopoietic expression of JAK3 has also been reported, although the functional significance of this has not yet to be clarified (J. Immunol. 168 (2002), pp. 2475-2482, herein incorporated by reference). Because bone marrow transplants for SCID are curative (Blood 103 (2004), pp. 2009-2018, herein incorporated by reference), it seems unlikely that JAK3 has essential non-redundant functions in other tissues or organs. Hence, in contrast with other targets of immunosuppressive drugs, the restricted distribution of JAK3 is appealing. Agents that act on molecular targets with expression limited to the immune system might lead to an optimal efficacy: toxicity ratio. Targeting JAK3 would, therefore, theoretically offer immune suppression where it is needed (*i.e.* on cells actively participating in immune responses) without resulting in any effects outside of these cell populations. Although defective immune responses have been described in various STAT^{-/-} strains (J. Investig. Med. 44 (1996), pp. 304-311; Curr. Opin. Cell Biol. 9 (1997), pp. 233-239, herein incorporated by reference), the ubiquitous distribution of STATs and the fact that those molecules lack enzymatic activity that could be targeted with small-molecule inhibitors has contributed to their non-selection as key targets for immunosuppression.

[0011] TYK2 associates with the type I interferon, IL-6, IL-10, IL-12 and IL-23 cytokine receptor complexes. Consistent with this, primary cells derived from a TYK2 deficient human are defective in type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling.

[0012] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0013] B-cell signaling through the B-cell receptor (BCR) can lead to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The

magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause dysregulated B-cell activation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, compromised T-cell-independent immune responses and marked attenuation of the sustained calcium signal upon BCR stimulation.

[0014] Evidence for the role of Btk in allergic disorders and/or autoimmune disease and/or inflammatory disease has been established in Btk-deficient mouse models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression.

[0015] A large body of evidence supports the role of B-cells and the human immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, and asthma. In addition, Btk has been reported to play a role in apoptosis; thus, inhibition of Btk activity can be useful for cancer, as well as the treatment of B-cell lymphoma and leukemia.

[0016] An epidermal growth factor receptor (EGFR) as a kind of receptor tyrosine kinase is a multifunction glycoprotein widely distributed on the cell membranes of the tissues of the human body, and is an oncogene homolog of avian erythroblastic leukemia viral (v-erb-b). Human EGFR/HER1/ErbB-1 and HER2 (human epidermal growth factor receptor-2)/ErbB-2/Trk/p185, HER3/ErbB-3, HER4/ErbB-4 and the like are grouped into the HER/ErbB family, and belong to protein tyrosine kinases (PTKs). They are each a single polypeptide chain, and respectively encoded by genes located on different chromosomes. EGFR and the like are expressed in the epithelia-derived tumors such as squamous cell carcinoma of head and neck, mammary cancer, rectal cancer, ovarian cancer, prostate carcinoma, non-small cell lung cancer, and the like, their expressions are related to cancer cell proliferation and metastasis and the like.

[0017] At present, acquired drug resistance has become a worldwide difficult problem in the drug therapy of cancer, and is also a reason of ineffective treatment of cancer. EGFR-TKI drug (erlotinib or gefitinib) is an important targeted drug in the treatment of advanced non-small cell

lung cancer, but occurrence of acquired drug resistance restricts its clinical application. Therefore, the formation mechanism of acquired drug resistance needs to be energetically explored. The mechanism of acquired drug resistance to EGFR-TKI drug remains unclear presently. The researches have shown that acquired drug resistance to EGFR-TKI drug may mainly relate to both mechanisms: secondary exon T790M mutation and secondary MET augmentation.

[0018] A secondary EGFR mutation, T790M, is a point mutant in exon 20, and is thought to be one of recognized drug resistance mechanisms. T790M is located in the entrance of ATP-binding pocket with EGFR, the size of the side chain thereof directly affects the combining capacity of EGFR with ATP. T790M mutation blocks the binding of EGFR inhibitor to ATP-binding point in space, and increases the affinity of EGFR for ATP, which leads to the cells resistant to EGFR inhibitor. At first, T790M was found just in the NSCLC patient sample with treatment failure, but thereafter, also in the NSCLC patient sample without treatment, so it is considered that this mutation also exists in tumor tissue of the patient without TKI treatment, but just in a few clone cells which were selected out due to their resistances to TKI after treatment.

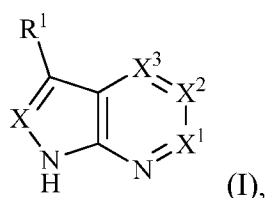
[0019] Therefore, it is need to provide compounds for inhibiting protein kinases to treat diseases such as an autoimmune disease, an inflammatory disease and cancer.

SUMMARY OF THE INVENTION

[0020] The compounds disclosed herein can effectively inhibit activity of protein kinases, these protein kinases include, but are not limited to, Ab1, Akt1, Akt2, Akt3, ALK, Alk5, A-Raf, B-Raf, Brk, BTK, Cdk2, CDK4, CDK5, CDK6, CHK1, C-Raf-1, Csk, EGFR, EphA1, EphA2, EphB2, EphB4, Erk2, Fak, FGFR1, FGFR2, FGFR3, FGFR4, Flt1, Flt3, Flt4, Fms, Frk, Fyn, Gsk3. alpha., Gsk3. beta, HCK, Her2/ErbB2, Her4/ErbB4, IGF1R, IKK. beta, Irak4, Itk, JAK1, JAK2, JAK3, Jnk1, Jnk2, Jnk3, Kdr, Kit, LCK, MAP2K1, MAP2K2, MAP4K4, MAPKAPK2, Met, Mnk1, MLK1, p38, PDGFRA, PDGFRB, PDPK1, Pim1, Pim2, Pim3, PKC. alpha, PKC. beta, PKC. theta, Plk1, Pyk2, Ret, ROCK1, ROCK2, Ron, Src, Stk6, Syk, TEC, Tie2, TrkA, TrkB, Yes and Zap70, as well as mutants thereof. Especially, the compounds disclosed herein can strongly inhibit activity of BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M; In particular, the compounds form complex with JAK3 irreversibly. These compounds will play a potential role in the treatment of an autoimmune disease and/or inflammatory disease and/or cancer.

[0021] The compounds disclosed herein have inhibitory activities against protein kinases. What's more satisfactory are, the compounds disclosed herein have multiple inhibitory activities, which could inhibit signal responses from BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M. In particular, the compounds and the pharmaceutically acceptable compositions can be effective inhibitors against BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M.

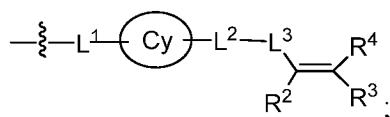
[0022] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

X is N or CR^x;

each of X¹ and X² is independently N, CR⁰ or CR^{x1} with the proviso of at least one of X¹ and X² is CR^{x1};



each R^{x1} is independently

X³ is CR or N, wherein R is H, deuterium, F, Cl, Br, I, CN, OH, NO₂, COOH, alkyl, alkoxy, alkenyl or alkynyl;

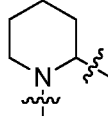
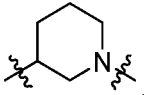
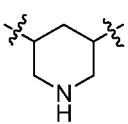
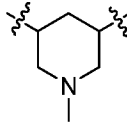
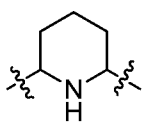
each R^x and R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

R¹ is cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, fused bicycyl, fused heterobicycyl, spiro bicycyl or spiro heterobicycyl;

each L¹ is independently -O-, -N(R^{1a})-, -S(=O)_p-, -C(=O)-, -C(=O)-N(R^{1a})-, -S(=O)_p-N(R^{1a})-, -(CR^mR^w)_g- or -(CR^mR^w)_n-CR^{1a}=CR^{1a}-(CR^mR^w)_n;

each L² is independently a bond, -O-, -N(R^{1a})-, -CH₂-N(R^{1a})-, -CH(CH₃)-N(R^{1a})-, -C(CH₃)₂-N(R^{1a})-, -C(=O)-N(R^{1a})- or -S(=O)_p-N(R^{1a})-;

each L³ is independently -C(=O)- or -S(=O)₂-;

each Cy is independently cycloalkyl, cycloalkenyl, C₂₋₄ heterocyclyl, , , , , , C₆₋₁₀ heterocyclyl, aryl, heteroaryl, fused bicyclyl, fused heterobicyclyl, spiro bicyclyl or spiro heterobicyclyl;

each R² is independently H, deuterium, F, Cl, Br, I, CN, alkyl, alkenyl or alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, fused bicyclyl, fused bicyclylalkyl, fused heterobicyclyl, fused heterobicyclylalkyl, spiro bicyclyl, spiro bicyclylalkyl, spiro heterobicyclyl or spiro heterobicyclylalkyl;

each n is independently 0, 1, 2, 3, or 4;

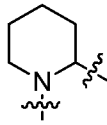
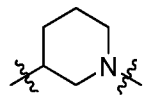
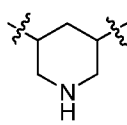
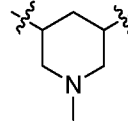
g is 1, 2, 3, or 4;

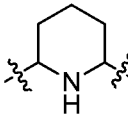
each p is independently 0, 1, or 2;

each R^{1a} is independently H, deuterium, alkyl, alkenyl or alkynyl;

each R^m and R^w is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclylalkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

wherein each alkyl, haloalkyl, cyano-substituted alkyl, alkoxy, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, carbocyclyl,

heterocycle, heterocyclyl, C₂₋₄ heterocyclyl, , , , ,

, C₆₋₁₀ heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, fused bicyclyl, fused bicyclylalkyl, fused heterobicyclyl, fused heterobicyclylalkyl, spiro bicyclyl, spiro bicyclylalkyl, spiro heterobicyclyl, spiro heterobicyclylalkyl, -N(R^{1a})-, -C(=O)-N(R^{1a})-, -S(=O)_p-N(R^{1a})-, -(CR^mR^w)_g- or -(CR^mR^w)_n-CR^{1a}=CR^{1a}-(CR^mR^w)_n- described in R, R^x, R^{x1}, R⁰, R¹, L¹, L², Cy, R², R³, R⁴, R^{1a}, R^m and/or R^w is optionally and independently

substituted with one or more R⁵;

wherein each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aryloxy, heteroaryloxy, heterocycloxy, arylalkoxy, heteroarylalkoxy, heterocyclalkoxy, alkylamino, alkylaminoalkyl, alkylaminoalkylamino, cycloalkylamino, alkylthio, haloalkyl, haloalkoxy, hydroxy-substituted alkyl, hydroxy-substituted alkylamino, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted alkylamino, amino-substituted alkyl, alkylacyl, heteroalkyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heterocyclalkylamino, heterocyclacyl, aryl, arylalkyl, arylamino, heteroaryl, heteroarylamino, NH₂-C(=O)-, alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-alkyl-, alkyl-N(R⁶)-S(=O)₂-alkyl-, alkyl-S(=O)₂-N(R⁶)-alkyl-, aryl-alkyl-N(R⁶)-C(=O)-, alkyl-C(=O)-N(R⁶)-, alkyl-N(R⁶)-C(=O)-alkyl-N(R⁶)-, alkyl-S(=O)₂-, alkyl-S(=O)₂-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-alkyl-;

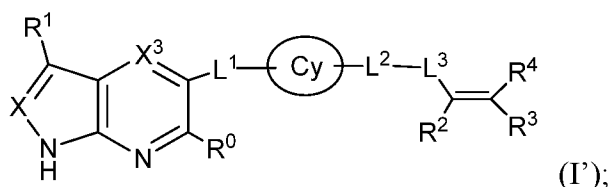
each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, alkyl, alkenyl or alkynyl;

each R¹¹ and R¹² is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocycl or heterocyclalkyl; or R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each R⁵ is optionally and independently substituted with one or more substituents selected from H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkyl-C(=O)-, cyano-substituted alkyl-C(=O)-, alkylamino, NH₂-S(=O)₂-, alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-alkyl-, alkyl-N(R¹³)-S(=O)₂-alkyl-, alkyl-S(=O)₂-N(R¹³)-alkyl-, haloalkyl, hydroxy-substituted alkyl, cyano-substituted alkyl, cycloalkyl, heterocycl, aryl, aryloxy or arylalkoxy; and

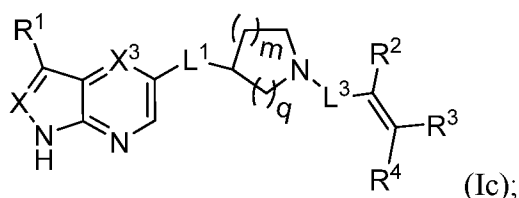
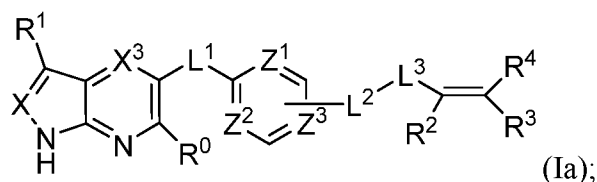
each R¹³ is independently H, deuterium, alkyl, alkenyl or alkynyl.

[0023] In some embodiments, provided herein is a compound having Formula (I') or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein each of X, X³, R¹, R⁰, L¹, Cy, L², L³, R², R³ and R⁴ is as defined herein.

[0024] In some embodiments, provided herein is a compound having Formula (Ia) or Formula (Ic) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein each of X, X³, R¹, R⁰, L¹, L², L³, R², R³ and R⁴ is as defined herein;

each of Z¹, Z² and Z³ is independently N or CR^y;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkylamino or halo-C₁₋₆-alkyl;

m is 0, 1 or 2; and

q is 1, 2 or 3.

[0025] In some embodiments, each R^x and R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl.

[0026] In other embodiments, each R^x and R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₅ heteroaryl.

[0027] In other embodiments, each R^x and R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, phenyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, triazolyl, tetrazolyl, oxazolyl, pyridyl, pyrimidinyl or pyrazinyl.

[0028] In some embodiments, R¹ is C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀

aryl, C₁₋₉ heteroaryl, C₅₋₁₂ fused bicycyl, C₅₋₁₂ fused heterobicycyl, C₅₋₁₂ spiro bicycyl or C₅₋₁₂ spiro heterobicycyl; and R¹ is optionally substituted with one or more R⁵.

[0029] In other embodiments, R¹ is C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₂₋₆ heterocycyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl; and R¹ is optionally substituted with one or more R⁵.

[0030] In other embodiments, R¹ is pyrrolidinyl, piperazinyl, piperidyl, morpholinyl, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydropyridyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexdienyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolinyl, pteridinyl, naphthyridinyl, benzotriazolyl, benzofuranyl, isobenzofuranyl, furo[3,2-*c*]pyridyl, furo[3,2-*b*]pyridyl, furo[2,3-*b*]pyridyl, furo[2,3-*c*]pyridyl, benzothienyl, benzothiazolyl, 1,2-benzoisothiazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyridyl, 3,4-dihydro-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridyl, thieno[2,3-*c*]pyridyl, thieno[2,3-*b*]pyridyl, 1,4-benzodioxinyl, pyridin-2(1*H*)-one-3-yl, pyridin-2(1*H*)-one-4-yl, pyridin-2(1*H*)-one-5-yl, pyridin-2(1*H*)-one-6-yl, pyrazin-2(1*H*)-one-3-yl, pyrazin-2(1*H*)-one-5-yl or pyrazin-2(1*H*)-one-6-yl; R¹ is optionally substituted with one or more R⁵.

[0031] In some embodiments, each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkylamino-C₁₋₆-alkyl, C₁₋₆ alkylthio-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocycyl, C₂₋₁₀ heterocycyl-C₁₋₆-alkyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₅₋₁₂ fused bicycyl, C₅₋₁₂ fused bicycyl-C₁₋₆-alkyl, C₅₋₁₂ fused heterobicycyl, C₅₋₁₂ fused heterobicycyl-C₁₋₆-alkyl, C₅₋₁₂ spiro bicycyl, C₅₋₁₂ spiro

bicycyl-C₁₋₆-alkyl, C₅₋₁₂ spiro heterobicycyl or C₅₋₁₂ spiro heterobicycyl-C₁₋₆-alkyl;

each n is independently 0, 1, 2, 3, or 4; and

each R^m and R^w is independently H, deuterium, C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[0032] In other embodiments, each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₃ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₃ alkylthio-C₁₋₃-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₃-alkyl, C₂₋₈ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₃-alkyl, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-C₁₋₃-alkyl, C₅₋₁₂ fused bicycyl, C₅₋₁₂ fused bicycyl-C₁₋₃-alkyl, C₅₋₁₂ fused heterobicycyl, C₅₋₁₂ fused heterobicycyl-C₁₋₃-alkyl, C₅₋₁₂ spiro bicycyl, C₅₋₁₂ spiro bicycyl-C₁₋₃-alkyl, C₅₋₁₂ spiro heterobicycyl or C₅₋₁₂ spiro heterobicycyl-C₁₋₃-alkyl;

each n is independently 0, 1, 2, 3, or 4; and

each R^m and R^w is independently H, deuterium, C₁₋₅ alkyl, cyano-substituted C₁₋₄ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[0033] In other embodiments, each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₃ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₃ alkylthio-C₁₋₃-alkyl, C₂₋₆ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl, C₅₋₁₂ fused bicycyl, C₅₋₁₂ fused bicycyl-C₁₋₃-alkyl, C₅₋₁₂ fused heterobicycyl, C₅₋₁₂ fused heterobicycyl-C₁₋₃-alkyl, C₅₋₁₂ spiro bicycyl, C₅₋₁₂ spiro bicycyl-C₁₋₃-alkyl, C₅₋₁₂ spiro heterobicycyl or C₅₋₁₂ spiro heterobicycyl-C₁₋₃-alkyl;

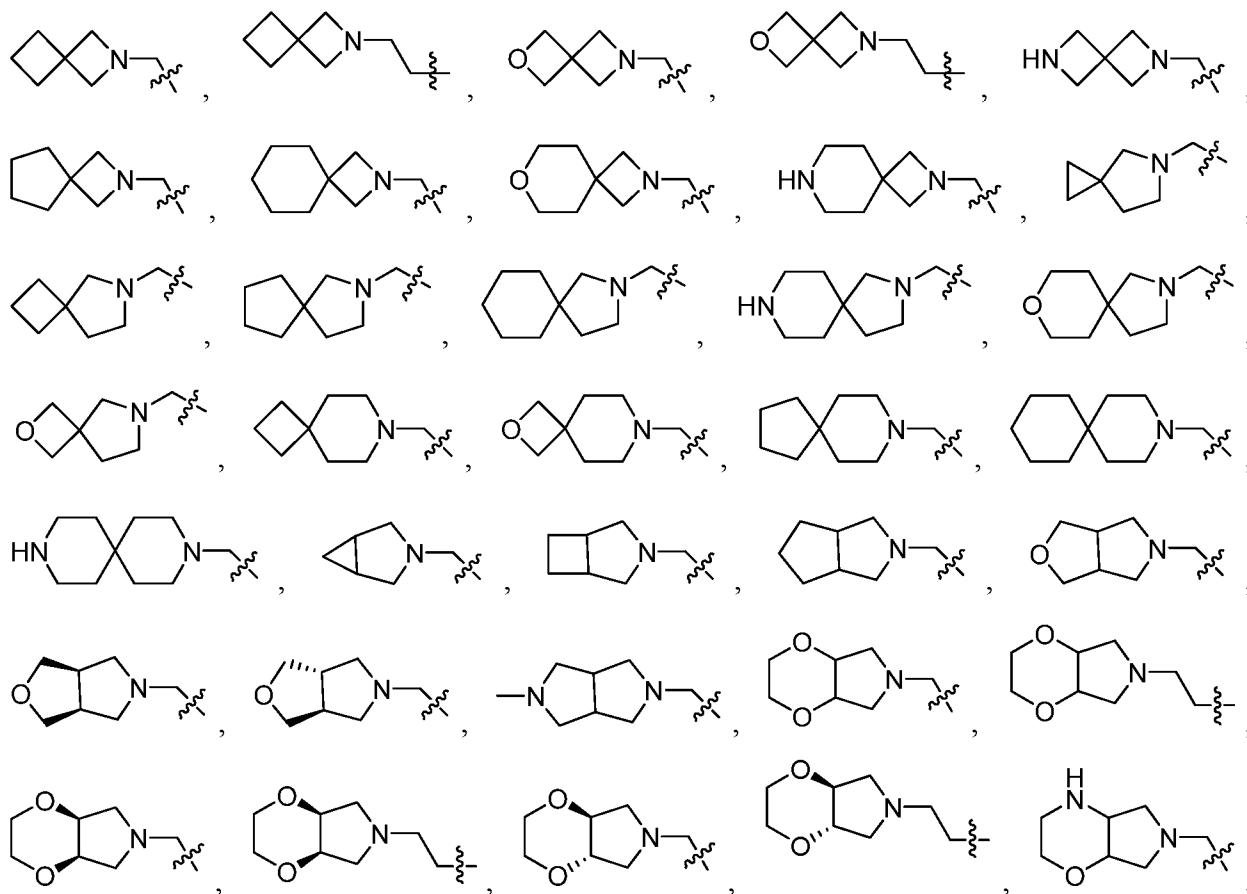
each n is independently 0, 1, 2, 3, or 4; and

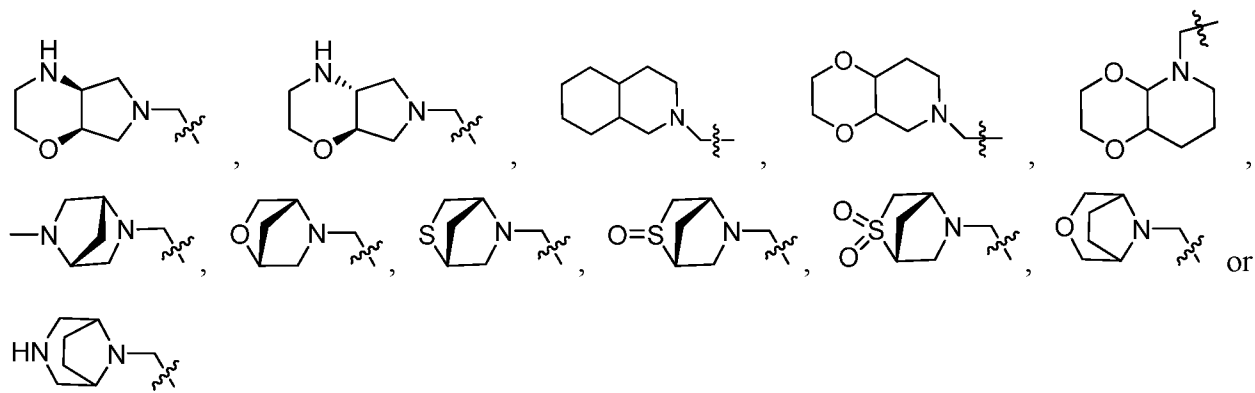
each R^m and R^w is independently H, deuterium, C₁₋₄ alkyl, cyano-substituted C₁₋₄ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀

heterocycl-yl-C₁₋₃-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

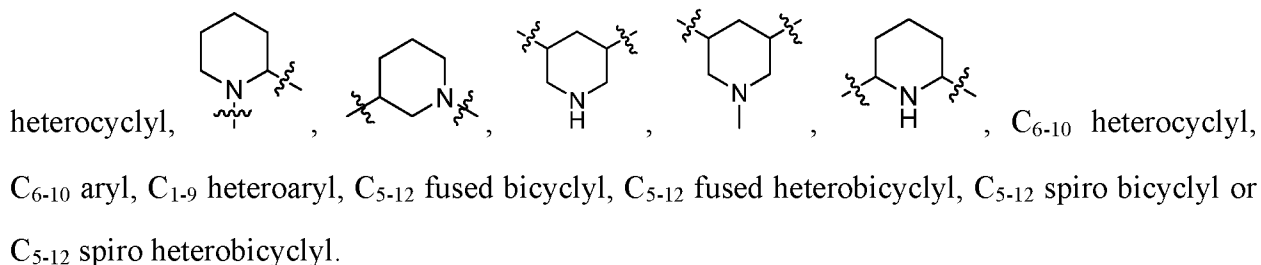
[0034] In other embodiments, each R² is independently H, deuterium, F, Cl, Br, I, CN, methyl, ethyl, propyl or isopropyl; and

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, -CH₂-NHMe, -CH₂-NMe₂, -(CH₂)₂-NMe₂, -(CH₂)₃-NMe₂, -CH₂-NEt, -CH₂-NEt₂, -(CH₂)₂-NEt₂, -(CH₂)₃-NEt₂, oxacyclobutyl, azacyclobutyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, piperazinyl, piperidyl, morpholinylmethyl, thiomorpholinylmethyl, 1-oxidothiomorpholinylmethyl, 1,1-dioxidothiomorpholinylmethyl, morpholinylethyl, thiomorpholinylethyl, 1-oxidothiomorpholinylethyl, 1,1-dioxidothiomorpholinylethyl, morpholinylpropyl, thiomorpholinylpropyl, 1-oxidothiomorpholinylpropyl, 1,1-dioxidothiomorpholinylpropyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, piperidylmethyl, piperidylethyl, piperidylpropyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydropyranylpropyl, pyrrolidinylmethyl, pyrrolidinylethyl or pyrrolidinylpropyl; or each R³ and R⁴ is independently

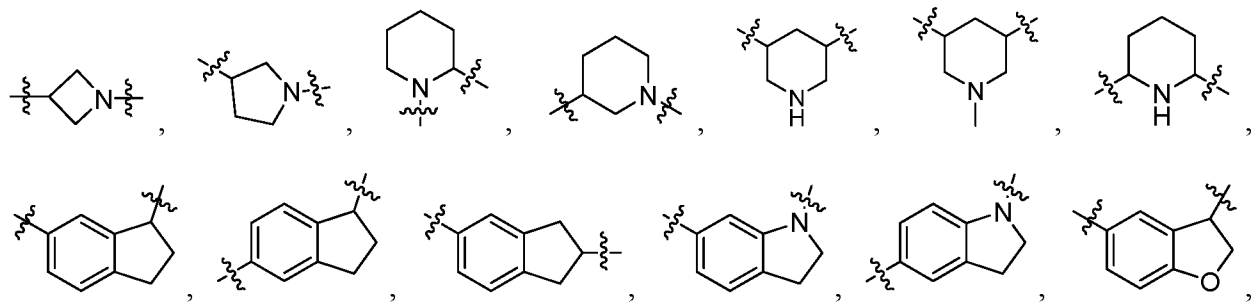


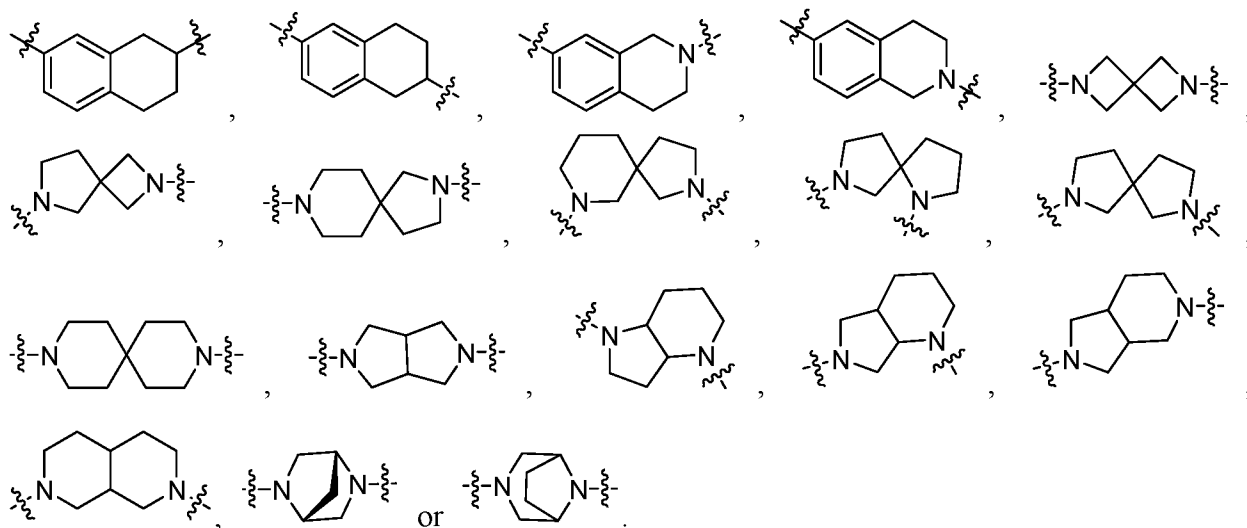


[0035] In some embodiments, each Cy is independently C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₂₋₄



[0036] In other embodiments, each Cy is independently cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolinyl, pteridinyl, naphthyridinyl, benzotriazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzothiazolyl, 1,2-benzisothiazolyl, benzoxazolyl, benzoisoxazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl or [1,2,4]triazolo[1,5-*a*]pyridyl; or Cy is one of the following groups:





[0037] In some embodiments, each R^5 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , $COOH$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, C_{1-6} alkoxy- C_{1-6} -alkoxy, C_{1-6} alkoxy- C_{1-6} -alkylamino, C_{6-10} aryloxy, C_{1-9} heteroaryloxy, C_{2-10} heterocycloxy, C_{6-10} aryl- C_{1-6} -alkoxy, C_{1-9} heteroaryl- C_{1-6} -alkoxy, C_{2-10} heterocyclyl- C_{1-6} -alkoxy, C_{1-6} alkylamino, C_{1-6} alkylamino- C_{1-6} -alkyl, C_{1-6} alkylamino- C_{1-6} -alkylamino, C_{3-8} cycloalkylamino, C_{1-6} alkylthio, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, hydroxy-substituted C_{1-6} alkyl, hydroxy-substituted C_{1-6} alkylamino, cyano-substituted C_{1-6} alkyl, cyano-substituted C_{1-6} alkoxy, cyano-substituted C_{1-6} alkylamino, amino-substituted C_{1-6} alkyl, C_{1-6} alkylacyl, C_{1-8} heteroalkyl, C_{3-6} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} cycloalkyl- C_{1-6} -alkyl, C_{2-10} heterocyclyl, C_{2-10} heterocyclyl- C_{1-6} -alkyl, C_{2-10} heterocyclyl- C_{1-6} -alkylamino, C_{2-10} heterocyclylacyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-6} -alkyl, C_{6-10} arylamino, C_{1-9} heteroaryl, C_{1-9} heteroarylamino, $NH_2-C(=O)-$, C_{1-6} alkyl- $N(R^6)-C(=O)-$, $NH_2-S(=O)_2-$, C_{1-6} alkyl- $N(R^6)-S(=O)_2-$, $NH_2-S(=O)_2-C_{1-6}$ alkyl-, C_{1-6} alkyl- $N(R^6)-S(=O)_2-C_{1-6}$ -alkyl-, C_{1-6} alkyl- $S(=O)_2-N(R^6)-C_{1-6}$ -alkyl-, C_{6-10} aryl- C_{1-6} -alkyl- $N(R^6)-C(=O)-$, C_{1-6} alkyl- $C(=O)-N(R^6)-$, C_{1-6} alkyl- $N(R^6)-C(=O)-C_{1-6}$ -alkyl- $N(R^6)-$, C_{1-6} alkyl- $S(=O)_2-$, C_{1-6} alkyl- $S(=O)_2-C_{1-6}$ -alkyl-, $-(CH_2)_n-N(R^6)-(CH_2)_n-S(=O)_p-R^7$, $-(CH_2)_n-N(R^6)-(CH_2)_n-N(R^6)-S(=O)_p-R^7$, $-(CR^8R^9)_n-COOR^{10}$ or $R^{11}R^{12}N-C(=O)-C_{1-6}$ alkyl-;

each n is independently 0, 1, 2, 3, or 4;

each p is independently 0, 1, or 2;

each R^6 , R^7 , R^8 , R^9 and R^{10} is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

each R^{11} and R^{12} is independently H, deuterium, C_{1-6} alkyl, cyano-substituted C_{1-6} alkyl,

halo-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl; or R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each R⁵ is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkyl-C(=O)-, cyano-substituted C₁₋₆ alkyl-C(=O)-, C₁₋₆ alkylamino, NH₂-S(=O)₂-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-N(R¹³)-C₁₋₆ alkyl-, halo-C₁₋₆-alkyl, hydroxy-substituted C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy or C₆₋₁₀ aryl-C₁₋₆-alkoxy; and

each R¹³ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl.

[0038] In other embodiments, each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy-C₁₋₄-alkyl, C₁₋₄ alkoxy-C₁₋₄-alkoxy, C₁₋₃ alkoxy-C₁₋₄-alkylamino, C₆₋₁₀ aryloxy, C₁₋₉ heteroaryloxy, C₂₋₁₀ heterocycloxy, C₆₋₁₀ aryl-C₁₋₃-alkoxy, C₁₋₉ heteroaryl-C₁₋₃-alkoxy, C₂₋₁₀ heterocyclyl-C₁₋₆-alkoxy, C₁₋₄ alkylamino, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₄ alkylamino-C₁₋₄-alkylamino, C₃₋₆ cycloalkylamino, C₁₋₄ alkylthio, halo-C₁₋₄-alkyl, halo-C₁₋₄-alkoxy, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkylamino, cyano-substituted C₁₋₄ alkyl, cyano-substituted C₁₋₄ alkoxy, cyano-substituted C₁₋₄ alkylamino, amino-substituted C₁₋₄ alkyl, C₁₋₄ alkylacyl, C₁₋₈ heteroalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₄-alkyl, C₂₋₆ heterocyclyl-C₁₋₄-alkylamino, C₂₋₁₀ heterocyclylacyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₆₋₁₀ arylamino, C₁₋₉ heteroaryl, C₁₋₉ heteroarylamino, NH₂-C(=O)-, C₁₋₄ alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-S(=O)₂-N(R⁶)-C₁₋₃-alkyl-, C₆₋₁₀ aryl-C₁₋₃ alkyl-N(R⁶)-C(=O)-, C₁₋₄ alkyl-C(=O)-N(R⁶)-, C₁₋₃ alkyl-N(R⁶)-C(=O)-C₁₋₆ alkyl-N(R⁶)-, C₁₋₄ alkyl-S(=O)₂-, C₁₋₃ alkyl-S(=O)₂-C₁₋₄-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-C₁₋₃-alkyl-;

each n is independently 0, 1, 2, 3, or 4;

each p is independently 0, 1, or 2;

each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl;

each R^{11} and R^{12} is independently H, deuterium, C_{1-3} alkyl, cyano-substituted C_{1-3} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-3} -alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, C_{1-5} heteroaryl, C_{2-6} heterocyclyl or C_{2-6} heterocyclyl- C_{1-3} -alkyl; or R^{11} and R^{12} , together with the N atom to which they are attached, form a 3- to 8-membered heterocycle;

each R^5 is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-4} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxy- C_{1-4} -alkyl, C_{1-3} alkyl-C(=O)-, cyano-substituted C_{1-3} alkyl-C(=O)-, C_{1-3} alkylamino, $NH_2-S(=O)_2-$, C_{1-3} alkyl-N(R^{13})- $S(=O)_2-$, $NH_2-S(=O)_2-C_{1-3}$ -alkyl-, C_{1-3} alkyl-N(R^{13})- $S(=O)_2-C_{1-3}$ -alkyl-, C_{1-3} alkyl-S(=O)₂-N(R^{13})- C_{1-3} -alkyl-, halo- C_{1-3} -alkyl, hydroxy-substituted C_{1-3} alkyl, cyano-substituted C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{6-10} aryloxy or C_{6-10} aryl- C_{1-3} -alkoxy; and

each R^{13} is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl.

[0039] In other embodiments, X is N or CR^x ;

X^3 is CR or N;

each of Z^1 , Z^2 and Z^3 is independently N or CR^y ;

wherein R is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , COOH, C_{1-3} alkyl or C_{1-3} alkoxy;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylamino- C_{1-4} -alkylamino or halo- C_{1-3} -alkyl;

L^1 is -O-, -N(R^{1a})-, -S(=O)_p-, -C(=O)-, -C(=O)-NH- or -S(=O)_p-NH-;

L^2 is a bond, -O-, -N(R^{1a})-, -CH₂-N(R^{1a})-, -CH(CH₃)-N(R^{1a})-, -C(CH₃)₂-N(R^{1a})-, -C(=O)-NH- or -S(=O)_p-NH-;

L^3 is -C(=O)- or -S(=O)₂-;

m is 0, 1 or 2;

q is 1, 2 or 3;

each p is independently 0, 1, or 2; and

each R^{1a} is independently H, deuterium, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[0040] In other embodiments, X is N or CH;

X^3 is CH or N;

each of Z^1 , Z^2 and Z^3 is independently N or CR^y ;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, methyl,

ethyl, propyl, $-\text{CF}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CCl}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, $-\text{CH}_2\text{CCl}_3$, methoxy, ethoxy, propoxy, isopropoxy, $-\text{NH}-\text{CH}_3$, $-\text{NH}-\text{CH}_2-\text{CH}_3$, $-\text{NH}-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{N}(\text{CH}_3)-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{NH}-(\text{CH}_2)_2-\text{NH}-\text{CH}_3$ or $-\text{N}(\text{CH}_3)-(\text{CH}_2)_2-\text{N}(\text{CH}_3)_2$;

L^1 is $-\text{O}-$, $-\text{NH}-$, $-\text{S}(=\text{O})_p-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})-\text{NH}-$ or $-\text{S}(=\text{O})_p-\text{NH}-$;

L^2 is a bond, $-\text{O}-$, $-\text{NH}-$, $-\text{CH}_2-\text{NH}-$, $-\text{CH}(\text{CH}_3)-\text{NH}-$ or $-\text{C}(\text{CH}_3)_2-\text{NH}-$;

L^3 is $-\text{C}(=\text{O})-$ or $-\text{S}(=\text{O})_2-$;

m is 0, 1 or 2; and

q is 1, 2 or 3; and each p is independently 0, 1, or 2.

[0041] In other aspect, provided herein is a pharmaceutical composition comprising a compound disclosed herein or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof.

[0042] In some embodiments, the pharmaceutical composition further comprises at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants and vehicles.

[0043] In some embodiments, the pharmaceutical composition disclosed herein further comprises an additional therapeutic agent selected from a chemotherapeutic agent or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, or an agent for treating autoimmune disease.

[0044] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing or treating an autoimmune disease or a proliferative disease in a patient, or lessening the severity thereof.

[0045] In other aspect, provided herein is a method for preventing, managing, treating or lessening an autoimmune disease or a proliferative disease in a patient comprising administering to the patient in need of such treatment a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein.

[0046] In other aspect, provided herein is the compound or the pharmaceutical composition disclosed herein for use in preventing, managing, treating or lessening an autoimmune disease or a proliferative disease in a patient.

[0047] In some embodiments, the autoimmune disease disclosed herein is lupus, multiple

sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, psoriasis, type I diabetes, complication from organ transplantation, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorder, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia or lymphoma.

[0048] In some embodiments, the proliferative disease is metastatic carcinoma, colon cancer, gastric adenocarcinoma, bladder carcinoma, breast carcinoma, renal carcinoma, liver cancer, lung cancer, thyroid cancer, head and neck cancer, prostatic cancer, pancreatic cancer, CNS (central nervous system) cancer, spongiblastoma, myeloproliferative diseases, or atherosclerosis or pulmonary fibrosis.

[0049] In other aspect, provided herein is use of the compound or the pharmaceutical composition containing the compound disclosed herein in the manufacture of a medicament for inhibiting or regulating the activities of protein kinases in a biological sample.

[0050] In other aspect, provided herein is a method for inhibiting or regulating the activity of protein kinase in a biological sample comprising contacting the compound or the pharmaceutical composition disclosed herein to the biological sample.

[0051] In other aspect, provided herein is the compound or the pharmaceutical composition disclosed herein for use inhibiting or regulating the activity of protein kinase in a biological sample.

[0052] In some embodiments, the protein kinase comprises BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M.

[0053] In other aspect, provided herein is a compound for preparing the compound of Formula (I), (I'), (Ia) or (Ic).

[0054] In other aspect, provided herein is a method of preparing, separating or purifying the compound of Formula (I), (I'), (Ia) or (Ic).

[0055] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0056] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. The invention is intended

to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described herein. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0057] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination.

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0059] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry” by Michael B. Smith and Jerry March, John Wiley & Sons, New York: 2007, the entire contents of which are hereby incorporated by reference.

[0060] The grammatical articles “a”, “an” and “the”, as used herein, are intended to include “at least one” or “one or more” unless otherwise indicated herein or clearly contradicted by the context. Thus, the articles are used herein to refer to one or more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example, “a component” means one or more components, and thus, possibly, more than one component is contemplated and may be employed or used in an implementation of the described embodiments.

[0061] As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain

embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[0062] As used herein, “patient” refers to a human (including adults and children) or other animal. In one embodiment, “patient” refers to a human.

[0063] The term “comprising” is meant to be open ended, including the indicated component but not excluding other elements.

[0064] “Stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include enantiomer, diastereomers, conformer (rotamer), geometric (cis/trans) isomer, atropisomer, *etc.*

[0065] “Chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

[0066] “Enantiomers” refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0067] “Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.* melting points, boiling points, spectral properties or biological activities. Mixture of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

[0068] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed. , McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S. , “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc. , New York, 1994.

[0069] Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes *D* and *L*, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes *d* and *l* or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with (−) or *l* meaning that the compound is levorotatory. A compound prefixed with (+) or *d* is dextrorotatory. A specific stereoisomer is referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[0070] Any asymmetric atom (*e.g.*, carbon or the like) of the compound(s) disclosed herein can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R*, *S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration.

[0071] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration.

[0072] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric isomers, enantiomers, diastereomers, for example, by chromatography and/or fractional crystallization.

[0073] Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by methods known to those skilled in the art, *e.g.*, by separation of the diastereomeric salts thereof. Racemic products can also be resolved by chiral chromatography, *e.g.*, high performance liquid product chromatography (HPLC) using a chiral adsorbent. Preferred enantiomers can also be prepared by asymmetric syntheses. See, for example, Jacques, et al. *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); *Principles of Asymmetric Synthesis* (2nd Ed. Robert E. Gawley, Jeffrey Aubé, Elsevier, Oxford, UK, 2012); Eliel, E. L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed. , Univ. of Notre Dame Press, Notre Dame, IN 1972); *Chiral Separation Techniques: A Practical Approach* (Subramanian, G. Ed. , Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2007).

[0074] The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. If tautomerism could happen (such as in a solvent), the chemical balance between tautomers can be reached. For example, proton

tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. The specific example of keto-enol tautomerisms is hexane-2,4-dione and 4-hydroxyhex-3-en-2-one tautomerism. Another example of tautomerisms is phenol-keto tautomerism. The specific example of phenol-keto tautomerisms is pyridin-4-ol and pyridin-4(1*H*)-one tautomerism. Unless otherwise stated, all tautomers of the present compounds are within the scope disclosed herein.

[0075] As described herein, compounds disclosed herein may optionally be substituted with one or more substituents, such as are illustrated generally below, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted”. In general, the term “substituted” refers to the replacement of one or more hydrogen radicals in a give a structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a give an structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. wherein substituents of compounds disclosed herein include, but are not limited to, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aryloxy, heteroaryloxy, heterocyclyloxy, arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, cycloalkylalkoxy, alkylamino, alkylaminoalkyl, alkylaminoalkylamino, cycloalkylamino, cycloalkylalkylamino, alkylthio, haloalkyl, haloalkoxy, hydroxy-substituted alkyl, hydroxy-substituted alkylamino, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted alkylamino, amino-substituted alkyl, alkylacyl, heteroalkyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylacyl, aryl, arylalkyl, arylamino, heteroaryl, heteroarylalkyl, heteroarylamino, acylamino, sulfonyl, aminosulfonyl, and the like.

[0076] Furthermore, unless otherwise stated, the phrase “each...is independently” is used interchangeably with the phrase “each (of)...and...is independently”. It should be understood broadly that the specific options expressed by the same symbol are independently of each other in different radicals; or the specific options expressed by the same symbol are independently of each other in same radicals. Take R⁶ for example, the R⁶ groups of structure

“alkyl-N(R⁶)-C(=O)-alkyl-N(R⁶)-” and structure “alkyl-N(R⁶)-S(=O)₂-” are independent each other. Meanwhile, the R⁶ groups of the same structure “alkyl-N(R⁶)-C(=O)-alkyl-N(R⁶)-” are independent each other.

[0077] At various places in the present specification, substituents of compounds disclosed herein are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁-C₆ alkyl” or “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

[0078] At various places in the present specification, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. Unless otherwise indicated, any way of written of structure of the linking substituents does not imply the linking orientation of the linking substituents. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl” or “aryl” then it is understood that the “alkyl” or “aryl” represents a linking alkylene group or arylene group, respectively. For example, the group Cy connects to the rest of the molecular through L¹ and L², and it lists aryl or heteroaryl as Cy then it is understood that the “aryl” or “heteroaryl” represents a linking arylene group or heteroarylene group, respectively.

[0079] The term “alkyl” or “alkyl group” refers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 20 carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. Unless otherwise specified, the alkyl group contains 1-20 carbon atoms. In some embodiments, the alkyl group contains 1-12 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In still other embodiments, the alkyl group contains 1-4 carbon atoms. In yet other embodiments, the alkyl group contains 1-3 carbon atoms.

[0080] Some non-limiting examples of the alkyl group include, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), *n*-propyl (*n*-Pr, -CH₂CH₂CH₃), isopropyl (*i*-Pr, -CH(CH₃)₂), *n*-butyl (*n*-Bu, -CH₂CH₂CH₂CH₃), isobutyl (*i*-Bu, -CH₂CH(CH₃)₂), *sec*-butyl (*s*-Bu, -CH(CH₃)CH₂CH₃), *tert*-butyl (*t*-Bu, -C(CH₃)₃), *n*-pentyl (-CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), *n*-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl

(-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), *n*-heptyl and *n*-octyl, *etc.*

[0081] The term “alkylene” refers to a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms. Unless otherwise specified, the alkylene group contains 1-12 carbon atoms. In some embodiments, the alkylene group contains 1-6 carbon atoms. In other embodiments, the alkylene group contains 1-4 carbon atoms. In still other embodiments, the alkylene group contains 1-3 carbon atoms. In yet other embodiments, the alkylene group contains 1-2 carbon atoms. Such examples include methylene (-CH₂-), ethylene (-CH₂CH₂-), isopropylene (-CH(CH₃)CH₂-), and the like. For alkylene, no orientation of the linking is implied by the direction in which the formula of the linking is written. For example, isopropylene represents both -CH(CH₃)CH₂- and -CH₂CH(CH₃)-

[0082] The term “alkenyl” refers to linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp² double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having “*cis*” and “*trans*” orientations, or alternatively, “*E*” and “*Z*” orientations. In some embodiments, the alkenyl contains 2 to 8 carbon atoms. In other embodiments, the alkenyl contains 2 to 6 carbon atoms. In still other embodiments, the alkenyl contains 2 to 4 carbon atoms. Some non-limiting examples of the alkenyl group include ethenyl or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), propenyl (CH₃-CH=CH-), and the like.

[0083] The term “alkynyl” refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted with one or more substituents described herein. In some embodiments, the alkynyl contains 2 to 8 carbon atoms. In other embodiments, the alkynyl contains 2 to 6 carbon atoms. In still other embodiments, the alkynyl contains 2 to 4 carbon atoms. Some non-limiting examples of the alkynyl group include ethynyl (-C≡CH), propargyl (-CH₂C≡CH), propynyl (-C≡C-CH₃), and the like.

[0084] The term “alkoxy” refers to an alkyl group attached to the rest part of the molecule through an oxygen atom, wherein the alkyl group is as defined herein. Unless otherwise specified, the alkoxy group contains 1-12 carbon atoms. In one embodiment, the alkoxy group contains 1-6 carbon atoms. In other embodiment, the alkoxy group contains 1-4 carbon atoms. In still other embodiment, the alkoxy group contains 1-3 carbon atoms. The alkoxy group may be optionally substituted with one or more substituents disclosed herein.

[0085] Some non-limiting examples of the alkoxy group include, but are not limited to, methoxy (MeO, -OCH₃), ethoxy (EtO, -OCH₂CH₃), 1-propoxy (*n*-PrO, *n*-propoxy, -OCH₂CH₂CH₃), 2-propoxy (*i*-PrO, *i*-propoxy, -OCH(CH₃)₂), 1-butoxy (*n*-BuO, *n*-butoxy, -OCH₂CH₂CH₂CH₃), 2-methyl-1-propoxy (*i*-BuO, *i*-butoxy, -OCH₂CH(CH₃)₂), 2-butoxy (*s*-BuO, *s*-butoxy, -OCH(CH₃)CH₂CH₃), 2-methyl-2-propoxy (*t*-BuO, *t*-butoxy, -OC(CH₃)₃), 1-pentoxy (*n*-pentoxy, -OCH₂CH₂CH₂CH₂CH₃), 2-pentoxy (-OCH(CH₃)CH₂CH₂CH₃), 3-pentoxy (-OCH(CH₂CH₃)₂), 2-methyl-2-butoxy (-OC(CH₃)₂CH₂CH₃), 3-methyl-2-butoxy (-OCH(CH₃)CH(CH₃)₂), 3-methyl-1-butoxy (-OCH₂CH₂CH(CH₃)₂), 2-methyl-1-butoxy (-OCH₂CH(CH₃)CH₂CH₃), and the like.

[0086] The term “alkoxyalkyl” refers to an alkyl group substituted with one or more alkoxy groups, wherein the alkyl group and alkoxy group are as defined herein. Some non-limiting examples of such groups include methoxymethyl, methoxyethyl, ethoxyethyl, and the like.

[0087] The term “alkoxyalkoxy” refers to an alkoxy group substituted with one or more alkoxy groups, wherein the alkoxy group is as defined herein. Some non-limiting examples of such groups include methoxymethoxy, methoxyethoxy, methoxypropoxy, ethoxymethoxy, ethoxyethoxy, and the like.

[0088] The terms “haloalkyl”, “haloalkenyl” or “haloalkoxy” refer to alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. Some non-limiting examples of “haloalkyl”, “haloalkenyl” or “haloalkoxy” groups include trifluoromethyl, trifluoromethoxy, -CH₂Cl, -CH₂CF₃, -CH₂CH₂CF₃, and the like.

[0089] The term “cyano-substituted alkyl”, “cyano-substituted alkoxy”, or “cyano-substituted alkylamino” refer to an alkyl group, an alkoxy group, or an alkylamino group, as the case may be, substituted with one or more CN. Some non-limiting examples of such groups include, -CH₂CN, -CH₂CH₂CN, -CH₂CH₂CH₂CN, -C(CH₃)₂CN, -OCH₂CN, -OCH₂CH₂CN, -OCH₂CH₂CH₂CN, -NHCH₂CN, -NHCH₂CH₂CN, -N(CH₃)CH₂CH₂CN, and the like.

[0090] The term “hydroxy-substituted alkyl”, or “hydroxy-substituted alkylamino” refer to an alkyl group or an alkylamino group, as the case may be, substituted with one or more OH. Some non-limiting examples of such groups include, -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂C(CH₃)₂OH, -NHCH₂CH₂OH, -NHCH(OH)CH₂OH, and the like.

[0091] The term “alkylthio” refers to a radical containing a linear or branched-alkyl radical of one to ten carbon atoms, attached to a divalent sulfur atom. Wherein the alkyl group is as defined herein. Some non-limiting examples of the alkylthio group include methylthio (CH₃S-) and ethylthio, *etc.*

[0092] The term “heteroalkyl” refers to a stable linear or branched-chain alkyl, comprising at least one carbon atom and at least one heteroatom selected from N, O, P and S; wherein N, O, P or S can locate in any inner position of the heteroalkyl or the position of connection of the group with the rest of the molecular; the carbon atom of the heteroalkyl group is optionally substituted with oxo to give a C(=O) group. The alkyl group is as defined herein. In some embodiments, the heteroalkyl group is a linear or branched-chain having 1 to 10 atoms (*e.g.*, 1 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, or PO or PO₂). In other embodiments, the heteroalkyl group is a linear or branched-chain having 1 to 8 atoms (*e.g.*, 1 to 7 carbon atoms and 1 to 3 heteroatoms selected from N, O, P and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, or PO or PO₂). In still other embodiments, the heteroalkyl group is a linear or branched-chain having 1 to 6 atoms (*e.g.*, 1 to 5 carbon atoms and 1 to 3 heteroatoms selected from N, O, P and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, or PO or PO₂). In still other embodiments, the heteroalkyl group is a linear or branched-chain having 1 to 4 atoms (*e.g.*, 1 to 3 carbon atoms and 1 to 3 heteroatoms selected from N, O, P and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, or PO or PO₂) or a linear or branched-chain having 1 to 3 atoms (*e.g.*, 1 to 2 carbon atoms and 1 to 2 heteroatoms selected from N, O, P and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, or PO or PO₂). Some non-limiting examples of the heteroalkyl group include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-C=N-OCH₃, -NH-CH₂-CH₃, -NH-CH₂-C(=O)-NH-CH₂-CH₃, -NH-CH(C(CH₃)₃)-C(=O)-NH-CH₂-CH₃, -NH-CH(CH(CH₃)₂)-C(=O)-NH-CH₂-CH₃,

-NH-CH₂-CH₂-CH₃, -NH-CH₂-CH₂-O-CH₃, -O-CH₂-CH₂-O-CH₃, -CH₂-NH-(CH₂)₂-NH-S(=O)₂CH₃, and the like. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as alkylamino, alkoxyalkyl or the like, it will be understood that the terms heteroalkyl and alkylamino or alkoxyalkyl, and the like, are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity.

[0093] The term “carbocyclyl”, “carbocycle” or “carbocyclic ring” refers to a monovalent or multivalent saturated or partially unsaturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic or tricyclic ring system. A carbobicyclyl group includes a spiro carbobicyclyl group or a fused carbobicyclyl group. Suitable carbocyclyl groups include, but are not limited to, cycloalkyl, cycloalkenyl and cycloalkynyl. Further examples of carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclohendecyl, cyclododecyl, benzocyclopentyl, benzocyclohexyl, and the like. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “carbocyclyl” then it is understood that the “carbocyclyl” represents a linking carbocyclylene group.

[0094] The term “cycloalkyl” refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. In one embodiment, the cycloalkyl contains 3 to 12 carbon atoms. In other embodiment, the cycloalkyl contains 3 to 8 carbon atoms. In still other embodiment, the cycloalkyl contains 3 to 6 carbon atoms. The cycloalkyl group may be optionally substituted with one or more substituents disclosed herein. Some examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclohendecyl and cyclododecyl, *etc.* Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “cycloalkyl” then it is understood that the “cycloalkyl” represents a linking cycloalkylene group.

[0095] The term “cycloalkenyl” refers to a monovalent or multivalent, non-aromatic ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system containing at

least one carbon-carbon double bond. In one embodiment, the cycloalkenyl contains 3 to 12 carbon atoms. In other embodiment, the cycloalkenyl contains 3 to 8 carbon atoms. In still other embodiment, the cycloalkenyl contains 3 to 6 carbon atoms. The cycloalkenyl group may be optionally substituted with one or more substituents disclosed herein. Some non-limiting examples include, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cyclooctenyl, cyclononenyl and cyclodecenyl, and the like. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "cycloalkenyl" then it is understood that the "cycloalkenyl" represents a linking cycloalkenylene group.

[0096] The term "cycloalkylalkyl" refers to an alkyl radical substituted with one or more cycloalkyl radicals, wherein the cycloalkyl and alkyl are as defined herein. Some non-limiting examples of the cycloalkylalkyl group include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and the like.

[0097] The term "heterocycle", "heterocyclyl", or "heterocyclic ring" as used interchangeably herein refers to a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring containing 3-12 ring atoms of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and monocyclic, bicyclic or tricyclic ring of which can not contain a aromatic ring. Unless otherwise specified, The heterocyclyl may be carbon or nitrogen linked, and of which a -CH₂- group can optionally be replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to S-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of heterocyclyl include, but are not limited to, oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, piperazinyl, dioxanyl, dithianyl, thioxanyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, tetrahydropyridyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl, 2-piperidinonyl and 3, 5-dioxopiperidinyl. Some non-limited examples of

heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholiny. The heterocyclyl group may be optionally substituted with one or more substituents disclosed herein. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "heterocyclyl" then it is understood that the "heterocyclyl" represents a linking heterocyclylene group.

[0098] In one embodiment, heterocyclyl may be 4-7 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4-7 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 4-7 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 4-7 ring atoms include, but are not limited to, azetidiny, oxetanyl, thietanyl, pyrrolidiny, 2-pyrroliny, 3-pyrroliny, pyrazolidiny, imidazolidiny, imidazolidiny, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidiny, tetrahydropyridyl, morpholiny, thiomorpholiny, piperaziny, dioxanyl, dithianyl, thioxanyl, homopiperaziny, homopiperidiny, oxepanyl and thiepanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidiny, oxo-1,3-thiazolidiny, 2-piperidinonyl and 3,5-dioxopiperidiny. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholiny. The heterocyclyl containing 4-7 ring atoms group may be optionally substituted with one or more substituents disclosed herein.

[0099] In one embodiment, heterocyclyl may be 4-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 4 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 4 ring atoms include azetidiny, oxetanyl and thietanyl. The heterocyclyl group containing 4 ring atoms may be optionally substituted with one or more

substituents disclosed herein.

[00100] In one embodiment, heterocyclyl may be 5-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 5 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 5 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 5 ring atoms include, but are not limited to, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl and dithiolanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidinyl and oxo-1,3-thiazolidinyl. Non-limited example of heterocyclyl wherein the ring sulfur atom is oxidized include sulfolanyl. The heterocyclyl group containing 5 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[00101] In one embodiment, heterocyclyl may be 6-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 6 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 6 ring atoms include, but are not limited to, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl and thioxanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-piperidinonyl and 3, 5-dioxopiperidinyl. Non-limited example of heterocyclyl wherein the ring sulfur atom is oxidized is 1,1-dioxo-thiomorpholinyl. The heterocyclyl group containing 6 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[00102] In other embodiment, heterocyclyl may be 7-12 membered heterocyclyl, which refers to a saturated or partially unsaturated spiro or fused bicycyl ring containing 7-12 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 7-12 ring atoms may be carbon or nitrogen linked,

and a $\text{-CH}_2\text{-}$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 7-12 ring atoms include 2-oxa-5-azabicyclo[2.2.1]hept-5-yl. The heterocyclyl group containing 7-12 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[00103] The term “ C_{x-y} heterocyclyl” refers to a heterocyclyl group containing x to y carbon atoms.

[00104] In some embodiments, the heterocyclyl group refers to C_{2-4} heterocyclyl, wherein the heterocyclyl contains 2 to 4 carbon atoms, such examples include, but are not limited to, azacyclopropyl, azacyclobutyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, morpholinyl, thiomorpholinyl, 1-oxidithiomorpholinyl, 1,1-dioxidithiomorpholinyl or piperazinyl.

[00105] In some embodiments, the heterocyclyl group refers to C_{6-10} heterocyclyl, wherein the heterocyclyl contains 6 to 10 carbon atoms, such examples include, but are not limited to, homopiperidyl.

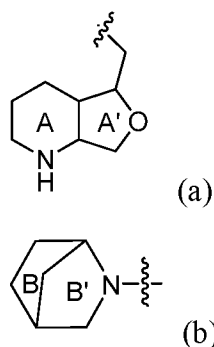
[00106] The term “heterocyclylalkyl” refers to an alkyl group substituted with heterocyclyl, wherein the heterocyclyl group and alkyl group are as defined herein. Some non-limiting examples of such groups include thiomorpholin-4-yl-methyl, 1-oxo-thiomorpholin-4-yl-methyl, 1,1-dioxo-thiomorpholin-4-yl-methyl, tetrahydropyran-3-yl-methyl, oxetan-3-yl-methyl, azetidin-1-yl-methyl, azetidin-1-yl-ethyl, azetidin-1-yl-propyl, pyrrol-2-yl-methyl, pyrrol-1-yl-ethyl, morpholin-4-yl-methyl, morpholin-4-yl-ethyl, morpholin-4-yl-propyl, and the like.

[00107] The term “heterocyclyloxy” refers to an optionally substituted heterocyclyl attached to the rest of molecular through an oxygen atom, wherein the heterocyclyl group is as defined herein. Some non-limiting examples of such groups include azetidin-2-yl-oxy, azetidin-3-yl-oxy, pyrrolidin-2-yl-oxy, pyrrolidin-3-yl-oxy, piperid-2-yl-oxy, piperid-3-yl-oxy, piperid-4-yl-oxy, and the like.

[00108] The term “heterocyclylalkoxy” refers to an alkoxy group substituted with heterocyclyl, attached to the rest of molecular through an oxygen atom. Wherein the heterocyclyl group and alkoxy group are as defined herein. Some non-limiting examples of such groups include pyrrolidin-2-yl-methoxy, morpholin-2-yl-ethoxy,

morpholin-3-yl-ethoxy, piperazin-2-yl-ethoxy, and the like.

[00109] The terms “fused bicycle” and “fused bicycyl” as used interchangeably herein refer to a monovalent or multivalent saturated or partially unsaturated bridged ring system, which refers to a bicyclic ring system. The term “bridged ring” refers to any two cycles of it share two C atoms which connect to each other directly or indirectly. For example, depicted in Formula a and b, ring A and ring A' share two carbon atoms which connect to each other directly, or ring B and ring B' share two carbon atoms which connect to each other indirectly. Each ring of the fused cycle is carbocycle or heterocycle. Some non-limiting examples of such groups include hexahydro-furo[3,2-*b*]furan, 2,3,3a,4,7,7a-hexahydro-1*H*-indene, 7-azabicyclo[2.2.1]heptane, fused bicyclo[3.3.0]octane, fused bicyclo[3.1.0]hexane and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene. The fused bicycle defined herein may be substituted or unsubstituted. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “fused bicycyl” then it is understood that the “fused bicycyl” represents a linking fused bicycylene group.



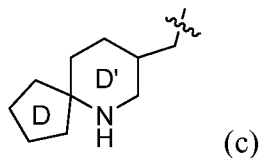
[00110] The term “fused heterobicycyl” refers to unsaturated or saturated fused cyclic system, and at least one ring in the system is inclusive of one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members, *e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, PO or PO₂. Some non-limiting examples of fused heterobicyclic ring system include hexahydro-furo[3,2-*b*]furan, 7-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.0]octane, 3,5,8-trioxabicyclo[5,1,0]octane, 1-aza-4,6-dioxabicyclo[3.3.0]octane, and the like. The fused heterobicycyl defined herein may be substituted or unsubstituted. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure

requires a linking group and the Markush group definition for that variable lists “fused heterobicycyl” then it is understood that the “fused heterobicycyl” represents a linking fused heterobicycylene group.

[00111] The term “fused bicycylalkyl” refers to an alkyl group substituted with one or more fused bicycyl groups, wherein the alkyl group and fused bicycyl group are as defined herein. Some non-limiting examples of such group include 1,2,3,4,4a,5,8,8a-octahydro-naphthylethyl, 1,2,3,4,4a,5,8,8a-octahydro-naphthylmethyl, 1,2,3,4,4a,5,8,8a-octahydro-naphthylpropyl, 7-azabicyclo[2.2.1]hept-7-yl-ethyl, 3-azabicyclo[3.1.0]hexylethyl, fused bicyclo[3.3.0]octylmethyl, fused bicyclo[3.1.0]hexylethyl, and the like.

[00112] The term “fused heterobicycylalkyl” refers to an alkyl group substituted with one or more fused heterobicycyl groups, wherein the alkyl group and fused heterobicycyl group are as defined herein. Some non-limiting examples of such group include hexahydro-furo[3,2-*b*]furan-2-yl-ethyl, hexahydro-furo[3,2-*b*]furan-2-yl-methyl, 7-azabicyclo[2.2.1]heptan-2-yl-methyl, 7-azabicyclo[2.2.1]heptan-2-yl-ethyl, 7-azabicyclo[2.2.1]heptan-4-yl-methyl, and the like.

[00113] The term “spiro bicycyl” or “spiro bicyclic” as used interchangeably herein refers to a monovalent or multivalent saturated or partially unsaturated ring system, wherein a ring originating from a particular annular carbon of another ring. For example, depicted in Formula c, ring D and ring D' share one carbon atom between the two saturated ring systems, which terms as a “spirocycyl” or “spiro bicycyl”. Each cyclic ring in the spirocycyl or spiro bicycyl can be either a carbocyclic or a heteroalicyclic, and optionally substituted with one or more substituents disclosed herein. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “spiro bicycyl” then it is understood that the “spiro bicycyl” represents a linking spiro bicycylene group.



[00114] The term “spiro heterobicycyl” refers to a ring originating from a particular annular carbon of another ring, wherein at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members and that contains 1 to 6 carbon

atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO, SO₂, PO or PO₂. Some non-limiting examples of the spiro heterobicycyl group include 4-azaspiro[2.4]hept-5-yl, 4-oxaspiro[2.4]hept-5-yl, 5-azaspiro[2.4]hept-5-yl, 7-hydroxy-5-azaspiro[2.4]hept-5-yl, and the like. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “spiro heterobicycyl” then it is understood that the “spiro heterobicycyl” represents a linking spiro heterobicycylene group.

[00115] The term “spiro bicycylalkyl” refers to an alkyl group substituted with one or more spiro bicycyl groups, wherein the alkyl group and spiro bicycyl group are as defined herein. Some non-limiting examples of the spiro bicycylalkyl group include (spiro[2.4]hept-1-yl)ethyl, (2,7-diazaspiro[4.4]non-2-yl)methyl, (4-azaspiro[2.4]hept-5-yl)ethyl, and the like.

[00116] The term “spiro heterobicycylalkyl” refers to an alkyl group substituted with one or more spiro heterobicycyl groups, wherein the alkyl group and spiro heterobicycyl group are as defined herein. Some non-limiting examples of the spiro heterobicycylalkyl group include (4-azaspiro[2.4]hept-5-yl)ethyl, and the like.

[00117] The term “n-membered”, where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6 membered heterocycloalkyl and 1,2,3,4-tetrahydro-naphthalene is an example of a 10 membered carbocycyl group.

[00118] The term “unsaturated” refers to a moiety having one or more units of unsaturation.

[00119] The term “heteroatom” refers to one or more of oxygen, sulfur, nitrogen, phosphorus and silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in *N*-substituted pyrrolidinyl).

[00120] The term “halogen” refers to fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

[00121] The term “azido” or “N₃” refers to an azide moiety. This radical may be attached other group, for example, to a methyl group to form azidomethane (methyl azide, MeN₃); or attached to a phenyl group to form phenyl azide (PhN₃).

[00122] The term “aryl” refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, or six to twelve ring members, or six to ten ring

members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term “aryl” and “aromatic ring” can be used interchangeably herein. Examples of the aryl group would include phenyl, indenyl, naphthyl, and anthracene. The aryl group may be optionally and independently substituted with one or more substituents disclosed herein. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “aryl” then it is understood that the “aryl” represents a linking arylene group.

[00123] The term “arylalkyl” or “aralkyl” refers to an alkyl group substituted with one or more aryl groups, wherein the alkyl group and aryl group are as defined herein. Some non-limiting examples of the arylalkyl group include phenylmethyl, phenylethyl, (*p*-tolyl)ethyl, and the like.

[00124] The term “aryloxy” refers to an optionally substituted aryl group, as defined herein, attached to an oxygen atom, wherein the oxygen atom serves as the attaching point to the rest of the molecule. Some non-limiting examples of the aryloxy group include phenyloxy, *p*-methylphenyloxy, *p*-ethylphenyloxy, and the like.

[00125] The term “arylalkoxy” refers to an alkoxy group substituted with one or more aryl groups, wherein the aryl group and alkoxy group are as defined herein. Some non-limiting examples of such groups include phenylmethoxy, phenylethoxy, *p*-methylphenylmethoxy, phenylpropoxy, and the like.

[00126] The term “heteroaryl” refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems having a total of five to twelve ring members, or five to ten ring members, or five to six ring members, wherein at least one ring in the system is aromatic, and in which at least one ring member is selected from heteroatom, and wherein each ring in the system contains 5 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term “heteroaryl” and “heteroaromatic ring” or “heteroaromatic compound” can be used interchangeably herein. The heteroaryl group is optionally substituted with one or more substituents disclosed herein. In one embodiment, a 5-10 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that

variable lists “heteroaryl” then it is understood that the “heteroaryl” represents a linking heteroarylene group.

[00127] Some non-limiting examples of heteroaryl rings include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (*e.g.*, 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (*e.g.*, 5-tetrazolyl), triazolyl (*e.g.*, 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (*e.g.*, 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, pyrimidinonyl, pyridinonyl, and the following non-limiting bicycles: benzimidazolyl, benzofuryl, benzothienyl, indolyl (*e.g.*, 2-indolyl), purinyl, quinolinyl (*e.g.*, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), tetrahydroquinolinyl (*e.g.*, 1,2,3,4-tetrahydroquinolinyl), isoquinolinyl (*e.g.*, 1-isoquinolinyl, 3-isoquinolinyl or 4-isoquinolinyl), tetrahydroisoquinolinyl (*e.g.*, 1,2,3,4-tetrahydroisoquinolinyl), imidazo[1,2-*a*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, or [1,2,4]triazolo[1, 5-*a*]pyridyl, and the like.

[00128] The term “heteroarylalkyl” refers to an alkyl group substituted with one or more heteroaryl groups, wherein the alkyl group and heteroaryl group are as defined herein. Some non-limiting examples of the heteroarylalkyl group include (pyrid-2-yl)methyl, (pyrid-2-yl)ethyl, (pyrid-3-yl)methyl, (pyrid-4-yl)methyl, (thiazol-2-yl)methyl, (imidazol-2-yl)ethyl, (pyrimidin-2-yl)propyl, and the like.

[00129] The term “heteroaryloxy” refers to an optionally substituted heteroaryl group, as defined herein, attached to an oxygen atom, wherein the oxygen atom serves as the attaching point to the rest of the molecule. Some non-limiting examples of the heteroaryloxy group include pyridyloxy, pyrimidyloxy, and the like.

[00130] The term “heteroarylalkoxy” refers to an alkoxy group substituted with one or more optionally substituted heteroaryl groups, wherein the alkoxy group and heteroaryl group are as defined herein. Some non-limiting examples of the heteroarylalkyl group include (pyrid-2-yl)methoxy, (thiazol-2-yl)ethoxy, (imidazol-2-yl)ethoxy, (pyrimidin-2-yl)propoxy, (pyrimidin-2-yl)methoxy, and the like.

[00131] The terms “carboxy” or “carboxyl”, whether used alone or with other terms, such as “carboxyalkyl”, refer to $\text{-CO}_2\text{H}$. The term “carbonyl”, whether used alone or with other terms, such as “aminocarbonyl”, “acyloxy”, “alkylacyl”, “cycloalkylacyl”, “heterocyclacyl”, “arylacyl” or “heteroarylacyl” denotes -(C=O)- .

[00132] The term “alkylacyl” refers to alkyl-C(=O)- , wherein the alkyl group is as defined herein. Some non-limiting examples of the alkylacyl group include $\text{CH}_3\text{-C(=O)-}$, $\text{CH}_3\text{-CH}_2\text{-C(=O)-}$, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-C(=O)-}$, $(\text{CH}_3)_2\text{CH-C(=O)-}$, and the like.

[00133] The term “arylacyl” refers to aryl-C(=O)- , wherein the aryl group is as defined herein. Some non-limiting examples of the arylacyl group include benzoyl.

[00134] The term “alkylamino” refers to “*N*-alkylamino” and “*N,N*-dialkylamino” wherein amino groups are independently substituted with one alkyl radical or two alkyl radicals, respectively. In some embodiments, the alkylamino radical is “lower alkylamino” radical having one or two C_{1-6} alkyl groups attached to a nitrogen atom. In other embodiments, the alkylamino radical is “lower alkylamino” radical having one or two C_{1-3} alkyl groups attached to a nitrogen atom. Some non-limiting examples of suitable alkylamino radical include mono or dialkylamino. Some examples include, but are not limited to, *N*-methylamino, *N*-ethylamino, *N,N*-dimethylamino and *N,N*-diethylamino, and the like.

[00135] The term “alkoxyalkylamino” refers to an alkylamino group optionally substituted with one or more alkoxy groups, wherein the alkoxy and alkylamino are as defined herein. Some non-limiting examples of such group include $\text{-NHCH}_2\text{OCH}_3$, $\text{-NHCH}_2\text{OCH}_2\text{CH}_3$, $\text{-NHCH}_2\text{CH}_2\text{OCH}_3$, $\text{-NHCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$, and the like.

[00136] The term “alkylaminoalkylamino” refers to an alkylamino group optionally substituted with one or more alkylamino groups, wherein the alkylamino is as defined herein. Some non-limiting examples of such group include $\text{-NHCH}_2\text{NHCH}_3$, $\text{-NHCH}_2\text{NHCH}_2\text{CH}_3$, $\text{-NHCH}_2\text{CH}_2\text{N(CH}_3)_2$, $\text{-N(CH}_3)_2\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_3$, and the like.

[00137] The term “cycloalkylamino” refers to an amino group is substituted with one or two cycloalkyl radicals. Some non-limiting examples of the cycloalkylamino group include cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino, and the like.

[00138] The term “alkylaminoalkyl” refers to an alkyl group substituted with one or more alkylamino groups, wherein the alkyl group and alkylamino group are as defined herein. Some non-limiting examples of the alkylaminoalkyl group include *N*-methyldiaminomethyl,

N-ethylaminomethyl, *N,N*-diethylaminomethyl, *N,N*-dimethylaminoethyl, *N,N*-diethylaminoethyl, -CH₂N(CH₃)CH₂CH₃, and the like.

[00139] The term “arylamino” refers to an amino group substituted with one or two aryl groups. Some non-limiting examples of such group included *N*-phenylamino. In some embodiments, the aryl group of the arylamino may be further substituted.

[00140] The term “heteroarylamino” refers to an amino group substituted with one or two optionally substituted heteroaryl groups, wherein the heteroaryl group is as defined herein. Some non-limiting examples of the heteroarylalkyl group include *N*-thienylamino, pyrid-4-yl-amino, *m*-fluoropyridylamino, dipyridylamino, 1*H*-pyrazol-4-yl-amino, and the like.

[00141] The term “aminoalkyl” or “amino-substituted alkyl” refers to a C₁₋₁₀ linear or branched-chain alkyl group substituted with one or more amino groups. In some embodiments, the aminoalkyl is a C₁₋₆ lower aminoalkyl derived from a C₁₋₆ alkyl which is substituted with one or more amino groups. Some non-limiting examples of the aminoalkyl group include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminoethyl.

[00142] The term “cycloalkylaminoalkyl” refers to an aminoalkyl substituted with cycloalkyl. Some non-limiting examples of such group include cyclopropylaminomethyl, cyclobutylaminomethyl, cyclopentylaminomethyl, cyclopropylaminoethyl, cyclobutylaminoethyl, cyclopropylaminopropyl, cyclobutylaminopropyl.

[00143] The term “heterocyclylalkylamino” refers to an alkylamino substituted with one or more heterocyclyl groups, wherein heterocyclyl group and alkylamino group are as defined herein. Some non-limiting examples of such group include morpholin-4-yl-propylamino, and the like.

[00144] The term “protecting group” or “PG” refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an “amino-protecting group” is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxy-carbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethylenoxy-carbonyl (Fmoc). Similarly, a “hydroxy-protecting group” refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A “carboxy-protecting group” refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include -CH₂CH₂SO₂Ph, cyanoethyl, 2-(trimethylsilyl)ethyl,

2-(trimethylsilyl)ethoxy-methyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfonyl)-ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991; and P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 2005.

[00145] The term “prodrug” refers to a compound that is transformed in vivo into a compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id). Such a transformation can be affected, for example, by hydrolysis of the prodrug form in blood or enzymatic transformation to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C₁₋₂₄) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains a hydroxy group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, those phosphate compounds derived from the phosphonation of a hydroxy group on the parent compound. A thorough discussion of prodrugs is provided in Higuchi et al., *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A. C. S. Symposium Series, Edward B. Roche, et al. ed. , Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; Rautio et al. , *Prodrugs: Design and Clinical Applications*, *Nature Review Drug Discovery*, 2008, 7, 255-270, and Hecker et al. , *Prodrugs of Phosphates and Phosphonates*, *J. Med. Chem.* , 2008, 51, 2328-2345, all of which are incorporated herein by reference in their entireties.

[00146] The term “metabolite” refers to a product produced through metabolism in the body of a specified compound or salt thereof. The metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein, including metabolites produced by contacting a compound disclosed herein with a mammal for a sufficient time period.

[00147] The term “pharmaceutically acceptable salt” disclosed herein refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1-19, which is incorporated herein by reference.

Examples of pharmaceutically acceptable, nontoxic salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid, or salts obtained by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil product soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[00148] The term “solvate” refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term “hydrate” refers to the complex where the solvent molecule is water.

[00149] As used herein, the term “treat”, “treating” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (*i.e.*, slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*,

stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

[00150] “Inflammatory disorder/disease” as used herein can refer to any disease, disorder, or syndrome in which an excessive or unregulated inflammatory response leads to excessive inflammatory symptoms, host tissue damage, or loss of tissue function. “Inflammatory disorder” also refers to a pathological state mediated by influx of leukocytes and/or neutrophil chemotaxis.

[00151] “Inflammation” as used herein refers to a localized, protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue. Inflammation is notably associated with influx of leukocytes and/or neutrophil chemotaxis. Inflammation can result from infection with pathogenic organisms and viruses and from noninfectious means such as trauma or reperfusion following myocardial infarction or stroke, immune response to foreign antigen, and autoimmune responses. Accordingly, inflammatory disorders amenable to treatment with the compounds disclosed herein encompass disorders associated with reactions of the specific defense system as well as with reactions of the nonspecific defense system.

[00152] “Autoimmune disease” as used herein refers to any group of disorders in which tissue injury is associated with humoral or cell-mediated responses to the body’s own constituents. The examples of the autoimmune disease include lupus, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, psoriasis, type I diabetes, complications from organ transplantation, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn’s disease, Alzheimer’s disease, leukemia or lymphoma.

[00153] “Arthritic disease” as used herein refers to any disease that is characterized by inflammatory lesions of the joints attributable to a variety of etiologies. “Dermatitis” as used herein refers to any of a large family of diseases of the skin that are characterized by inflammation of the skin attributable to a variety of etiologies. “Transplant rejection” as used herein refers to any immune reaction directed against grafted tissue, such as organs or cells (*e.g.*, bone marrow), characterized by a loss of function of the grafted and surrounding tissues, pain, swelling, leukocytosis, and thrombocytopenia. The therapeutic methods of the present invention include methods for the treatment of disorders associated with inflammatory cell activation.

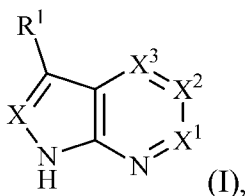
[00154] The terms “cancer” and “cancerous” refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A “tumor” comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small cell lung cancer, non-small cell lung cancer (“NSCLC”), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

[00155] The term “biological sample” as used herein, means a sample outside a living organism and includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of kinase activity, particularly BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M kinase activity, in a biological sample is useful for a variety of purposes known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[00156] The compound or pharmaceutical composition thereof disclosed herein has potential effect on autoimmune diseases or cancer.

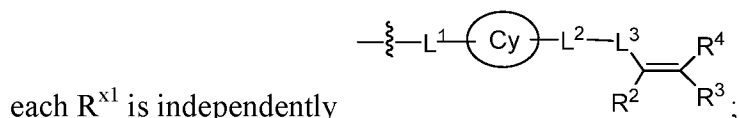
[00157] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

X is N or CR^x;

each of X^1 and X^2 is independently N, CR^0 or CR^{x1} with the proviso of at least one of X^1 and X^2 is CR^{x1} ;



X^3 is CR or N, wherein R is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , COOH, alkyl, alkoxy, alkenyl or alkynyl;

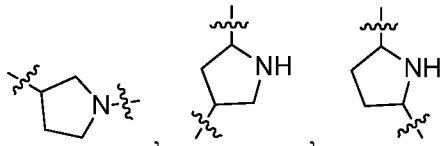
each R^x and R^0 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

each L^1 is independently $-O-$, $-N(R^{1a})-$, $-S(=O)_p-$, $-C(=O)-$, $-C(=O)-N(R^{1a})-$, $-S(=O)_p-N(R^{1a})-$, $-(CR^mR^w)_g-$ or $-(CR^mR^w)_n-CR^{1a}=CR^{1a}-(CR^mR^w)_n-$;

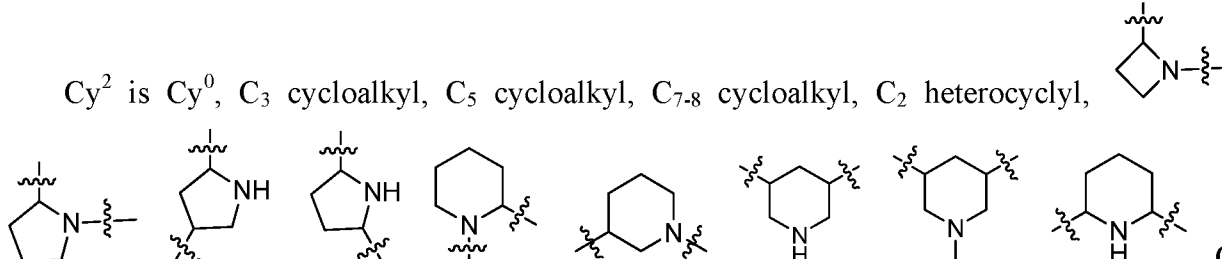
1) R^1 is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , methyl, C_{2-10} alkyl, cycloalkylaminoalkyl, alkoxy, alkylamino, alkylthio, alkenyl, alkynyl, cycloalkylalkyl, heterocyclalkyl, arylalkyl, heteroarylalkyl, $-(CR^mR^w)_n-C(=O)-R^{1a}$, $-(CR^mR^w)_n-COOR^{1a}$, $-(CR^mR^w)_n-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-NR^aR^b$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w$, $-(CR^mR^w)_n-NR^mR^w$, cycloalkylacyl, heterocyclacyl, arylacyl, heteroarylacyl, fused bicyclalkyl, fused heterobicyclalkyl, spiro bicyclalkyl or spiro heterobicyclalkyl;

each Cy is independently Cy^0 , cycloalkyl, heterocyclyl, fused bicyclyl or fused heterobicyclyl;

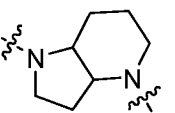
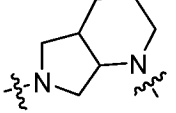
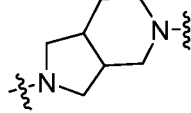
i) when L^1 is $-NH-C(=O)-$, each Cy is independently Cy^1 ;

Cy^1 is Cy^0 , cycloalkyl, C_{2-3} heterocyclyl, , C_{5-10} heterocyclyl, fused bicyclyl or fused heterobicyclyl;

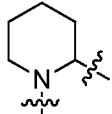
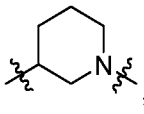
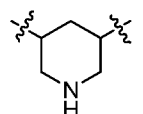
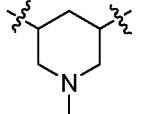
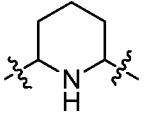
ii) when L^1 is $-NH-$, each Cy is independently Cy^2 ;

Cy^2 is Cy^0 , C_3 cycloalkyl, C_5 cycloalkyl, C_{7-8} cycloalkyl, C_2 heterocyclyl, , C_6

heterocyclyl, C₈₋₁₀ heterocyclyl, , C₆ fused bicyclyl, C₈₋₁₂ fused bicyclyl, C₆ fused

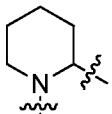
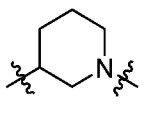
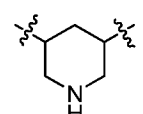
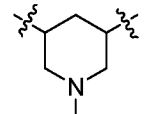
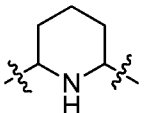
heterobicyclyl, , , , or C₈₋₁₂ fused heterobicyclyl;

iii) when L¹ is -O-, each Cy is independently fused heterobicyclyl Cy³;

Cy³ is Cy⁰, cycloalkyl, C₂₋₄ heterocyclyl, , , , , , C₆₋₁₀ heterocyclyl, fused bicyclyl or fused heterobicyclyl;

2) R¹ is cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, fused bicyclyl, fused heterobicyclyl, spiro bicyclyl or spiro heterobicyclyl;

each Cy is independently Cy⁴;

Cy⁴ is Cy⁰, cycloalkyl, C₂₋₄ heterocyclyl, , , , , , C₆₋₁₀ heterocyclyl, fused bicyclyl or fused heterobicyclyl;

each Cy⁰ is independently cycloalkenyl, aryl, heteroaryl, spiro bicyclyl or spiro heterobicyclyl;

each L² is independently a bond, -O-, -N(R^{1a})-, -CH₂-N(R^{1a})-, -CH(CH₃)-N(R^{1a})-, -C(CH₃)₂-N(R^{1a})-, -C(=O)-N(R^{1a})- or -S(=O)_p-N(R^{1a})-;

each L³ is independently -C(=O)- or -S(=O)₂-;

each R² is independently H, deuterium, F, Cl, Br, I, CN, alkyl, alkenyl or alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, fused bicyclyl, fused bicyclylalkyl, fused heterobicyclyl, fused heterobicyclylalkyl, spiro bicyclyl, spiro bicyclylalkyl, spiro heterobicyclyl or spiro heterobicyclylalkyl;

each n is independently 0, 1, 2, 3, or 4;

g is 1, 2, 3, or 4;

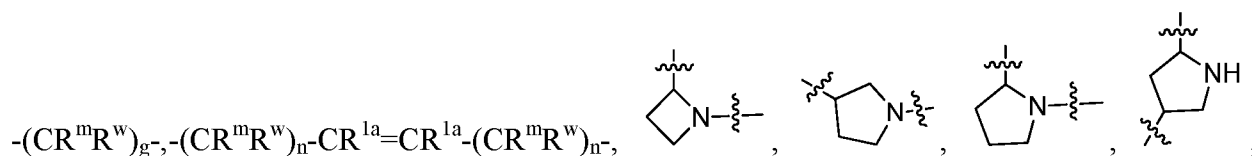
each p is independently 0, 1, or 2;

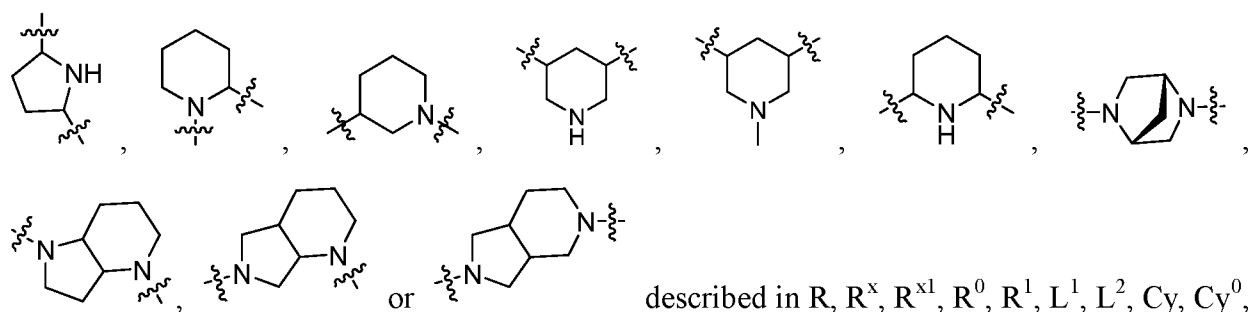
each R^{1a} is independently H, deuterium, alkyl, alkenyl or alkynyl;

each of R^a and R^b is independently H, deuterium, C₁₋₃ alkyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, C₅₋₁₀ alkyl, cyano-substituted alkyl, hydroxy-substituted alkyl, amino-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl; or R^a and R^b, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each R^m and R^w is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclalkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

wherein each alkyl, methyl, C₂₋₁₀ alkyl, C₁₋₃ alkyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, C₅₋₁₀ alkyl, haloalkyl, cyano-substituted alkyl, hydroxy-substituted alkyl, amino-substituted alkyl, cycloalkylaminoalkyl, alkoxy, alkoxyalkyl, alkylamino, alkylaminoalkyl, alkylthio, alkylthioalkyl, alkenyl, alkynyl, cycloalkyl, C₃ cycloalkyl, C₅ cycloalkyl, C₇₋₈ cycloalkyl, cycloalkenyl, cycloalkylalkyl, carbocyclyl, heterocycle, heterocyclyl, C₂ heterocyclyl, C₂₋₃ heterocyclyl, C₂₋₄ heterocyclyl, C₅₋₁₀ heterocyclyl, C₆ heterocyclyl, C₆₋₁₀ heterocyclyl, C₈₋₁₀ heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -(CR^mR^w)_n-C(=O)-R^{1a}, -(CR^mR^w)_n-COOR^{1a}, -(CR^mR^w)_n-S(=O)_p-R^{1a}, -(CR^mR^w)_n-S(=O)_p-NR^mR^w, -(CR^mR^w)_n-C(=O)-NR^aR^b, -(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-R^{1a}, -(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-NR^mR^w, -(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}, -(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w, -(CR^mR^w)_n-NR^mR^w, cycloalkylacyl, heterocyclacyl, arylacyl, heteroarylacyl, fused bicyclyl, C₆ fused bicyclyl, C₈₋₁₂ fused bicyclyl, fused bicyclylalkyl, fused heterobicyclyl, C₆ fused heterobicyclyl, C₈₋₁₂ fused heterobicyclyl, fused heterobicyclalkyl, spiro bicyclyl, spiro bicyclalkyl, spiro heterobicyclyl, spiro heterobicyclalkyl, -N(R^{1a})-, -C(=O)-N(R^{1a})-, -S(=O)_p-N(R^{1a})-,





Cy¹, Cy², Cy³, Cy⁴, R², R³, R⁴, R^{1a}, R^a, R^b, R^m and/or R^w is optionally and independently substituted with one or more R⁵;

wherein each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aryloxy, heteroaryloxy, heterocycloxy, arylalkoxy, heteroarylalkoxy, heterocyclalkoxy, alkylamino, alkylaminoalkyl, alkylaminoalkylamino, cycloalkylamino, alkylthio, haloalkyl, haloalkoxy, hydroxy-substituted alkyl, hydroxy-substituted alkylamino, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted alkylamino, amino-substituted alkyl, alkylacyl, heteroalkyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heterocyclalkylamino, heterocyclacyl, aryl, arylalkyl, arylamino, heteroaryl, heteroarylamino, NH₂-C(=O)-, alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-alkyl-, alkyl-N(R⁶)-S(=O)₂-alkyl-, alkyl-S(=O)₂-N(R⁶)-alkyl-, aryl-alkyl-N(R⁶)-C(=O)-, alkyl-C(=O)-N(R⁶)-, alkyl-N(R⁶)-C(=O)-alkyl-N(R⁶)-, alkyl-S(=O)₂-, alkyl-S(=O)₂-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-alkyl-;

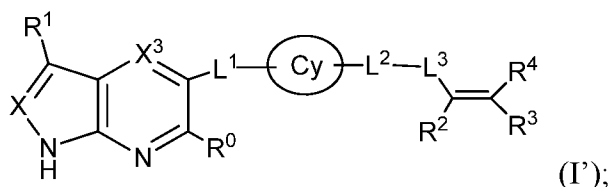
each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, alkyl, alkenyl or alkynyl;

each R¹¹ and R¹² is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocycl or heterocyclalkyl; or R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each R⁵ is optionally and independently substituted with one or more substituents selected from H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkyl-C(=O)-, cyano-substituted alkyl-C(=O)-, alkylamino, NH₂-S(=O)₂-, alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-alkyl-, alkyl-N(R¹³)-S(=O)₂-alkyl-, alkyl-S(=O)₂-N(R¹³)-alkyl-, haloalkyl, hydroxy-substituted alkyl, cyano-substituted alkyl, cycloalkyl, heterocycl, aryl, aryloxy or arylalkoxy; and

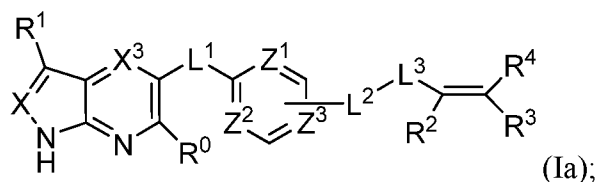
each R¹³ is independently H, deuterium, alkyl, alkenyl or alkynyl.

[00158] In some embodiments, provided herein is a compound having Formula (I') or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein each of X, X³, R¹, R⁰, L¹, Cy, L², L³, R², R³ and R⁴ is as defined herein.

[00159] In some embodiments, provided herein is a compound having Formula (Ia) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

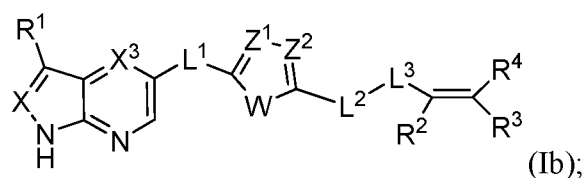


wherein each of X, X³, R¹, R⁰, L¹, L², L³, R², R³ and R⁴ is as defined herein;

each of Z¹, Z² and Z³ is independently N or CR^y; and

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkylamino or halo-C₁₋₆-alkyl.

[00160] In some embodiments, provided herein is a compound having Formula (Ib) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein each of X, X³, R¹, L¹, L², L³, R², R³ and R⁴ is as defined herein;

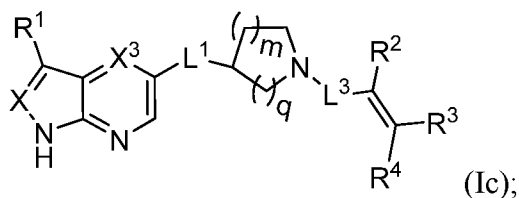
each of Z¹ and Z² is independently N or CR^y;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkylamino or halo-C₁₋₆-alkyl; and

W is O, S, CH₂ or NH.

[00161] In some embodiments, provided herein is a compound having Formula (Ic) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a

metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

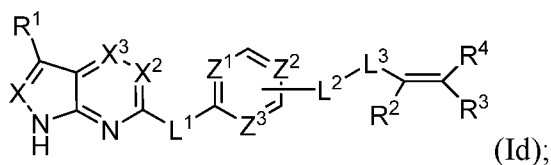


wherein each of X, X³, R¹, L¹, L³, R², R³ and R⁴ is as defined herein;

m is 0, 1 or 2; and

q is 1, 2 or 3.

[00162] In some embodiments, provided herein is a compound having Formula (Id) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein each of X, X², X³, R¹, L¹, L², L³, R², R³ and R⁴ is as defined herein;

each of Z¹, Z² and Z³ is independently N or CR^y; and

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkylamino or halo-C₁₋₆-alkyl.

[00163] In some embodiments, each R^x is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl.

[00164] In some embodiments, each R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl.

[00165] In other embodiments, each R^x is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₅ heteroaryl.

[00166] In other embodiments, each R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₅ heteroaryl.

[00167] In other embodiments, each R^x is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, phenyl, furyl,

imidazolyl, pyrazolyl, pyrrolyl, triazolyl, tetrazolyl, oxazolyl, pyridyl, pyrimidinyl or pyrazinyl.

[00168] In other embodiments, each R^0 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , $COOH$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, phenyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, triazolyl, tetrazolyl, oxazolyl, pyridyl, pyrimidinyl or pyrazinyl.

[00169] In some embodiments, R^1 is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , methyl, C_{2-6} alkyl, C_{3-8} cycloalkylamino- C_{1-6} -alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl- C_{1-6} -alkyl, C_{2-10} heterocyclyl- C_{1-6} -alkyl, C_{6-10} aryl- C_{1-6} -alkyl, C_{1-9} heteroaryl- C_{1-6} -alkyl, $-(CR^mR^w)_n-C(=O)-R^{1a}$, $-(CR^mR^w)_n-COOR^{1a}$, $-(CR^mR^w)_n-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-NR^aR^b$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w$, $-(CR^mR^w)_n-NR^mR^w$, C_{3-8} cycloalkylacyl, C_{2-10} heterocyclacyl, C_{6-10} arylacyl, C_{1-9} heteroarylacyl, C_{5-12} fused bicyclyl- C_{1-6} -alkyl, C_{5-12} fused heterobicyclyl- C_{1-6} -alkyl, C_{5-12} spiro bicyclyl- C_{1-6} -alkyl or C_{5-12} spiro heterobicyclyl- C_{1-6} -alkyl; R^1 is optionally substituted with one or more R^5 ;

wherein each R^5 , R^{1a} , R^a , R^b , R^m and R^w is as defined herein;

each n is independently 0, 1, 2, 3 or 4; and

each p is independently 0, 1 or 2.

[00170] In some embodiments, each R^{1a} is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl.

[00171] In some embodiments, each of R^a and R^b is independently H, deuterium, C_{1-3} alkyl, n -butyl, isobutyl, *sec*-butyl, *tert*-butyl, C_{5-6} alkyl, cyano-substituted C_{1-6} alkyl, hydroxy-substituted C_{1-6} alkyl, amino-substituted C_{1-6} alkyl, halo- C_{1-6} -alkyl, C_{1-6} alkoxy- C_{1-6} -alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} -alkyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-6} -alkyl, C_{1-9} heteroaryl, C_{1-9} heteroaryl- C_{1-6} -alkyl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-6} -alkyl.

[00172] In some embodiments, R^a and R^b , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00173] In some embodiments, each R^m and R^w is independently H, deuterium, C_{1-6} alkyl, cyano-substituted C_{1-6} alkyl, halo- C_{1-6} -alkyl, C_{1-6} alkoxy- C_{1-6} -alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-6} -alkyl.

[00174] In some embodiments, R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00175] In some embodiments, R^1 is C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{5-12} fused bicyclyl, C_{5-12} fused heterobicyclyl, C_{5-12} spiro bicyclyl or C_{5-12} spiro heterobicyclyl; R^1 is optionally substituted with one or more R^5 ; and wherein each R^5 is as defined herein.

[00176] In other embodiments, R^1 is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , methyl, C_{2-4} alkyl, C_{3-8} cycloalkylamino- C_{1-3} -alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl- C_{1-3} -alkyl, C_{2-10} heterocyclyl- C_{1-4} -alkyl, C_{6-10} aryl- C_{1-3} -alkyl, C_{1-9} heteroaryl- C_{1-3} -alkyl, $-(CR^mR^w)_n-C(=O)-R^{1a}$, $-(CR^mR^w)_n-COOR^{1a}$, $-(CR^mR^w)_n-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-NR^aR^b$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w$, $-(CR^mR^w)_n-NR^mR^w$, C_{3-8} cycloalkylacyl, C_{2-10} heterocyclylacyl, C_{6-10} arylacyl, C_{1-9} heteroarylacyl, C_{5-12} fused bicyclyl- C_{1-3} -alkyl, C_{5-12} fused heterobicyclyl- C_{1-3} -alkyl, C_{5-12} spiro bicyclyl- C_{1-3} -alkyl, or C_{5-12} spiro heterobicyclyl- C_{1-3} -alkyl; R^1 is optionally substituted with one or more R^5 ;

each R^5 , R^{1a} , R^a , R^b , R^m and R^w is as defined herein;

each n is independently 0, 1, 2, 3 or 4; and

each p is independently 0, 1 or 2.

[00177] In other embodiments, each R^{1a} is independently H, deuterium, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[00178] In other embodiments, each of R^a and R^b is independently H, deuterium, C_{1-3} alkyl, n -butyl, isobutyl, *sec*-butyl, *tert*-butyl, cyano-substituted C_{1-4} alkyl, hydroxy-substituted C_{1-5} alkyl, amino-substituted C_{1-5} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-3} -alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-3} -alkyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-3} -alkyl, C_{1-9} heteroaryl, C_{1-9} heteroaryl- C_{1-3} -alkyl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-3} -alkyl.

[00179] In other embodiments, R^a and R^b , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00180] In other embodiments, each R^m and R^w is independently H, deuterium, C_{1-5} alkyl, cyano-substituted C_{1-4} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-4} -alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-3} -alkyl.

[00181] In other embodiments, R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00182] In some embodiments, R^1 is C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{2-8} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{5-12} fused bicyclyl, C_{5-12} fused heterobicyclyl, C_{5-12} spiro bicyclyl or C_{5-12} spiro heterobicyclyl; R^1 is optionally substituted with one or more R^5 ; and wherein each R^5 is as defined herein.

[00183] In other embodiments, R^1 is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , methyl, C_{2-4} alkyl, C_{3-6} cycloalkylamino- C_{1-3} -alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl- C_{1-3} -alkyl, C_{2-10} heterocyclyl- C_{1-4} -alkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-(CR^mR^w)_n-C(=O)-R^{1a}$, $-(CR^mR^w)_n-COOR^{1a}$, $-(CR^mR^w)_n-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-NR^aR^b$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-R^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-S(=O)_p-NR^mR^w$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w$, $-(CR^mR^w)_n-NR^mR^w$, C_{3-8} cycloalkylacyl, C_{2-10} heterocyclylacyl, C_{6-10} arylacyl or C_{1-5} heteroarylacyl; R^1 is optionally substituted with one or more R^5 ;

wherein each R^5 , R^{1a} , R^a , R^b , R^m and R^w is as defined herein;

each n is independently 0, 1, 2, 3 or 4; and

each p is independently 0, 1 or 2.

[00184] In other embodiments, each R^{1a} is independently H, deuterium, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[00185] In other embodiments, each of R^a and R^b is independently H, deuterium, C_{1-3} alkyl, n -butyl, isobutyl, *sec*-butyl, *tert*-butyl, cyano-substituted C_{1-4} alkyl, hydroxy-substituted C_{1-5} alkyl, amino-substituted C_{1-5} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-3} -alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} -alkyl, C_{6-10} aryl- C_{1-3} -alkyl, C_{1-5} heteroaryl- C_{1-3} -alkyl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-3} -alkyl.

[00186] In other embodiments, R^a and R^b , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00187] In other embodiments, each R^m and R^w is independently H, deuterium, C_{1-4} alkyl, cyano-substituted C_{1-4} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-4} -alkyl, C_{3-6} cycloalkyl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-3} -alkyl.

[00188] In other embodiments, R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00189] In some embodiments, R^1 is C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{2-6} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl or C_{5-12} fused bicyclyl; R^1 is optionally substituted with one or more R^5 ; and

wherein each R^5 is as defined herein.

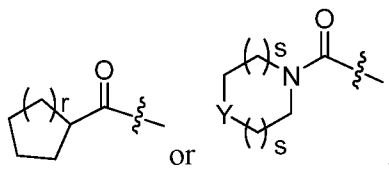
[00190] In other embodiments, R^1 is H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, methyl, ethyl, propyl, isopropyl, cyclopropylaminomethyl, cyclobutylaminomethyl, cyclopentylaminomethyl, cyclopropylaminoethyl, cyclobutylaminoethyl, cyclopropylaminopropyl, cyclobutylaminopropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, piperidylmethyl, piperidylethyl, piperidylpropyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydropyranylpropyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, $-(CH_2)_n-C(=O)-R^{1a}$, $-(CH_2)_n-COOR^{1a}$, $-(CR^mR^w)_n-C(=O)-NR^aR^b$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-OR^{1a}$, $-(CR^mR^w)_n-C(=O)-N(R^{1a})-(CR^mR^w)_n-C(=O)-NR^mR^w$, $-(CR^mR^w)_n-NR^mR^w$, benzoyl or C₁₋₅ heteroarylacyl; R^1 is optionally substituted with one or more R^5 ;

wherein each R^5 , R^{1a} , R^a , R^b , R^m and R^w is as defined herein;

each n is independently 0, 1, 2, 3 or 4; and

each p is independently 0, 1 or 2.

[00191] In other embodiments, R^1 is



R^1 is optionally substituted with one or more R^5 ;

wherein each R^5 , R^{1a} , R^m and R^w is as defined herein;

Y is O, S, NR^{1a} or CR^mR^w ; and

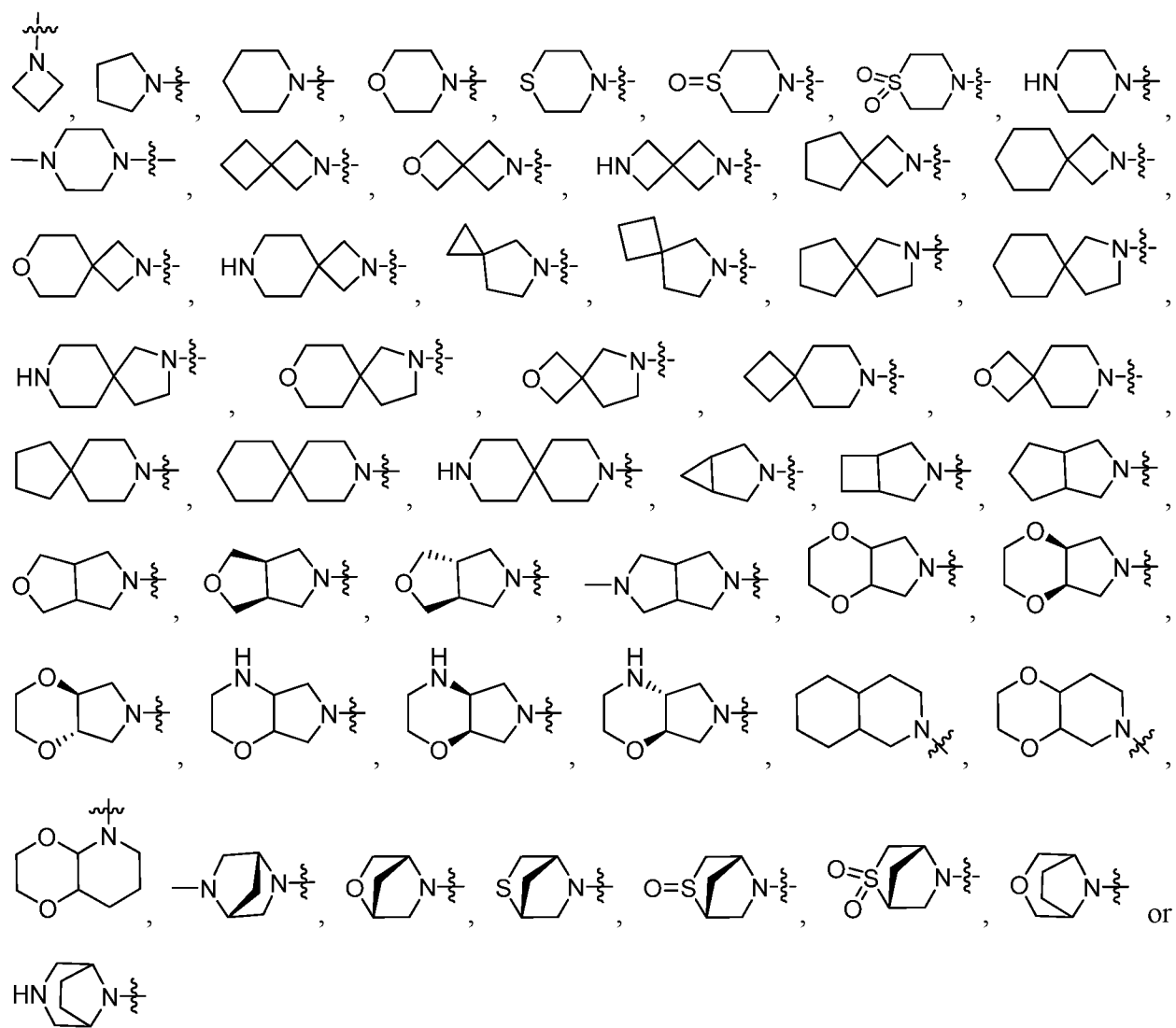
each r and s is independently 0, 1, 2 or 3.

[00192] In other embodiments, each R^{1a} is independently H, deuterium, methyl, ethyl, propyl or isopropyl.

[00193] In other embodiments, each of R^a and R^b is independently H, deuterium, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, cyano-substituted C₁₋₃ alkyl, hydroxy-substituted C₁₋₄ alkyl, amino-substituted C₁₋₄ alkyl, halo-C₁₋₃-alkyl, methoxymethyl, methoxyethyl, methoxypropyl, 1-methoxyprop-2-yl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, isopropoxyethyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, cyclobutyl, cyclobutylmethyl, cyclobutylethyl, cyclopentyl, cyclopentylmethyl,

cyclopentylethyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl, benzyl, phenylethyl, pyridylmethyl, pyridylethyl, pyridylpropyl, pyrimidinylmethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrazolylmethyl, pyrazolyethyl, pyrazolylpropyl, imidazolylmethyl, imidazolethyl, imidazolylpropyl, 4*H*-imidazolylmethyl, 4*H*-imidazolethyl, azacyclobutyl, azacyclobutylmethyl, azacyclobutylethyl, azacyclobutylpropyl, oxacyclobutyl, oxacyclobutylmethyl, oxacyclobutylethyl, oxacyclobutylpropyl, pyrrolidinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, tetrahydrofuranyl, tetrahydrofuranylmethyl, tetrahydrofuranylethyl, tetrahydrofuranylpropyl, tetrahydropyranyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydropyranylpropyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, 1-oxidothiomorpholinyl or 1,1-dioxidothiomorpholinyl.

[00194] In other embodiments, R^a and R^b, together with the N atom to which they are attached, form a group described below:

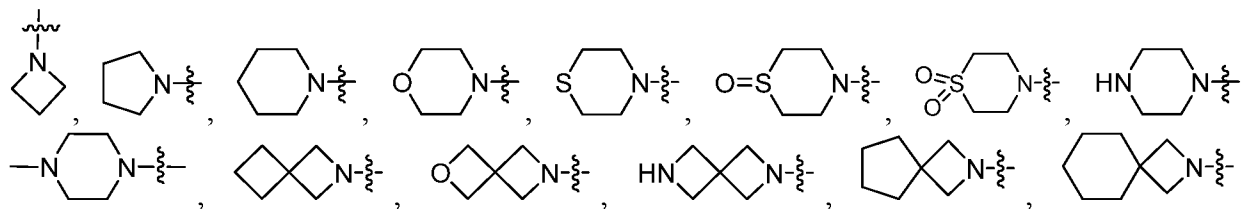


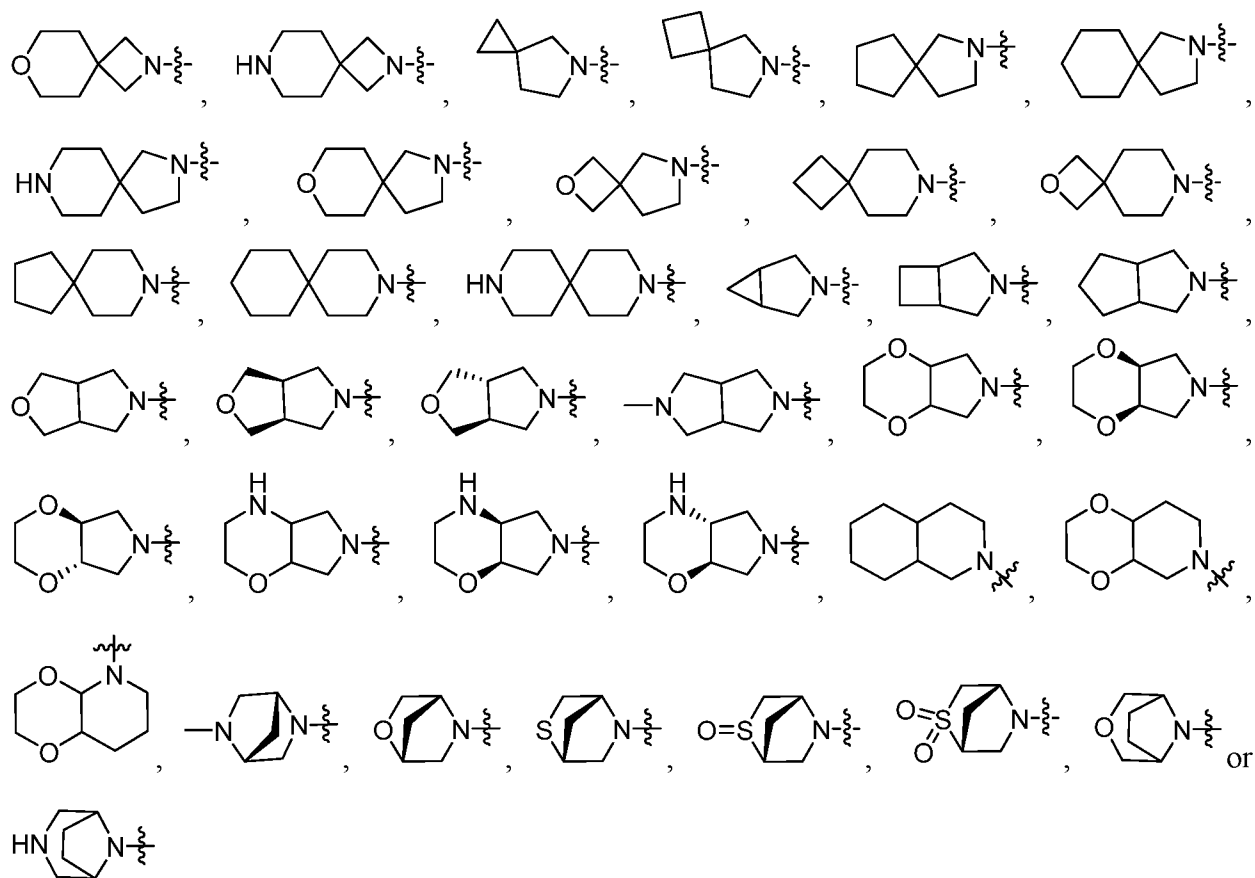
[00195] In other embodiments, R¹ is pyrrolidinyl, piperazinyl, piperidyl, morpholinyl,

1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydropyridyl, thiomorpholinyl, 1-oxidithiomorpholinyl, 1,1-dioxithiomorpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl cyclohexdienyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, pteridyl, naphthyridinyl, benzotriazolyl, benzofuranyl, isobenzofuranyl, furo[3,2-*c*]pyridyl, furo[3,2-*b*]pyridyl, furo[2,3-*b*]pyridyl, furo[2,3-*c*]pyridyl, benzothienyl, benzothiazolyl, 1,2-benzoisothiazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridinopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyridyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridyl, thieno[2,3-*c*]pyridyl, thieno[2,3-*b*]pyridyl, 1,4-benzodioxinyl, pyridin-2(1*H*)-one-3-yl, pyridin-2(1*H*)-one-4-yl, pyridin-2(1*H*)-one-5-yl, pyridin-2(1*H*)-one-6-yl, pyrazin-2(1*H*)-one-3-yl, pyrazin-2(1*H*)-one-5-yl, pyrazin-2(1*H*)-one-6-yl, R¹ is optionally substituted with one or more R⁵; and wherein each R⁵ is as defined herein.

[00196] In other embodiments, each R^m and R^w is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, cyano-substituted C₁₋₃ alkyl, halo-C₁₋₃-alkyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, isopropoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[00197] In other embodiments, R^m and R^w, together with the N atom to which they are attached, form a group described below:





[00198] In some embodiments, each R^2 is independently H, deuterium, F, Cl, Br, I, CN, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl.

[00199] In some embodiments, each R^3 and R^4 is independently H, deuterium, F, Cl, Br, I, CN, $COOH$, $-(CR^mR^w)_n-NR^mR^w$, C_{1-6} alkyl, halo- C_{1-6} -alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy- C_{1-6} -alkyl, C_{1-6} alkylamino- C_{1-6} -alkyl, C_{1-6} alkylthio- C_{1-6} -alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} -alkyl, C_{2-10} heterocyclyl, C_{2-10} heterocyclyl- C_{1-6} -alkyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-6} -alkyl, C_{1-9} heteroaryl, C_{1-9} heteroaryl- C_{1-6} -alkyl, C_{5-12} fused bicycyl, C_{5-12} fused bicycyl- C_{1-6} -alkyl, C_{5-12} fused heterobicycyl, C_{5-12} fused heterobicycyl- C_{1-6} -alkyl, C_{5-12} spiro bicycyl, C_{5-12} spiro bicycyl- C_{1-6} -alkyl, C_{5-12} spiro heterobicycyl or C_{5-12} spiro heterobicycyl- C_{1-6} -alkyl;

wherein each R^m and R^w is as defined herein; and

each n is independently 0, 1, 2, 3, or 4.

[00200] In some embodiments, each R^m and R^w is independently H, deuterium, C_{1-6} alkyl, cyano-substituted C_{1-6} alkyl, halo- C_{1-6} -alkyl, C_{1-6} alkoxy- C_{1-6} -alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-6} -alkyl.

[00201] In some embodiments, R^m and R^w , together with the N atom to which they are attached,

form a 3- to 12-membered heterocycle.

[00202] In other embodiments, each R^2 is independently H, deuterium, F, Cl, Br, I, CN, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[00203] In other embodiments, each R^3 and R^4 is independently H, deuterium, F, Cl, Br, I, CN, COOH, $-(CR^mR^w)_n-NR^mR^w$, C_{1-3} alkyl, halo- C_{1-3} -alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-3} alkoxy- C_{1-3} -alkyl, C_{1-3} alkylamino- C_{1-3} -alkyl, C_{1-3} alkylthio- C_{1-3} -alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-3} -alkyl, C_{2-8} heterocyclyl, C_{2-10} heterocyclyl- C_{1-3} -alkyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-3} -alkyl, C_{1-9} heteroaryl, C_{1-9} heteroaryl- C_{1-3} -alkyl, C_{5-12} fused bicycyl, C_{5-12} fused bicycyl- C_{1-3} -alkyl, C_{5-12} fused heterobicycyl, C_{5-12} fused heterobicycyl- C_{1-3} -alkyl, C_{5-12} spiro bicycyl, C_{5-12} spiro bicycyl- C_{1-3} -alkyl, C_{5-12} spiro heterobicycyl or C_{5-12} spiro heterobicycyl- C_{1-3} -alkyl;

wherein each R^m and R^w is as defined herein; and

each n is independently 0, 1, 2, 3, or 4.

[00204] In other embodiments, each R^m and R^w is independently H, deuterium, C_{1-5} alkyl, cyano-substituted C_{1-4} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-4} -alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{2-10} heterocyclyl or C_{2-10} heterocyclyl- C_{1-3} -alkyl.

[00205] In other embodiments, R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00206] In other embodiments, each R^2 is independently H, deuterium, F, Cl, Br, I, CN, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[00207] In other embodiments, each R^3 and R^4 is independently H, deuterium, F, Cl, Br, I, CN, COOH, $-(CR^mR^w)_n-NR^mR^w$, C_{1-3} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-3} -alkyl, C_{1-3} alkylamino- C_{1-3} -alkyl, C_{1-3} alkylthio- C_{1-3} -alkyl, C_{2-6} heterocyclyl, C_{2-10} heterocyclyl- C_{1-3} -alkyl, C_{5-12} fused bicycyl, C_{5-12} fused bicycyl- C_{1-3} -alkyl, C_{5-12} fused heterobicycyl, C_{5-12} fused heterobicycyl- C_{1-3} -alkyl, C_{5-12} spiro bicycyl, C_{5-12} spiro bicycyl- C_{1-3} -alkyl, C_{5-12} spiro heterobicycyl or C_{5-12} spiro heterobicycyl- C_{1-3} -alkyl;

wherein each R^m and R^w is as defined herein; and

each n is independently 0, 1, 2, 3, or 4.

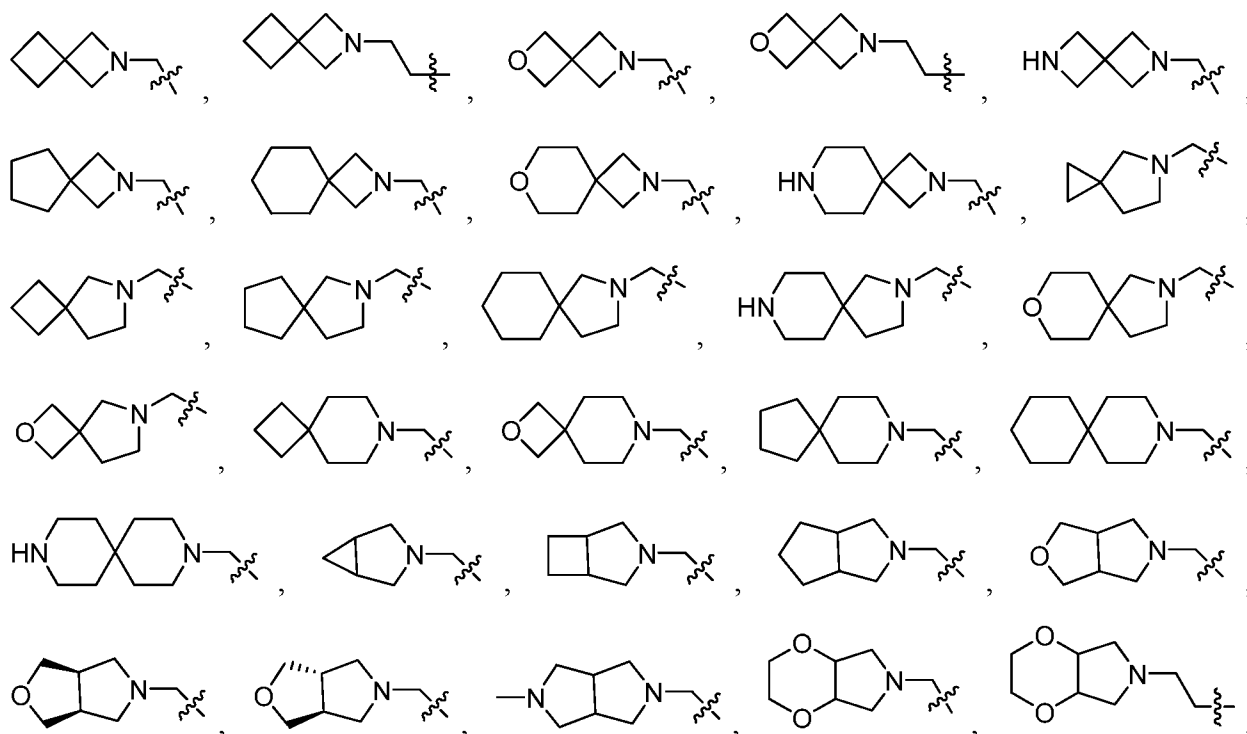
[00208] In other embodiments, each R^m and R^w is independently H, deuterium, C_{1-4} alkyl, cyano-substituted C_{1-4} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-4} -alkyl, C_{3-6} cycloalkyl, C_{2-10} heterocyclyl, C_{2-10} heterocyclyl- C_{1-3} -alkyl.

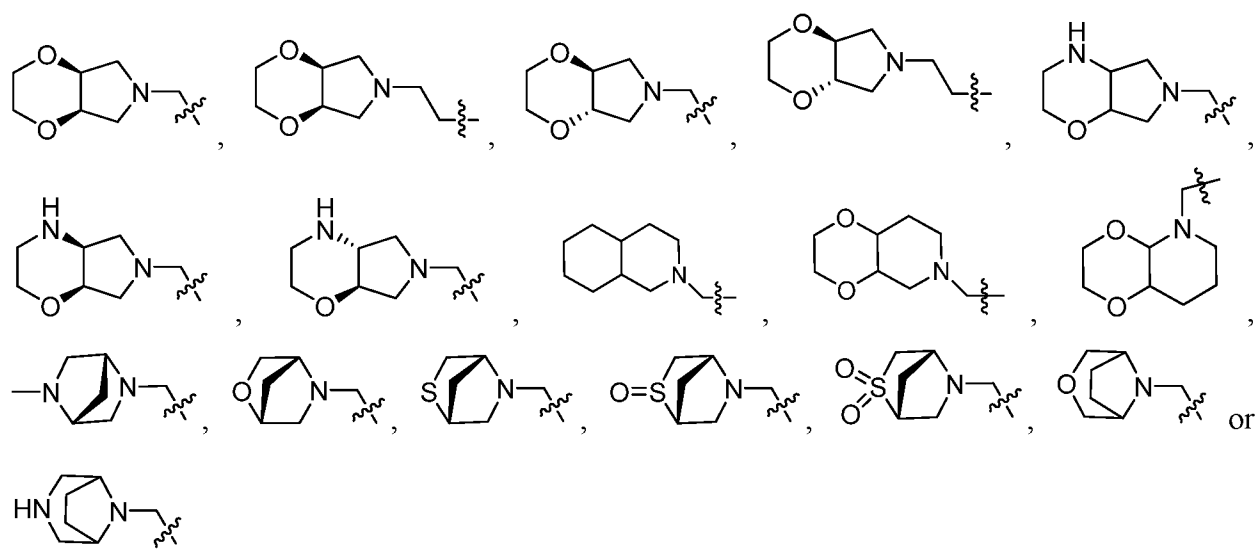
[00209] In other embodiments, R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00210] In other embodiments, each R^2 is independently H, deuterium, F, Cl, Br, I, CN, methyl, ethyl, propyl or isopropyl.

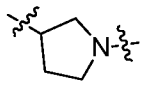
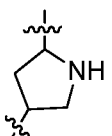
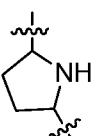
[00211] In other embodiments, each R^3 and R^4 is independently H, deuterium, F, Cl, Br, I, CN, COOH, C_{1-3} alkyl, halo- C_{1-3} -alkyl, C_{1-3} alkoxy- C_{1-3} -alkyl, $-\text{CH}_2\text{-NHMe}$, $-\text{CH}_2\text{-NMe}_2$, $-(\text{CH}_2)_2\text{-NMe}_2$, $-(\text{CH}_2)_3\text{-NMe}_2$, $-\text{CH}_2\text{-NHEt}$, $-\text{CH}_2\text{-NEt}_2$, $-(\text{CH}_2)_2\text{-NEt}_2$, $-(\text{CH}_2)_3\text{-NEt}_2$, oxacyclobutyl, azacyclobutyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, piperazinyl, piperidyl, morpholinylmethyl, thiomorpholinylmethyl, 1-oxidothiomorpholinylmethyl, 1,1-dioxidothiomorpholinylmethyl, morpholinylethyl, thiomorpholinylethyl, 1-oxidothiomorpholinylethyl, 1,1-dioxidothiomorpholinylethyl, morpholinylpropyl, thiomorpholinylpropyl, 1-oxidothiomorpholinylpropyl, 1,1-dioxidothiomorpholinylpropyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, piperidylmethyl, piperidylethyl, piperidylpropyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydropyranylpropyl, pyrrolidinylmethyl, pyrrolidinylethyl or pyrrolidinylpropyl.

[00212] In other embodiments, each R^3 and R^4 is independently

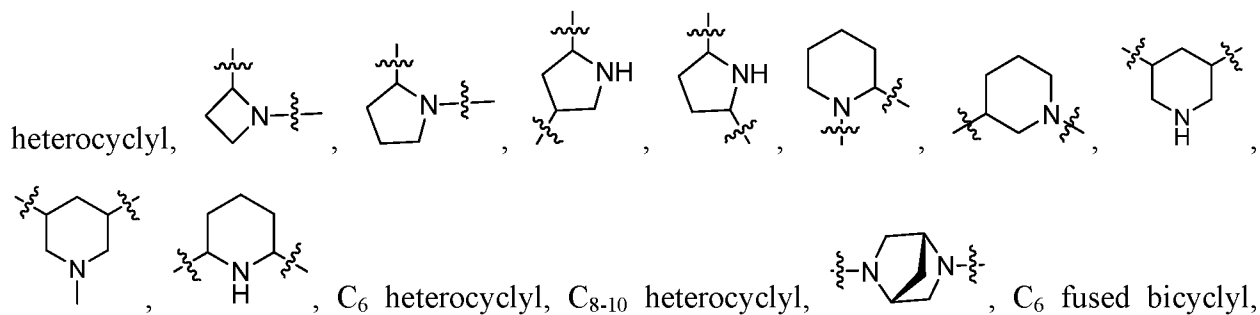


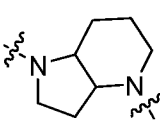
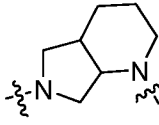
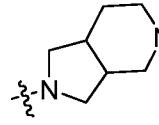


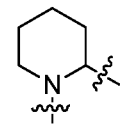
[00213] In some embodiments, each Cy is independently Cy^0 , C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{5-12} fused bicyclyl or C_{5-12} fused heterobicyclyl, and wherein Cy^0 is as defined herein.

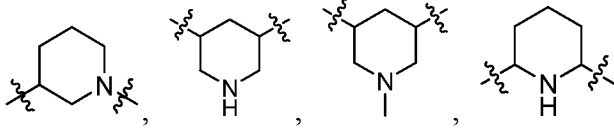
[00214] In some embodiments, Cy^1 is Cy^0 , C_{3-8} cycloalkyl, C_{2-3} heterocyclyl, , , , C_{5-10} heterocyclyl, C_{5-12} fused bicyclyl or C_{5-12} fused heterobicyclyl; and wherein Cy^0 is as defined herein.

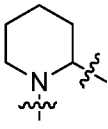
[00215] In some embodiments, Cy^2 is Cy^0 , C_3 cycloalkyl, C_5 cycloalkyl, C_{7-8} cycloalkyl, C_2

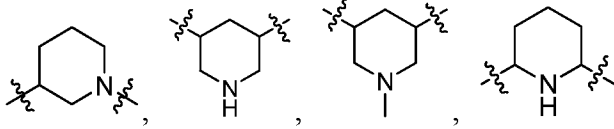


C_{8-12} fused bicyclyl, C_6 fused heterobicyclyl, , ,  or C_{8-12} fused heterobicyclyl; and wherein Cy^0 is as defined herein.

[00216] In some embodiments, Cy^3 is Cy^0 , C_{3-8} cycloalkyl, C_{2-4} heterocyclyl, ,

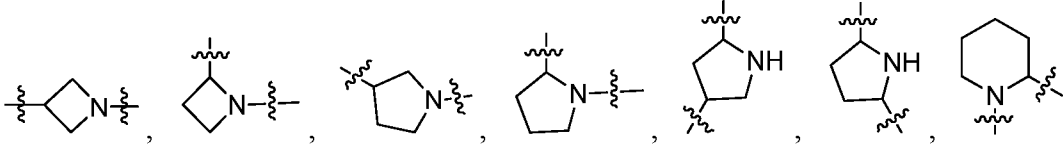
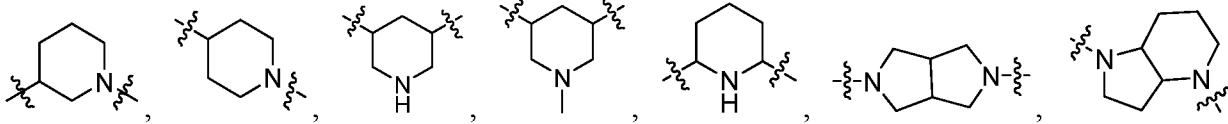
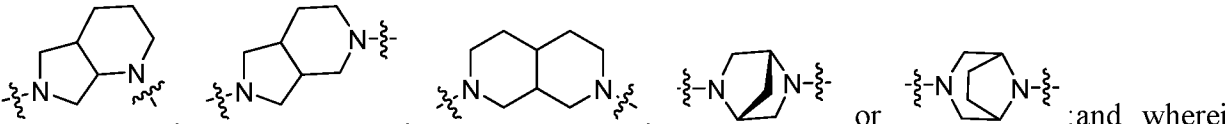
, C₆₋₁₀ heterocyclyl, C₅₋₁₂ fused bicyclyl or C₅₋₁₂ fused heterobicyclyl; and wherein Cy⁰ is as defined herein.

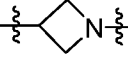
[00217] In some embodiments, Cy⁴ is Cy⁰, C₃₋₈ cycloalkyl, C₂₋₄ heterocyclyl, ,

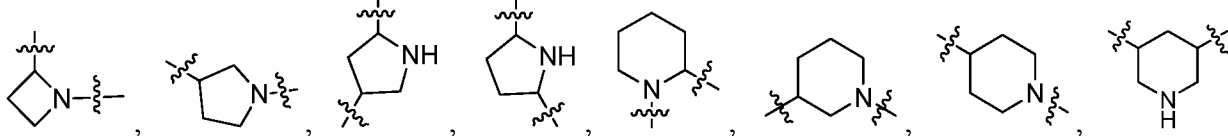
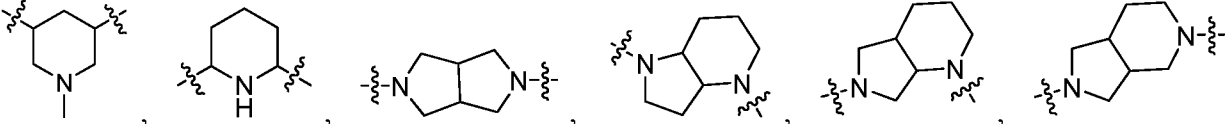
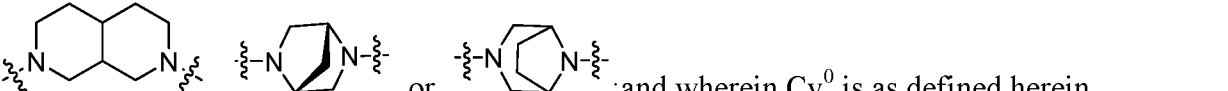
, C₆₋₁₀ heterocyclyl, C₅₋₁₂ fused bicyclyl or C₅₋₁₂ fused heterobicyclyl; and wherein Cy⁰ is as defined herein.

[00218] In some embodiments, each Cy⁰ is independently C₃₋₈ cycloalkenyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₅₋₁₂ spiro bicyclyl or C₅₋₁₂ spiro heterobicyclyl.

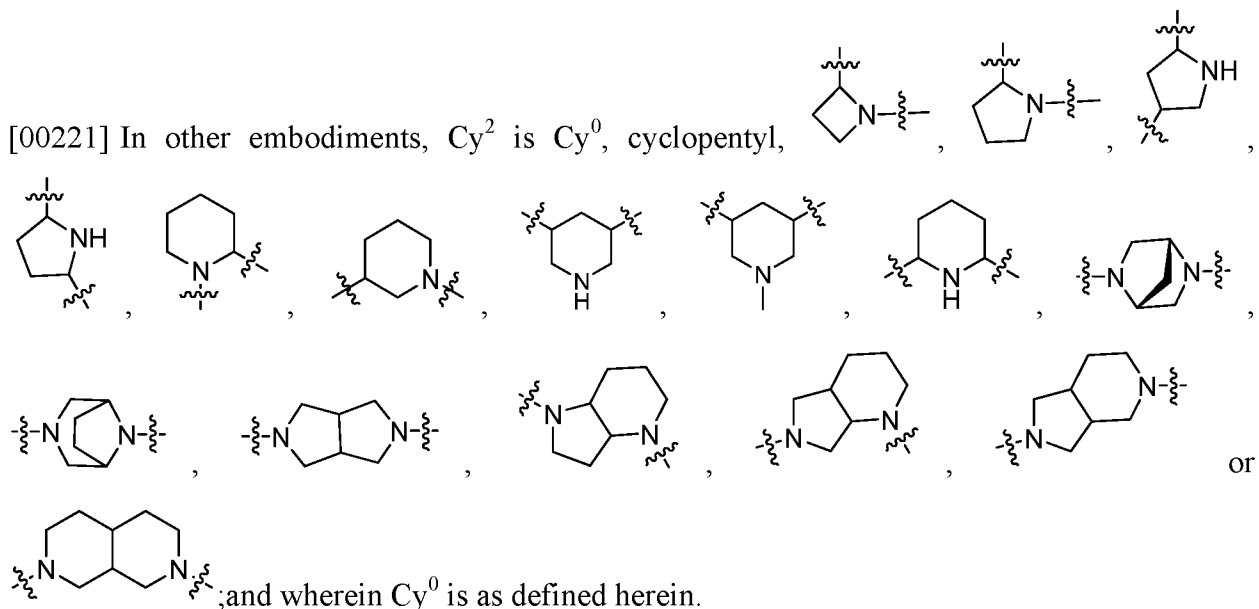
[00219] In other embodiments, each Cy is independently Cy⁰, cyclobutyl, cyclopentyl,

cyclohexyl, , , , and wherein Cy⁰ is as defined herein.

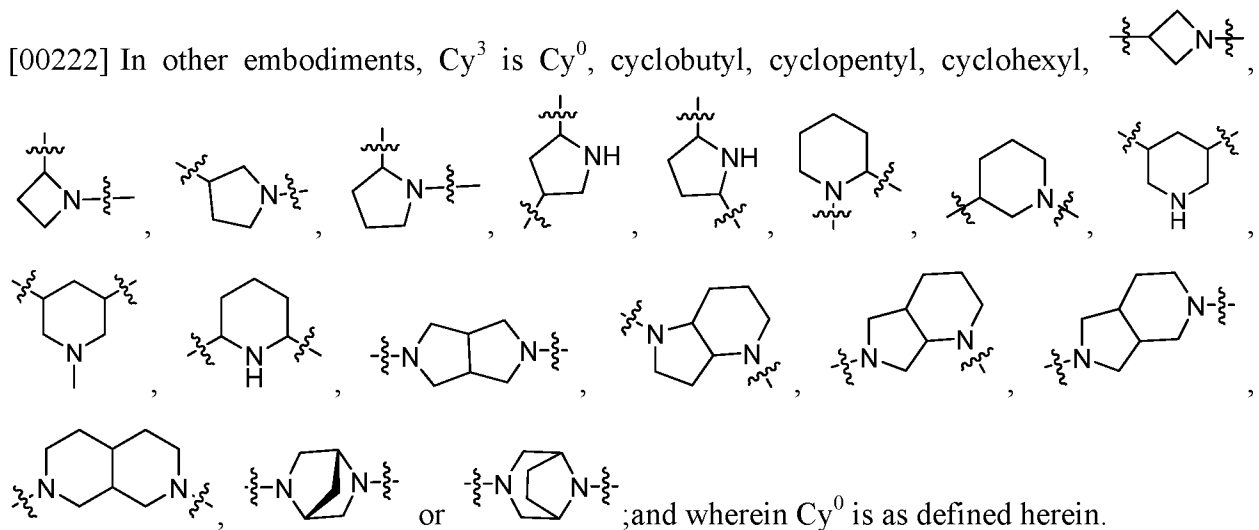
[00220] In other embodiments, Cy¹ is Cy⁰, cyclobutyl, cyclopentyl, cyclohexyl, ,

, , , and wherein Cy⁰ is as defined herein.

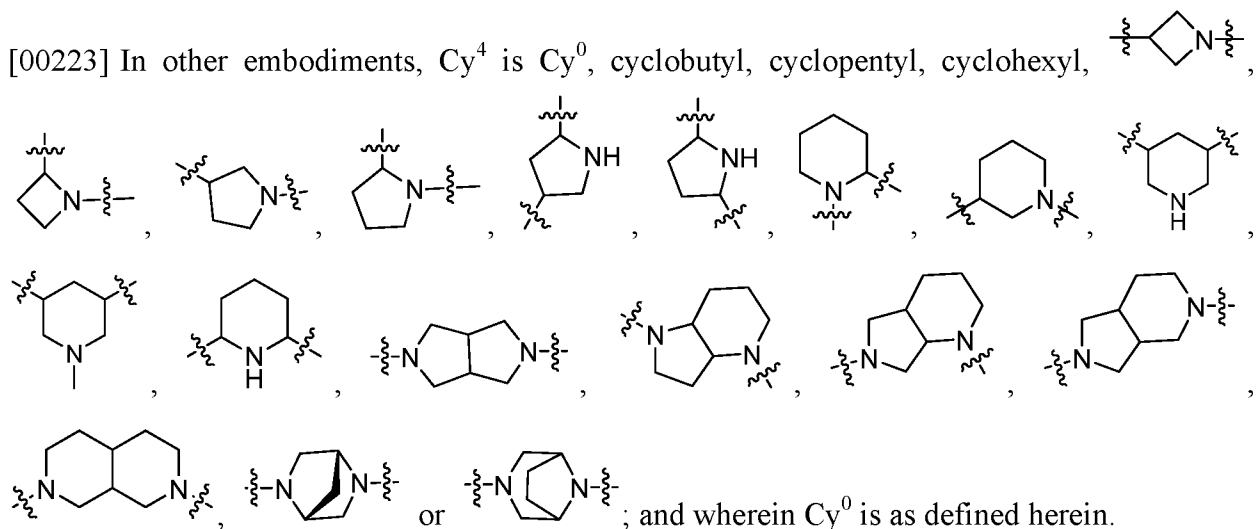
[00221] In other embodiments, Cy^2 is Cy^0 , cyclopentyl,



[00222] In other embodiments, Cy^3 is Cy^0 , cyclobutyl, cyclopentyl, cyclohexyl,

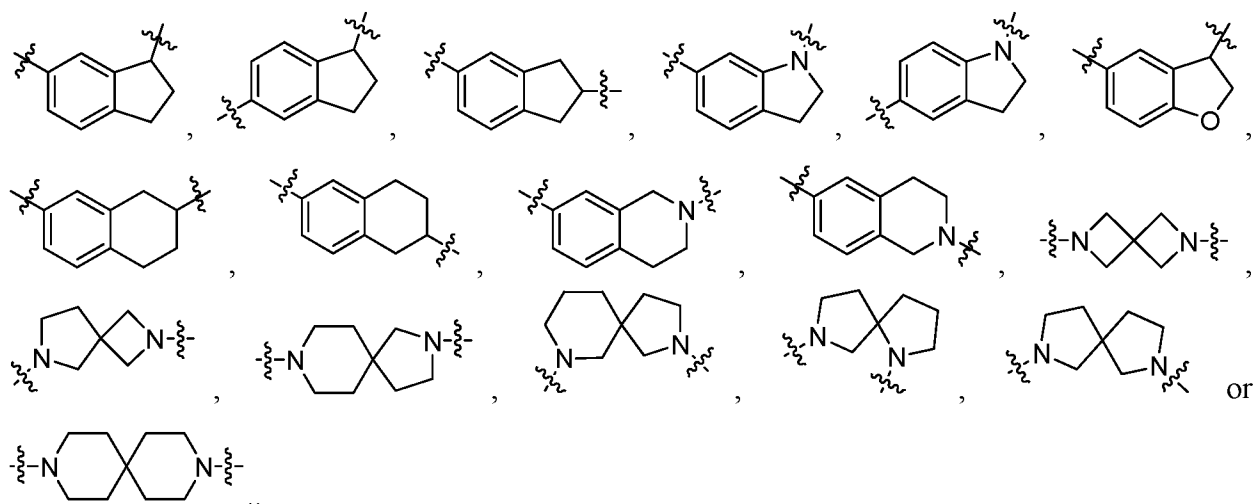


[00223] In other embodiments, Cy^4 is Cy^0 , cyclobutyl, cyclopentyl, cyclohexyl,



[00224] In other embodiments, each Cy^0 is independently cyclobutenyl, cyclopentenyl, cyclohexenyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolinyl, pteridiny, naphthyridinyl,

benzotriazolyl, benzofuranyl, isobenzofuranyl, benzothieryl, benzothiazolyl, 1,2-benzisothiazolyl, benzoxazolyl, benzoisoxazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridinopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl or [1,2,4]triazolo[1,5-*a*]pyridyl. or each Cy⁰ is one of the following groups:



[00225] In some embodiments, each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkylamino, C₆₋₁₀ aryloxy, C₁₋₉ heteroaryloxy, C₂₋₁₀ heterocycloxy, C₆₋₁₀ aryl-C₁₋₆-alkoxy, C₁₋₉ heteroaryl-C₁₋₆-alkoxy, C₂₋₁₀ heterocyclyl-C₁₋₆-alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkyl, C₁₋₆ alkylamino-C₁₋₆-alkylamino, C₃₋₈cycloalkylamino, C₁₋₆ alkylthio, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkylamino, cyano-substituted C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkoxy, cyano-substituted C₁₋₆ alkylamino, amino-substituted C₁₋₆ alkyl, C₁₋₆ alkylacyl, C₁₋₈ heteroalkyl, C₃₋₆ cycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkylamino, C₂₋₁₀ heterocyclylacyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₆₋₁₀ arylamino, C₁₋₉ heteroaryl, C₁₋₉ heteroarylamino, NH₂-C(=O)-, C₁₋₆ alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, C₁₋₆ alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-N(R⁶)-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-N(R⁶)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-C₁₋₆-alkyl-N(R⁶)-C(=O)-, C₁₋₆ alkyl-C(=O)-N(R⁶)-, C₁₋₆

alkyl-N(R⁶)-C(=O)-C₁₋₆-alkyl-N(R⁶)-, C₁₋₆ alkyl-S(=O)₂-, C₁₋₆ alkyl-S(=O)₂-C₁₋₆-alkyl-,
 -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰
 or R¹¹R¹²N-C(=O)-C₁₋₆ alkyl-;

wherein each R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² is as defined herein;

each n is independently 0, 1, 2, 3, or 4; and

each p is independently 0, 1, or 2.

[00226] In some embodiments, each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl.

[00227] In some embodiments, each R¹¹ and R¹² is independently H, deuterium, C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl.

[00228] In some embodiments, R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

[00229] In some embodiments, each R⁵ is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkyl-C(=O)-, cyano-substituted C₁₋₆ alkyl-C(=O)-, C₁₋₆ alkylamino, NH₂-S(=O)₂-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-N(R¹³)-C₁₋₆ alkyl-, halo-C₁₋₆-alkyl, hydroxy-substituted C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy or C₆₋₁₀ aryl-C₁₋₆-alkoxy; and

wherein R¹³ is as defined herein.

[00230] In some embodiments, each R¹³ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl.

[00231] In other embodiments, each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy-C₁₋₄-alkyl, C₁₋₄ alkoxy-C₁₋₄-alkoxy, C₁₋₃ alkoxy-C₁₋₄-alkylamino, C₆₋₁₀ aryloxy, C₁₋₉ heteroaryloxy, C₂₋₁₀ heterocyclloxy, C₆₋₁₀ aryl-C₁₋₃-alkoxy, C₁₋₉ heteroaryl-C₁₋₃-alkoxy, C₂₋₁₀ heterocyclyl-C₁₋₆-alkoxy, C₁₋₄ alkylamino, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₄ alkylamino-C₁₋₄-alkylamino, C₃₋₆ cycloalkylamino, C₁₋₄ alkylthio, halo-C₁₋₄-alkyl, halo-C₁₋₄-alkoxy, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkylamino, cyano-substituted C₁₋₄ alkyl, cyano-substituted C₁₋₄ alkoxy, cyano-substituted C₁₋₄ alkylamino, amino-substituted C₁₋₄ alkyl, C₁₋₄ alkylacyl, C₁₋₈ heteroalkyl, C₃₋₆ cycloalkyl, C₃₋₆

cycloalkenyl, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₄-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₄-alkylamino, C₂₋₁₀ heterocyclylacyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₆₋₁₀ arylamino, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-amino, NH₂-C(=O)-, C₁₋₄ alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-S(=O)₂-N(R⁶)-C₁₋₃-alkyl-, C₆₋₁₀ aryl-C₁₋₃ alkyl-N(R⁶)-C(=O)-, C₁₋₄ alkyl-C(=O)-N(R⁶)-, C₁₋₃ alkyl-N(R⁶)-C(=O)-C₁₋₆ alkyl-N(R⁶)-, C₁₋₄ alkyl-S(=O)₂-, C₁₋₃ alkyl-S(=O)₂-C₁₋₄-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-C₁₋₃-alkyl-;

wherein each R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² is as defined herein;

each n is independently 0, 1, 2, 3, or 4; and

each p is independently 0, 1, or 2.

[00232] In other embodiments, each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl.

[00233] In other embodiments, each R¹¹ and R¹² is independently H, deuterium, C₁₋₃ alkyl, cyano-substituted C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₂₋₆ heterocyclyl or C₂₋₆ heterocyclyl-C₁₋₃-alkyl.

[00234] In other embodiments, R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 8-membered heterocycle.

[00235] In other embodiments, each R⁵ is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₁₋₃ alkyl-C(=O)-, cyano-substituted C₁₋₃ alkyl-C(=O)-, C₁₋₃ alkylamino, NH₂-S(=O)₂-, C₁₋₃ alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-N(R¹³)-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-S(=O)₂-N(R¹³)-C₁₋₃-alkyl-, halo-C₁₋₃-alkyl, hydroxy-substituted C₁₋₃ alkyl, cyano-substituted C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy or C₆₋₁₀ aryl-C₁₋₃-alkoxy; and wherein R¹³ is as defined herein.

[00236] In other embodiments, each R¹³ is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl.

[00237] In other embodiments, X is N or CR^x; and wherein R^x is as defined herein.

[00238] In other embodiments, X³ is CR or N; and wherein R is as defined herein.

[00239] In other embodiments, each of Z¹, Z² and Z³ is independently N or CR^y; and wherein R^y is as defined herein.

[00240] In other embodiments, R is H, deuterium, F, Cl, Br, I, CN, OH, NO₂, COOH, C₁₋₃ alkyl or C₁₋₃ alkoxy.

[00241] In other embodiments, each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylamino, C₁₋₃ alkylamino-C₁₋₄-alkylamino or halo-C₁₋₃-alkyl.

[00242] In other embodiments, L¹ is -O-, -N(R^{1a})-, -S(=O)_p-, -C(=O)-, -C(=O)-NH- or -S(=O)_p-NH-; and wherein R^{1a} is as defined herein.

[00243] In other embodiments, L² is a bond, -O-, -N(R^{1a})-, -CH₂-N(R^{1a})-, -CH(CH₃)-N(R^{1a})-, -C(CH₃)₂-N(R^{1a})-, -C(=O)-NH- or -S(=O)_p-NH-; and wherein R^{1a} is as defined herein.

[00244] In other embodiments, L³ is -C(=O)- or -S(=O)₂-.

[00245] In other embodiments, each p is independently 0, 1, or 2.

[00246] In other embodiments, each R^{1a} is independently H, deuterium, C₁₋₃ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl.

[00247] In other embodiments, X is N or CR^x; and wherein R^x is as defined herein.

[00248] In other embodiments, X³ is CR or N; and wherein R is as defined herein.

[00249] In other embodiments, each of Z¹, Z² and Z³ is independently N or CR^y; and wherein R^y is as defined herein.

[00250] In other embodiments, R is H, deuterium, F, Cl, Br, I, CN, OH, NO₂, COOH, methyl, ethyl or methoxy.

[00251] In other embodiments, each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, methyl, ethyl, propyl, -CF₃, -CH₂Cl, -CCl₃, -CH₂CF₃, -CF₂CF₃, -CH₂CCl₃, methoxy, ethoxy, propoxy, isopropoxy, -NH-CH₃, -NH-CH₂-CH₃, -NH-CH₂-NH-CH₃, -N(CH₃)-CH₂-NH-CH₃, -NH-(CH₂)₂-NH-CH₃ or -N(CH₃)-(CH₂)₂-N(CH₃)₂.

[00252] In other embodiments, L¹ is -O-, -NH-, -S(=O)_p-, -C(=O)-, -C(=O)-NH- or -S(=O)_p-NH-.

[00253] In other embodiments, L² is a bond, -O-, -NH-, -CH₂-NH-, -CH(CH₃)-NH- or -C(CH₃)₂-NH-.

[00254] In other embodiments, L³ is -C(=O)- or -S(=O)₂-.

[00255] In other embodiments, each p is independently 0, 1 or 2.

[00256] In other embodiments, X is N or CH.

[00257] In other embodiments, X³ is CH or N.

[00258] In other embodiments, each of Z^1 and Z^2 is independently N or CR^y ; and wherein each R^y is as defined herein.

[00259] In other embodiments, W is O, S, CH_2 or NH.

[00260] In other embodiments, each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, methyl, ethyl, methoxy or ethoxy.

[00261] In other embodiments, L^1 is -O-, -NH-, $-S(=O)_p$ -, $-C(=O)$ -, $-C(=O)-NH$ - or $-S(=O)_p-NH$ -.

[00262] In other embodiments, L^2 is a bond, -O-, -NH-, $-CH_2-NH$ -, $-CH(CH_3)-NH$ - or $-C(CH_3)_2-NH$ -.

[00263] In other embodiments, L^3 is $-C(=O)$ - or $-S(=O)_2$ -.

[00264] In other embodiments, X is N or CR^x ; and wherein R^x is as defined herein.

[00265] In other embodiments, X^3 is CR or N; and wherein R is as defined herein.

[00266] In other embodiments, R is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , COOH, C_{1-3} alkyl or C_{1-3} alkoxy.

[00267] In other embodiments, L^1 is -O-, $-N(R^{1a})$ -, $-S(=O)_p$ -, $-C(=O)$ - or $-S(=O)_p-NH$ -; and wherein R^{1a} is as defined herein.

[00268] In other embodiments, L^3 is $-C(=O)$ - or $-S(=O)_2$ -.

[00269] In other embodiments, m is 0, 1 or 2.

[00270] In other embodiments, q is 1, 2 or 3.

[00271] In other embodiments, each p is independently 0, 1 or 2.

[00272] In other embodiments, R^{1a} is H, deuterium, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

[00273] In other embodiments, X is N or CH.

[00274] In other embodiments, X^3 is N or CH.

[00275] In other embodiments, L^1 is -O-, -NH-, $-S(=O)_p$ -, $-C(=O)$ - or $-S(=O)_p-NH$ -.

[00276] In other embodiments, L^3 is $-C(=O)$ - or $-S(=O)_2$ -.

[00277] In other embodiments, m is 0, 1 or 2.

[00278] In other embodiments, q is 1, 2 or 3.

[00279] In other embodiments, each p is independently 0, 1 or 2.

[00280] In other embodiments, X is CH or N.

[00281] In other embodiments, X^2 is CH or N.

[00282] In other embodiments, X^3 is CH or N.

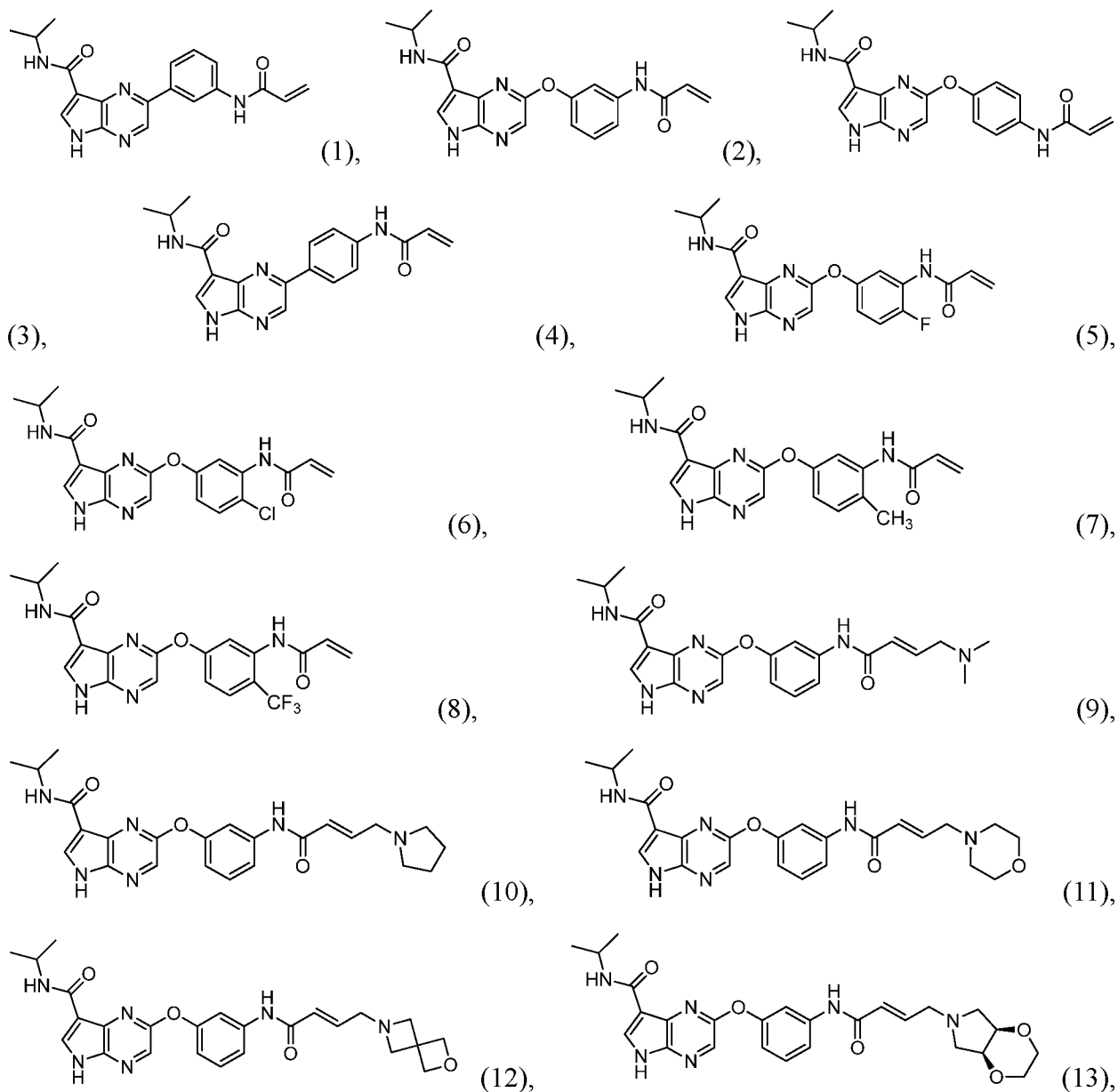
[00283] In other embodiments, each of Z^1 , Z^2 and Z^3 is independently N or CH.

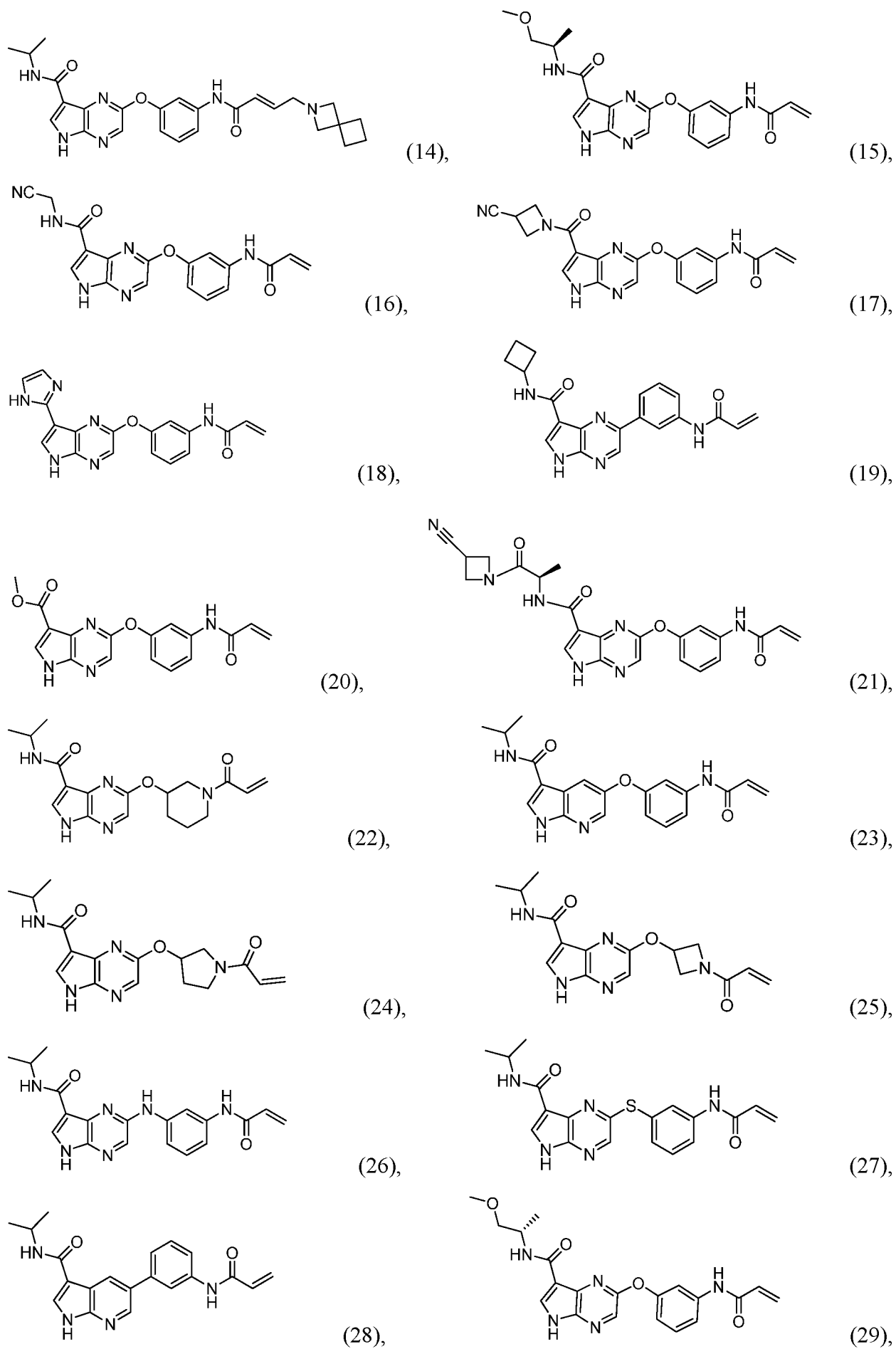
[00284] In other embodiments, L^1 is -O-, -NH-, -S(=O)_p-, -C(=O)-, -C(=O)-NH- or -S(=O)_p-NH-.

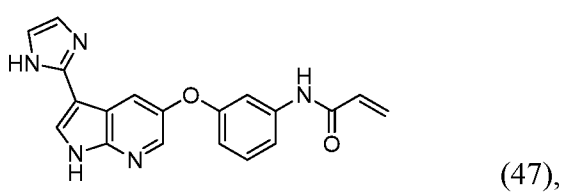
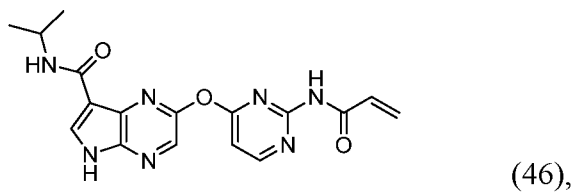
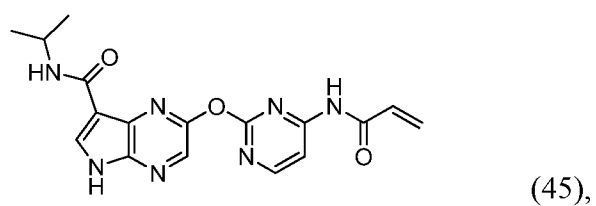
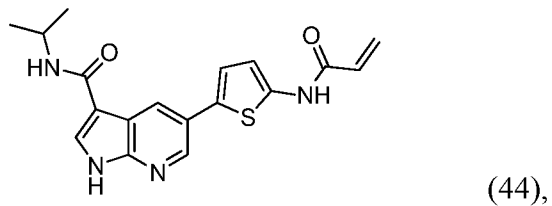
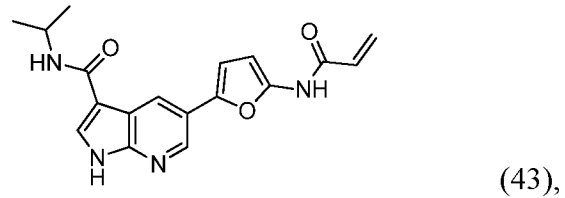
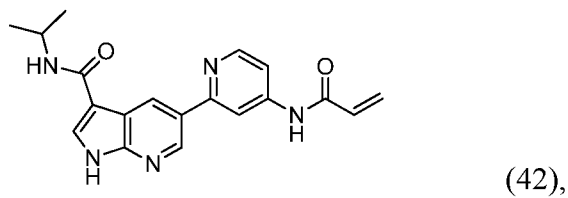
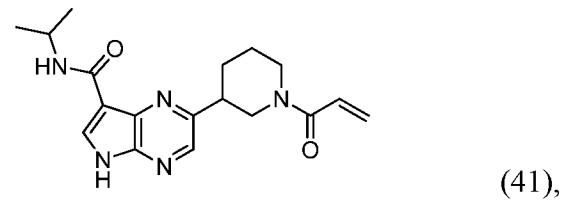
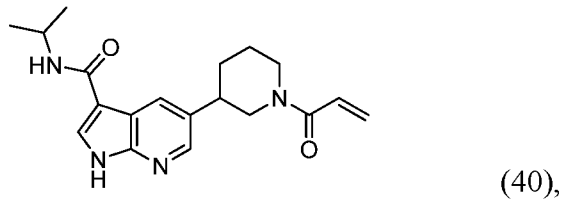
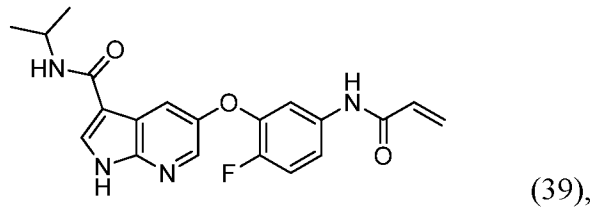
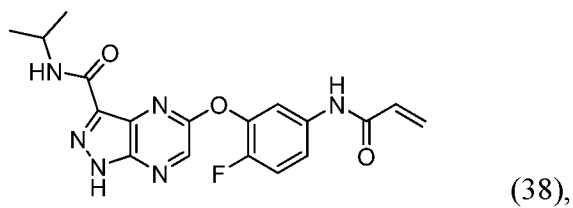
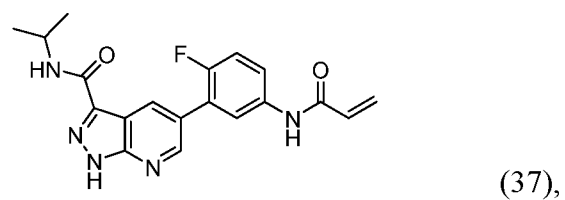
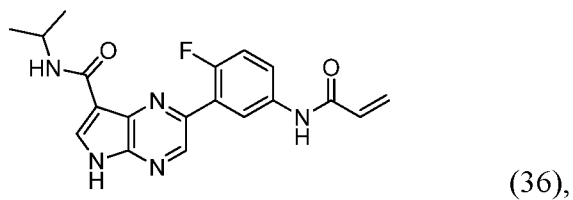
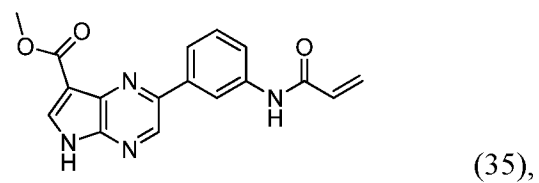
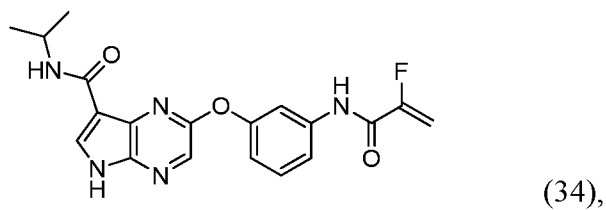
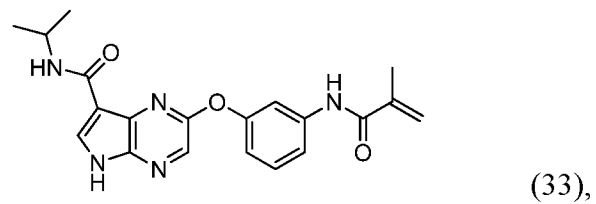
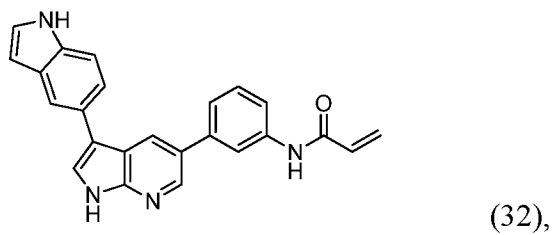
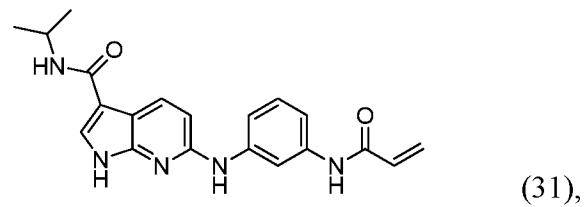
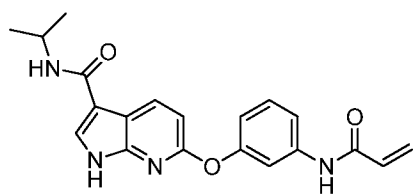
[00285] In other embodiments, L^2 is a bond, -O-, -NH-, -CH₂-NH-, -CH(CH₃)-NH- or -C(CH₃)₂-NH-.

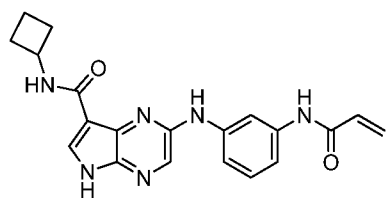
[00286] In other embodiments, L^3 is -C(=O)- or -S(=O)₂-.

[00287] In one aspect, provided herein is a compound having one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

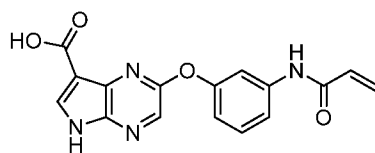




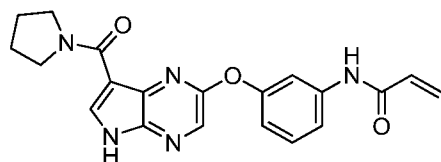




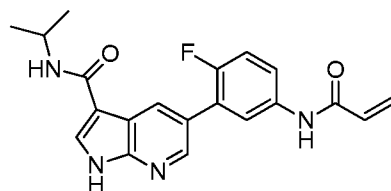
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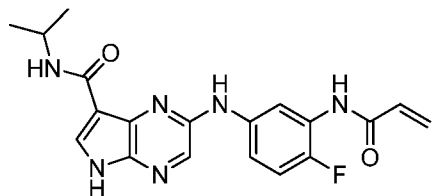
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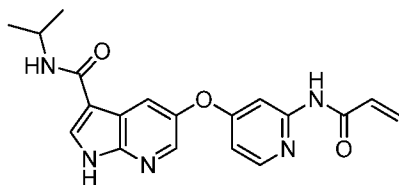
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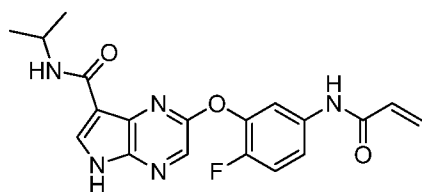
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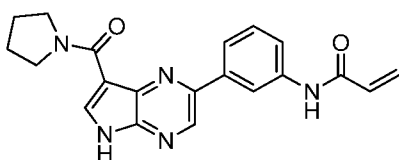
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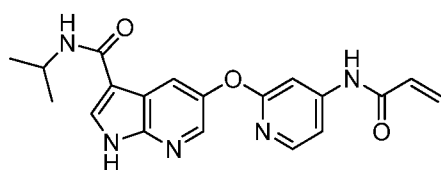
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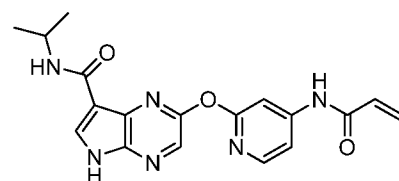
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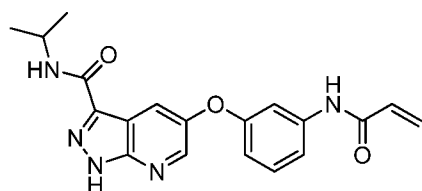
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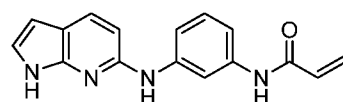
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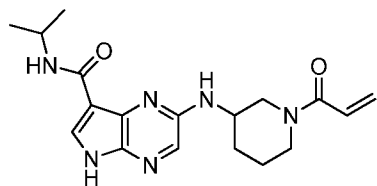
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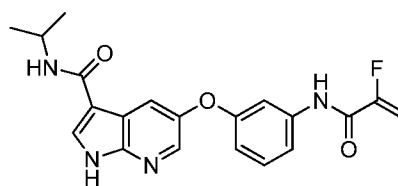
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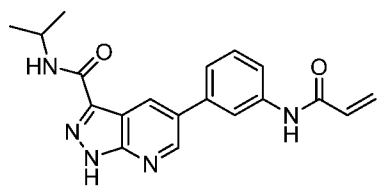
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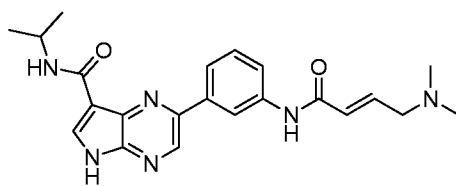
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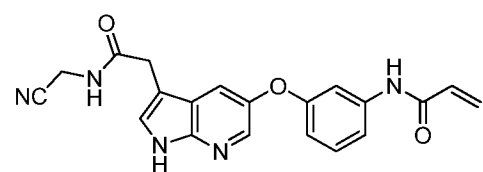
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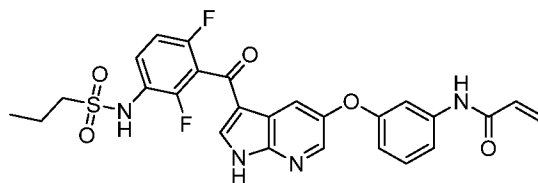
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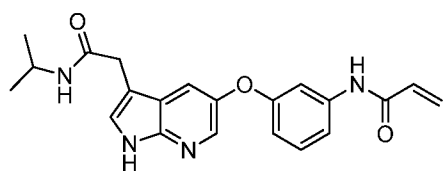
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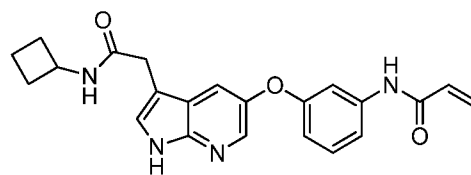
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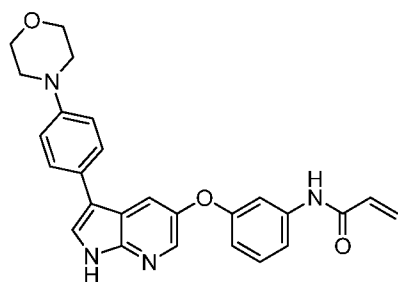
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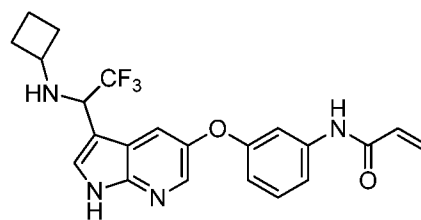
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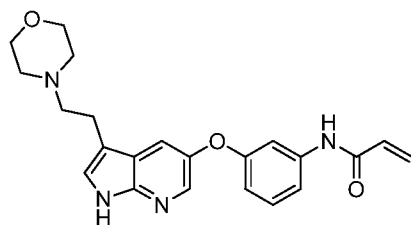
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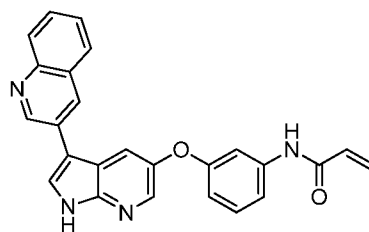
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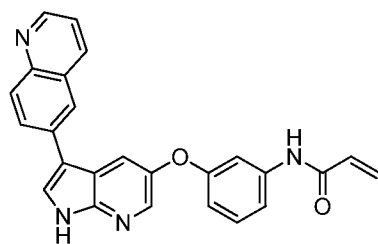
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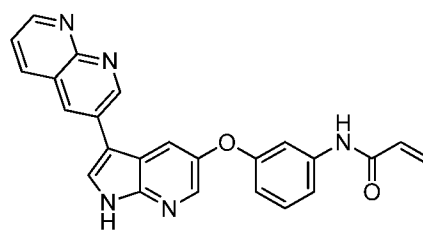
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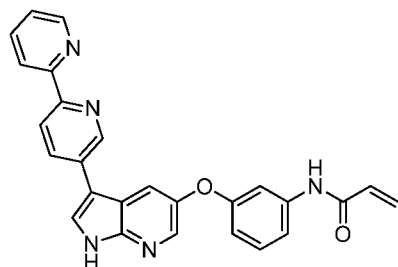
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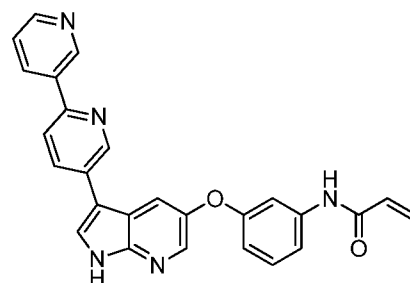
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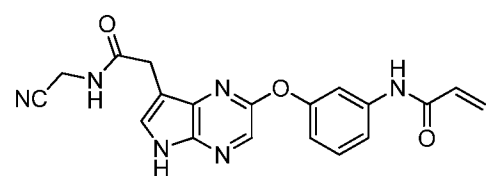
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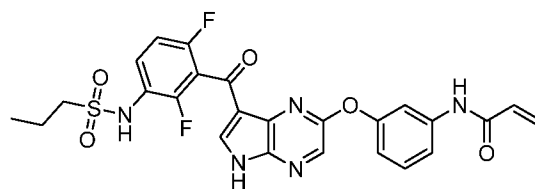
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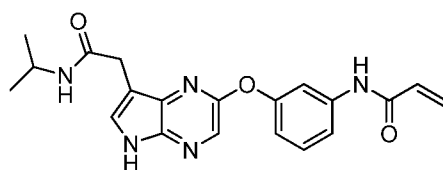
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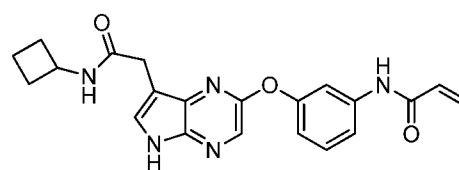
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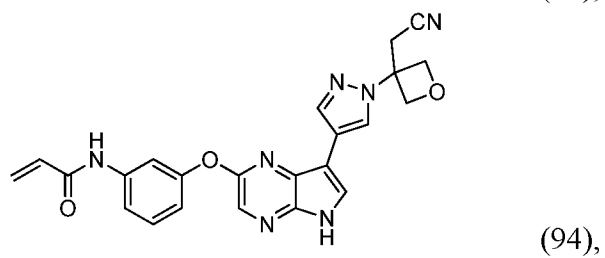
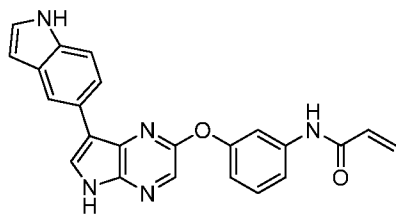
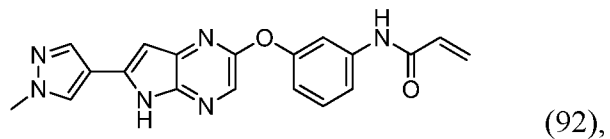
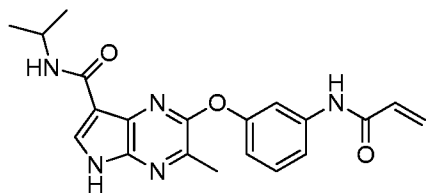
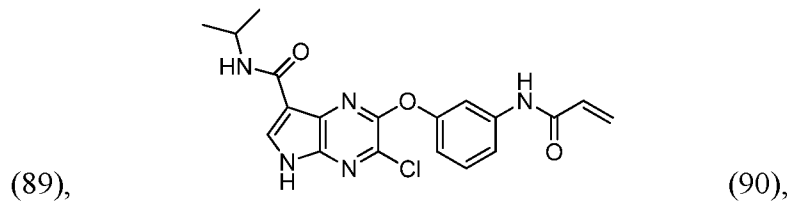
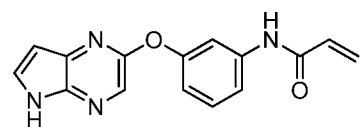
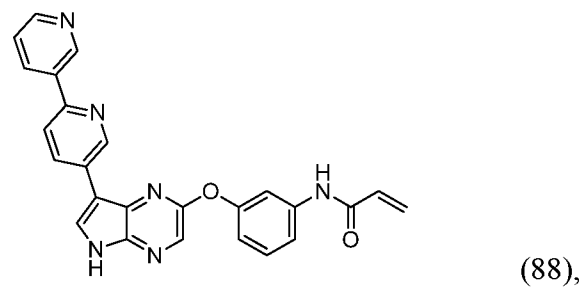
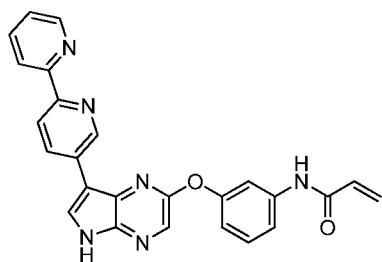
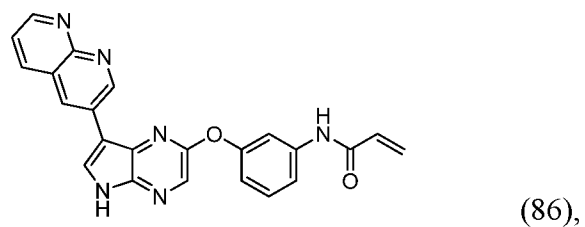
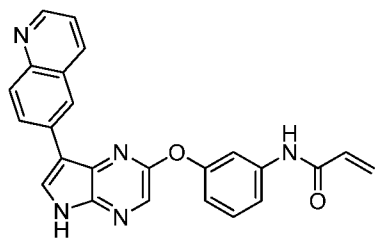
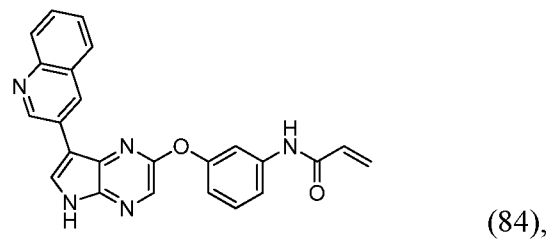
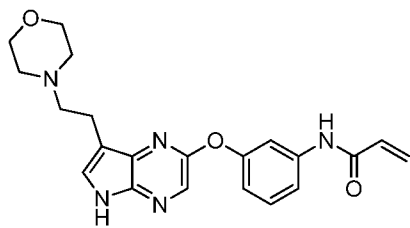
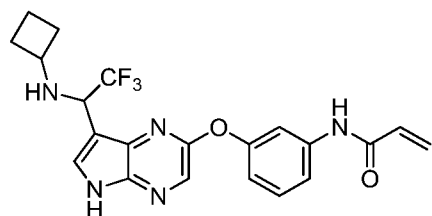
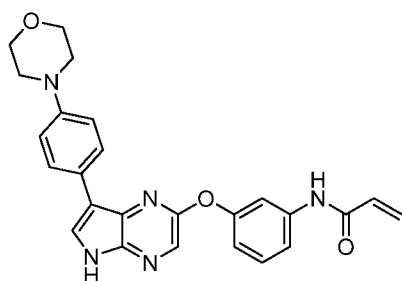
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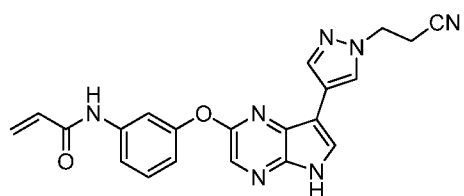


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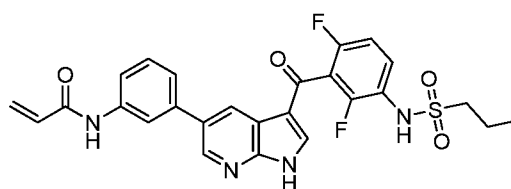


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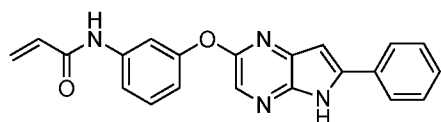




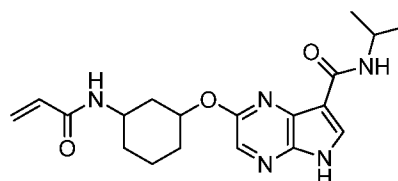
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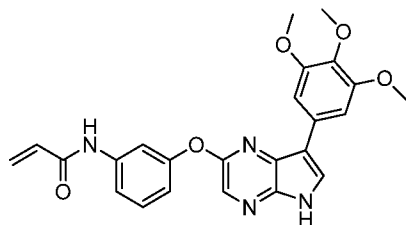
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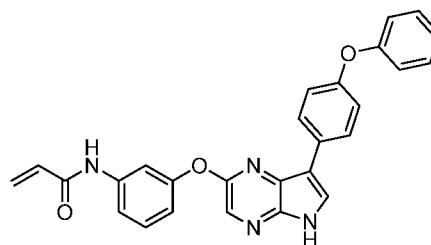
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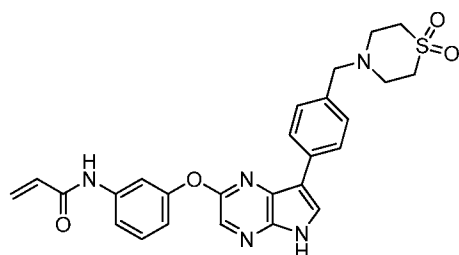
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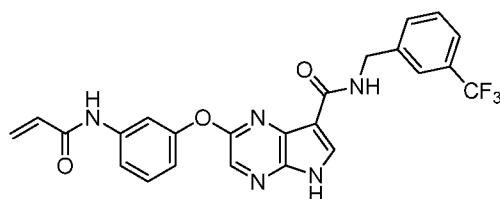
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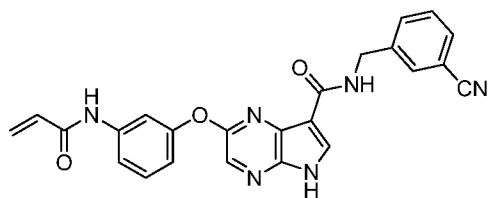
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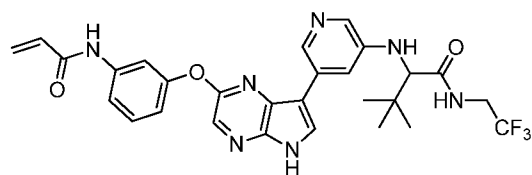
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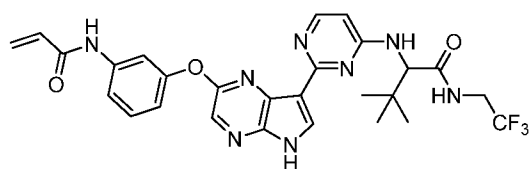
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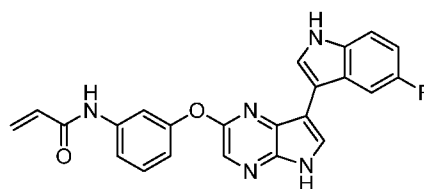
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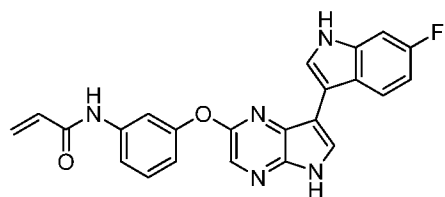
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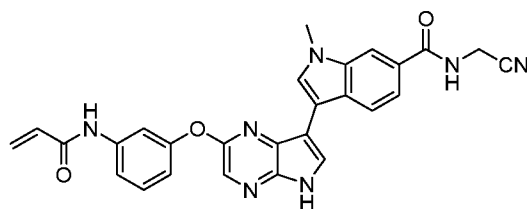
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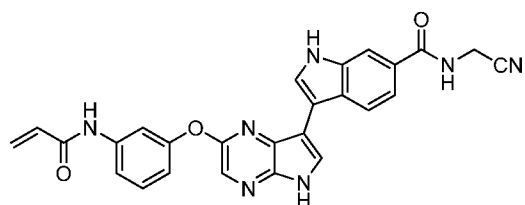
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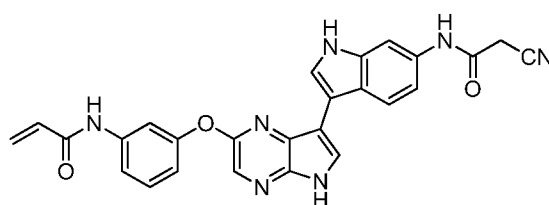
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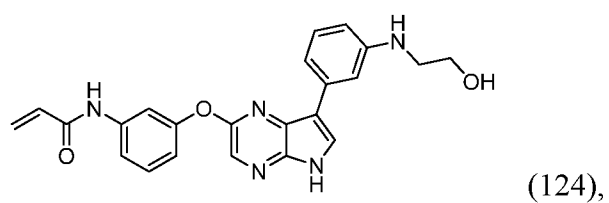
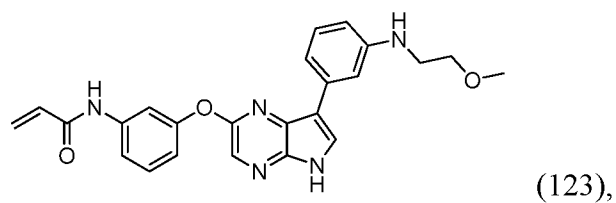
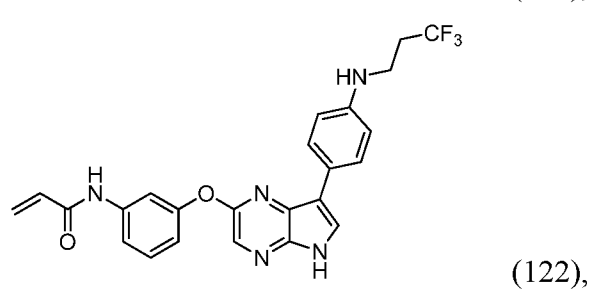
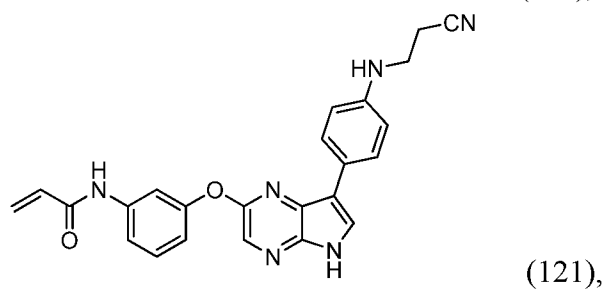
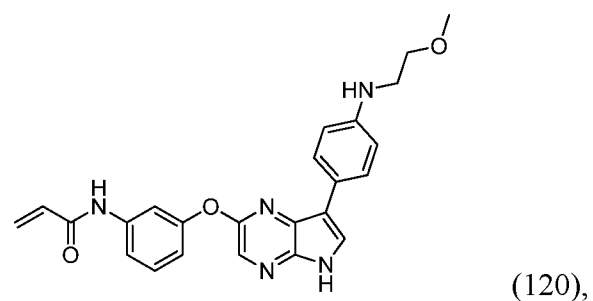
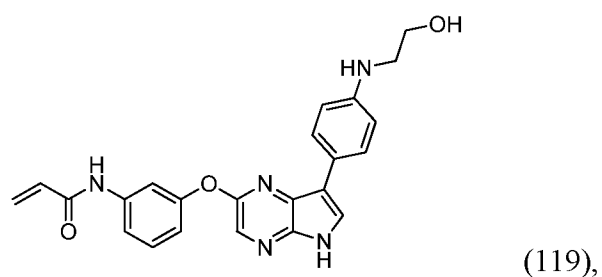
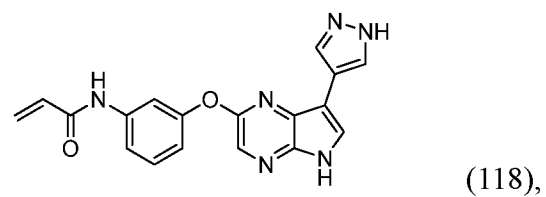
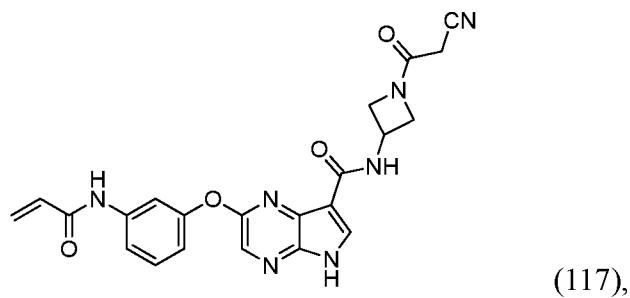
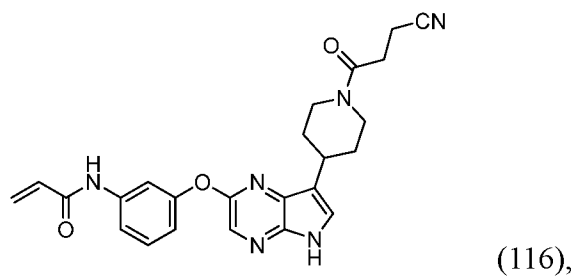
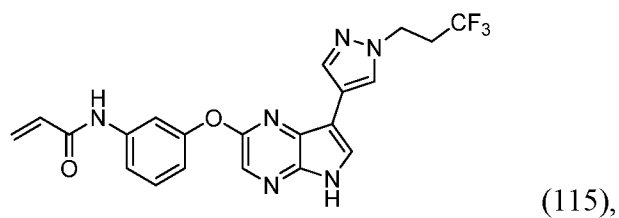
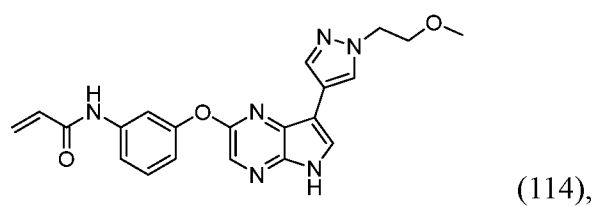
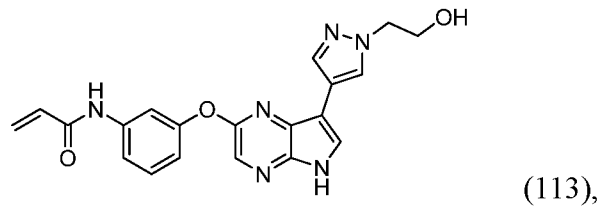
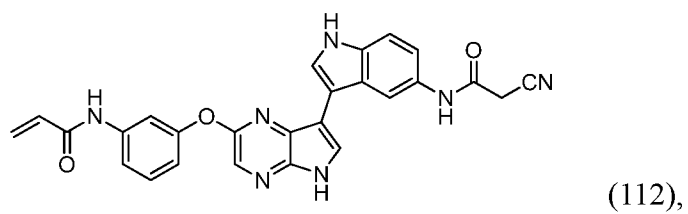
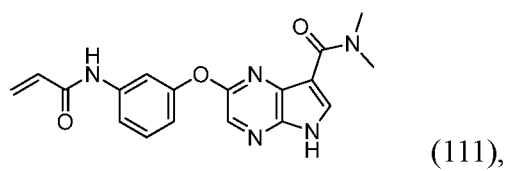
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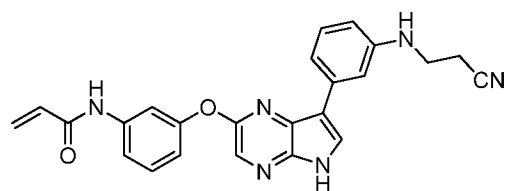


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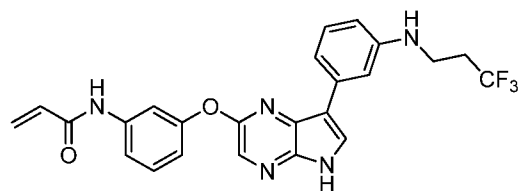


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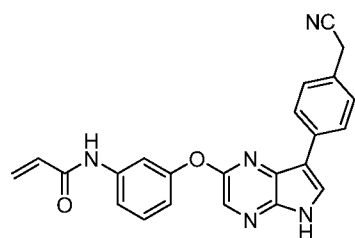




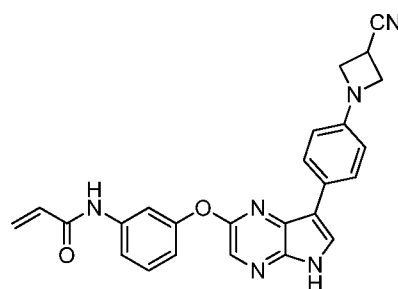
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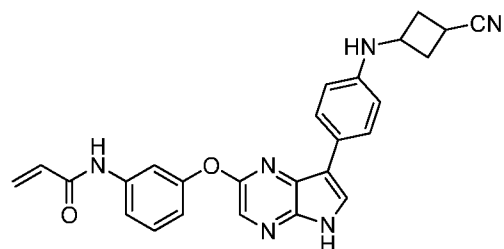
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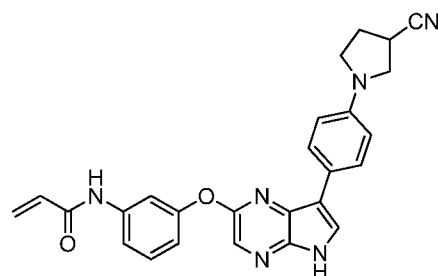
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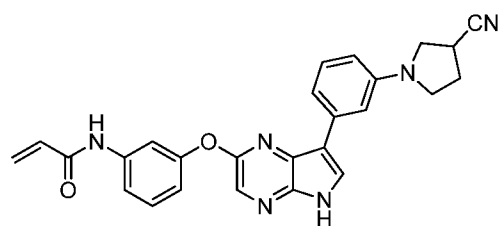
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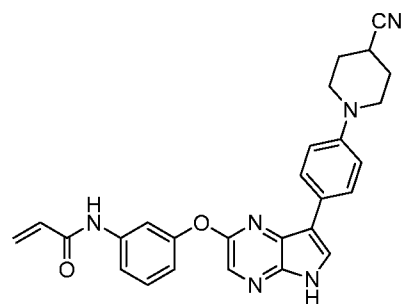
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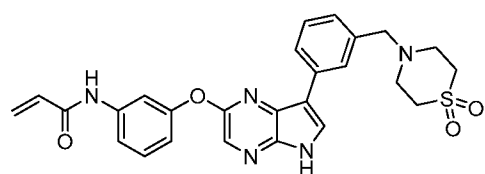
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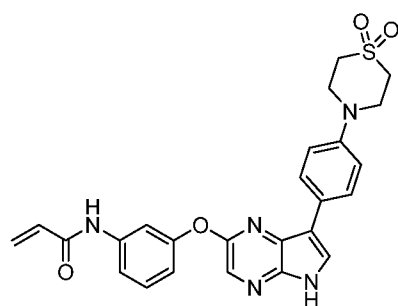
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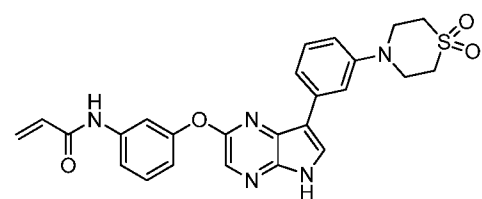
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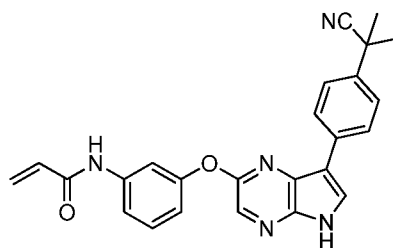
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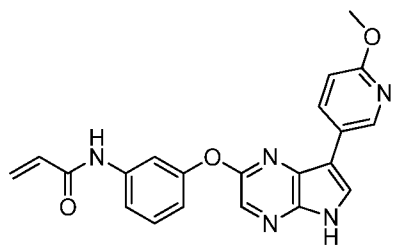
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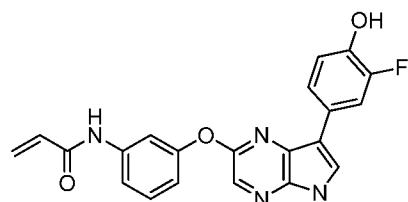
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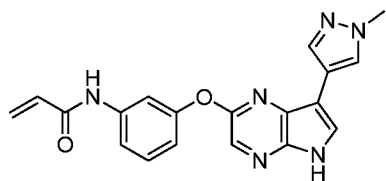
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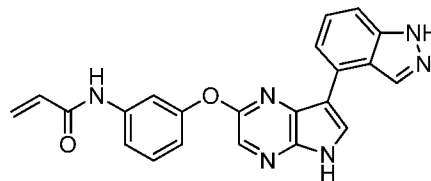
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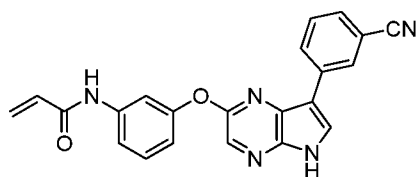
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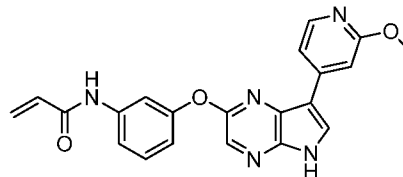
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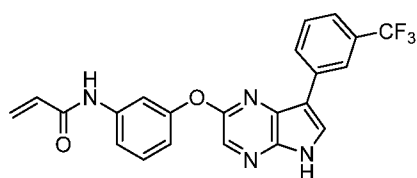
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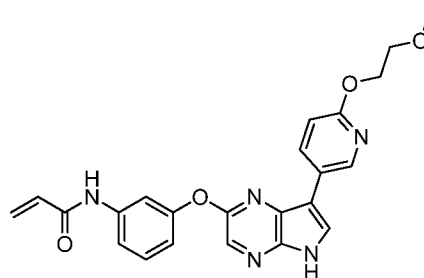
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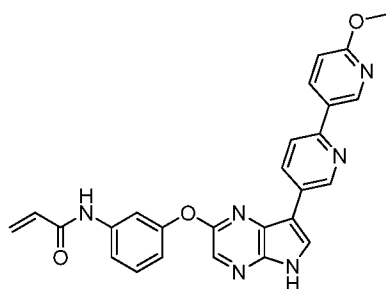
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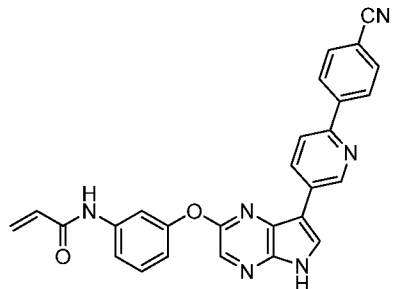
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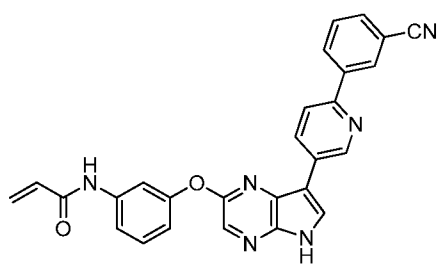
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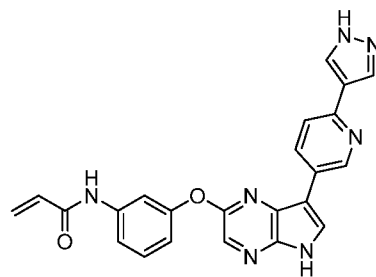
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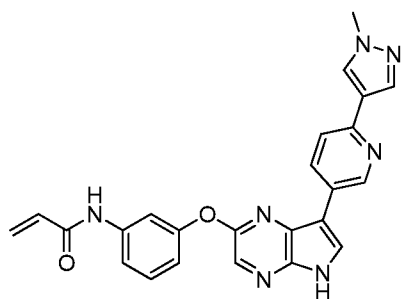
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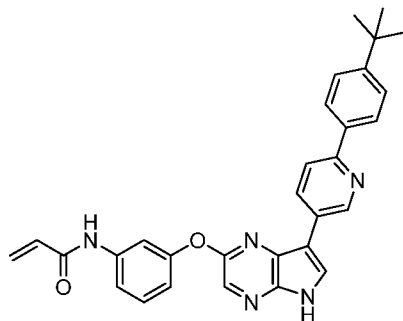
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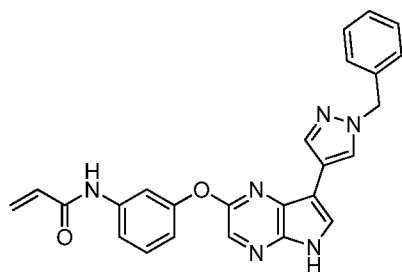
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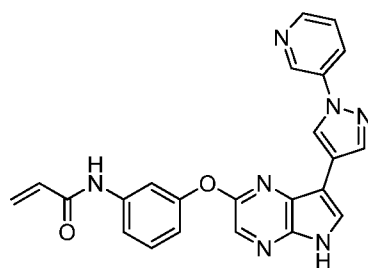
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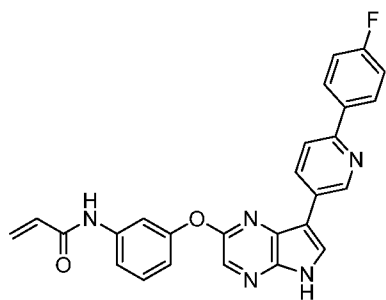
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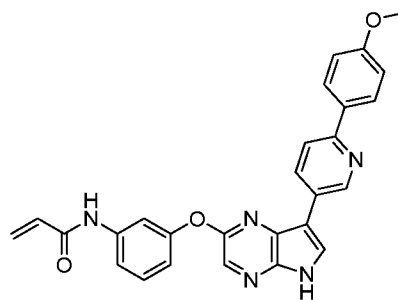
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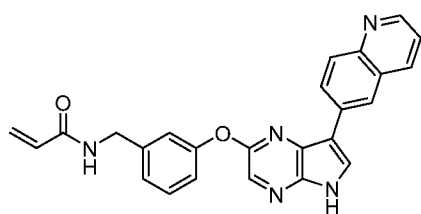
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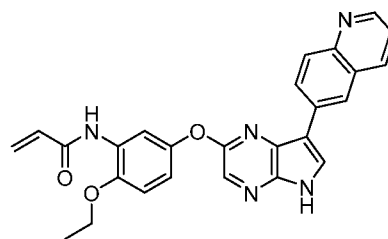
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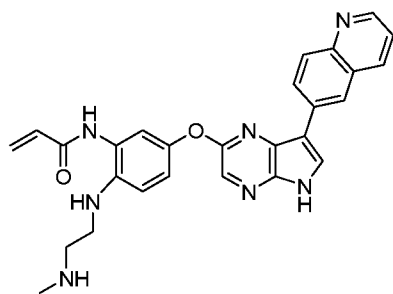
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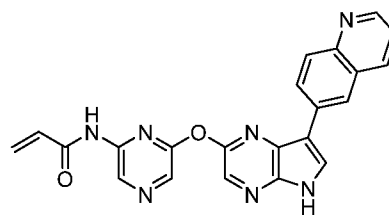
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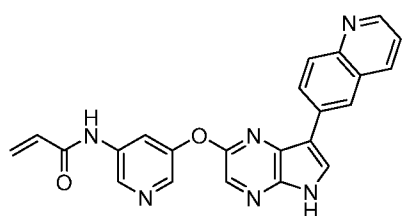
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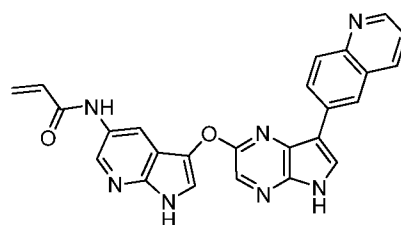
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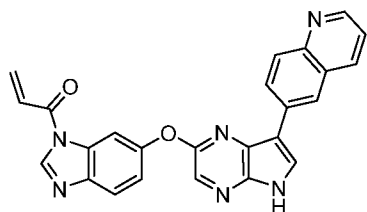
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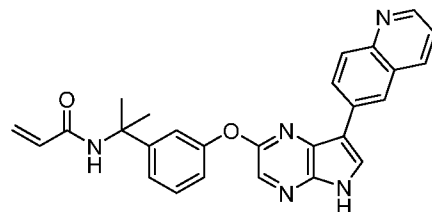
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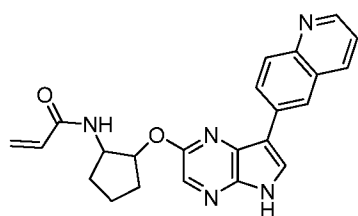
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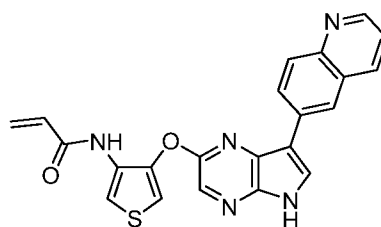
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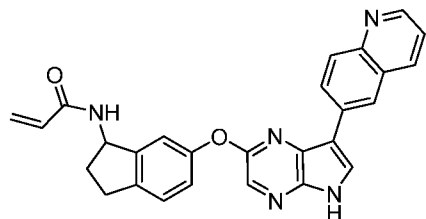
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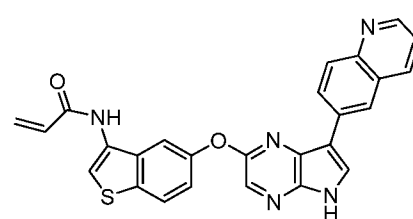
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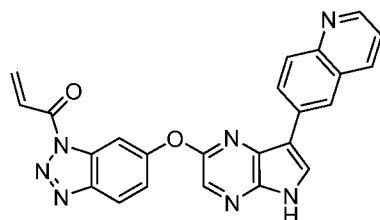
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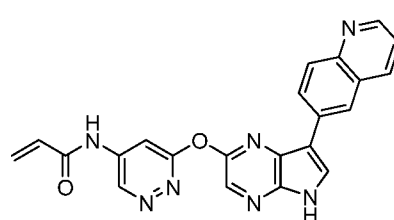
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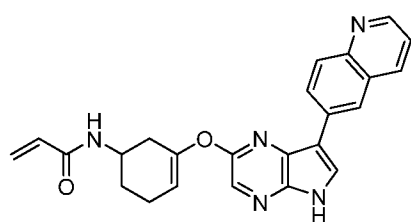
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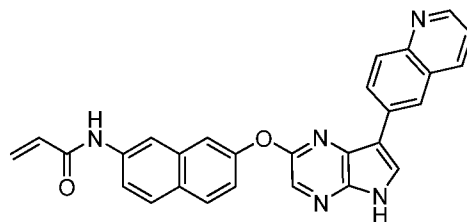
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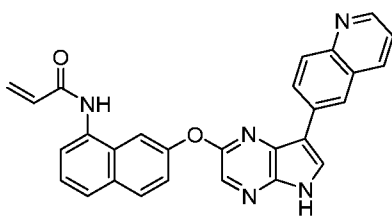
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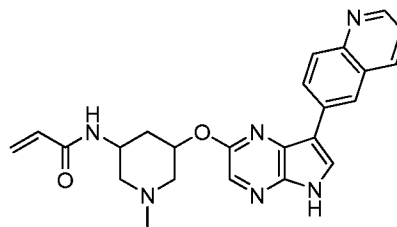
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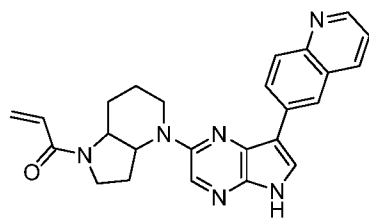
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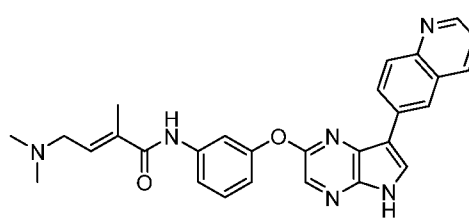
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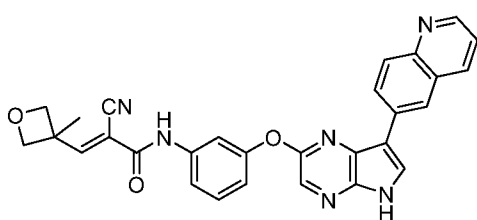
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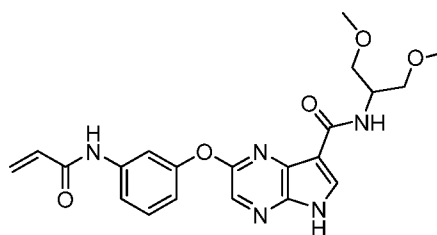
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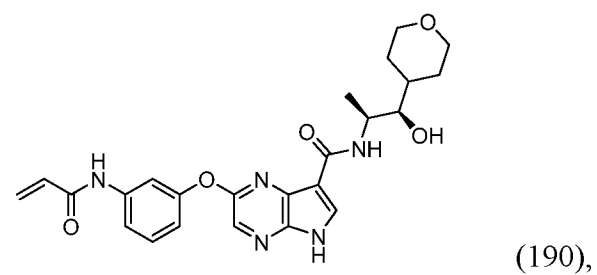
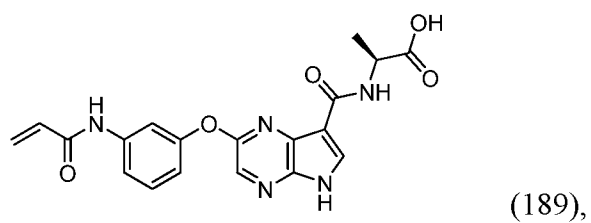
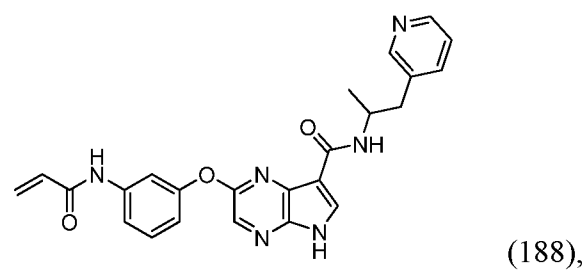
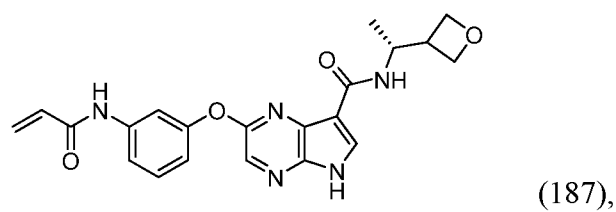
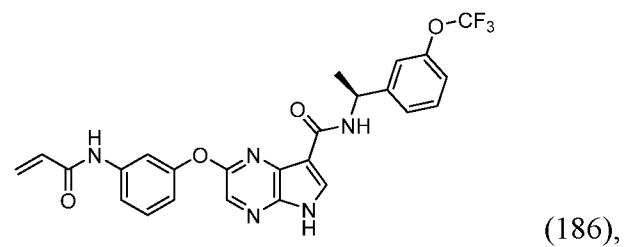
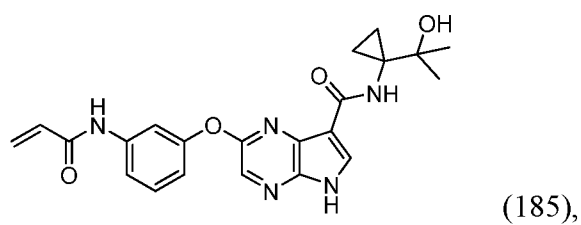
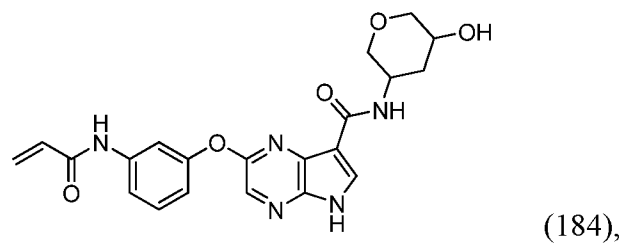
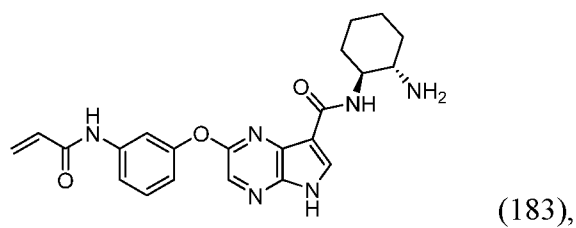
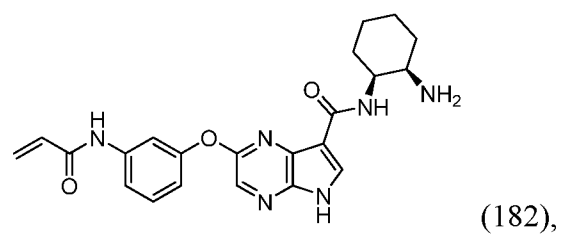
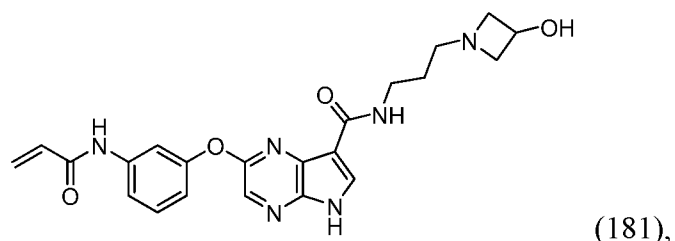
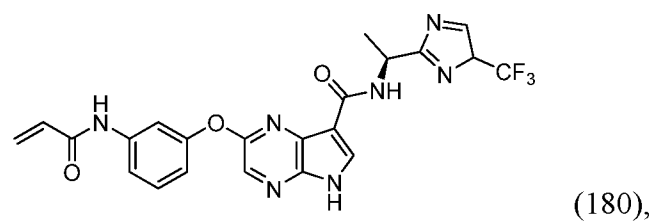
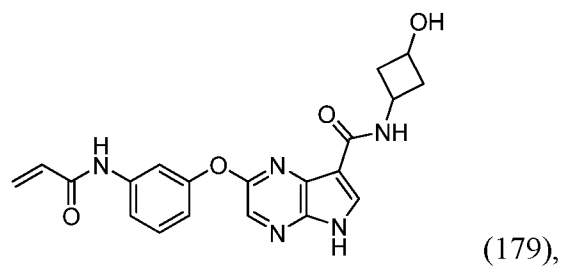
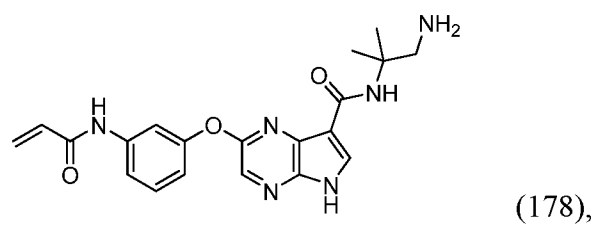
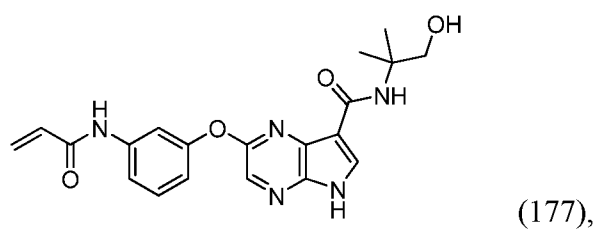
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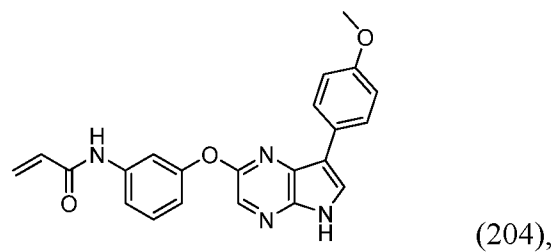
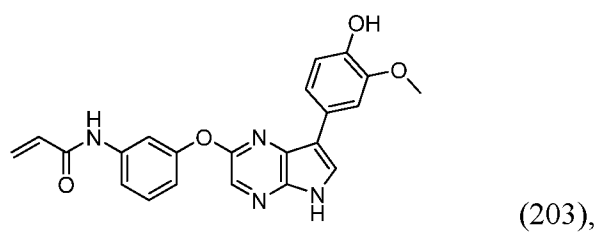
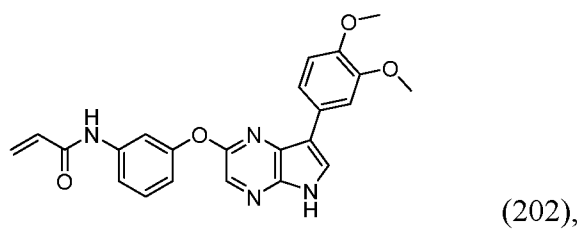
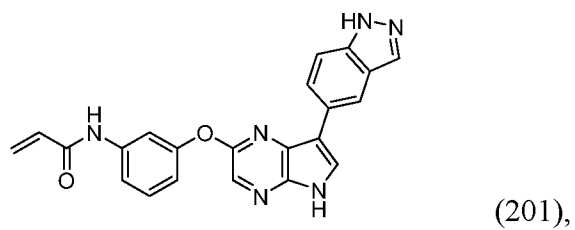
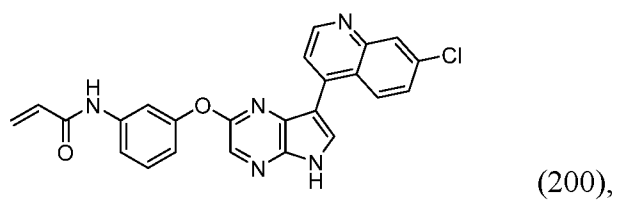
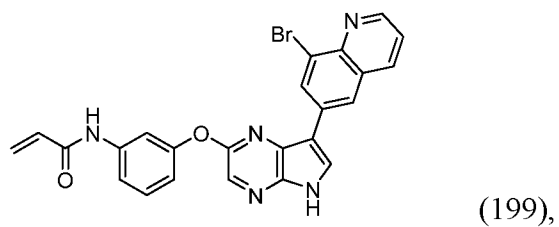
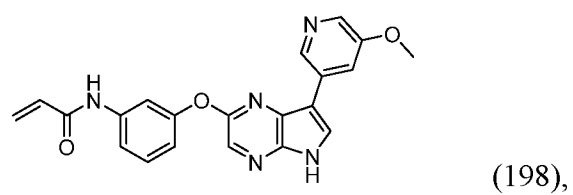
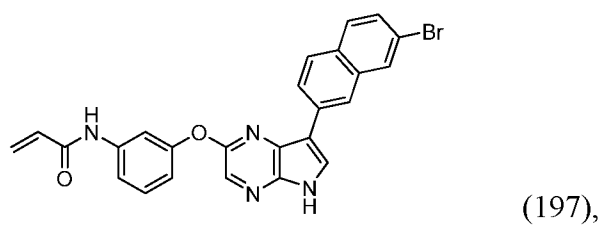
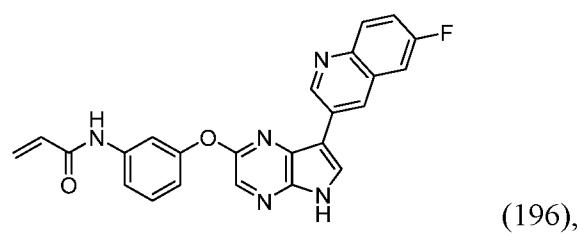
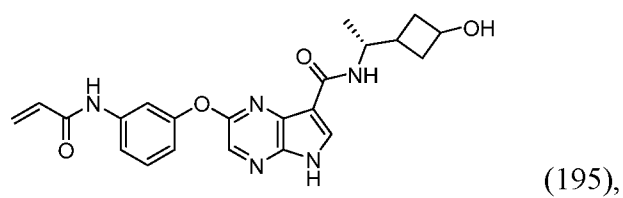
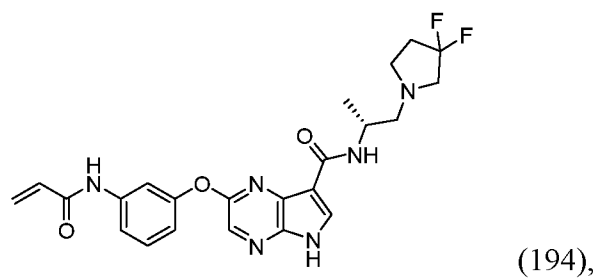
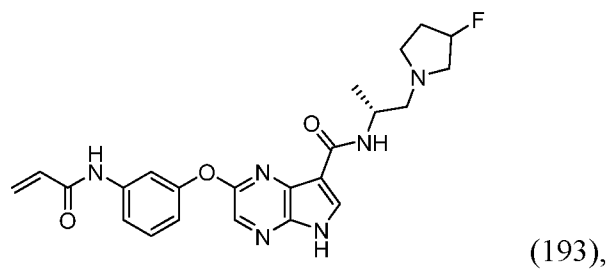
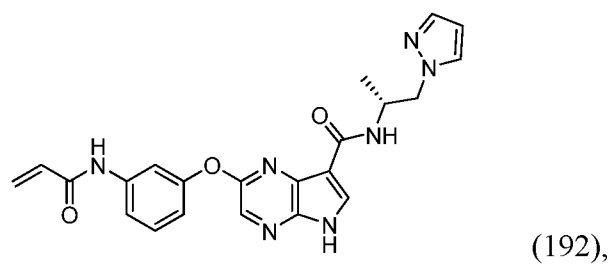
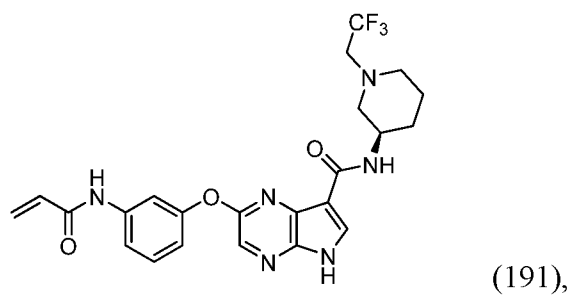


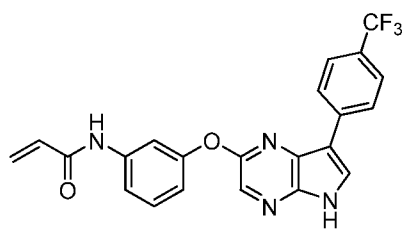
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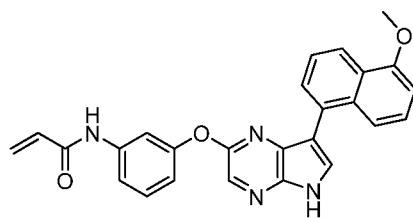
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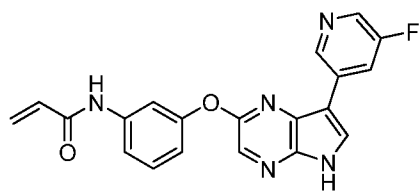




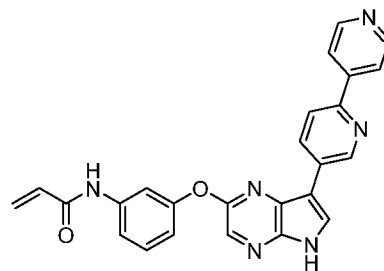
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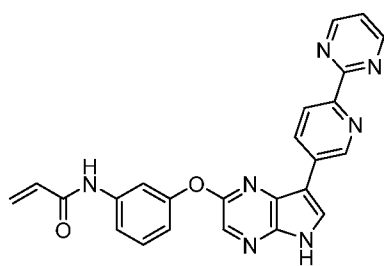
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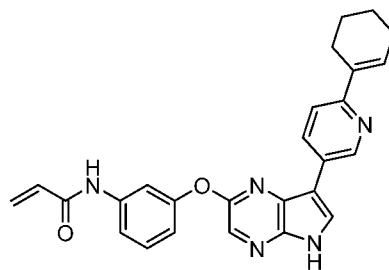
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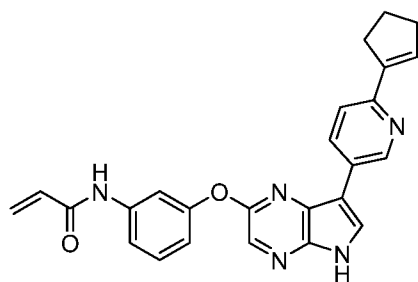
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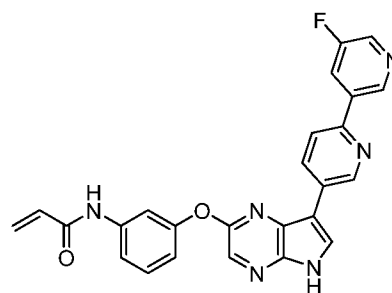
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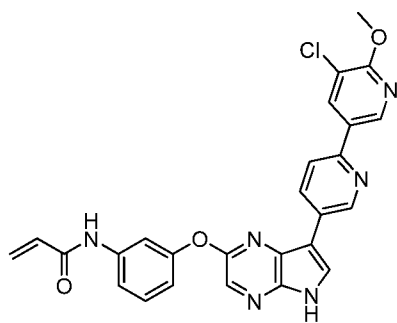
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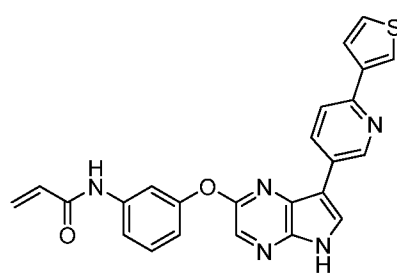
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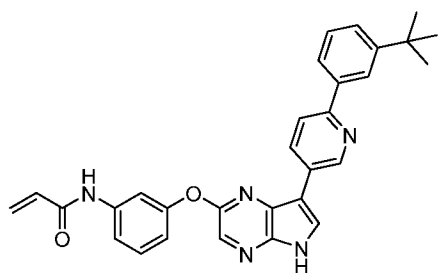
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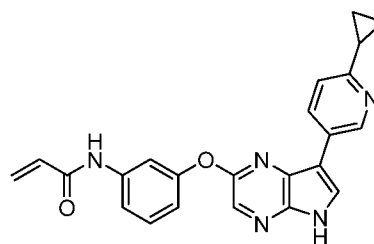
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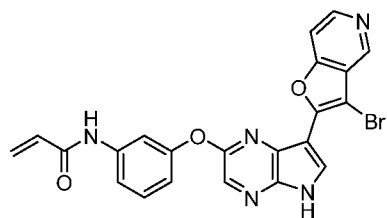
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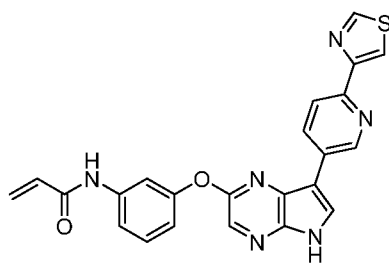
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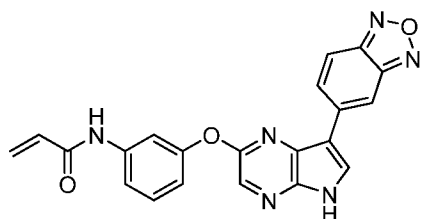
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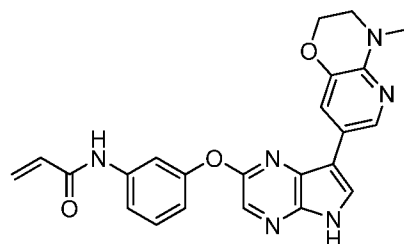
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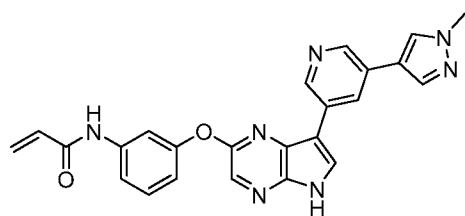
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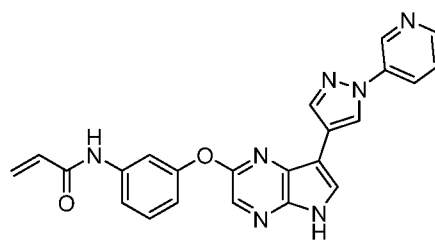
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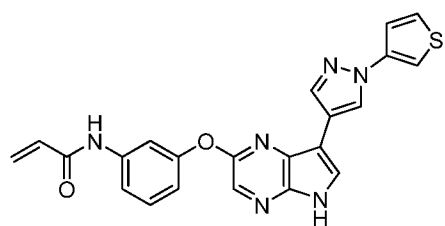
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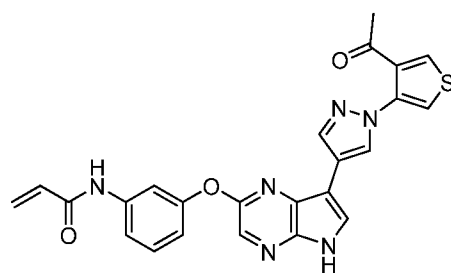
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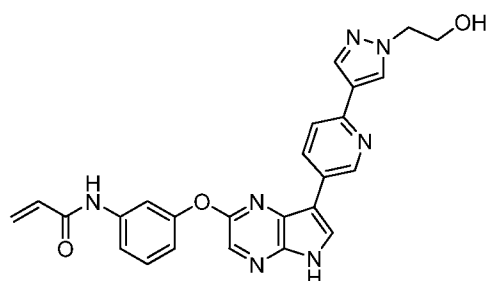
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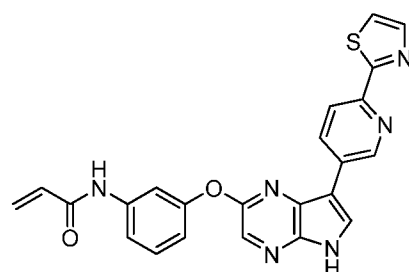
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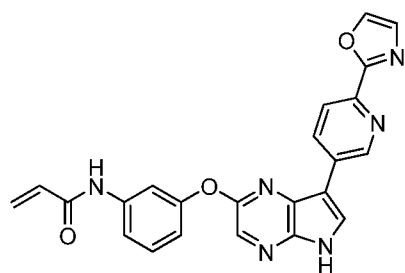
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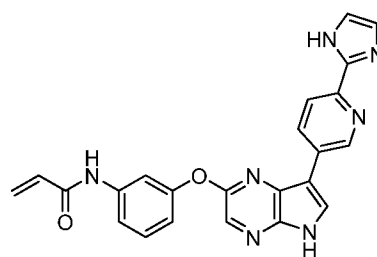
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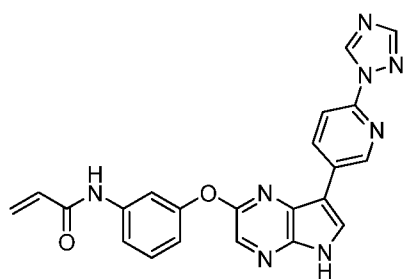
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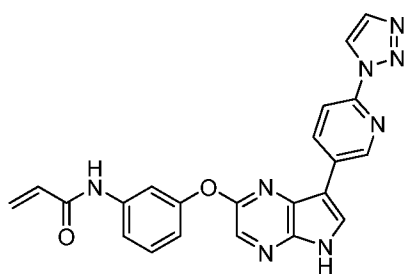
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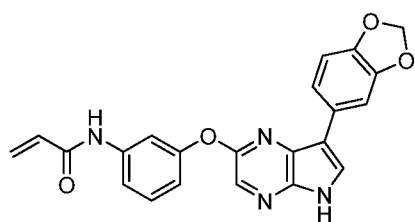
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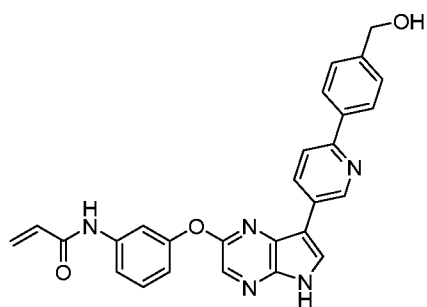
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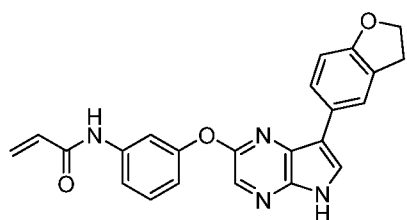
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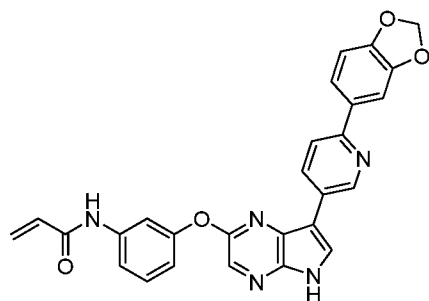
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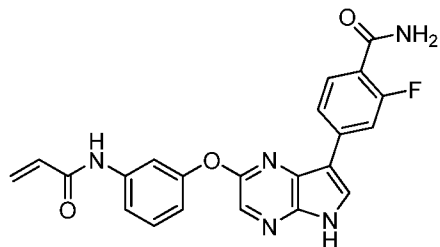
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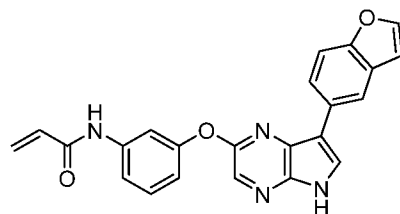
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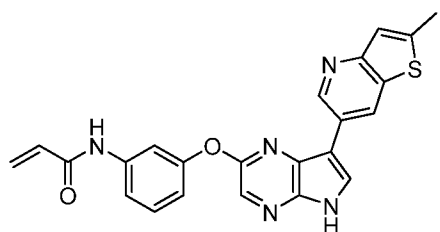
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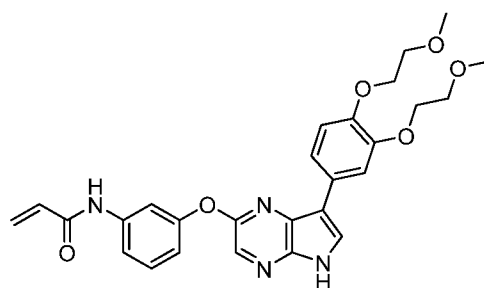
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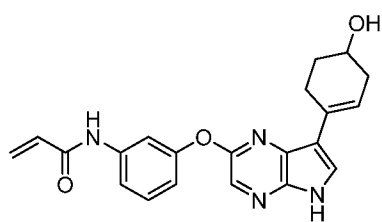
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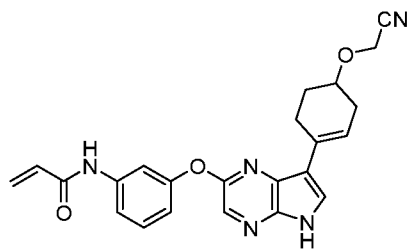
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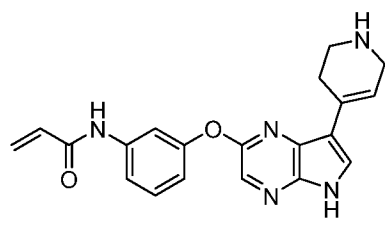
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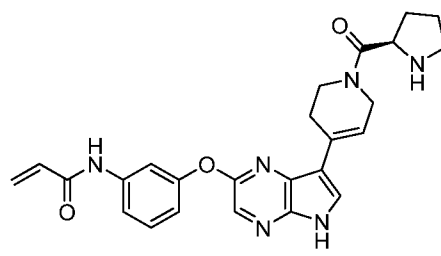
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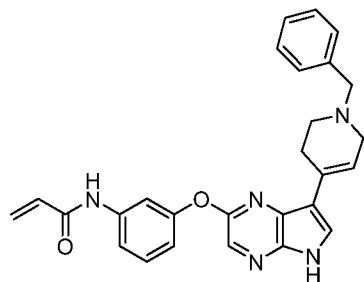
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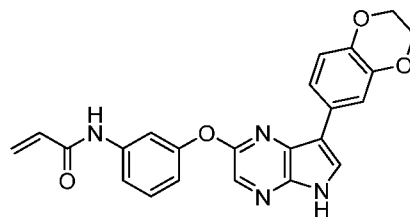
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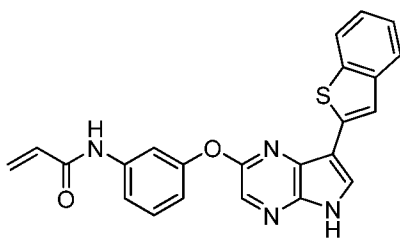
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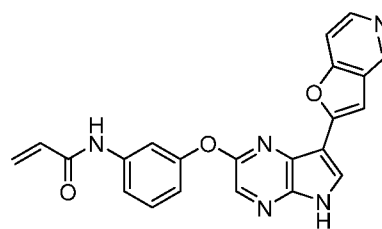
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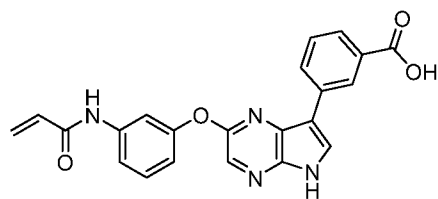
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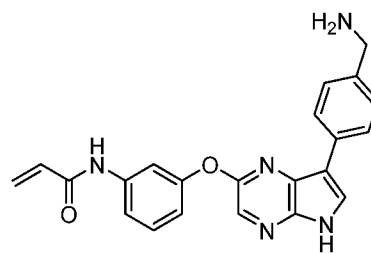
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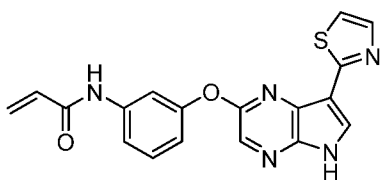
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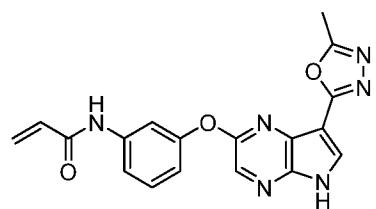
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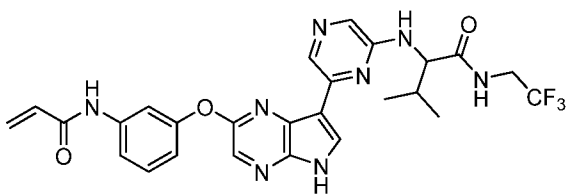
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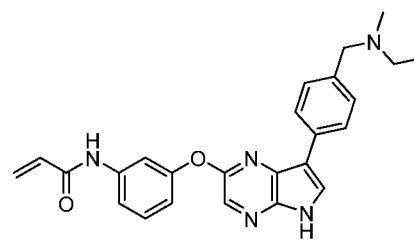
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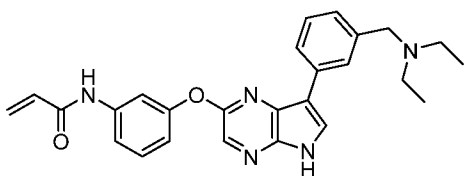
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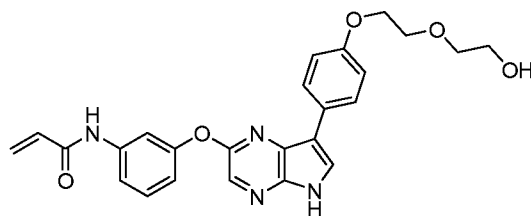
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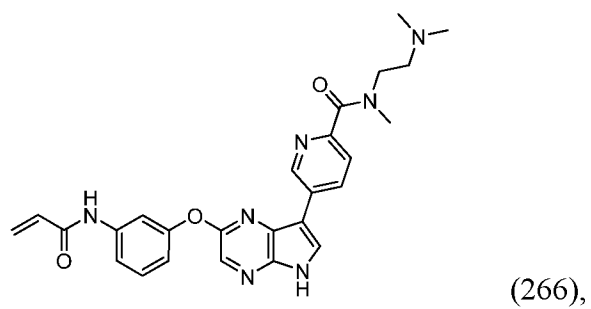
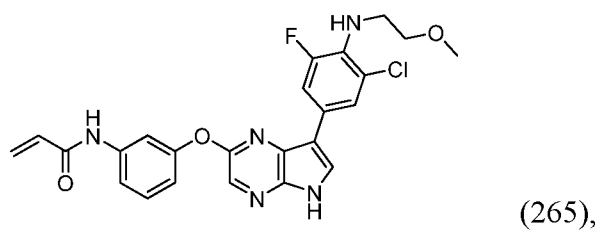
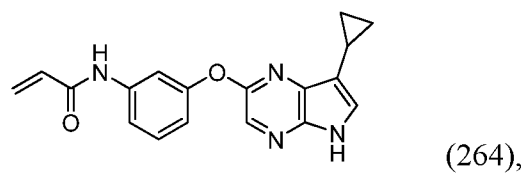
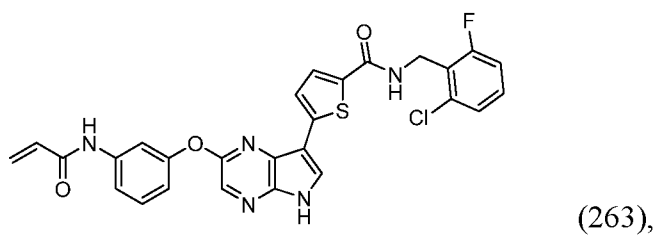
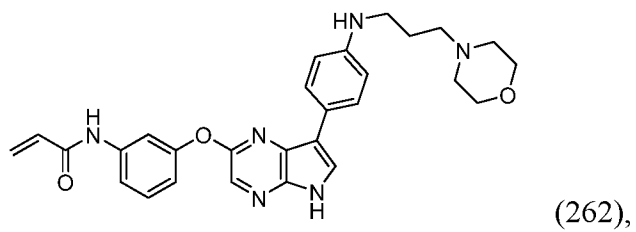
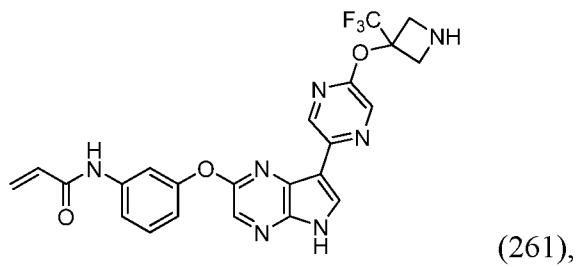
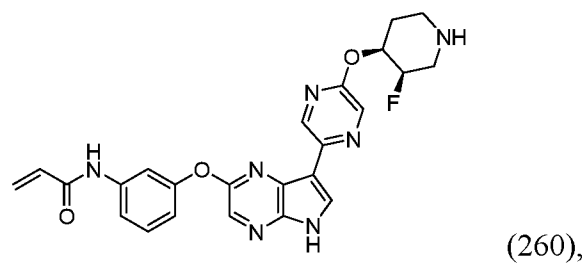
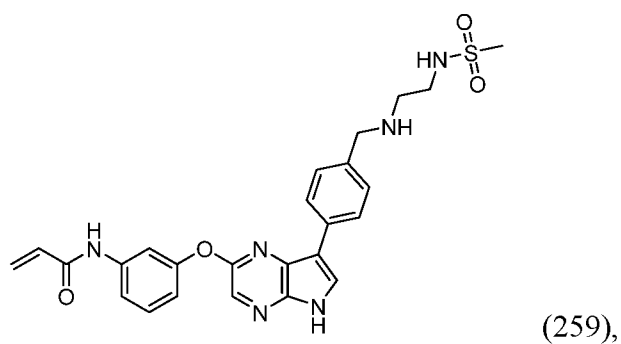
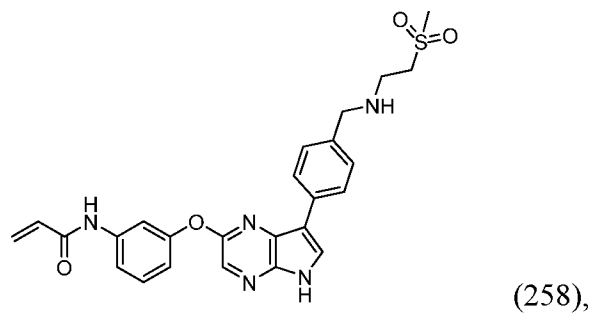
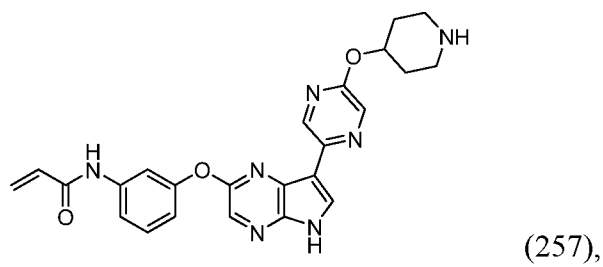
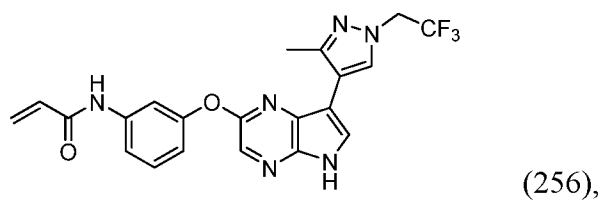
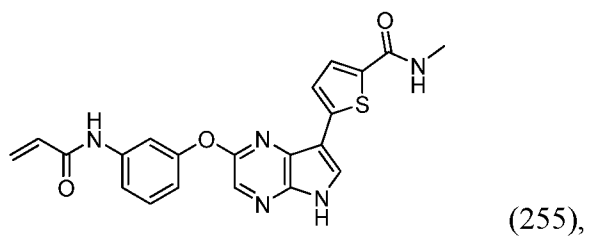
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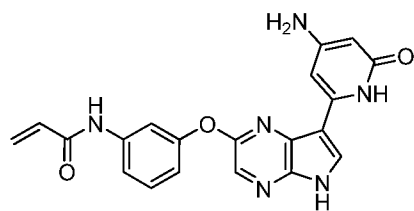


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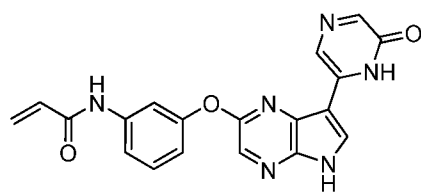


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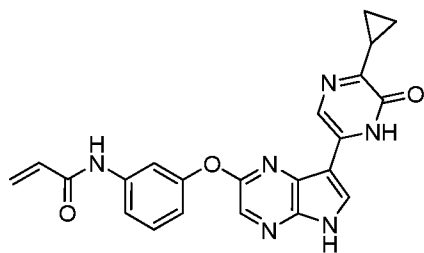




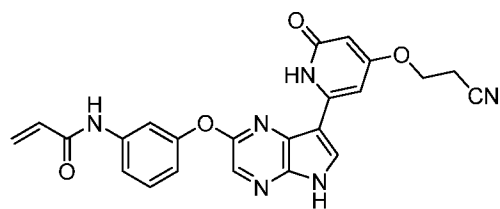
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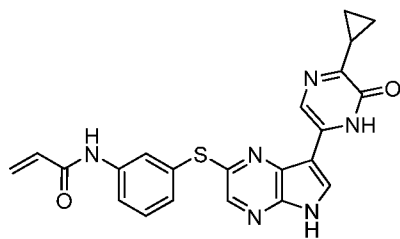
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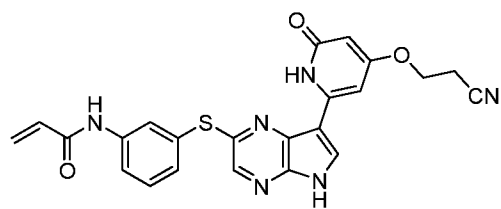
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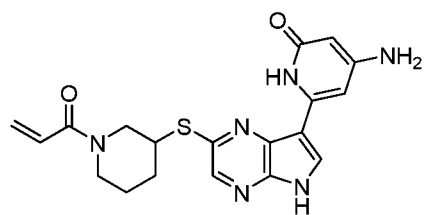
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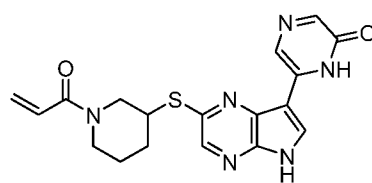
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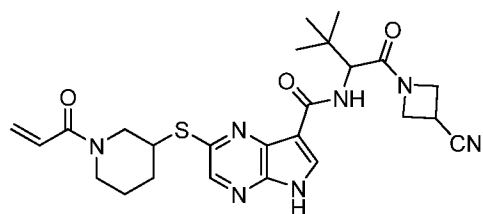
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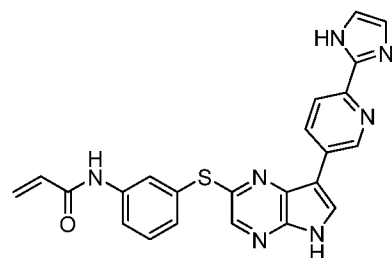
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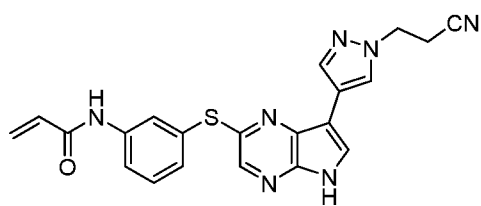
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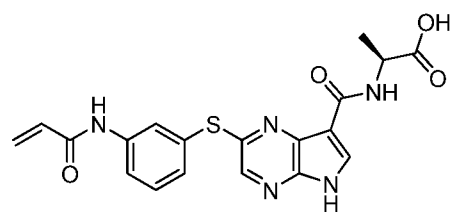
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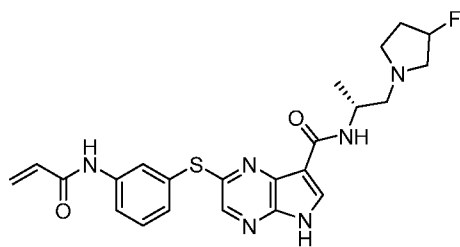
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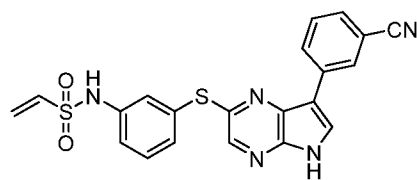
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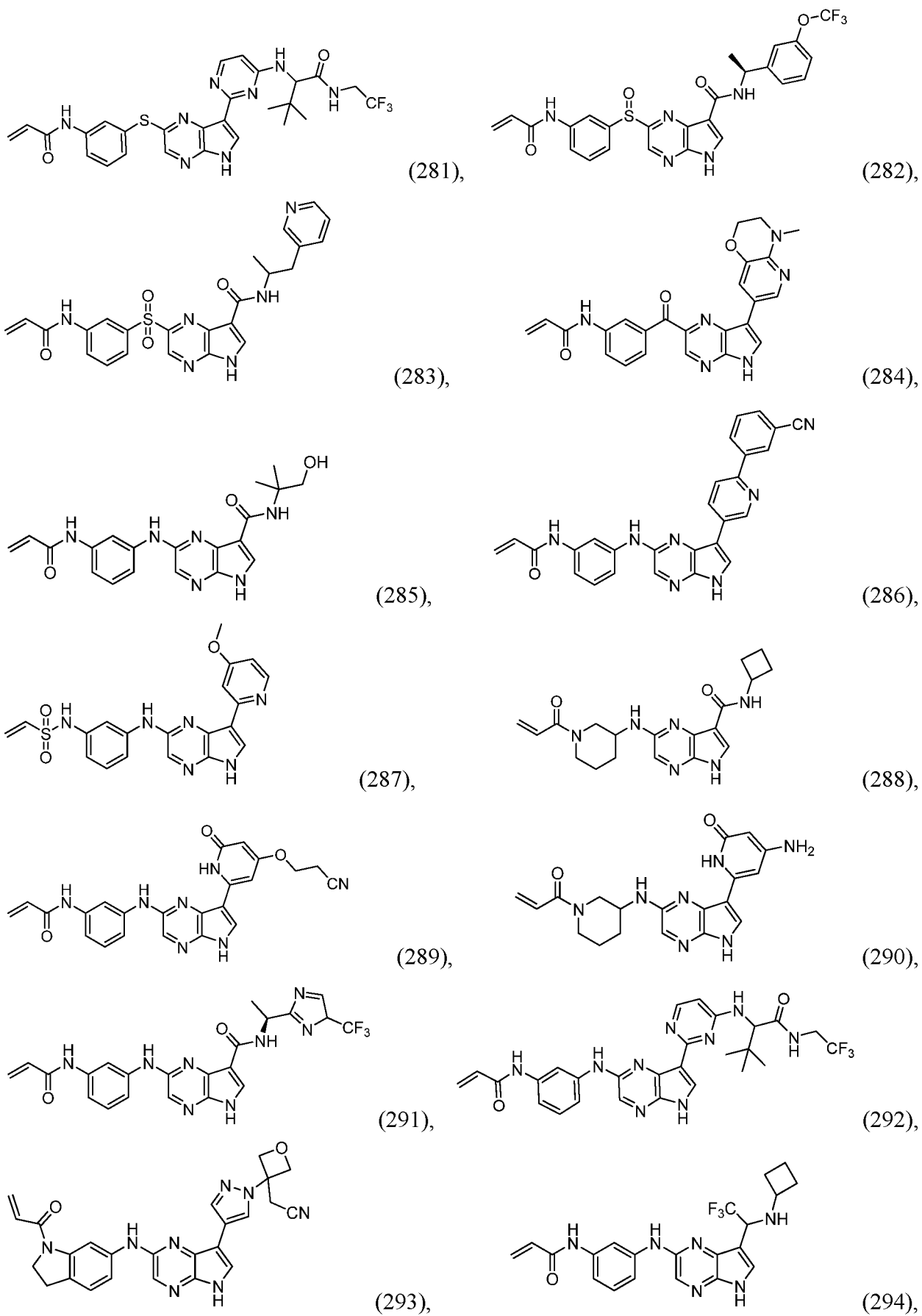
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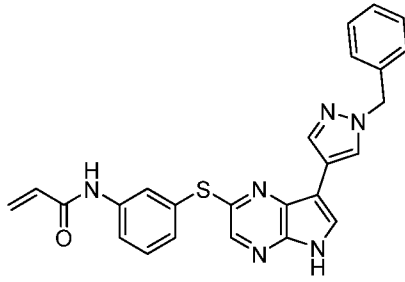
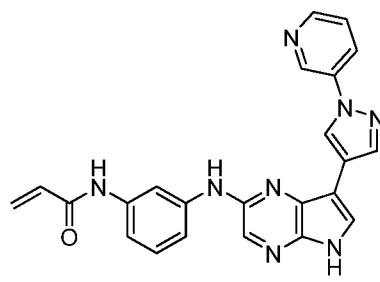
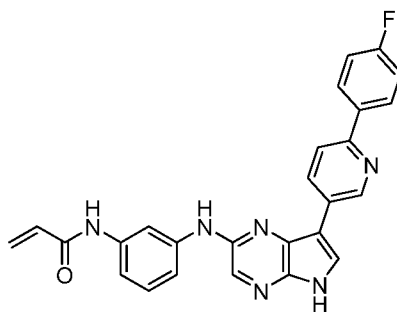
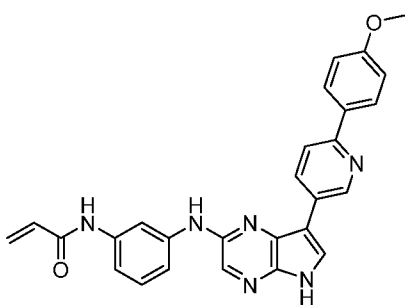
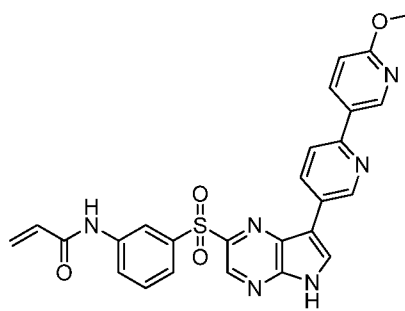
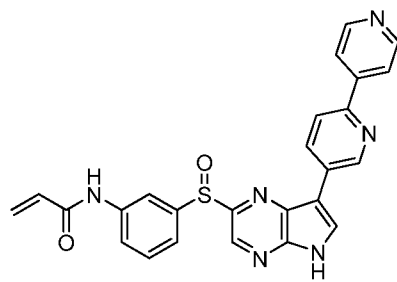
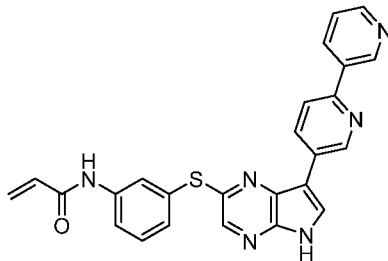
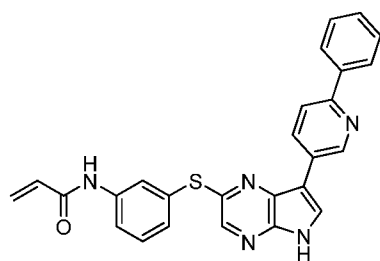
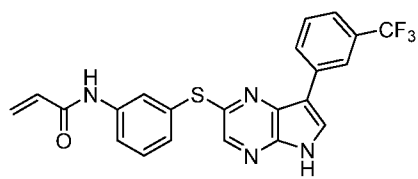
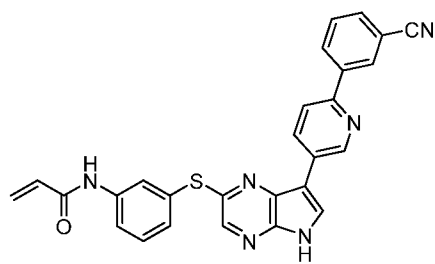
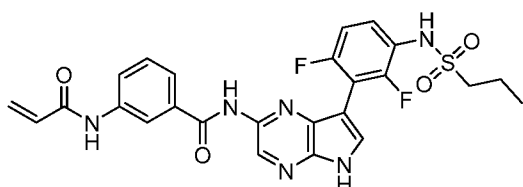
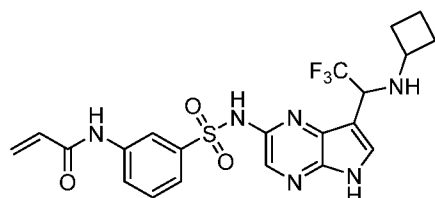


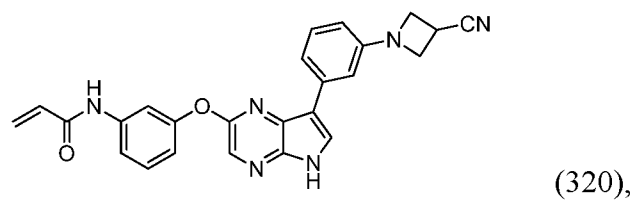
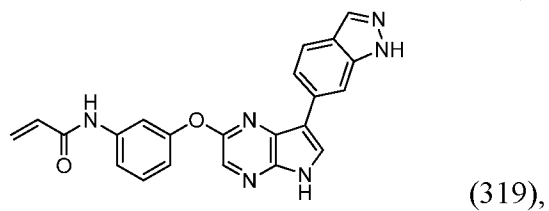
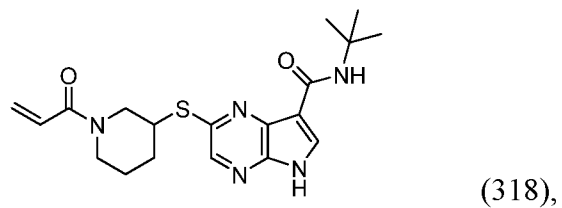
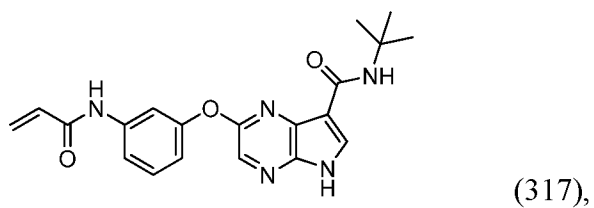
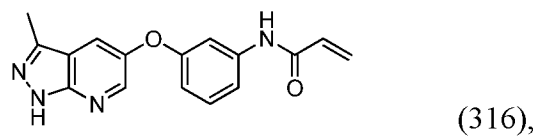
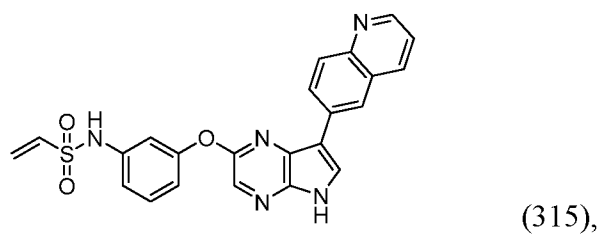
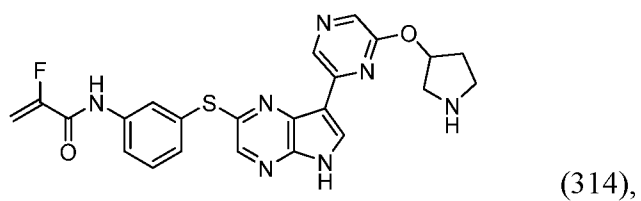
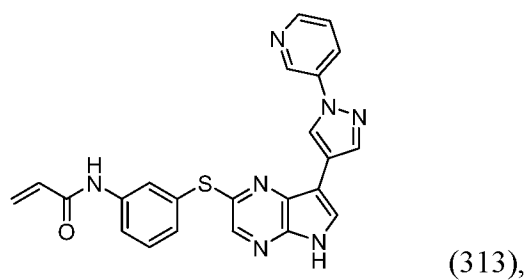
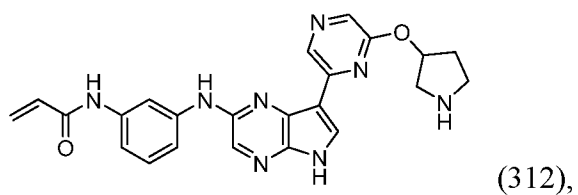
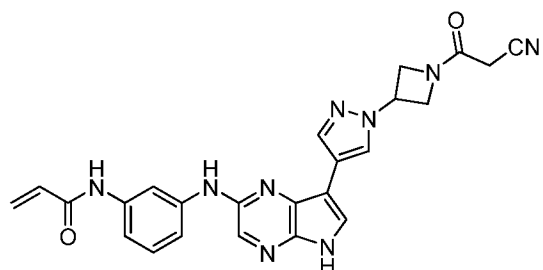
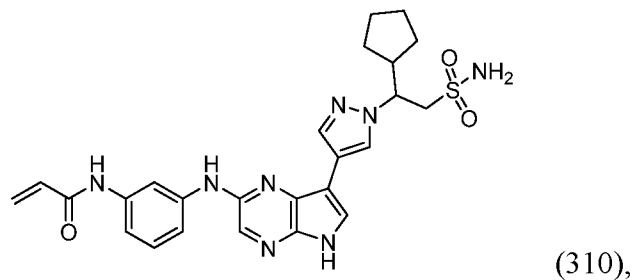
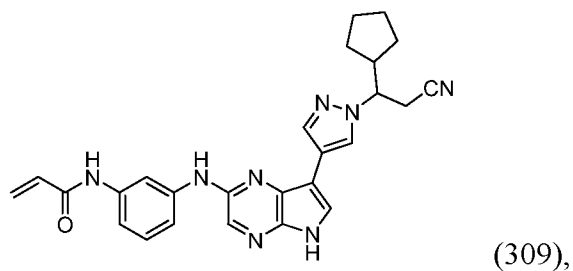
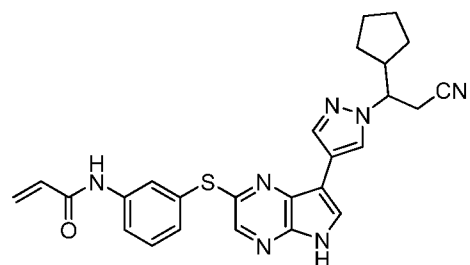
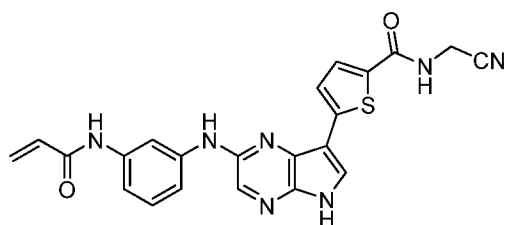
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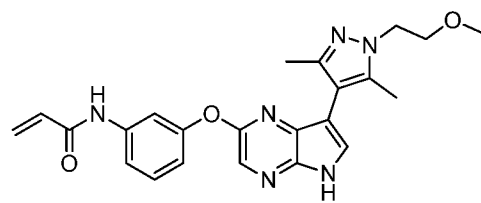
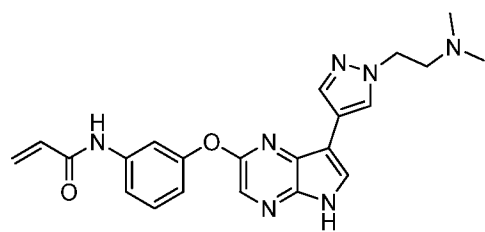
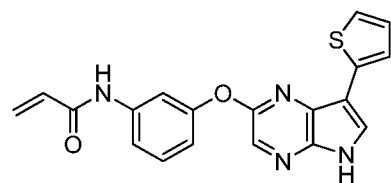
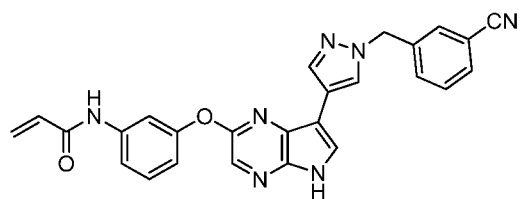
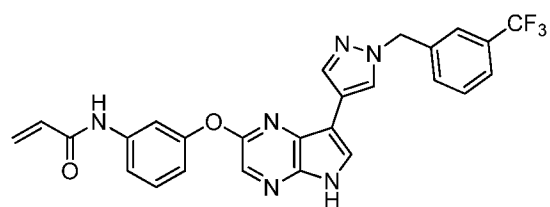
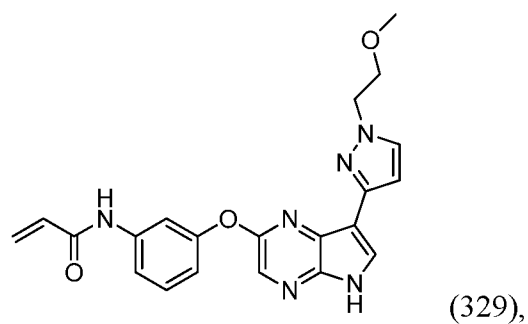
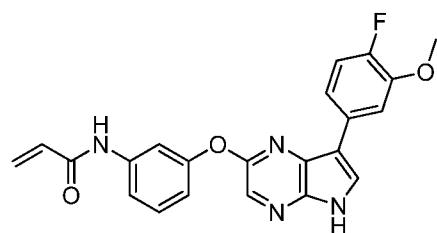
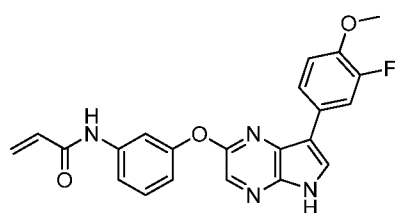
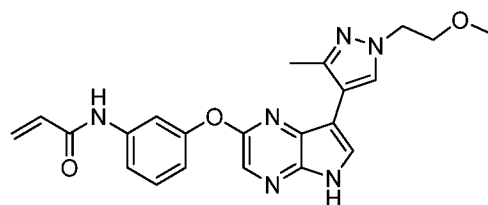
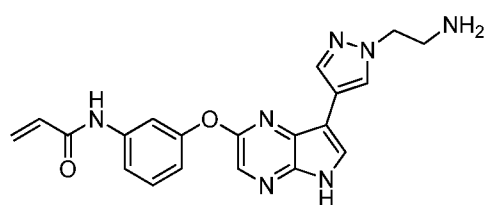
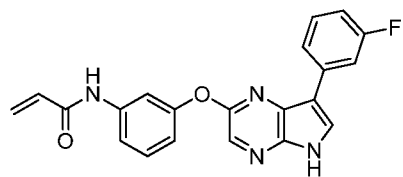
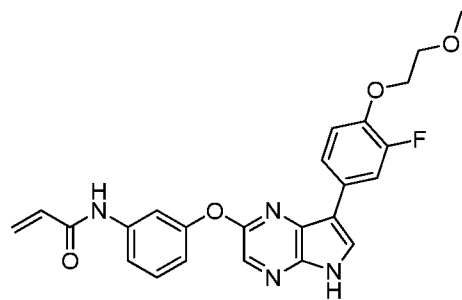
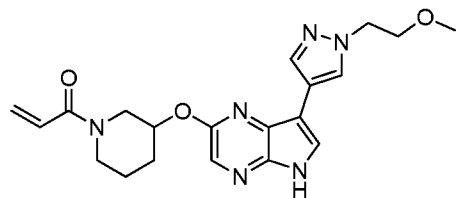
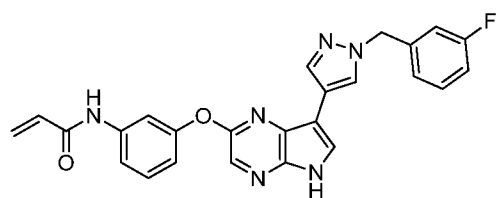


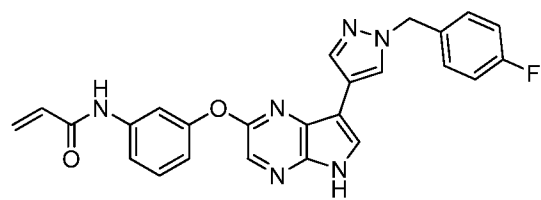
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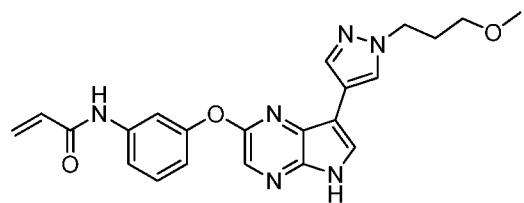




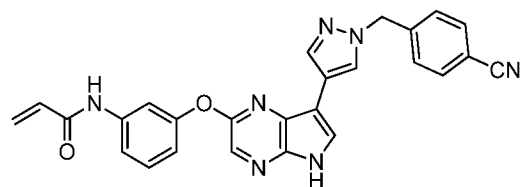




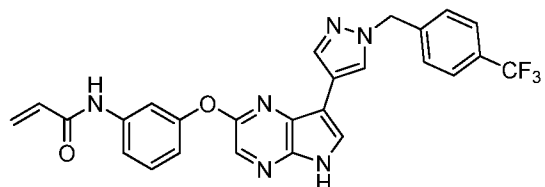
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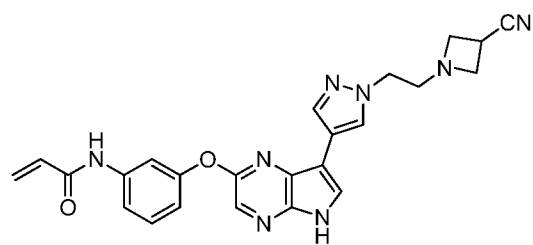
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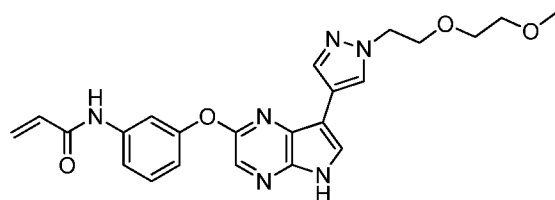
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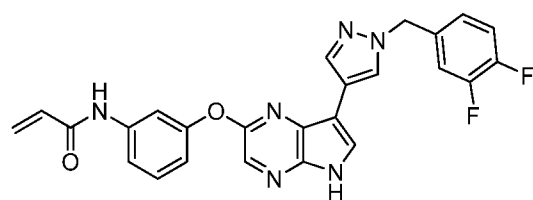
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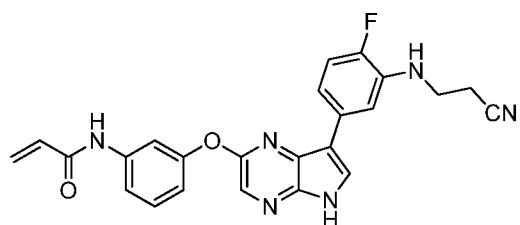
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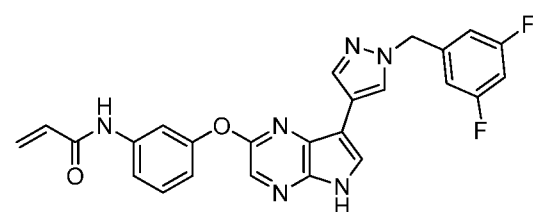
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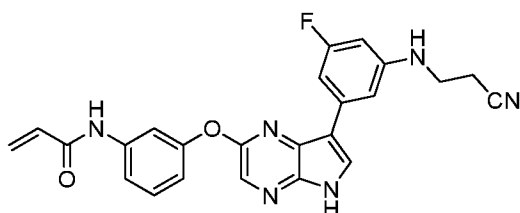
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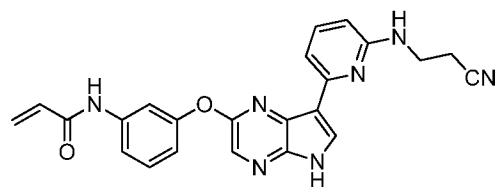
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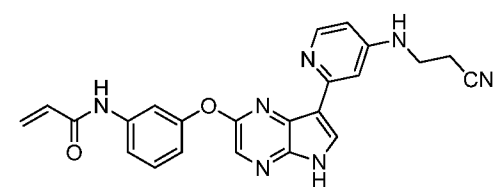
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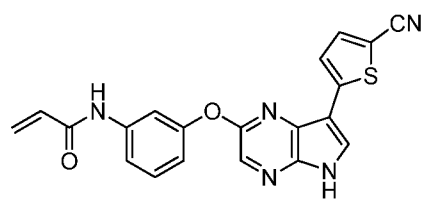
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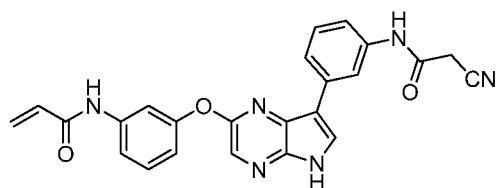
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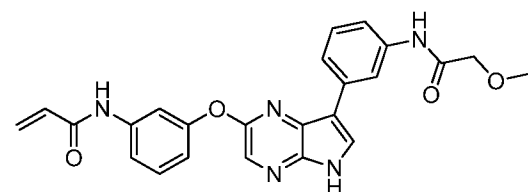
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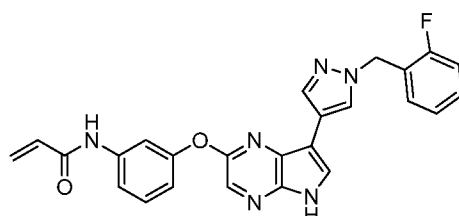
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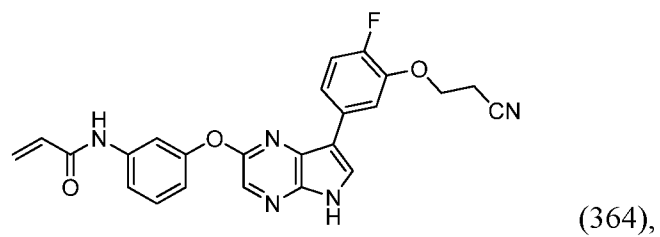
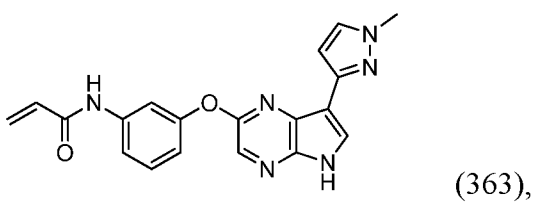
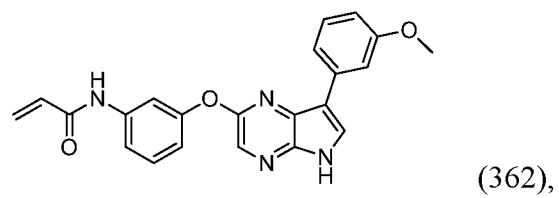
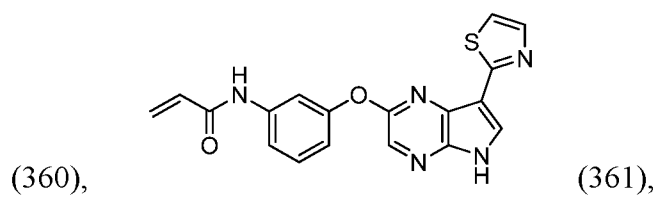
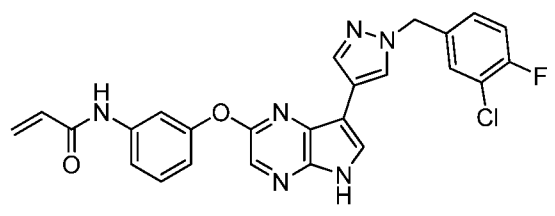
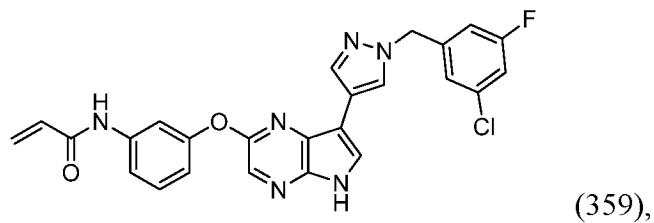
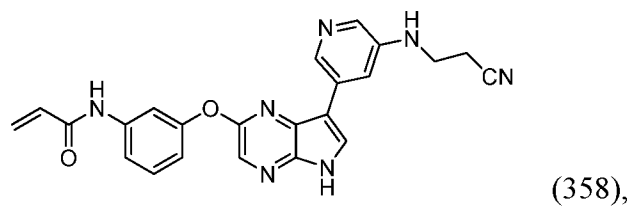
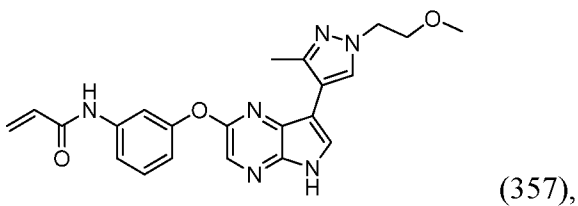
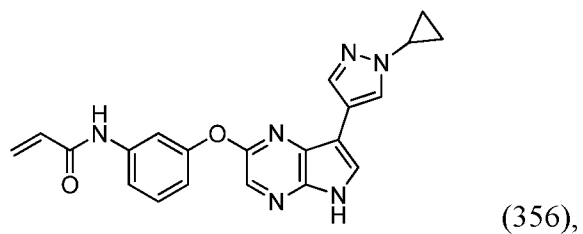
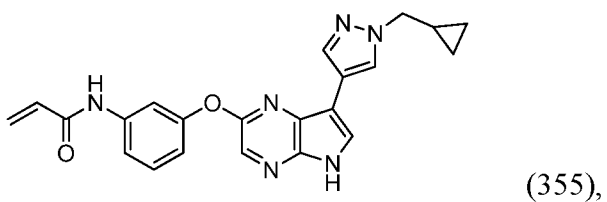
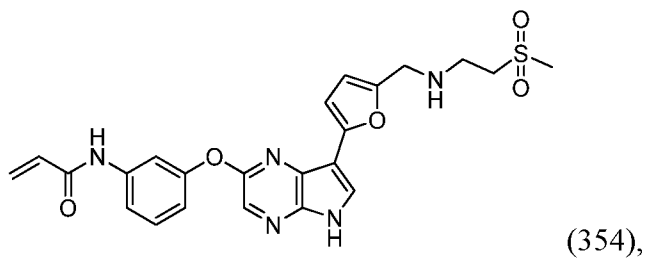
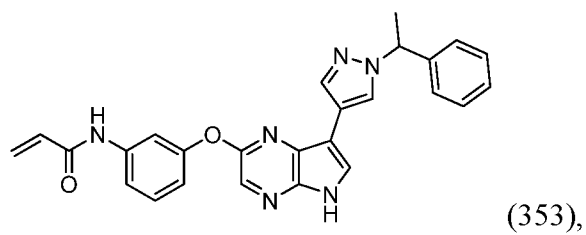
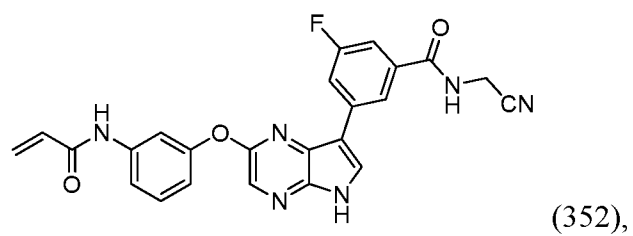
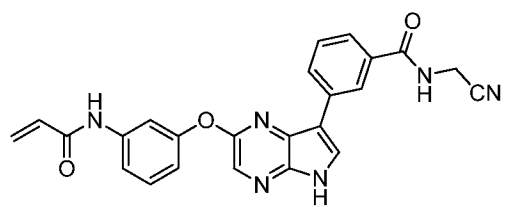
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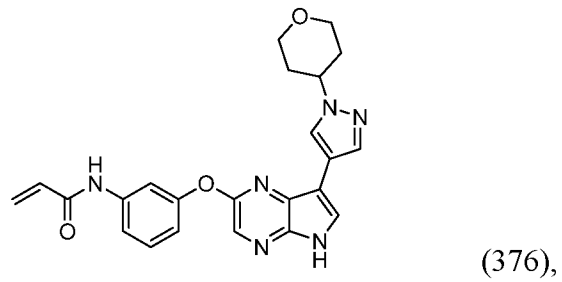
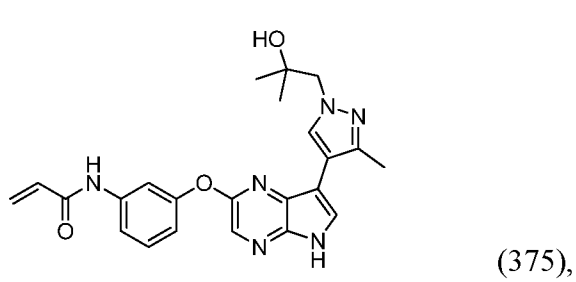
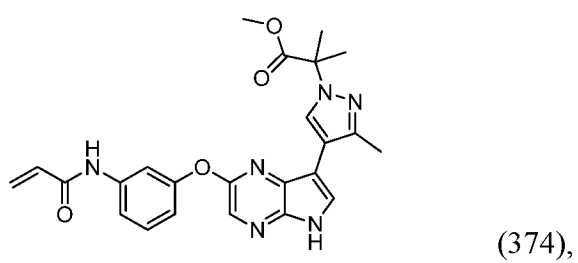
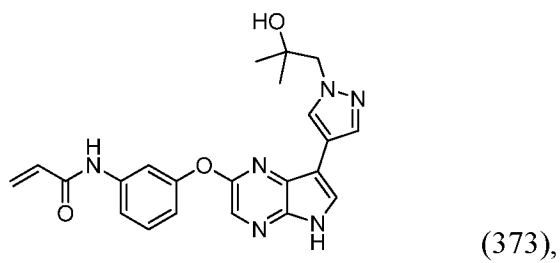
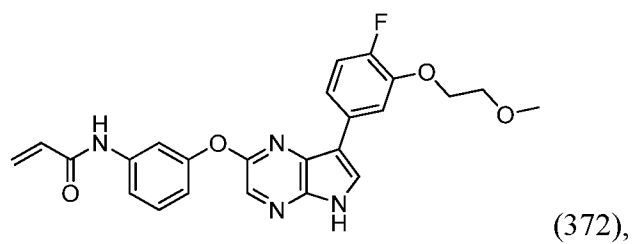
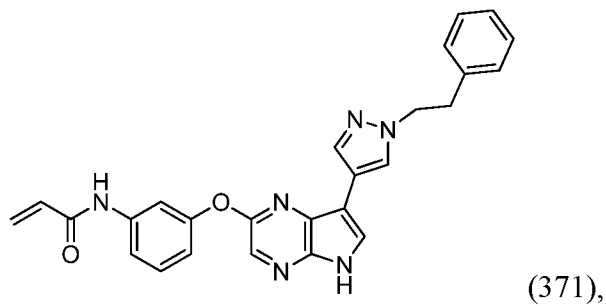
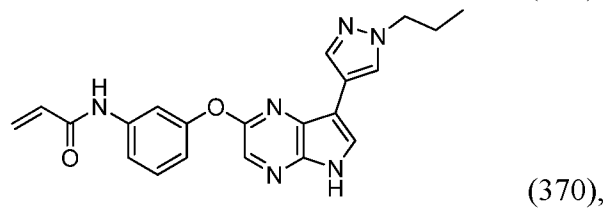
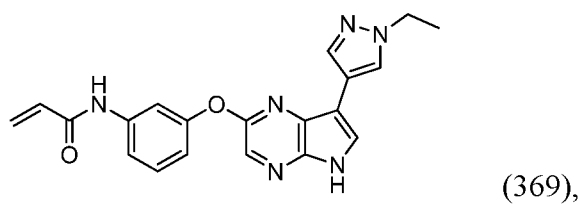
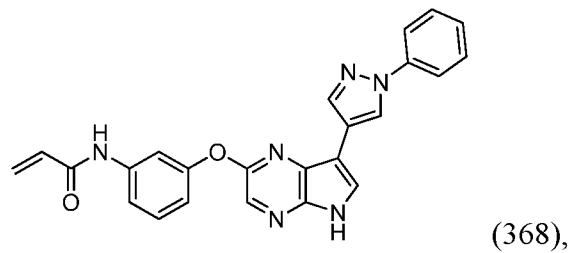
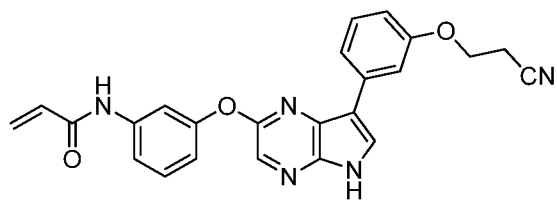
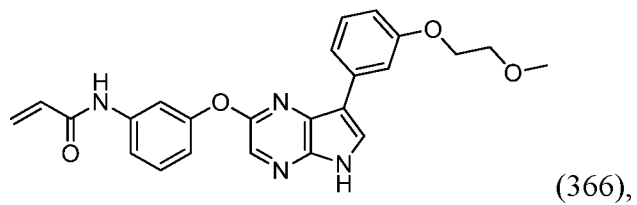
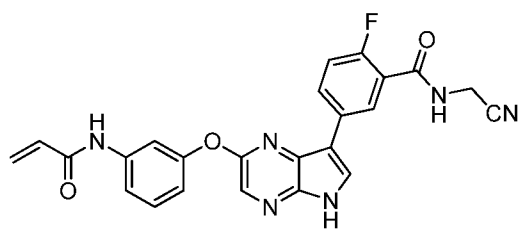


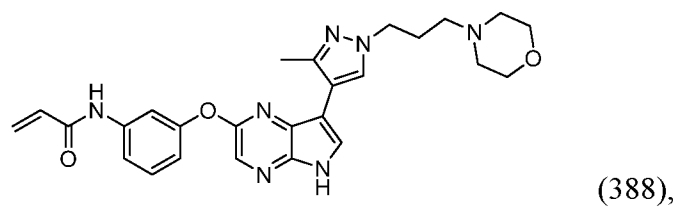
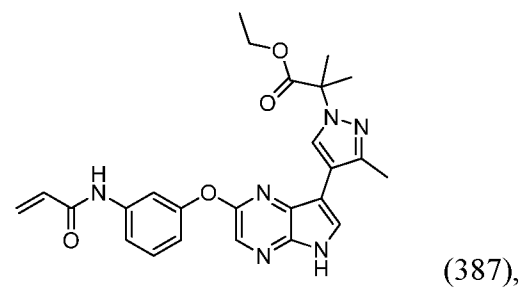
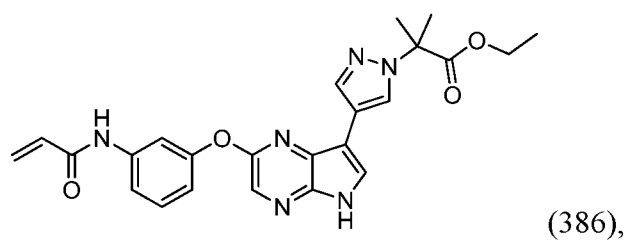
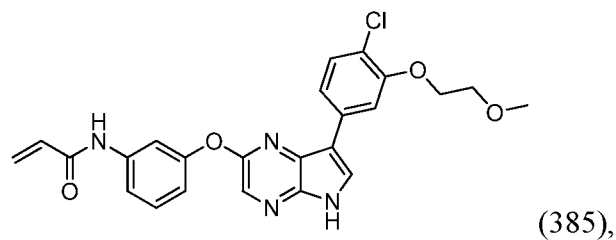
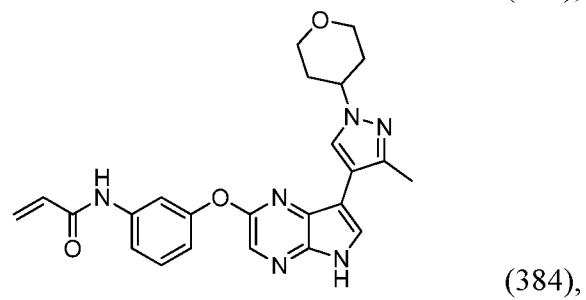
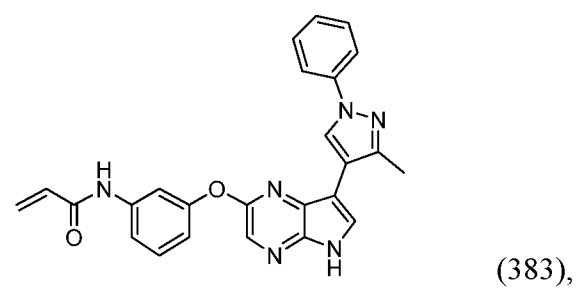
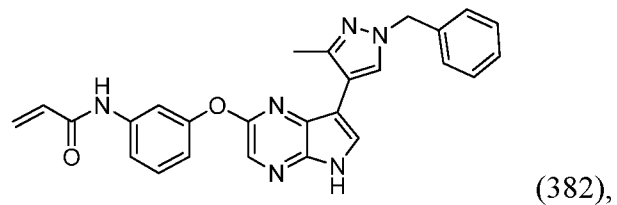
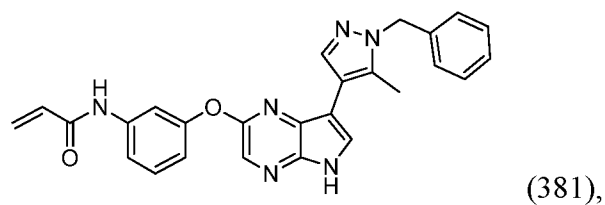
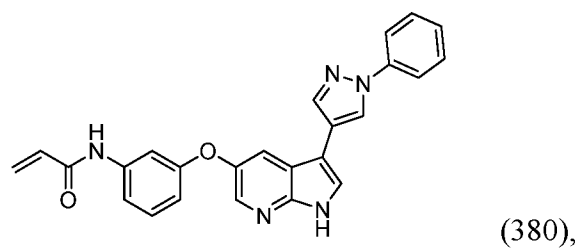
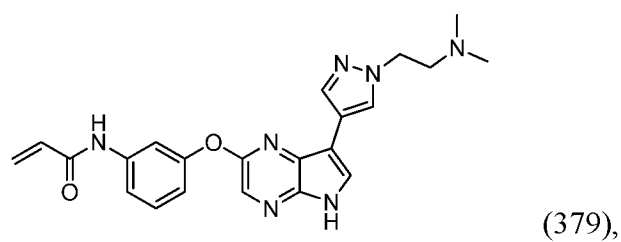
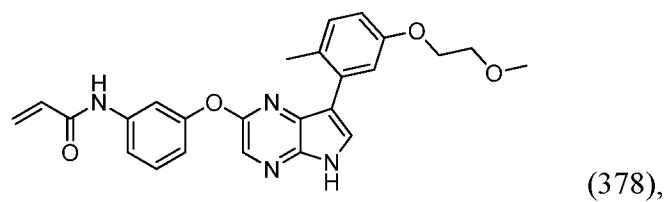
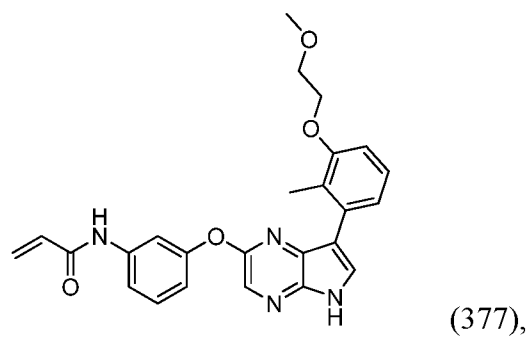
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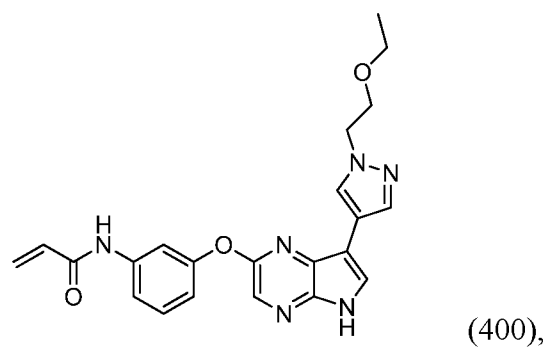
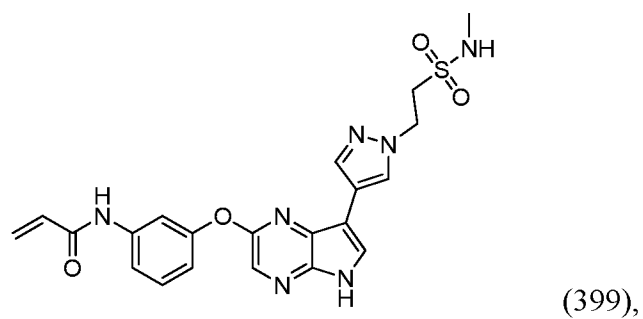
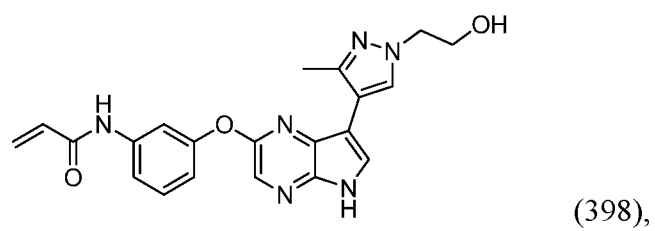
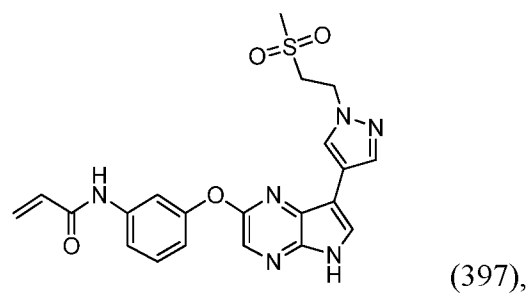
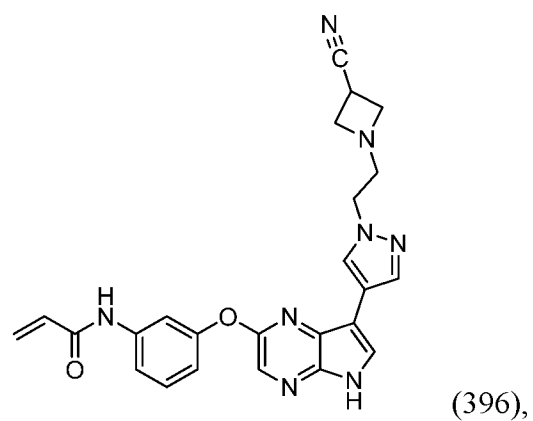
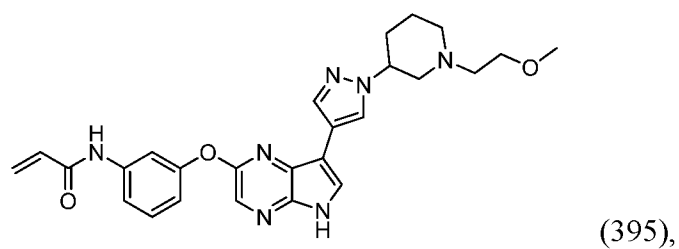
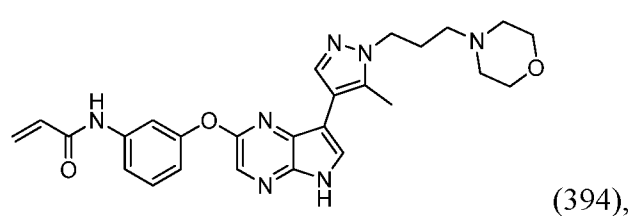
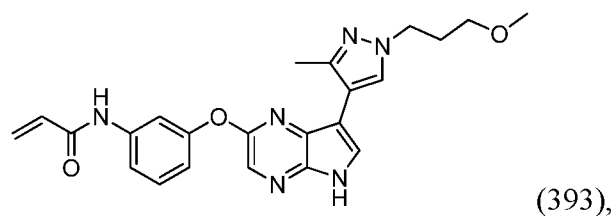
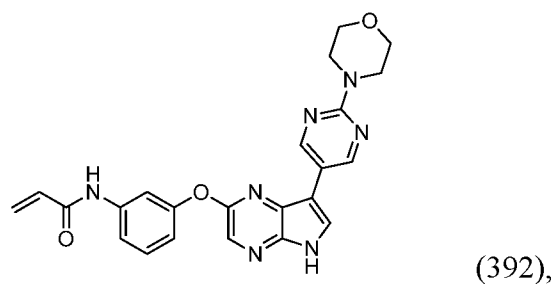
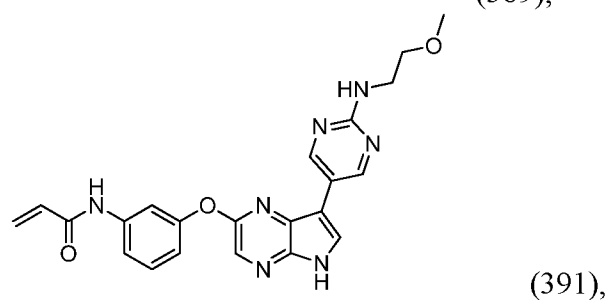
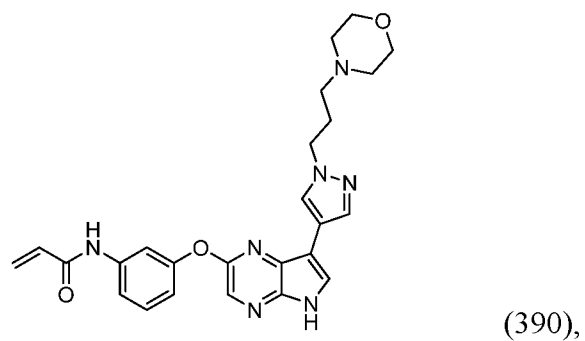
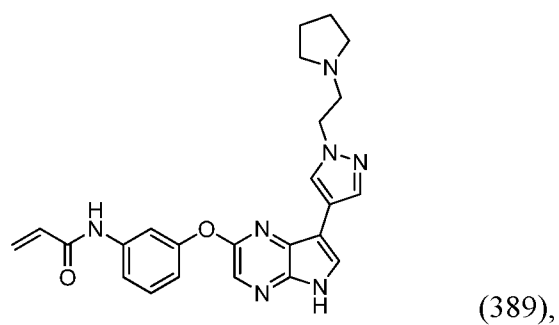


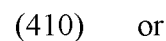
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proliferative diseases including those described in the invention. The compound disclosed herein also can be used in the manufacture of a medicament for lessening, preventing, managing or treating diseases mediated by BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M.

[00289] The present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id), in association with at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants, vehicles.

[00290] The present invention also provides a method of treating autoimmune diseases or proliferative diseases, or sensitive to these diseases in a patient comprising administering to the patient a therapeutically effective amount of the compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id).

[00291] Unless otherwise indicated, all stereoisomers, geometric isomers, tautomers, racemates, *N*-oxides, hydrates, solvates, metabolites, pharmaceutically acceptable salts or prodrugs of the compounds disclosed herein are within the scope of the present invention.

[00292] Specifically, the salt is a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable" refers to that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[00293] The salt of the compounds disclosed herein also include salts of the compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id) and/or for separating enantiomers of compounds of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id).

[00294] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, *e.g.*, acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate

and trifluoroacetate salts.

[00295] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[00296] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, sulfosalicylic acid, and the like.

[00297] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

[00298] Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[00299] Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[00300] The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, *e.g.*, in “Remington’s Pharmaceutical Sciences”, 20th ed. , Mack Publishing Company, Easton, Pa. , (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00301] Furthermore, the compounds disclosed herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents such as ethanol, DMSO, and the like, used

for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms.

[00302] Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Isotopically enriched compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as ^2H (deuterium, D), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl and ^{125}I , respectively.

[00303] In another aspect, the compounds of the invention include isotopically enriched compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{14}C and ^{18}F , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically enriched compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F -enriched compound may be particularly desirable for PET or SPECT studies. Isotopically-enriched compounds of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[00304] Further, substitution with heavier isotopes, particularly deuterium (*i.e.*, ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability. For example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated

deuterium atom of at least 3500 (52. 5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67. 5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82. 5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333. 3 (95% deuterium incorporation), at least 6466. 7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633. 3 (99. 5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D₂O, *d*₆-acetone, DMSO-*d*₆.

PHARMACEUTICAL COMPOSITION OF THE COMPOUND OF THE INVENTION AND PREPARATIONS AND ADMINISTRATION

[00305] The present invention provides a pharmaceutical composition comprising the compounds disclosed herein and pharmaceutically acceptable excipient, carrier, adjuvant, solvent and a combination thereof. The amount of the compound of the pharmaceutical composition disclosed herein refers to an amount which can be effectively detected to inhibit protein kinase of biology sample and patient.

[00306] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need thereof is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00307] The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id) disclosed herein can be extracted and then give an to the patient, such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic) or (Id) disclosed herein. When prepared in unit dosage form, the pharmaceutical compositions of the invention commonly contain from about 0. 5 mg to 1 g, or 1 mg to 700 mg, or 5 mg to 100 mg, of the compound of the invention.

[00308] “Pharmaceutically acceptable excipient” as used herein means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled, such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and would result in pharmaceutically unacceptable compositions are avoided. In addition, each excipient must of course be pharmaceutically acceptable, such as, sufficiently high purity.

[00309] Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting the compound of the present invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

[00310] Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

[00311] Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically acceptable excipients and may be useful in selecting suitable pharmaceutically acceptable excipients. Examples include Remington’s Pharmaceutical Sciences

(Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

[00312] In Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[00313] The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

[00314] Therefore, another aspect of the present invention is related to a method for preparing a pharmaceutical composition, the pharmaceutical composition contains the compound disclosed herein and pharmaceutically acceptable excipient, carrier, adjuvant, vehicle or a combination thereof, the method comprises mixing various ingredients. The pharmaceutical composition containing the compound disclosed herein can be prepared at for example environment temperature and under barometric pressure.

[00315] The compound of the invention will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols, solutions, and dry powders; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

[00316] In one embodiment, the compounds disclosed herein can be prepared to oral. In the other embodiment, the compounds disclosed herein can be prepared to inhalation. In the still

other embodiment, the compounds disclosed herein can be prepared to nasal administration. In the yet other embodiment, the compounds disclosed herein can be prepared to transdermal administration. In the still yet other embodiments, the compounds disclosed herein can be prepared to topical administration.

[00317] The pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from contacting the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates.

[00318] Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00319] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00320] Exemplary pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid product lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oil products; vegetable oil products, such as peanut oil product, cottonseed oil product, sesame oil product, olive oil product, and corn oil product; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol;

alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENS; wetting agents, such as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[00321] The pharmaceutical compositions provided herein may be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid product, semisolid product, and solid product dosage forms provided herein may be encapsulated in a capsule. Suitable liquid product and semisolid product dosage forms include solutions and suspensions in propylene carbonate, vegetable oil products, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00322] The pharmaceutical compositions provided herein may be provided in liquid product and semisolid product dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid product is dispersed in the form of small globules throughout another liquid product, which can be oil product-in-water or water-in-oil product. Emulsions may include a pharmaceutically acceptable non-aqueous liquid products or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxy groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid product dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid product carrier, *e.g.*, water, to be measured conveniently for administration.

[00323] Other useful liquid product and semisolid product dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thioldipropionic acid and its esters, and dithiocarbamates.

[00324] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

[00325] The pharmaceutical compositions provided herein for oral administration may be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00326] The pharmaceutical compositions provided herein may be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid product dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00327] Coloring and flavoring agents can be used in all of the above dosage forms.

[00328] The compounds disclosed herein can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyranes, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

[00329] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release forms.

[00330] The pharmaceutical compositions provided herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action.

[00331] The pharmaceutical compositions provided herein may be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[00332] The pharmaceutical compositions provided herein may be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid product forms suitable for solutions or suspensions in liquid product prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, Remington: The Science and Practice of Pharmacy, *supra*).

[00333] The pharmaceutical compositions intended for parenteral administration may include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00334] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oil products of vegetable origin, castor oil product, corn oil product, cottonseed oil product, olive oil product, peanut oil product, peppermint oil product, safflower oil product, sesame oil product, soybean oil product, hydrogenated vegetable oil products, hydrogenated soybean oil product, and medium-chain triglycerides of coconut oil

product, and palm seed oil product. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid product polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N*, *N*-dimethylacetamide, and dimethyl sulfoxide.

[00335] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α -cyclodextrin, β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin, and sulfobutylether 7- β -cyclodextrin (CAPTISOL[®], CyDex, Lenexa, Kans.).

[00336] The pharmaceutical compositions provided herein may be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampoule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00337] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle

prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00338] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00339] The pharmaceutical compositions may be formulated as a suspension, solid product, semi-solid product, or thixotropic liquid product, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid product inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00340] Suitable inner matrixes include polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00341] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

[00342] In another aspect, the pharmaceutical composition of the invention is prepared to a dosage form adapted for administration to a patient by inhalation, for example as a dry powder, an aerosol, a suspension, or a solution composition. In one embodiment, the invention is directed to a dosage form adapted for administration to a patient by inhalation as a dry powder. In other embodiment, the invention is directed to a dosage form adapted for administration to a patient by inhalation through a sprayer. Dry powder compositions for delivery to the lung by inhalation typically comprise a compound disclosed herein or a pharmaceutically acceptable salt thereof as a finely divided powder together with one or more pharmaceutically-acceptable excipients as

finely divided powders. Pharmaceutically-acceptable excipients particularly suited for use in dry powders are known to those skilled in the art and include lactose, starch, mannitol, and mono-, di-, and polysaccharides. The finely divided powder may be prepared by, for example, micronisation and milling. Generally, the size-reduced (eg micronised) compound can be defined by a D_{50} value of about 1 to about 10 microns (for example as measured using laser diffraction).

[00343] Aerosols may be formed by suspending or dissolving a compound disclosed herein or a pharmaceutically acceptable salt thereof in a liquified propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (HFA-134a), 1,1-difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA-227a), perfluoropropane, perfluorobutane, perfluoropentane, butane, isobutane, and pentane. Aerosols comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof will typically be administered to a patient via a metered dose inhaler (MDI). Such devices are known to those skilled in the art.

[00344] The aerosol may contain additional pharmaceutically-acceptable excipients typically used with MDIs such as surfactants, lubricants, cosolvents and other excipients to improve the physical stability of the formulation, to improve valve performance, to improve solubility, or to improve taste.

[00345] Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the patient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986).

[00346] Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oil products. Ointments, creams and gels, may, for example, be formulated with an aqueous or oil producty base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil product such as liquid product paraffin or a vegetable oil product such as arachis oil product or castor oil product, or a solvent such as polyethylene glycol. Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene

glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

[00347] Lotions may be formulated with an aqueous or oil producty base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

[00348] Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

[00349] Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions may be applied as a topical ointment or cream. When formulated in an ointment, the compound of the invention may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, a compound of the invention may be formulated in a cream with an oil product-in-water cream base or a water-in-oil product base.

USE OF THE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

[00350] The present invention provides methods of using the compounds and pharmaceutical compositions disclosed herein to treat, prevent, or improve diseases or disorders mediated by JAK kinase including JAK1, JAK2, JAK3 or TYK2 kinase activity, or influenced by other ways; or one or more symptoms of the diseases or disorders mediated by JAK kinase including JAK1, JAK2, JAK3 or TYK2 kinase activity, or influenced by other ways.

[00351] JAK kinase may be wild type and/or mutation of JAK1, JAK2, JAK3 or TYK2 kinase.

[00352] In one embodiment, the present invention provides a compound or a composition containing the compound disclosed herein used for treating, preventing, or improving diseases or disorders mediated by aberrant JAK1 kinase activity, or influenced by other ways; or one or more symptoms of the diseases or disorders mediated by aberrant JAK1 kinase activity, or influenced by other ways.

[00353] In other embodiment, the diseases or disorders or one or more symptoms of the diseases or disorders are related to aberrant JAK2 kinase activities.

[00354] In yet other embodiment, the diseases or disorders or one or more symptoms of the diseases or disorders are related to aberrant JAK3 kinase activities.

[00355] “Aberrant JAK kinase activity” refers to the JAK kinase activity occurred in special patient deviated from normal JAK kinase activity. Aberrant JAK kinase activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of JAK kinase activity. Such aberrant activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation. Therefore, the present invention provides the methods of treating these diseases and disorders.

[00356] Consistent with the description above, such diseases or disorders include without limitation: myeloproliferative disorders such as polycythemia vera (PCV), essential thrombocythemia and idiopathic myelofibrosis (IMF); leukemia such as myeloid leukemia including chronic myeloid leukemia (CML), imatinib-resistant forms of CML, acute myeloid leukemia (AML), and a subtype of AML, acute megakaryoblastic leukemia (AMKL); lymphoproliferative diseases such as myeloma; cancer including head and neck cancer, prostate cancer, breast cancer, ovarian cancer, melanoma, lung cancer, brain tumor, pancreatic cancer and renal carcinoma; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency, immunomodulation, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn’s disease and ulcerative colitis (UC), systemic lupus erythematosus (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma and chronic obstructive pulmonary disease (COPD) and dry eye syndrome (or keratoconjunctivitis sicca (KCS)).

[00357] In one aspect, the present invention provides a compound or a composition containing the compound disclosed herein used for preventing and/or treating proliferative diseases, autoimmune diseases, anaphylactic diseases, inflammatory diseases or transplant rejection in a mammal (including human).

[00358] In other aspect, methods are provided herein for treating the diseases disclosed herein in a mammal suffering from (or at risk for), comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In other aspect, methods are provided herein for

treating proliferative diseases, autoimmune diseases, anaphylactic diseases, inflammatory diseases or transplant rejection in a mammal animal suffering from (or at risk for).

[00359] In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with a proliferative disease, comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In a particular embodiment, the proliferative disease is selected from cancer (*e.g.* solid product tumors such as uterine leiomyosarcoma or prostate cancer), polycythemia vera, primary thrombocythemia, myelofibrosis, leukemia (*e.g.* AML, CML, ALL or CLL) and multiple myeloma.

[00360] In another aspect the present invention provides a compound of the invention for use in the treatment and/or prevention or prophylaxis of a proliferative disease. In a particular embodiment, the proliferative disease is selected from cancer (*e.g.* solid product tumors such as uterine leiomyosarcoma or prostate cancer), polycythemia vera, primary thrombocythemia, myelofibrosis, leukemia (*e.g.* AML, CML, ALL or CLL) and multiple myeloma.

[00361] In another aspect the present invention provides a compound of the invention or a composition containing the compound of the invention for use in the manufacture of a medicine used in treatment or prevention or prophylaxis of a proliferative disease. In a particular embodiment, the proliferative disease is selected from cancer (*e.g.* solid product tumors such as uterine leiomyosarcoma or prostate cancer), polycythemia vera, primary thrombocythemia, myelofibrosis, leukemia (*e.g.* AML, CML, ALL or CLL) and multiple myeloma.

[00362] In another aspect, this invention provides methods of treating a mammal susceptible to or afflicted with an autoimmune disease, comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In a particular embodiment, the autoimmune disease is selected from chronic obstructive pulmonary disease (COPD), asthma, systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, sicca syndrome, psoriasis, type I diabetes and inflammatory bowel disease.

[00363] In another aspect the present invention provides a compound of the invention for use in the treatment and/or prevention or prophylaxis of an autoimmune disease. In a particular embodiment, the autoimmune disease is selected from chronic obstructive pulmonary disease (COPD), asthma, systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis,

dermatomyositis, sicca syndrome, psoriasis, type I diabetes and inflammatory bowel disease.

[00364] In another aspect the present invention provides a compound of the invention or a composition containing the compound of the invention for use in the manufacture of a medicine used in treatment or prevention or prophylaxis of an autoimmune disease. In a particular embodiment, the autoimmune disease is selected from chronic obstructive pulmonary disease (COPD), asthma, systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, sicca syndrome, psoriasis, type I diabetes and inflammatory bowel disease.

[00365] In another aspect, this invention provides methods of treating a mammal susceptible to or afflicted with an anaphylactic disease, comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In a particular embodiment, the anaphylactic disease is selected from respiratory allergic disease, nasosinusitis, eczema and measles, food allergy and insect venom allergy.

[00366] In another aspect the present invention provides a compound of the invention for use in the treatment and/or prevention or prophylaxis of an anaphylactic disease. In a particular embodiment, the anaphylactic disease is selected from respiratory allergic disease, nasosinusitis, eczema and measles, food allergy and insect venom allergy.

[00367] In another aspect the present invention provides a compound of the invention or a composition containing the compound of the invention for use in the manufacture of a medicine used in treatment or prevention or prophylaxis of an anaphylactic disease. In a particular embodiment, the anaphylactic disease is selected from respiratory allergic disease, nasosinusitis, eczema and measles, food allergy and insect venom allergy.

[00368] In another aspect, this invention provides methods of treating a mammal susceptible to or afflicted with an inflammatory disease, comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In particular embodiment, the inflammatory disease is selected from inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, juvenile arthritis and psoriasis arthritis.

[00369] In another aspect the present invention provides a compound of the invention for use in the treatment and/or prevention or prophylaxis of an inflammatory disease. In particular embodiment, the inflammatory disease is selected from inflammatory bowel disease, Crohn's

disease, rheumatoid arthritis, juvenile arthritis and psoriasis arthritis.

[00370] In another aspect the present invention provides a compound of the invention or a composition containing the compound of the invention for use in the manufacture of a medicine used in treatment or prevention or prophylaxis of an inflammatory disease. In particular embodiment, the inflammatory disease is selected from inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, juvenile arthritis and psoriasis arthritis.

[00371] In another aspect, this invention provides methods of treating a mammal susceptible to or afflicted with transplantation rejection, comprising administering to the mammal a therapeutically or prophylactically effective amount of one or more the pharmaceutical composition or compound disclosed herein. In a particular embodiment, the transplantation rejection is selected from organ transplant rejection, tissue graft rejection and cell transplantation rejection.

[00372] In another aspect the present invention provides a compound of the invention for use in the treatment and/or prevention or prophylaxis of transplantation rejection. In a particular embodiment, the transplantation rejection is selected from organ transplant rejection, tissue graft rejection and cell transplantation rejection.

[00373] In another aspect the present invention provides a compound of the invention or a composition containing the compound of the invention for use in the manufacture of a medicine used in treatment or prevention or prophylaxis of transplantation rejection. In a particular embodiment, the transplantation rejection is selected from organ transplant rejection, tissue graft rejection and cell transplantation rejection.

[00374] In another aspect, the present invention provides a compound of the invention used as a medicine particularly for treating and/or preventing the diseases described above, also provides a medicine prepared from the compound disclosed herein used for treating and/or preventing the diseases described above.

[00375] A particular regimen of the present method comprises the administration to a subject suffering from a disease involving inflammation, of an effective amount of a compound of the invention for a period of time sufficient to reduce the level of inflammation in the subject, and preferably terminate the processes responsible for said inflammation. A special embodiment of the method comprises administering of an effective amount of the compound of the invention to a subject patient suffering from or susceptible to the development of rheumatoid arthritis, for a

period of time sufficient to reduce or prevent, respectively, inflammation in the joints of said patient, and preferably terminate, the processes responsible for said inflammation.

[00376] A further particular regimen of the present method comprises the administration to a subject suffering from a disease involving proliferation, of an effective amount of a compound of the invention for a period of time sufficient to reduce the level of proliferation in the subject, and preferably terminate the processes responsible for said proliferation. A special embodiment of the method comprises administering of an effective amount of the compound of the invention to a patient suffering from or susceptible to the development of cancer, for a period of time sufficient to reduce or prevent, respectively, the cancer in the said patient, and preferably terminate, the processes responsible for said cancer.

[00377] The compounds or pharmaceutical compositions thereof disclosed herein are kinases inhibitors, in particular Btk inhibitors. These inhibitors can be useful for treating one or more diseases responsive to kinase inhibition, including diseases responsive to Btk inhibition and/or inhibition of B-cell proliferation, in mammals. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of the invention with Btk results in the inhibition of Btk activity and thus in the pharmaceutical utility of these compounds. Accordingly, the invention includes a method of treating a mammal, for instance a human, having a disease responsive to inhibition of Btk activity, and/or inhibiting B-cell proliferation, comprising administering to the mammal having such a disease, an effective amount of at least one chemical entity provided herein. An effective concentration may be ascertained experimentally, for example by assaying blood concentration of the compound, or theoretically, by calculating bioavailability, determining the effective concentration. Other kinases that may be affected in addition to Btk include, but are not limited to, other tyrosine kinases and serine/threonine kinases.

[00378] To the extent, the disease, alleviation of the disease symptoms, preventative, and prophylactic treatment, which are all associated with Btk, are within the scope of this invention.

[00379] In some embodiments, the condition responsive to inhibition of Btk activity and/or B-cell and/or myeloid-cell activity is cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction.

[00380] The invention includes a method of treating a patient having cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute

inflammatory reaction, by administering an effective amount of a compound disclosed herein and pharmaceutically acceptable salts, solvates, and mixtures thereof.

[00381] In some embodiments, the conditions and diseases that can be affected using compounds disclosed herein, include, but are not limited to: allergic disorders, including but not limited to eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions; autoimmune and/or inflammatory diseases, including but not limited to psoriasis, Crohn's disease, irritable bowel syndrome, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, asthma, systemic lupus erythematosus (and associated glomerulonephritis), dermatomyositis, multiple sclerosis, scleroderma, vasculitis (ANCA-associated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, rheumatoid arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Alzheimer's disease, Diabetes mellitus (type 1), septic shock, myasthenia gravis, Ulcerative Colitis, Aplastic anemia, Coeliac disease, Wegener's granulomatosis and other diseases in which the cells and antibodies arise from and are directed against the individual's own tissues; acute inflammatory reactions, including but not limited to skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, uveitis, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, and cholecystitis; cancer, including but not limited to hematological malignancies, such as B-cell lymphoma, and acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic and acute lymphocytic leukemia, hairy cell leukemia, Hodgkin's disease, Non-Hodgkin lymphoma, multiple myeloma, and other diseases that are characterized by cancer of the blood or lymphatic system; and bone disorders, including but not limited to osteoporosis.

[00382] Btk is a known inhibitor of apoptosis in lymphoma B-cells. Defective apoptosis contributes to the pathogenesis and drug resistance of human leukemias and lymphomas. Thus, further provided is a method of promoting or inducing apoptosis in cells expressing Btk comprising contacting the cell with a compound disclosed, pharmaceutically acceptable salts, solvates, and mixtures thereof.

COMBINATION THERAPY

[00383] The compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compounds that demonstrate the same or a similar therapeutic activity, and that are determined to be safe and efficacious for such combined administration.

[00384] In one aspect, the present invention provides methods used in the treatment, prevention or improvement of diseases or symptoms thereof, comprising administering to a patient a safe and effective combination drug containing a compound of the invention and one or more therapeutic active agents. In one embodiment, the combination drug contains one or two other therapeutic agents.

[00385] Some examples of the other therapeutic agent include, but are not limited to, anticancer agent, including chemotherapeutic agent and anti-proliferation agent; anti-inflammatory agent; and immunomodulator or immunosuppressor.

[00386] In other aspect, the invention provides a product comprising a compound of the invention and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by JAK kinases. Products provided as a combined preparation include a composition comprising the compound of the invention and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of the invention and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

[00387] In other aspect, the invention provides a pharmaceutical composition comprising a compound of the invention and one or more other therapeutic agents. In one embodiment, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, carrier, adjuvant or vehicle as described above.

[00388] In other aspect, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil product packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

[00389] The invention provides the use of a compound of the invention for treating a disease or condition mediated by JAK kinases, wherein the patient is administered with another therapeutic agent before (such as in 24 hours). The invention also provides the use of another therapeutic

agent for treating a disease or condition mediated by JAK kinases, wherein the patient is administered with a compound of the invention before (such as in 24 hours).

[00390] The compounds of the invention may be administered as the sole active ingredient or in conjunction with, *e.g.* as an adjuvant to, other drugs *e.g.* immunosuppressive or immunomodulating agents or other anti-inflammatory agents, *e.g.* for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, *e.g.* a malignant cell anti-proliferative agent. For example, the compounds of the invention may be used in combination with other active agent, *e.g.* a calcineurin inhibitor, *e.g.* cyclosporin A or FK 506; a mTOR inhibitor, *e.g.* rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, AP23573, TAFA-93, biolimus-7 or biolimus-9; an ascomycin having immunosuppressive properties, *e.g.* ABT-281, ASM981, *etc.*; corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide; mizoribine; mycophenolic acid or salt; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; a PKC inhibitor, *e.g.* as disclosed in WO 02/38561 or WO 03/82859, *e.g.* the compound of Example 56 or 70; immunosuppressive monoclonal antibodies, *e.g.*, monoclonal antibodies to leukocyte receptors, *e.g.*, MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, *e.g.* a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, *e.g.* an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, *e.g.* CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, *e.g.* LEA29Y; adhesion molecule inhibitors, *e.g.* LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent, *e.g.* paclitaxel, gemcitabine, cisplatin, doxorubicin or 5-fluorouracil; or an anti-infectious agent.

[00391] Where the compounds of the invention are administered in conjunction with other immunosuppressive/immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious compound will of course vary depending on the type of co-drug employed, *e.g.* whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth.

[00392] In one aspect, the invention encompasses a combination comprising a compound of the

invention together with a β_2 -adrenoreceptor agonist. Examples of β_2 -adrenoreceptor agonists include salmeterol, salbutamol, formoterol, salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuteol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. In one embodiment the β_2 -adrenoreceptor agonists are long-acting β_2 -adrenoreceptor agonists, for example, compounds which provide effective bronchodilation for about 12 hours or longer.

[00393] The β_2 -adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

[00394] In other aspect, the present invention provides a combination comprising a compound of the invention together with a corticosteroid. Suitable corticosteroids refer to oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples of corticosteroids include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl- 17α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester, $6\alpha,9\alpha$ -difluoro- 17α -[(2-furanylcarbonyl)oxy]- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester (fluticasone furoate), $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl-3-oxo- 17α -propionyloxy-androsta-1,4-diene- 17β -carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl-3-oxo- 17α -(2,2,3,3-tetramethylcyclopropyl carbonyl)oxy-androsta-1,4-diene- 17β -carbothioic acid *S*-cyanomethyl ester and $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl- 17α -(1-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester, beclomethasone esters (for example the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolid, mometasone esters (for example mometasone furoate), triamcinolone acetonide, rofleponide, ciclesonide ($16\alpha,17$ -[[*(R)*-cyclohexylmethylene]bis(oxy)]- $11\beta,21$ -dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. In one embodiment corticosteroids include fluticasone propionate, $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl- 17α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester, $6\alpha,$

9 α -difluoro-17 α -(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid *S*-cyanomethyl ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester. In one embodiment the corticosteroid is 6 α ,9 α -difluoro-17 α -(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester.

[00395] In other aspect, the present invention provides a combination comprising a compound of the invention together with a non-steroidal compound having glucocorticoid agonism, which may possess selectivity for transrepression over transactivation and may be useful in combination therapy include those covered in the following published patent applications and patents: WO 03/082827, WO 98/54159, WO 04/005229, WO 04/009017, WO 04/018429, WO 03/104195, WO 03/082787, WO 03/082280, WO 03/059899, WO 03/101932, WO 02/02565, WO 01/16128, WO 00/66590, WO 03/086294, WO 04/026248, WO 03/061651, WO 03/08277, further non-steroidal compounds are covered in the following published patent applications and patents: WO2006/000401, WO2006/000398 and WO2006/015870.

[00396] In other aspect, the present invention provides a combination comprising a compound of the invention together with a non-steroidal anti-inflammatory drug (NSAID's). Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (for example montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (*e.g.* adenosine 2a agonists), cytokine antagonists (for example chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. In one embodiment, the invention encompasses iNOS (inducible nitric oxide synthase) inhibitors for oral administration. Examples of iNOS inhibitors include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Examples of CCR3 inhibitors include those disclosed in WO 02/26722.

[00397] In one embodiment the invention provides the use of the compounds of the invention in combination with a phosphodiesterase 4 (PDE4) inhibitor, for example in the case of a

formulation adapted for inhalation. The PDE4-specific inhibitor useful in this aspect is any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family, such as PDE3 and PDE5. Compounds include *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Also, *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S. Pat. No. 5,552,438 issued 3 Sep. 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

[00398] In other aspect, the present invention provides a combination comprising a compound of the invention together with an anticholinergic agent. Examples of anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M₁ or M₃ receptors, dual antagonists of the M₁/M₃ or M₂/M₃ receptors or pan-antagonists of the M₁/M₂/M₃ receptors. Exemplary compounds for administration via inhalation include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent[®]), oxitropium (for example, as the bromide, CAS 30286-75-0) and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva[®]). Also of interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO2001/04118. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex[®]), oxybutynin (CAS 5633-20-5, sold under the name Ditropan[®]), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol[®]), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen[®]), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare[®]).

[00399] In other aspect, the invention provides a combination comprising a compound of the invention together with an H₁ antagonist. Examples of H₁ antagonists include, without limitation, amlexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine,

cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrillamine, promethazine, terfenadine, tripeleminamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine. In a further embodiment the invention provides a combination comprising a compound of the invention together with an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include those compounds disclosed in WO2004/035556 and in WO2006/045416. Other histamine receptor antagonists which may be used in combination with the compounds of the present invention include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski et al. , J. Med. Chem. 46:3957-3960 (2003).

[00400] In a further aspect, the invention thus provides a combination comprising a compound of the invention together with a PDE4 inhibitor and a β_2 -adrenoreceptor agonist.

[00401] The invention thus provides, in a further aspect, a combination comprising a compound of the invention together with an anticholinergic and a PDE-4 inhibitor.

[00402] The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

[00403] The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will readily be appreciated by those skilled in the art.

[00404] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with another therapeutically active agent.

[00405] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a PDE4 inhibitor.

[00406] The invention thus provides, in a further aspect, a pharmaceutical composition

comprising a combination of a compound of the invention together with a β_2 -adrenoreceptor agonist.

[00407] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a corticosteroid.

[00408] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with a non-steroidal GR agonist.

[00409] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with an anticholinergic agent.

[00410] The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with an antihistamine.

[00411] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology, the one or more other components of such conjoint treatment in addition to the composition may be surgery, radiotherapy, chemotherapy, single transduction inhibitors or regulators (such as, kinases inhibitors or regulators) and/or monoclonal antibody.

[00412] The compound of the invention may be used to advantage in combination with other compounds, or with other therapeutic agents, especially antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; temozolomide (TEMODAL[®]); and calcium folinate.

[00413] The term “aromatase inhibitor” as used herein relates to a compound which inhibits the

estrogen production, *i.e.* the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark AROMASIN[®]. Formestane can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark LENTARON[®]. Fadrozole can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark AFEMA[®]. Anastrozole can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ARIMIDEX[®]. Letrozole can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark FEMARA[®] or FEMAR[®]. Aminoglutethimide can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ORIMETEN[®]. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, *e.g.* breast tumors.

[00414] The term “antiestrogen” as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark NOLVADEX[®]. Raloxifene hydrochloride can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark EVISTA[®]. Fulvestrant can be formulated as disclosed in U.S. Pat. No. 4,659,516 or it can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark FASLODEX[®]. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, *e.g.* breast tumors.

[00415] The term “anti-androgen” as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX[®]), which can be formulated, *e.g.* as disclosed in U.S. Pat. No. 4,636,505.

[00416] The term “gonadorelin agonist” as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Pat. No. 4,100,274 and can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ZOLADEX[®]. Abarelix can be formulated, *e.g.* as disclosed in U.S. Pat. No. 5,843,901.

[00417] The term “topoisomerase I inhibitor” as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804). Irinotecan can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark CAMPTOSAR[®]. Topotecan can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark HYCAMTIN[®].

[00418] The term “topoisomerase II inhibitor” as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, *e.g.* CAELYX[®]), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the epipodophyllotoxins etoposide and teniposide. Etoposide can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark ETOPOPHOS[®]. Teniposide can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark VM 26-BRISTOL[®]. Doxorubicin can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark ADRIBLASTIN[®] or ADRIAMYCIN[®]. Epirubicin can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark PHARMORUBICIN[®]. Idarubicin can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark ZAVEDOS[®]. Mitoxantrone can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark NOVANTRON[®].

[00419] The term “microtubule active agent” relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, *e.g.* paclitaxel and docetaxel, vinca alkaloids, *e.g.*, vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, *e.g.* epothilone B or D or derivatives thereof. Paclitaxel may be administered *e.g.* in the form as it is marketed, *e.g.* TAXOL[®]. Docetaxel can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark TAXOTERE[®]. Vinblastine sulfate can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark VINBLASTIN R. P[®]. Vincristine sulfate can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark FARMISTIN[®]. Discodermolide can be obtained, *e.g.*, as disclosed in U. S. Pat. No. 5, 010, 099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, U. S. Pat. No. 6, 194, 181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

[00420] The term “alkylating agent” as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark CYCLOSTIN®. Ifosfamide can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark HOLOXAN®.

[00421] The term “histone deacetylase inhibitors” or “HDAC inhibitors” relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO02/22577, especially *N*-hydroxy-3-[4-[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

[00422] The term “antineoplastic antimetabolite” includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark XELODA®. Gemcitabine can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark GEMZAR®. The term also includes monoclonal antibody trastuzumab, *e.g.*, in the form as it is marketed, *e.g.* under the trademark HERCEPTIN®.

[00423] The term “platin compound” as used herein includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark CARBOPLAT®. Oxaliplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ELOXATIN®.

[00424] The term “compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds” as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, *e.g.*,

[00425] a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, *e.g.* a *N*-phenyl-2-pyrimidine-amine derivative, *e.g.* imatinib, SU101, SU6668 and GFB-111, and the like;

[00426] b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

[00427] c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599;

[00428] d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family;

[00429] e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

[00430] f) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor;

[00431] g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase;

[00432] h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases—(part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, *e.g.* imatinib;

[00433] i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (*e.g.* BCR-Abl kinase), such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products comprising a N-phenyl-2-pyrimidine-amine derivative, *e.g.* imatinib PD180970; AG957; NSC 680410; PD173955 from ParkeDavis;

[00434] j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C(PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK, and Ras/MAPK family members, PI(3) kinases family members, or PI(3) kinases related kinases family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in U. S. Pat. No. 5, 093, 330, *e.g.* midostaurin; examples of further compounds include *e.g.* UCN-01, safingol, BAY 43-9006, Bryostatins 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697 (a P13K inhibitor);

[00435] k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC[®]) or tyrphostin. A tyrphostin is preferably a low molecular weight ($M_r < 1500$) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the *S*-arylbenzenemalonitrile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2, 5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); and

[00436] l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, *e.g.* EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, *e.g.* the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, U. S. Pat. No. 5, 747, 498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (*e.g.* compound known as CP 358774), WO 96/33980 (*e.g.* compound ZD 1839) and WO 95/03283 (*e.g.* compound ZM105180); *e.g.* trastuzumab (Herceptin[®]), cetuximab, Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7*H*-pyrrolo-[2,3-*d*]pyrimidine derivatives which are disclosed in WO 03/013541; and

[00437] Further anti-angiogenic compounds include compounds having another mechanism for their activity, *e.g.* unrelated to protein or lipid kinase inhibition *e.g.* thalidomide (THALOMID[®]) and TNP-470.

[00438] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are *e.g.* inhibitors of phosphatase 1, phosphatase 2A, or CDC25, *e.g.* okadaic acid or a derivative thereof.

[00439] Compounds which induce cell differentiation processes are *e.g.* retinoic acid, α - γ - or

δ -tocopherol or α - γ - or δ -tocotrienol.

[00440] The term “cyclooxygenase inhibitor” as used herein includes, but is not limited to, *e.g.* Cox-2 inhibitors, 5-alkyl substituted 2-arylamino phenylacetic acid and derivatives, such as celecoxib (CELEBREX[®]), rofecoxib (VIOXX[®]), etoricoxib, valdecoxib or a 5-alkyl-2-arylamino phenylacetic acid, *e.g.* 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00441] The term “bisphosphonates” as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. “Etridonic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark DIDRONEL[®]. “Clodronic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark BONEFOS[®]. “Tiludronic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark SKELID[®]. “Pamidronic acid” can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark AREDIA[™]. “Alendronic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark FOSAMAX[®]. “Ibandronic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark BONDRANAT[®]. “Risedronic acid” can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ACTONEL[®]. “Zoledronic acid” can be administered, *e.g.* in the form as it is marketed, *e.g.* under the trademark ZOMETA[®].

[00442] The term “mTOR inhibitors” relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune[®]), everolimus (Certican[™]), CCI-779 and ABT578.

[00443] The term “heparanase inhibitor” as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

[00444] The term “biological response modifier” as used herein refers to a lymphokine or interferons, *e.g.* interferon γ .

[00445] The term “inhibitor of Ras oncogenic isoforms”, *e.g.* H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras *e.g.* a “farnesyl transferase inhibitor” *e.g.* L-744832, DK8G557 or R115777 (Zarnestra).

[00446] The term “telomerase inhibitor” as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor. *e.g.*

telomestatin.

[00447] The term “methionine aminopeptidase inhibitor” as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are *e.g.* bengamide or a derivative thereof.

[00448] The term “proteasome inhibitor” as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include *e.g.* PS-341 and MLN 341.

[00449] The term “matrix metalloproteinase inhibitor” or “MMP” inhibitor as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, *e.g.* hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

[00450] The term “compounds used in the treatment of hematologic malignancies” as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors. Compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1- β -D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors *e.g.* compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00451] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, *e.g.* PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00452] The term “HSP90 inhibitors” as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 *e.g.*, 17-allylamino, 17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00453] The term “antiproliferative antibodies” as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erlotinib (TARCEVA™), bevacizumab

(Avastin™), rituximab (Rituxan®), PR064553 (anti-CD40) and 2C4 Antibody. By antibodies is meant *e.g.* intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity. For the treatment of acute myeloid leukemia (AML), compounds of the invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the invention can be administered in combination with, *e.g.*, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00454] The compound of the invention may be used to advantage in combination with other compounds, or with other therapeutic agents, especially anti-malarial agents. Such anti-malarial agents include, but are not limited to proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulfonamides drugs, artemisinin, arteflene, artemether, artesunate, primaquine, inhaled NO, *L*-arginine, dipropylene triamine NONO ester (NO donor), rosiglitazone (PPAR γ agonist), activated carbon, hemopoietin, levamisole and pyronaridine.

[00455] The compound of the invention may be used to advantage in combination with other compounds, or with other therapeutic agents, for example, the other therapeutic agent used for treating leishmaniasis, trypanosomosis, toxoplasmosis and cerebral cysticercosis. Such drugs include, but are not limited to, chloroquine sulfate, atovaquone-proguanil, artemether-benflumetol, quinine sulfate, artesunate, quinine, doxycycline, clindamycin, meglumine antimoniate, sodium stibogluconate, miltefosine, ketoconazole, pentamidine, AmphotericinB (AmB), AmB lipidosome, paromomycin, eflornithine, nifurtimox, suramin, melarsoprol, prednisolone, benzimidazole, sulfadiazine, pyrimethamine, synergy sulfamethoxazole, sulfamethoxazole, azitromycin, atovaquone, dexamethasone, praziquantel, albendazole, β -lactam, fluoroquinolones, macrolides, aminoglycosides, sulfadiazine and pyrimethamine.

[00456] The structure of the active ingredients identified by code nos. , generic or trade names and their preparation may be taken from the actual edition of the standard compendium "The Merck Index" (*e.g.* M. J. O'Neil et al. , ed. , 'The Merck Index', 13th ed. , Merck Research

Laboratories, 2001) or from databases, *e.g.* Patents International (*e.g.* IMS World Publications).

[00457] The compounds described above can be used in combination with the compound of the invention, which can be prepared and administered by the person skilled in the art according to the method disclosed in the above reference.

[00458] The compounds disclosed herein can be further used in combination with therapeutic processes, improving curative effect. For example, with hormone therapy or special radiation therapy. The compounds disclosed herein are used especially as radiosensitizer, in particular for the oncotherapy which has insensitive of radiation therapy.

[00459] By “combination” according to the invention, there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, *e.g.* synergistic effect. The terms “co-administration” or “combined administration” or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term “pharmaceutical combination” as used herein refers to a product obtained from mixing or combining active ingredients, and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, *e.g.* a compound disclosed herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, *e.g.* a compound of the invention and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the active ingredients in the body of the patient. The latter also applies to cocktail therapy, *e.g.* the administration of three or more active ingredients.

THERAPEUTIC METHODS

[00460] In one embodiment, the therapeutic methods disclosed herein comprise administering to a patient in need of the treatment a safe and effective amount of the compound of the invention or the pharmaceutical composition containing the compound of the invention. Each

example disclosed herein comprises the method of treating the above disorders or diseases comprising administering to a patient in need of the treatment a safe and effective amount of the compound of the invention or the pharmaceutical composition containing the compound of the invention.

[00461] In one embodiment, the compound of the invention or the pharmaceutical composition thereof may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration and rectal administration. Parenteral administration refers to routes of administration other than enteral or transdermal, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Topical administration includes application to the skin as well as intraocular, otic, intravaginal, inhaled and intranasal administration. In one embodiment, the compound of the invention or the pharmaceutical composition thereof may be administered orally. In another embodiment, the compound of the invention or the pharmaceutical composition thereof may be administered by inhalation. In a further embodiment, the compound of the invention or the pharmaceutical composition thereof may be administered intranasally.

[00462] In one embodiment, the compound of the invention or the pharmaceutical composition thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. In one embodiment, a dose is administered once per day. In a further embodiment, a dose is administered twice per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for the compound of the invention or the pharmaceutical composition thereof depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for the compound of the invention or the pharmaceutical composition thereof depend on the disorder being treated, the severity of the disorder being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens

may require adjustment give an individual patient's response to the dosing regimen or over time as individual patient needs change.

[00463] The compounds of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agents. The compounds of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents.

[00464] The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredients for a subject of about 50-70 kg, preferably about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

[00465] The above-cited dosage properties are demonstrable in vitro and in vivo tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and specimens thereof. The compounds of the present invention can be applied in vitro in the form of solutions, *e.g.*, preferably aqueous solutions, and in vivo either enterally or parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution.

[00466] In one embodiment, a therapeutically effective dosage of the compound disclosed herein from about 0.1 mg to about 2,000 mg per day. The pharmaceutical compositions should provide a dosage of from about 0.1 mg to about 2000 mg of the compound. In a special embodiment, pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 2,000 mg, about 10 mg to about 1,000 mg, about 20 mg to about 500 mg, or about 25 mg to about 250 mg of the active ingredient or a combination of essential ingredients per dosage unit form. In a special embodiment, pharmaceutical dosage unit forms are prepared to provide about 10 mg, 20 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg or 2000 mg of the active ingredient.

[00467] Additionally, the compounds of the invention may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in

vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of action of the compound in vivo; (b) modify the duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, amides, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

[00468] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formula (I), (I'), (Ia), (Ib), (Ic) or (Id) above, except where further noted. The following non-limiting schemes and examples 1 to 318 are presented to further exemplify the invention.

[00469] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00470] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius (°C). Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00471] Anhydrous THF, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous CH_2Cl_2 and CHCl_3 were obtained by refluxing the solvent with CaH_2 . EtOAc, PE, hexane, DMAC and DMF were treated with anhydrous Na_2SO_4 prior use.

[00472] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00473] Column chromatography was conducted using a silica gel column. Silica gel (300 - 400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were recorded with a Bruker 400 MHz or 600 MHz spectrometer using CDCl_3 , d_6 -DMSO, CD_3OD or d_6 -acetone as solutions (reported in ppm), and using TMS (0 ppm) or chloroform (7.26 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), dd (doublet of doublets), ddd (doublet of doublet of triplets), dt (doublet of triplets). Coupling constants, when give an, are reported in Hertz (Hz).

[00474] Low-resolution mass spectral (MS) data were determined on an Agilent 6120 Quadrupole HPLC-MS spectrometer equipped with an Agilent Zorbax SB-C18 (2.1 x 30 mm, 3.5 μm). The flow rate was 0.6 mL/min; the mobile phases consisted of a combination of A (0.1% formic acid in CH_3CN) and B (0.1% formic acid in H_2O) in gradient mode (5% to 95%), and an ESI source was used, the peak of HPLC was recorded with UV-Vis detection at 210/254 nm.

[00475] Purification of compound by preparative chromatography was implemented on Agilent 1260 Series high performance liquid product chromatography (Pre-HPLC) or Calesep Pump 250 Series high performance liquid product chromatography (Pre-HPLC) with UV detection at 210/254 nm (NOVASEP, 50/80 mm. DAC).

[00476] The following abbreviations are used throughout the application:

HPLC high performance liquid chromatography

H_2O water

CH_3OH , MeOH methanol

CD_3OD methanol-*d*

EtOH, ethanol ethanol

HCOOH formic acid

CH₃CN, MeCN acetonitrile
DCM, CH₂Cl₂ dichloromethane
CHCl₃ chloroform, trichloromethane
CDCl₃ chloroform-*d*
Cyclohexane cyclohexane
CDI 1, 1'-carbonyldiimidazole
DCC dicyclohexylcarbodiimide
DMSO dimethyl sulfoxide
DIEA, DIPEA ethyldiisopropylamine
DMF *N,N*-dimethylformamide
DME dimethyl ether
DPPA diphenylphosphoryl azide
DMF-DMA *N,N*-dimethylformamide dimethyl acetal
Et₃N, TEA, NEt₃ triethylamine
EA, EtOAc ethyl acetate
PE petroleum ether
EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBT 1-hydroxybenzotriazole
HATU 2-(7-aza-1*H*-benzotriazole-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate
BnOH phenylcarbinol
LiOH lithium hydroxide
NaH sodium hydride
NaOH sodium hydroxide
NaHCO₃ sodium bicarbonate
Na₂SO₄ sodium sulfate
NaBH(OAc)₃ sodium triacetoxyborohydride
KOH potassium hydroxide
K₂CO₃ potassium carbonate
Cs₂CO₃ cesium carbonate
CuI cuprous iodide
HCl hydrogen chloride

H₂SO₄ sulfuric acid

TFA trifluoroacetic acid

THF tetrahydrofuran

Pd/C Palladium on activated carbon

TsCl tosyl chloride

Pd(dppf)Cl₂ [1, 1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

Xantphos dimethylbis(diphenylphosphino)xanthene

X-Phos 2-(dicyclohexylphosphino)-2', 4', 6'-tri-*i*-propyl-1, 1'-biphenyl

Pd₂(dba)₃ tris(dibenzylideneacetone)dipalladium

t-BuDavePhos 2-di-*t*-butylphosphino-2'-(*N*, *N*-dimethylamino)biphenyl

DBU 1, 8-diazabicyclo[5. 4. 0]undec-7-ene

g gram

mg milligram

mol mole

mmol millimole

h hour, hours

min minute, minutes

L litre

mL, ml millilitre

r. t, RT room temperature

Rt retention time

HEPES 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

Brij-35 polyethylene glycol dodecyl ether

DTT dithiothreitol

EDTA ethylenediaminetetraacetic acid

EGFR epidermal growth factor receptor

BTK Bruton's tyrosine kinase

EGFR T790M epidermal growth factor receptor T790M mutant

Peptide FAM-P22 fluorescein-labeled peptide 22

ATP triphosphadenine

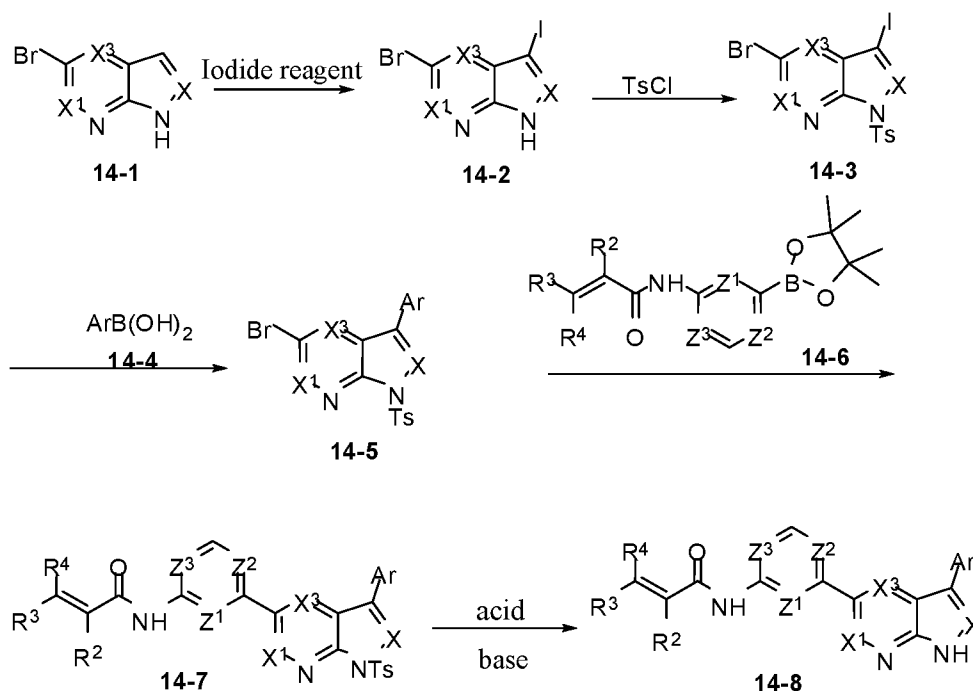
96-well plate 96-well plate

384-well plate 384-well plate

Staurosporine Staurosporine

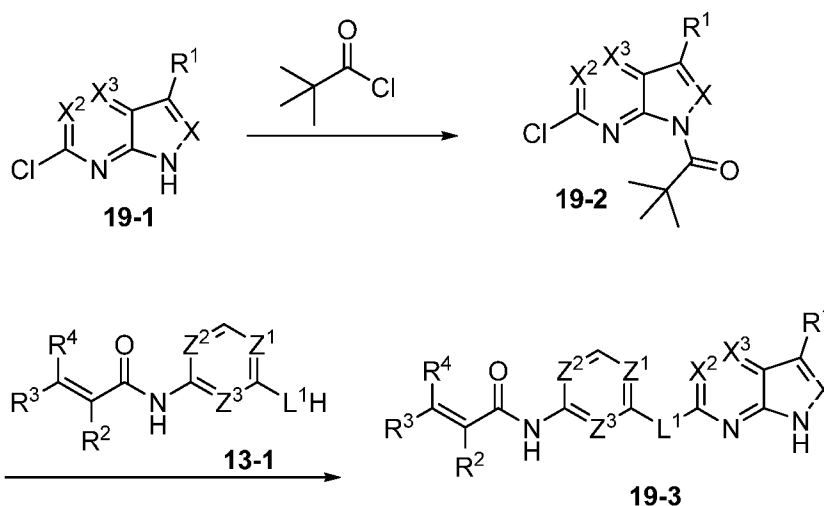
Coating Reagent #3 Coating Reagent #3

SEMCl 2-(trimethylsilyl)ethoxymethyl chloride

Scheme 1

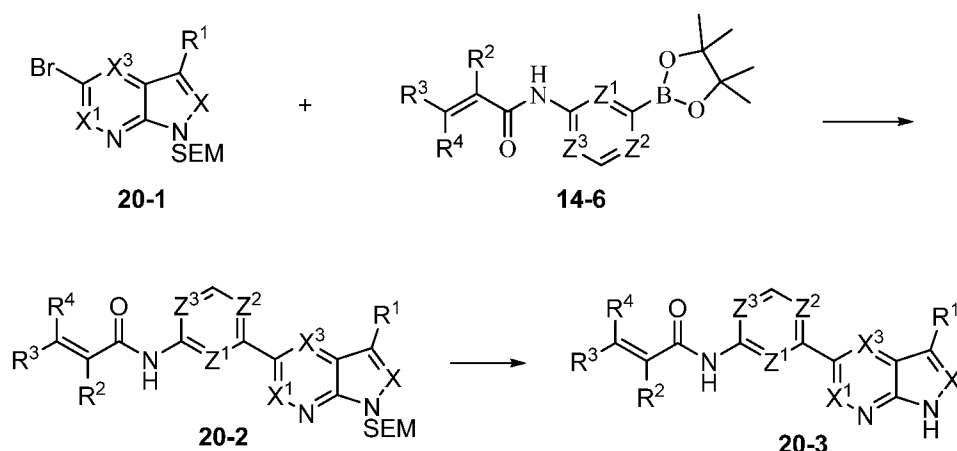
[00477] Compound **14-8** can be prepared by the process illustrated in **Scheme 1**, wherein X^1 , X^3 , X , Z^1 , Z^2 , Z^3 , R^2 , R^3 and R^4 are as defined herein; Ar has the definition of R^1 disclosed herein. Compound **14-1** can react with iodide reagent in a polar solvent (such as DMSO, DMF, actone and the like) to afford compound **14-2**; compound **14-2** can react with paratoluensulfonyl chloride in a base to afford compound **14-3**; compound **14-3** can react with compound **14-4** in the present of a transition metal catalyst by Suzuki cross coupling reaction to afford compound **14-5**; compound **14-5** can react with compound **14-6** in the present of a transition metal catalyst by Suzuki cross coupling reaction to afford compound **14-7**; compound **14-7** can react under an acidic condition (such as trifluoroacetic acid, hydrogen chloride and the like) and the reaction mixture can be concentrated, then the residue can react under an alkaline condition (such as ethanediamine, triethylamine, sodium hydroxide, sodium bicarbonate and the like) to afford target compound **14-8**.

Scheme 2



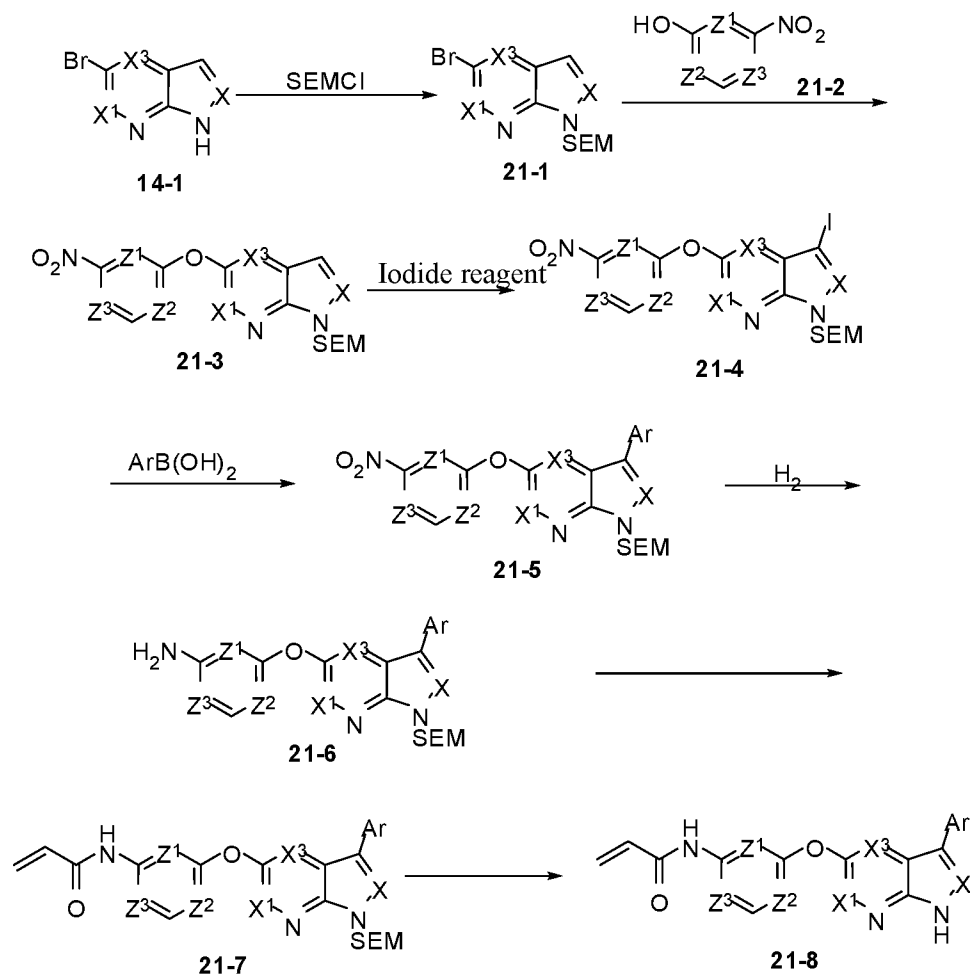
[00478] Compound **19-3** can be prepared by the process illustrated in **Scheme 2**, wherein X^2 , X^3 , X , R^1 , L^1 , Z^1 , Z^2 , Z^3 , R^2 , R^3 and R^4 are as defined herein. Compound **19-1** can react with acyl chloride in the present of a base (such as triethylamine, diisopropylethylamine, potassium carbonate and the like) to afford compound **19-2**; compound **19-2** can react with compound **13-1** in the present of a metal catalyst (such as copper (0), copper (I), copper (II), palladium (0), Ni (0), and the like) and a base (such as potassium carbonate, cesium carbonate, potassium phosphate and the like) to afford the target compound **19-3**.

Scheme 3



[00479] Compound **20-3** can be prepared by the process illustrated in **Scheme 3**, wherein X^1 , X^3 , X , R^1 , Z^1 , Z^2 , Z^3 , R^2 , R^3 and R^4 are as defined herein. Compound **20-1** can react with compound **14-6** in the present of a transition metal catalyst by Suzuki cross coupling reaction to afford compound **20-2**; compound **20-2** can react under an acidic condition (such as trifluoroacetic acid, hydrogen chloride and the like) and the reaction mixture can be concentrated, then the residue can react under an alkaline condition (such as ethanediamine, triethylamine, sodium hydroxide, sodium bicarbonate and the like) to afford target compound **20-3**.

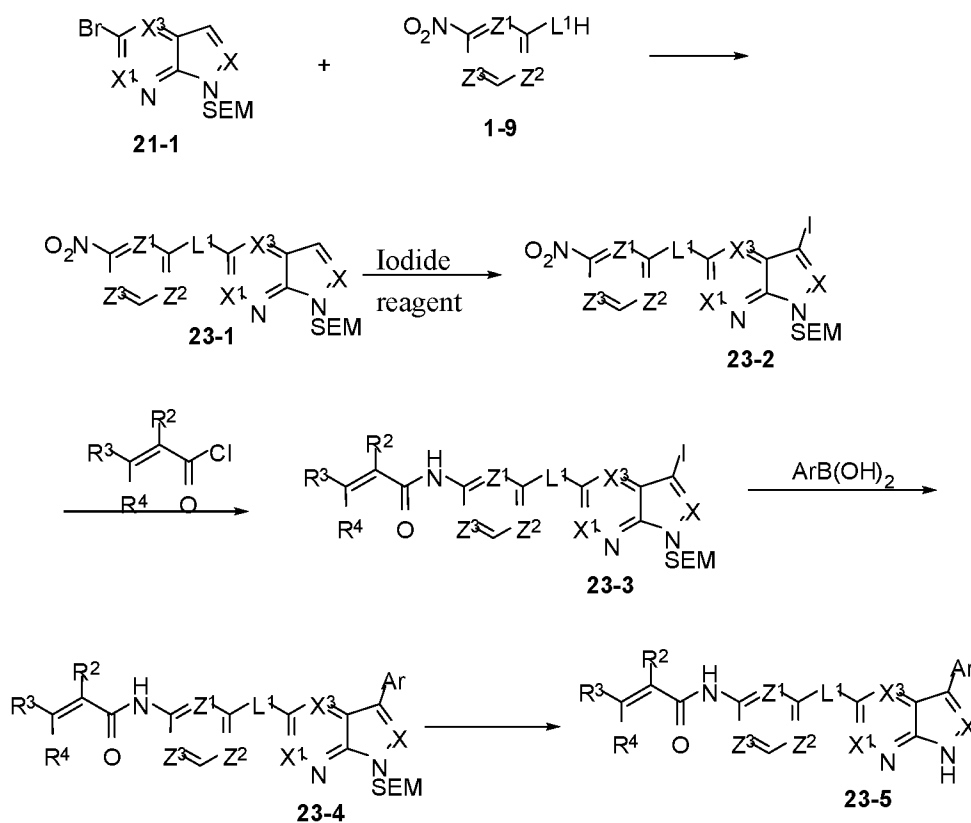
Scheme 4



[00480] Compound **21-8** can be prepared by the process illustrated in **Scheme 4**, wherein X^1 , X^3 , X, Z^1 , Z^2 and Z^3 are as defined herein; Ar has the definition of R^1 disclosed herein. Compound **14-1** can react with SEMCl in the present of a base (such as sodium hydride, potassium *tert*-butoxide and the like) to afford compound **21-1**; compound **21-1** can react with compound **21-2** in the present of a metal catalyst (such as copper (0), copper (I), copper (II), palladium (0), Ni (0), and the like) and a base (such as potassium carbonate, cesium carbonate, potassium phosphate and the like) to afford compound **21-3**; Compound **21-3** can react with iodide reagent in a polar solvent (such as DMSO, DMF, actone and the like) to afford compound **21-4**; compound **21-4** can react with ArB(OH)_2 in the present of a transition metal catalyst by Suzuki cross coupling reaction to afford compound **21-5**; catalytic hydrogenation of compound **21-5** can afford compound **21-6**; compound **21-6** can react with acyl chloride in the present of a base (such as triethylamine, diisopropylethylamine, potassium carbonate and the like) to afford compound **21-7**; compound **21-7** can react under an acidic condition (such as trifluoroacetic acid, hydrogen chloride and the like) and the reaction mixture can be concentrated, then the residue can be react

under an alkaline condition (such as ethanediamine, triethylamine, sodium hydroxide, sodium bicarbonate and the like) to afford target compound **21-8**.

Scheme 5



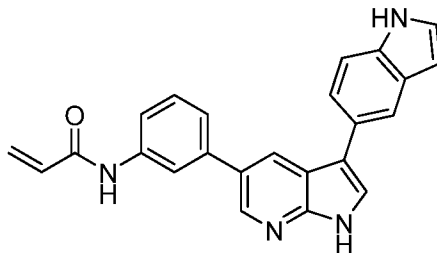
[00481] Compound **23-5** can be prepared by the process illustrated in **Scheme 5**, wherein X^1 , X^3 , X , L^1 , Z^1 , Z^2 , Z^3 , R^2 , R^3 and R^4 are as defined herein; Ar has the definition of R^1 disclosed herein. compound **21-1** can react with compound **1-9** in the present of a metal catalyst (such as copper (0), copper (I), copper (II), palladium (0), Ni (0), and the like) and a base (such as potassium carbonate, cesium carbonate, potassium phosphate and the like) to afford compound **23-1**; Compound **23-1** can react with iodide reagent in a polar solvent (such as DMSO, DMF, actone and the like) to afford compound **23-2**; catalytic hydrogenation of compound **23-2** can afford a phenylamine derivative, which can react with acyl chloride in the present of a base (such as triethylamine, diisopropylethylamine, potassium carbonate and the like) to afford compound **23-3**; compound **23-3** can react with ArB(OH)_2 in the present of a transition metal catalyst by Suzuki cross coupling reaction to afford compound **23-4**; compound **23-4** can react under an acidic condition (such as trifluoroacetic acid, hydrogen chloride and the like) and the reaction mixture can be concentrated, then the residue can be react under an alkaline condition (such as ethanediamine, triethylamine, sodium hydroxide, sodium bicarbonate and the like) to afford

target compound **23-5**.

Example

Example 1

N-(3-(3-(1*H*-Indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)acrylamide



Step 1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole

[00482] To a solution of 5-bromo-1*H*-indole (200 mg, 1.02 mmol) in dioxane (10 mL) were added bis(pinacolato)diboron (309.8 mg, 1.22 mmol), potassium acetate (300 mg, 3.06 mmol), X-Phos (48.5 mg, 0.10 mmol) and tris(dibenzylideneacetone)dipalladium (46.7 mg, 0.05 mmol). The mixture was stirred under N₂ at 115 °C for 18 h. After the reaction was completed, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a yellow solid product (280 mg).

MS (ESI, pos.ion) *m/z*: 244.2[M+1]⁺.

Step 2) 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine

[00483] To a solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (100 mg, 0.51 mmol) in acetone (10 mL) was added *N*-iodosuccinimide (125.6 mg, 0.56 mmol). The mixture was stirred at rt for 1.5 h and filtered, the filter cake was washed with acetone to give a gray solid product (150 mg, 86.1%).

MS (ESI, pos.ion) *m/z*: 322.9[M+1]⁺.

Step 3) 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine

[00484] To a solution of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (510 mg, 1.58 mmol) in anhydrous THF (15 mL) was added sodium hydride (60%, 94.7 mg, 3.95 mmol) in an ice-bath. The mixture was stirred for 0.5 h, and paratoluensulfonyl chloride (364 mg, 1.91 mmol) was added. The mixture was continued to stir overnight, and then saturated aqueous NaCl (20 mL) was added. The resulting mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a white solid

product (510 mg, 67.7%).

MS (ESI, pos.ion) m/z : 476.9[M+1]⁺.

Step 4) 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine

[00485] To a solution of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (20 mg, 0.042 mmol) in acetonitrile (4 mL) were added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (11.2 mg, 0.046 mmol), aqueous Na₂CO₃ solution (1 M, 0.11 mL, 0.11 mmol) and Pd(dppf)Cl₂ (6.5 mg, 0.009 mmol) in turn. The mixture was stirred at rt under N₂ for 2 h, and then saturated aqueous NaCl (10 mL) was added. The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a brown solid product (7 mg, 35.8%).

MS (ESI, pos.ion) m/z : 466.0[M+1]⁺.

Step 5) *N*-(3-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)acrylamide

[00486] To a 25 mL of one-neck flask were added 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (10 mg, 0.02 mmol), *N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylamide (8.8 mg, 0.03 mmol), Pd(dppf)Cl₂ (3.1 mg, 0.004 mmol) and aqueous Na₂CO₃ solution (1 M, 0.05 mL, 0.05 mmol). Then 1,4-dioxane (4 mL) was added. The mixture was stirred at 115 °C for 5 h, and then saturated aqueous NaCl (10 mL) solution was added. The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a brown solid product (3 mg, 26.3%).

MS (ESI, pos.ion) m/z : 533.2[M+1]⁺.

Step 6) *N*-(3-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)acrylamide

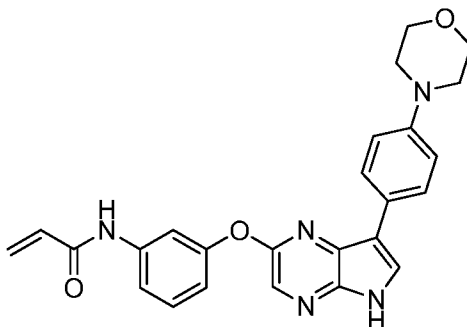
[00487] To a solution of *N*-(3-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)acrylamide (61 mg, 0.11 mmol) in DCM (5 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 6 h and concentrated *in vacuo*. The residue was dissolved in THF (5 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7, and stirred at rt. The resulting mixture was diluted with water (10 mL), and extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow solid product (17 mg, 39.3%).

MS (ESI, pos.ion) m/z : 379.1[M+1]⁺; and

¹H NMR (600 MHz, CD₃OD): δ (ppm) 8.50 (s, 2H), 7.97 (s, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.45 (m, 4H), 7.27 (s, 1H), 6.38-6.52 (m, 3H), 5.78 (d, J = 10.2 Hz, 1H).

Example 2

N-(3-((7-(4-Morpholinophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 4-(4-(2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)morpholine

[00488] To a mixture of 7-iodo-2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (0.30 g, 0.59 mmol), (4-morpholinophenyl)boronic acid (0.15 g, 0.72 mmol), Pd(dppf)Cl₂ (21 mg, 0.03 mmol) and sodium carbonate (0.10 g, 0.90 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) via syringe under N₂. The mixture was stirred at 65°C for 4.5 h. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with DCM. The combined filtrates were washed with saturated aqueous NaCl (30 mL). The aqueous layer was extracted with DCM (30 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a light yellow oily product (280 mg, 87.3%).

MS (ESI, pos.ion) m/z : 548.4[M+1]⁺.

Step 2) 3-((7-(4-morpholinophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)aniline

[00489] To a solution of 4-(4-(2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)morpholine (0.21 g, 0.38 mmol) in methanol (20 mL) was added Pd/C (10%, 20 mg). The mixture was stirred at rt under H₂ for 1 h. The mixture was filtered through a Celite pad to give a light yellow filtrate. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give light yellow oil (150 mg, 75.6%).

MS (ESI, pos.ion) m/z : 518.0[M+1]⁺.

Step 3) *N*-(3-((7-(4-morpholinophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00490] To a solution of 3-((7-(4-morpholinophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)aniline (0.15 mg, 0.29 mmol) in anhydrous DCM (10 mL) was added triethylamine (0.03 mL, 0.20 mmol), and followed by addition of 3-chloropropanoyl chloride (0.02 mL, 0.20 mmol) in an ice-bath. The mixture was warmed to rt naturally and stirred at rt for 6 h. The reaction was quenched with water (35 mL). The resulting mixture was extracted with DCM (35 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL), and then DBU (0.30 mL, 1.99 mmol) was added. The mixture was stirred at rt overnight. The reaction was quenched with water (35 mL). The resulting mixture was extracted with DCM (35 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 50/1 to give a light yellow oily product (100 mg, 60.4%).

MS (ESI, pos.ion) m/z : 572.0[M+1]⁺.

Step 4) *N*-(3-((7-(4-morpholinophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

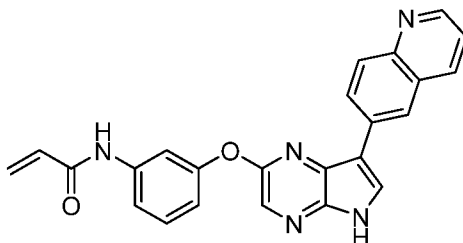
[00491] To a solution of *N*-(3-((7-(4-morpholinophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.1 g, 0.17 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred overnight (the reaction was not finished completely). The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in THF (6 mL), then triethylamine (1 mL) was added. The mixture was stirred at 40 °C overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 50/1 to give a light yellow solid product (25 mg, 32.4%).

MS (ESI, pos.ion) m/z : 442.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.23 (s, 1H), 10.24 (s, 1H), 8.26 (s, 1H), 8.15 (s, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.59 (s, 1H), 7.49-7.33 (m, 2H), 6.90 (m, 3H), 6.41 (dd, J_1 = 16.8 Hz, J_2 = 10.2 Hz, 1H), 6.24 (dd, J_1 = 16.8 Hz, J_2 = 1.8 Hz, 1H), 5.75 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.76-3.71 (m, 4H), 3.12-3.06 (m, 4H).

Example 3

N-(3-((7-(Quinolin-6-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine

[00492] To a solution of 2-bromo-5*H*-pyrrolo[2,3-*b*]pyrazine (1.94 g, 9.8 mmol) in DMF (20 mL) was added sodium hydride (60%, 525.3 mg, 13.13 mmol) in an ice bath. The mixture was stirred at this temperature for 30 min and then SEMCl (2.26 mL, 12.6 mmol) was added. The mixture was stirred at rt overnight. The reaction mixture was quenched with water (40 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/1 to give a light yellow oily product (2.40 g, 75.0%).

MS (ESI, pos.ion) m/z : 328.15[M+1]⁺.

Step 2) 2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine

[00493] To a solution of 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (600 mg, 1.83 mmol) in 1,4-dioxane (8 mL) were added cuprous iodide (348.1 mg, 1.83 mmol), 3-nitrophenol (305.11 mg, 2.19 mmol), *N,N*-dimethylglycine (188.5 mg, 1.82 mmol) and cesium carbonate (891.77 mg, 2.73 mmol). The mixture was stirred at 115 °C under N₂ for 6 h. The mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a light yellow oily product (590 mg, 83.5%).

MS (ESI, pos.ion) m/z : 387.20[M+1]⁺.

Step 3) 7-iodo-2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]

pyrazine

[00494] To a solution of 2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (340 mg, 0.88 mmol) in acetone (8 mL) was added *N*-iodosuccinimide (297 mg, 1.32 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a light yellow oil product (350 mg, 77.7%).

MS (ESI, pos.ion) *m/z*: 513.20[M+1]⁺.

Step 4) 6-(2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)quinoline

[00495] To a solution of 7-iodo-2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (800 mg, 1.56 mmol) in 1,4-dioxane (6 mL) were added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (518.2 mg, 2.03 mmol), potassium carbonate (539 mg, 3.90 mmol) and Pd(dppf)Cl₂ (114.2 mg, 0.15 mmol) in turn. The mixture was stirred at 115 °C under N₂ for 6 h. The mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a yellow oil product (290 mg, 36.2%).

MS (ESI, pos.ion) *m/z*: 514.10[M+1]⁺.

Step 5) 3-((7-(quinolin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)aniline

[00496] To a solution of 6-(2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)quinoline (290 mg, 0.56 mmol) in methanol (8 mL) was added Pd/C (10%, 29 mg). The mixture was stirred under H₂ at rt for 8 h. The mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a yellow oily product (95 mg, 34.8%).

MS (ESI, pos.ion) *m/z*: 484.30[M+1]⁺.

Step 6) *N*-(3-((7-(quinolin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00497] To a solution of 3-((7-(quinolin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)aniline (95 mg, 0.19 mmol) in anhydrous DCM (5 mL) was

added triethylamine (138 μ L, 0.99 mmol), and followed by the addition of 3-chloropropanoyl chloride (90 mg, 0.99 mmol) at rt. The mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a yellow solid (110 mg, 104.1%, containing triethylamine hydrochloride).

MS (ESI, pos.ion) m/z : 538.35[M+1]⁺.

Step 7) *N*-(3-((7-(quinolin-6-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

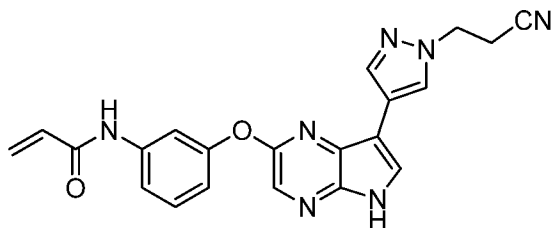
[00498] To a solution of *N*-(3-((7-(quinolin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (100 mg, 0.19 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 2 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a yellow solid product (30 mg, 39.6%).

MS (ESI, pos.ion) m/z : 408.20[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.50 (s, 1H), 10.34 (s, 1H), 8.80 (dd, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz, 1H), 8.66 (d, $J = 1.7$ Hz, 1H), 8.58 (s, 1H), 8.38 (dd, $J_1 = 8.9$ Hz, $J_2 = 1.9$ Hz, 1H), 8.25 (s, 1H), 8.03 (d, $J = 7.5$ Hz, 1H), 7.97 (d, $J = 8.9$ Hz, 1H), 7.77 (t, $J = 2.0$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.50-7.40 (m, 2H), 7.03 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H), 6.42 (dd, $J_1 = 10.0$ Hz, $J_2 = 16.8$ Hz, 1H), 6.24 (dd, $J_1 = 2.0$ Hz, $J_2 = 16.8$ Hz, 1H), 5.75 (dd, $J_1 = 2.0$ Hz, $J_2 = 10.0$ Hz, 1H).

Example 4

***N*-(3-((7-(1-(2-Cyanoethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 3-(4-bromo-1*H*-pyrazol-1-yl)propanenitrile

[00499] To a mixture of 4-bromo-1*H*-pyrazole (5 g, 34.02 mmol), 3-bromopropanenitrile (4.30

mL, 52.00 mmol) and cesium carbonate (17.50 g, 51.00 mmol) was added DMF (25 mL). The mixture was stirred at 75 °C for 15 h. The reaction mixture was diluted with water (120 mL). The resulting mixture was extracted with EtOAc (120 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a colorless crystalline solid product (6.00 g, 72.3%).

MS (ESI, pos.ion) *m/z*: 200.0[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 8.06 (s, 1H), 7.63 (s, 1H), 4.39 (t, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.4 Hz, 2H).

Step 2) 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl) propanenitrile

[00500] To a mixture of 3-(4-bromo-1H-pyrazol-1-yl)propanenitrile (20.00 mmol, 4.00 g), bis(pinacolato)diboron (6.00 g, 23.63 mmol), Pd(dppf)Cl₂ (0.74 g, 1.00 mmol) and potassium acetate (4.00 g, 39.53 mmol) was added 1,4-dioxane (40 mL) via syringe under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with DCM. The combined filtrates were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (1.80 g, 36.0%, containing bis(pinacolato)diboron).

MS (ESI, pos.ion) *m/z*: 248.1[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 8.03 (s, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.66 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 6.28 (t, *J* = 2.0 Hz, 1H), 4.40 (dt, *J*₁ = 9.5 Hz, *J*₂ = 6.4 Hz, 4H), 3.06 (dt, *J*₁ = 13.0 Hz, *J*₂ = 6.4 Hz, 4H), 1.26 (s, 12H).

Step 3) N-(3-((7-(1-(2-cyanoethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00501] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.28 g, 0.52 mmol), 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl) propanenitrile (400 mg, 1.60 mmol), Pd(dppf)Cl₂ (20 mg, 0.03 mmol) and sodium carbonate (88 mg, 0.79 mmol) were added 1,4-dioxane (20 mL) and water (5 mL) via syringe under N₂. The mixture was stirred at 70 °C for 6 h. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with DCM. The combined filtrates were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue

was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a brown solid product (200 mg, 72.3%).

MS (ESI, pos.ion) m/z : 530.4[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-cyanoethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

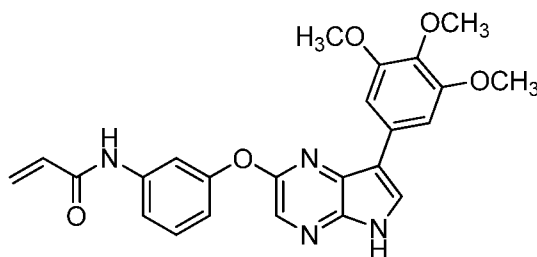
[00502] To a solution of *N*-(3-((7-(1-(2-cyanoethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.18 g, 0.34 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 20/1 to give a light yellow solid product (22 mg, 16.2%).

MS (ESI, pos.ion) m/z : 400.3[M+1]⁺; and

¹H NMR (600 MHz, CD₃OD): δ (ppm) 8.17 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 7.93 (s, 1H), 7.69 (t, J = 2.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 6.99 (ddd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, J_3 = 0.6 Hz, 1H), 6.44 (dd, J_1 = 17.4 Hz, J_2 = 10.2 Hz, 1H), 6.36 (dd, J_1 = 16.8 Hz, J_2 = 1.8 Hz, 1H), 5.78 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 4.41 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H).

Example 5

***N*-(3-((7-(3,4,5-Trimethoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N*-(3-((7-(3,4,5-trimethoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00503] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (200 mg, 0.37 mmol), (3,4,5-trimethoxyphenyl)boronic acid

(100 mg, 0.47 mmol), Pd(dppf)Cl₂ (14 mg, 0.02 mmol) and sodium carbonate (65 mg, 0.58 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) via syringe under N₂. The mixture was stirred at 65 °C for 4 h. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with DCM. The combined filtrates were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 50/1 to give a light yellow oily product (160 mg, 74.4%).

MS (ESI, pos.ion) *m/z*: 577.4[M+1]⁺.

Step 2) *N*-(3-((7-(3,4,5-trimethoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

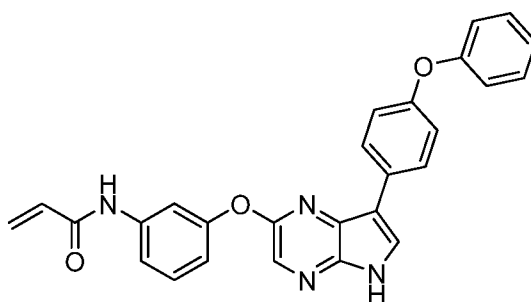
[00504] To a solution of *N*-(3-((7-(3,4,5-trimethoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (150 mg, 0.26 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 40/1 to give a light yellow solid product (25 mg, 21.5%).

MS (ESI, neg.ion) *m/z*: 447.3[M+1]⁺; and

¹H NMR (400 MHz, CD₃OD): δ (ppm) 8.12 (d, *J* = 8.0 Hz, 2H), 7.66 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.43-7.32 (m, 3H), 7.06-6.93 (m, 1H), 6.49-6.31 (m, 2H), 5.78 (dd, *J*₁ = 9.6 Hz, *J*₂ = 2.0 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 7H).

Example 6

***N*-(3-((7-(4-Phenoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 7-iodo-2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine

[00505] To a solution of 2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (2.20 g, 5.70 mmol) in acetone (30 mL) was added *N*-iodosuccinimide (2.01 g, 8.50 mmol) at rt. After the reaction was stirred at rt for 7 h, the raw material was consumed monitored by TLC, then to the reaction mixture was added silica gel. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a light yellow solid product (1.62 g, 54.5%).

MS (ESI, pos.ion) *m/z*: 513.2[M+1]⁺.

Step 2) 7-iodo-2-(3-aminophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine

[00506] To a mixture of Fe powder (56 mg, 1.00 mmol), ammonium chloride (91 mg, 1.69 mmol) and 7-iodo-2-(3-nitrophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (136 mg, 0.27 mmol) were added water (3 mL) and ethanol (10 mL) at rt. After the mixture was stirred at 95 °C for 4 h, the raw material was consumed monitored by TLC. The mixture was filtered through a Celite pad. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a light yellow oily product (32 mg, 25.0%).

MS (ESI, pos.ion) *m/z*: 483.2[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.03 (s, 1H), 7.68 (s, 1H), 7.36 (d, *J* = 3.2 Hz, 1H), 7.04-6.91 (m, 3H), 5.60 (s, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 0.91 (t, *J* = 6.4 Hz, 2H), -0.04 (s, 9H).

Step 3) *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00507] To a mixture of 7-iodo-2-(3-aminophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (170 mg, 0.35 mmol) and triethylamine (178 mg, 1.77 mmol) in DCM (15 mL) was added acryloyl chloride (36 mg, 0.41 mmol). After the reaction was stirred at rt overnight, the raw material was consumed monitored by TLC. The mixture was quenched with water (50 mL). The resulting mixture was extracted with DCM (150 mL). The organic layer was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a white solid product (146 mg, 77.2%).

MS (ESI, pos.ion) *m/z*: 537.2[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.05 (s, 1H), 7.69 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H),

7.37-7.31 (m, 3H), 6.40 (d, $J = 17.2$ Hz, 1H), 6.22 (dd, $J = 17.2$ Hz, 10.4 Hz, 1H), 5.76 (d, $J = 10.4$ Hz, 1H), 5.61 (s, 2H), 3.55 (t, $J = 8.4$ Hz, 2H), 0.92 (t, $J = 8.4$ Hz, 2H), -0.04 (s, 9H).

Step 4) *N*-(3-((7-(4-phenoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00508] To a mixture of (4-phenoxyphenyl)boronic acid (40 mg, 0.18 mmol), potassium carbonate (60 mg, 0.44 mmol), Pd(dppf)Cl₂ (20 mg, 0.028 mmol) and *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (100 mg, 0.19 mmol) were added water (4 mL) and dioxane (20 mL) at rt. The mixture was stirred at 50 °C under N₂. After the reaction was stirred for 6 h, to the reaction mixture was added silica gel. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (50 mg, 50.0%).

MS (ESI, pos.ion) m/z : 579.3[M+1]⁺.

Step 5) *N*-(3-((7-(4-phenoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

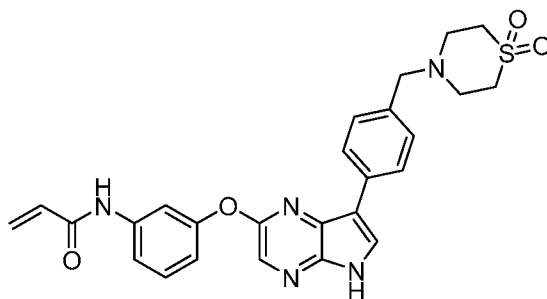
[00509] A mixture of *N*-(3-((7-(4-phenoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (232 mg, 0.41 mmol) in DCM (8 mL) and TFA (8 mL) was stirred at rt for 14 h. After the raw material was consumed monitored by TLC and LC-MS, the mixture was concentrated *in vacuo*. The residue was diluted with THF (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL). After stirring 6 h, the reaction was completed monitored by LC-MS. The resulting mixture was extracted with DCM (25 mL × 8). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (50 mg, 30.0%).

MS (ESI, neg.ion) m/z : 449.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.37 (d, $J = 2.4$ Hz, 1H), 10.22 (br, s, 1H), 8.87 (d, $J = 3$ Hz, 1H), 8.18 (s, 1H), 8.06 (d, $J = 9.0$ Hz, 2H), 7.64 (s, 1H), 7.41-7.35 (m, 4H), 7.13 (t, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 9.0$ Hz, 4H), 6.91 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H), 6.39-6.35 (m, 1H), 6.21 (dd, $J_1 = 16.8$ Hz, $J_2 = 1.2$ Hz, 1H), 5.72 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.2$ Hz, 1H).

Example 7

***N*-(3-((7-(4-((1,1-Dioxidothiomorpholino)methyl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-(4-bromobenzyl)thiomorpholine 1, 1-dioxide

[00510] To a mixture of 1-bromo-4-(bromomethyl)benzene (500 mg, 2.00 mmol) and thiomorpholine 1,1-dioxide (513 mg, 2.99 mmol) was added THF (10 mL) and triethylamine (0.84 mL) in turn. After the mixture was stirred at rt for 15 h, the raw material was consumed monitored by TLC. The reaction mixture was diluted with EtOAc (200 mL) and washed with saturated aqueous NaCl (50 mL) three times. The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a white solid product (310 mg, 50.9%).

MS (ESI, pos.ion) m/z : 304.1[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.46 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 3.59 (s, 2H), 3.07-3.05 (m, 4H), 2.98-2.95 (m, 4H).

Step 2) *N*-(3-((7-(4-((1,1-dioxidothiomorpholino)methyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00511] To a mixture of potassium acetate (77 mg, 0.77 mmol), Pd(dppf)Cl₂ (14 mg, 0.02 mmol), 4-(4-bromobenzyl)thiomorpholine 1,1-dioxide (120 mg, 0.39 mmol) and bis(pinacolato)diboron (105 mg, 0.41 mmol) was added 1,4-dioxane (20 mL). The system was exchanged with N₂ and equipped with a nitrogen balloon, and stirred at 95 °C. After stirring for 5 h, the raw material was consumed monitored by TLC. After the mixture was cooled to rt, Pd(dppf)Cl₂ (14 mg, 0.02 mmol), potassium carbonate (100 mg, 0.72 mmol), *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (158 mg, 0.29 mmol) and H₂O (4 mL) were added. The resulting mixture was stirred at 60 °C for 11 h under N₂, then the reaction was completed monitored by LC-MS and TLC. The mixture was filtered through a Celite pad. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a light yellow oil product (146 mg, 58.4%).

MS (ESI, pos.ion) m/z : 634.0[M+1]⁺.

Step 3) *N*-(3-((7-(4-((1,1-dioxidothiomorpholino)methyl)phenyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

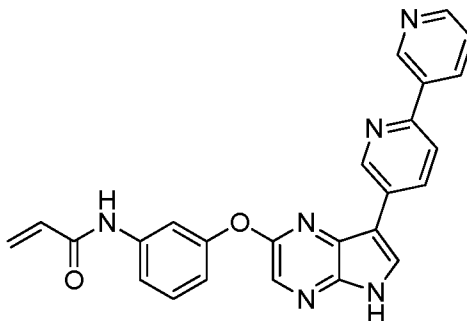
[00512] A mixture of *N*-(3-((7-(4-((1,1-dioxidothiomorpholino)methyl)phenyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (146 mg, 0.23 mmol) in DCM (8 mL) and trifluoroacetic acid (8 mL) was stirred at rt for 14 h. The raw material was consumed monitored by TLC and LC-MS. The mixture was concentrated *in vacuo*. The residue was diluted with THF (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL). After stirring 6 h, the reaction was completed monitored by LC-MS. The resulting mixture was extracted with DCM (50 mL × 8). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (26 mg, 22.4%).

MS (ESI, pos.ion) *m/z*: 504.3[M+1]⁺; and

¹H NMR (600 MHz, CD₃OD): δ (ppm) 8.11 (d, *J* = 6.6 Hz, 2H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.68 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.00 (dd, *J*₁ = 7.8 Hz, *J*₂ = 1.2 Hz, 1H), 6.47-6.43 (m, 1H), 6.36 (dd, *J*₁ = 16.8 Hz, *J*₂ = 1.2 Hz, 1H), 5.79 (dd, *J*₁ = 9.6 Hz, *J*₂ = 1.2 Hz, 1H), 3.67 (s, 2H), 3.12 (t, *J* = 4.8 Hz, 4H), 2.99 (s, 4H).

Example 8

***N*-(3-((7-([2, 3'-Bipyridin]-5-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) [2,3'-bipyridin]-5-ylboronic acid

[00513] To a solution of 5-bromo-2,3'-bipyridine (400 mg, 1.70 mmol) in 1,4-dioxane (10 mL) were added bis(pinacolato)diboron (840 mg, 3.31 mmol), potassium acetate (420 mg, 4.28 mmol) and Pd(dppf)Cl₂ (120 mg, 0.16 mmol). The mixture was refluxed at 110 °C under N₂ for 11 h. The mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a brown oily product (260 mg, 76%).

MS (ESI, pos.ion) *m/z*: 201.2[M+1]⁺.

Step 2) *N*-(3-((7-([2,3'-bipyridin]-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00514] To a solution of [2,3'-bipyridin]-5-ylboronic acid (240 mg, 1.20 mmol) in 1,4-dioxane (12 mL) were added *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (400 mg, 0.75 mmol), potassium carbonate (160 mg, 1.16 mmol), Pd(dppf)Cl₂ (60 mg, 0.08 mmol) and water (3 mL) in turn. The mixture was stirred at 65 °C under N₂ for 2 h and diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a brown oily product (390 mg, 92.6%).

MS (ESI, pos.ion) *m/z*: 565.4[M+1]⁺.

Step 3) *N*-(3-((7-([2,3'-bipyridin]-5-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

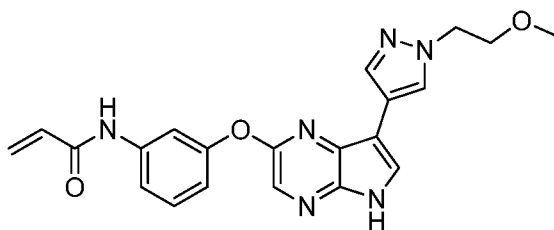
[00515] To a solution of *N*-(3-((7-([2,3'-bipyridin]-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (420 mg, 0.74 mmol) in DCM (10 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 6 h. The mixture was diluted with water (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a light yellow solid product (40 mg, 12.38%).

MS (ESI, pos.ion) *m/z*: 435.20[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.61 (s, 1H), 10.26 (s, 1H), 9.37 (d, *J* = 1.9 Hz, 1H), 9.27 (d, *J* = 1.7 Hz, 1H), 8.63 (s, 1H), 8.61 (dd, *J*₁ = 4.6 Hz, *J*₂ = 1.2 Hz, 1H), 8.52 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.1 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.25 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.50 (dd, *J*₁ = 7.9 Hz, *J*₂ = 4.8 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 6.96 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.9 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.6 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.6 Hz, 1H).

Example 9

***N*-(3-((7-(1-(2-Methoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-iodo-1-(2-methoxyethyl)-1H-pyrazole

[00516] To a solution of 4-iodo-1H-pyrazole (1.00 g, 5.20 mmol) in DMF (20 mL) were added 1-bromo-2-methoxyethane (0.89 g, 6.40 mmol) and cesium carbonate (2.65 g, 7.73 mmol). The mixture was stirred at rt for 5 h. The reaction mixture was quenched with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (50 mL $\times$ 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a colorless liquid product (1.10 g, 85.0%).

MS (ESI, pos.ion) *m/z*: 253.1[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.52 (dd, $J_1 = 7.4$ Hz, $J_2 = 2.3$ Hz, 2H), 4.29 (dd, $J_1 = 8.3$ Hz, $J_2 = 5.1$ Hz, 2H), 3.71 (dd, $J_1 = 8.3$ Hz, $J_2 = 5.1$ Hz, 2H), 3.33 (d, $J = 3.5$ Hz, 3H).

Step 2) 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00517] A mixture of 4-iodo-1-(2-methoxyethyl)-1H-pyrazole (1.00 g, 3.97 mmol), bis(pinacolato)diboron (1.51 g, 5.95 mmol), potassium acetate (1.2 g, 12.00 mmol) and PdCl₂(dppf)₂ (150 mg, 0.20 mmol) in DMSO (20 mL) was stirred at 80 °C under N₂ overnight. The mixture was cooled to rt and quenched with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (50 mL $\times$ 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/2 to give a light yellow oily product (480 mg, 48.0%).

MS (ESI, pos.ion) *m/z*: 253.3[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.80 (s, 1H), 7.77 (s, 1H), 4.31 (t, $J = 5.3$ Hz, 2H), 3.75 (t, $J = 5.3$ Hz, 2H), 3.33 (s, 3H), 1.25 (s, 12H).

Step 3) N-(3-((7-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00518] To a mixture of N-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (220 mg, 0.41 mmol), 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (160 mg, 0.63

mmol), sodium carbonate (80 mg, 0.72 mmol) and Pd(dppf)Cl₂ (17 mg, 0.023 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) under N₂. The mixture was stirred at 65 °C for 4 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 4/1 to give a brown oil product (150 mg, 68.4%).

MS (ESI, pos.ion) *m/z*: 535.0[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

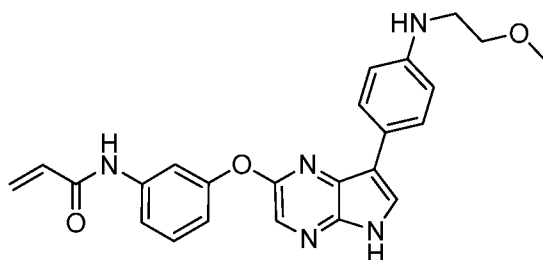
[00519] To a solution of *N*-(3-((7-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (150 mg, 0.22 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 4.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 20/1 to give a light yellow solid product (30 mg, 33.1%).

MS (ESI, pos.ion) *m/z*: 405.0[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.24 (s, 1H), 8.14 (s, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.93 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.6 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H), 4.22 (t, *J* = 5.3 Hz, 2H), 3.64 (t, *J* = 5.3 Hz, 2H), 3.19 (s, 3H).

Example 10

***N*-(3-((7-(4-((2-Methoxyethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *tert*-butyl (4-bromophenyl)(2-methoxyethyl)carbamate

[00520] A mixture of sodium hydride (60%, 160 mg, 4.00 mmol) and *tert*-butyl

(4-bromophenyl)carbamate (598 mg, 2.20 mmol) in DMF (20 mL) was stirred at 0 °C under N₂ for 0.5 h. To the mixture was added 1-bromo-2-methoxyethane (400 mg, 2.88 mmol). The resulting mixture was warmed to 80 °C and stirred for 3 h. The reaction mixture was cooled to rt and quenched with saturated aqueous NaCl (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 15/1 to give a light yellow solid product (696 mg, 96.1%).

MS (ESI, pos.ion) *m/z*: 230.2[M-99]⁺.

Step 2) *tert*-butyl (2-methoxyethyl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate

[00521] A mixture of *tert*-butyl (4-bromophenyl)(2-methoxyethyl)carbamate (550 mg, 2.01 mmol), bis(pinacolato)diboron (660 mg, 2.60 mmol), potassium acetate (500 mg, 5.10 mmol) and Pd(dppf)Cl₂ (60 mg, 0.08 mmol) in dioxane (15.00 mL) was stirred at 100 °C under N₂ for 12 h. The mixture was cooled to rt and quenched with saturated aqueous NH₄Cl (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a yellow oily product (610 mg, 96.8%).

MS (ESI, pos.ion) *m/z*: 278.3[M-99]⁺.

Step 3) *tert*-butyl (4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)(2-methoxyethyl)carbamate

[00522] To a mixture of *tert*-butyl (2-methoxyethyl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (400 mg, 1.06 mmol), *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (360 mg, 0.67 mmol), potassium carbonate (231 mg, 1.67 mmol) and Pd(dppf)Cl₂ (24 mg, 0.03 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N₂. The mixture was stirred at 110 °C for 12 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 2/1 to give a light yellow oily product (125 mg, 28.2%).

MS (ESI, pos.ion) *m/z*: 604.0[M-55]⁺.

Step 4) *N*-(3-((7-(4-((2-methoxyethyl)amino)phenyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00523] To a solution of *tert*-butyl (4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)

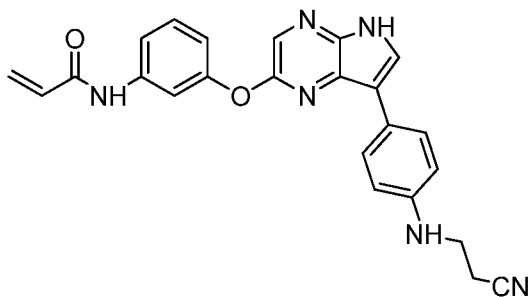
methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)(2-methoxyethyl)carbamate (125 mg, 0.19 mmol) in DCM (6 mL) was added trifluoroacetic acid (6 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with THF (4 mL) and saturated aqueous sodium bicarbonate solution (4 mL). The resulting mixture was stirred at rt for 5 h and extracted with EtOAc (50 mL × 6). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a light yellow solid product (24 mg, 29.5%)

MS (ESI, pos.ion) *m/z*: 430.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (d, *J* = 2.4 Hz, 1H), 10.21 (s, 1H), 8.14 (d, *J* = 2.8 Hz, 1H), 8.12 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.7 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 5.49 (t, *J* = 5.7 Hz, 1H), 3.48 (t, *J* = 5.7 Hz, 2H), 3.28 (s, 3H), 3.18 (q, *J* = 5.7 Hz, 2H).

Example 11

***N*-(3-((7-(4-((2-Cyanoethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acryl amide**



Step 1) 3-((4-bromophenyl)amino)propanenitrile

[00524] To a solution of bromo-4-iodobenzene (1.0 g, 3.53 mmol) in DMSO (16 mL) were added 3-aminopropanenitrile (400 μL, 5.32 mmol), cesium carbonate (1.7 g, 5.2 mmol), *N,N*-dimethylglycine (400 mg, 3.80 mmol) and cuprous iodide (675 mg, 3.54 mmol) in turn. The mixture was stirred at 70 °C for 7.5 h and quenched with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a light yellow solid product (300 mg, 37.7%).

MS (ESI, pos.ion) *m/z*: 225.0, 227.0[M+1]⁺.

Step 2) 3-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile

[00525] To a solution of 3-((4-bromophenyl)amino)propanenitrile (300 mg, 1.33 mmol) in 1,4-dioxane (8 mL) were added bis(pinacolato)diboron (410 mg, 1.61 mmol), potassium acetate (330 mg, 3.36 mmol) and Pd(dppf)Cl₂ (100 mg, 0.14 mmol). The mixture was stirred at 110 °C for 24 h and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (290 mg, 79.93%)

MS (ESI, pos.ion) *m/z*: 273.30[M+1]⁺.

Step 3) *N*-(3-((7-(4-((2-cyanoethyl)amino)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00526] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (300 mg, 0.56 mmol), 3-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile (230 mg, 0.85 mmol), sodium carbonate (100 mg, 0.90 mmol) and Pd(dppf)Cl₂ (20 mg, 0.03 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) under N₂. The mixture was stirred at 65 °C for 8 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/1 to give an earthy yellow solid product (110 mg, 35.5%).

MS (ESI, pos.ion) *m/z*: 555.1[M+1]⁺.

Step 4) *N*-(3-((7-(4-((2-cyanoethyl)amino)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00527] To a solution of *N*-(3-((7-(4-((2-cyanoethyl)amino)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (105 mg, 0.19 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a light yellow solid product (12 mg, 14.9%).

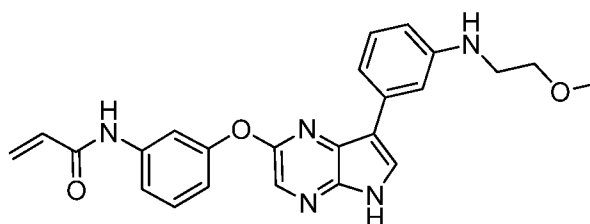
MS (ESI, pos.ion) *m/z*: 425.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.14 (d, *J* = 2.0 Hz, 1H), 10.21 (s, 1H), 8.17 (d, *J*

= 2.8 Hz, 1H), 8.13 (s, 1H), 7.79 (d, $J = 8.5$ Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 7.37 (t, $J = 8.1$ Hz, 1H), 6.90 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.9$ Hz, 1H), 6.61 (d, $J = 8.6$ Hz, 2H), 6.41 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, 1H), 6.24 (dd, $J_1 = 17.0$ Hz, $J_2 = 1.6$ Hz, 1H), 5.87 (t, $J = 5.9$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.6$ Hz, 1H), 3.34 (s, 2H), 2.71 (t, $J = 6.5$ Hz, 2H).

Example 12

N-(3-((7-(3-((2-Methoxyethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *tert*-butyl (3-bromophenyl)carbamate

[00528] A mixture of 3-bromoaniline (2.51 g, 15.01 mmol), di-*tert*-butyl dicarbonate (13.00 mL, 57.00 mmol) and triethylamine (6.10 mL, 44.00 mmol) in methanol (60.00 mL) was stirred at 75°C for 12 h. To the mixture was added silica gel. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 20/1) to give a yellow oily product (3.01 g, 76.1%).

MS (ESI, pos.ion) m/z : 216.10, 218.10[M-55]⁺.

Step 2) *tert*-butyl (3-bromophenyl)(2-methoxyethyl)carbamate

[00529] A mixture of sodium hydride (250 mg, 6.25 mmol) and *tert*-butyl (3-bromophenyl)carbamate (590 mg, 2.17 mmol) in DMF (15.00 mL) was stirred at 0 °C under N₂ for 0.5 h. To the mixture was added 1-bromo-2-methoxyethane (520 mg, 3.74 mmol). The resulting mixture was warmed to 80 °C and stirred for 3 h. The reaction mixture was cooled to rt and quenched with saturated aqueous NaCl (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 15/1 to give a colorless oily product (667 mg, 93.2%).

MS (ESI, pos.ion) m/z : 230.2[M-99]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.44 (s, 1H), 7.35-7.30 (m, 1H), 7.22-7.15 (m, 2H), 3.77 (t, $J = 5.9$ Hz, 2H), 3.52 (t, $J = 5.9$ Hz, 2H), 3.32 (s, 3H), 1.44 (s, 9H).

Step 3) *tert*-butyl (2-methoxyethyl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate

[00530] A mixture of *tert*-butyl (3-bromophenyl)(2-methoxyethyl)carbamate (662 mg, 2.01

mmol), bis(pinacolato)diboron (810 mg, 3.19 mmol), potassium acetate (590 mg, 6.01 mmol) and Pd(dppf)Cl₂ (71 mg, 0.10 mmol) in dioxane (15.00 mL) was stirred at 100 °C under N₂ for 12 h. The mixture was cooled to rt and quenched with saturated aqueous NaCl (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a light yellow oil product (750 mg, 99.2%).

MS (ESI, pos.ion) *m/z*: 278.3[M-99]⁺.

Step 4) *tert*-butyl (3-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)(2-methoxyethyl)carbamate

[00531] To a mixture of *tert*-butyl (2-methoxyethyl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (200 mg, 0.53 mmol), *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (200 mg, 0.37 mmol), potassium carbonate (130 mg, 0.94 mmol) and Pd(dppf)Cl₂ (14 mg, 0.02 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N₂. The mixture was stirred at 110 °C for 12 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 2/1 to give a light yellow oil product (72 mg, 29.3%).

MS (ESI, pos.ion) *m/z*: 560.1[M-99]⁺.

Step 5) *N*-(3-((7-(3-((2-methoxyethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00532] To a solution of *tert*-butyl (3-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)phenyl)(2-methoxyethyl)carbamate (72 mg, 0.11 mmol) in DCM (6 mL) was added trifluoroacetic acid (6 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with THF (4 mL) and saturated aqueous sodium bicarbonate solution (4 mL). The resulting mixture was stirred at rt for 5 h and extracted with EtOAc (50 mL × 6). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a white solid product (35 mg, 72.5%).

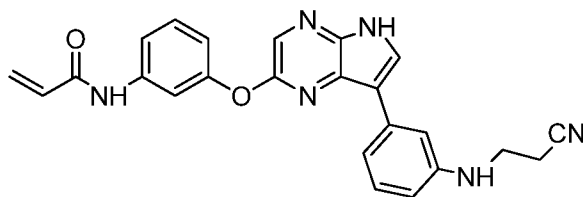
MS (ESI, pos.ion) *m/z*: 430.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.27 (d, *J* = 2.5 Hz, 1H), 10.23 (s, 1H), 8.27 (d, *J* = 3.0 Hz, 1H), 8.17 (s, 1H), 7.57 (t, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.94-6.91 (m,

1H), 6.45 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H), 6.41 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, 1H), 6.24 (dd, $J_1 = 17.0$ Hz, $J_2 = 1.9$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.8$ Hz, 1H), 5.26 (s, 1H), 3.41 (t, $J = 5.4$ Hz, 2H), 3.25 (s, 3H), 2.99 (t, $J = 4.7$ Hz, 2H).

Example 13

N-(3-((7-(3-((2-Cyanoethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 3-((3-bromophenyl)amino)propanenitrile

[00533] To a solution of 1-bromo-3-iodobenzene (4.0 g, 14.1 mmol) in DMSO (40 mL) were added 3-aminopropanenitrile (1.5 mL, 20 mmol), cuprous iodide (2.8 g, 15 mmol), cesium carbonate (7.0 g, 21.5 mmol) and *N,N*-dimethylglycine (1.5 g, 14 mmol) in turn. The mixture was stirred at 70 °C for 5 h and quenched with water (40 mL). The resulting mixture was extracted with DCM (40 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (3.0 g, 94%).

MS (ESI, pos.ion) m/z : 225.0, 227.0 $[\text{M}+1]^+$.

Step 2) 3-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile

[00534] To a solution of 3-((3-bromophenyl)amino)propanenitrile (3.0 g, 13 mmol) in DMSO (36 mL) were added bis(pinacolato)diboron (5.1 g, 20 mmol), potassium acetate (3.3 g, 34 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (950 mg, 1.28 mmol). The mixture was stirred at 100°C under N_2 for 8 h and quenched with water (40 mL). The resulting mixture was extracted with DCM (40 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (1.6 g, 44%).

MS (ESI, pos.ion) m/z : 273.0 $[\text{M}+1]^+$.

Step 3) *N*-(3-((7-(3-((2-cyanoethyl)amino)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00535] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.58 mmol), 3-((4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile (230 mg, 0.85 mmol), potassium carbonate (120 mg, 0.86 mmol) and Pd(dppf)Cl₂ (20 mg, 0.03 mmol) were added 1,4-dioxane (16 mL) and water (3 mL) under N₂. The mixture was stirred at 65 °C for 5 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/1 to give a gray yellow oil product (150 mg, 46.8%).

MS (ESI, pos.ion) *m/z*: 555.3[M+1]⁺.

Step 4) *N*-(3-((7-(3-((2-cyanoethyl)amino)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

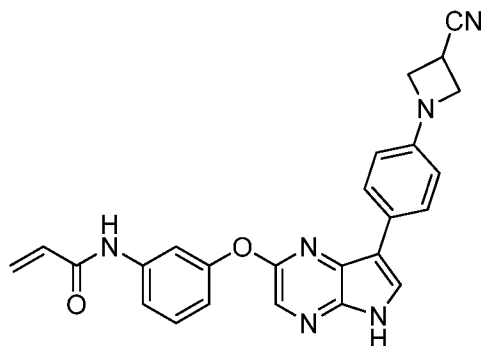
[00536] To a solution of *N*-(3-((7-(3-((2-cyanoethyl)amino)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (105 mg, 0.19 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (17 mg, 21.2%).

MS (ESI, pos.ion) *m/z*: 425.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.30 (d, *J* = 2.6 Hz, 1H), 10.23 (s, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 8.18 (s, 1H), 7.56 (t, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.30 (s, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.93 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.7 Hz, 1H), 6.46 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.7 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.80-5.71 (m, 2H), 3.15 (q, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 6.3 Hz, 2H).

Example 14

***N*-(3-((7-(4-(3-Cyanoazetidin-1-yl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(4-bromophenyl)azetidine-3-carbonitrile

[00537] To a solution of 1-bromo-4-iodobenzene (1.0 g, 3.53 mmol) in DMSO (16 mL) were added azetidine-3-carbonitrile hydrochloride (420 mg, 3.54 mmol), cesium carbonate (1.7 g, 5.2 mmol), *N,N*-dimethylglycine (400 mg, 3.80 mmol) and cuprous iodide (675 mg, 3.54 mmol) in turn. The mixture was stirred at 70 °C for 5 h and quenched with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a light yellow solid product (200 mg, 23.86%).

MS (ESI, pos.ion) *m/z*: 237.1, 238.9[M+1]⁺.

Step 2) 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-3-carbonitrile

[00538] To a solution of 1-(4-bromophenyl)azetidine-3-carbonitrile (190 mg, 0.80 mmol) in 1,4-dioxane (8 mL) were added bis(pinacolato)diboron (250 mg, 0.98 mmol), potassium acetate (200 mg, 2.04 mmol) and Pd(dppf)Cl₂ (60 mg, 0.08 mmol). The mixture was stirred at 110 °C for 24 h under N₂ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a brown oily product (230 mg, 87.82%).

MS (ESI, pos.ion) *m/z*: 285.15[M+1]⁺.

Step 3) *N*-(3-((7-(4-(3-cyanoazetidin-1-yl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00539] To a solution of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-3-carbonitrile (170 mg, 0.60 mmol) in 1,4-dioxane (8 mL) were added *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (261 mg, 0.49 mmol), potassium carbonate (108 mg, 0.78 mmol), Pd(dppf)Cl₂ (41 mg, 0.06 mmol) and water (2 mL) in turn. The mixture was stirred at 70 °C under N₂ for 2 h, cooled to rt and quenched with saturated aqueous NaCl (10 mL). The resulting mixture was extracted

with DCM (10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a yellow oily product (120 mg, 43.2%).

MS (ESI, pos.ion) m/z : 567.0[M+1]⁺.

Step 4) *N*-(3-((7-(4-(3-cyanoazetidin-1-yl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

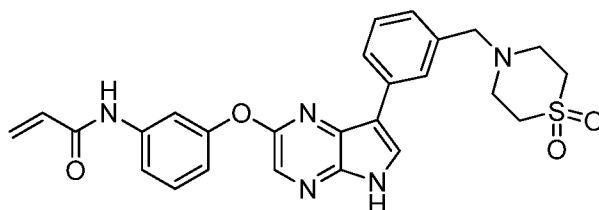
[00540] To a solution of *N*-(3-((7-(4-(3-cyanoazetidin-1-yl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (120 mg, 0.21 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO_3 to pH > 7 and stirred at rt for 12 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a yellow solid product (2 mg, 2.16%).

MS (ESI, pos.ion) m/z : 437.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.20 (d, J = 13.9 Hz, 1H), 10.21 (d, J = 16.8 Hz, 1H), 8.23 (t, J = 5.6 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.88 (t, J = 8.3 Hz, 2H), 7.58 (d, J = 19.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.36 (dd, J_1 = 17.1 Hz, J_2 = 8.9 Hz, 1H), 6.91 (dd, J_1 = 7.7 Hz, J_2 = 2.0 Hz, 1H), 6.47 (d, J = 8.6 Hz, 2H), 6.40 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 1H), 6.23 (m, 1H), 5.76 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 4.07 (m, 2H), 3.94 (dd, J_1 = 7.0 Hz, J_2 = 5.7 Hz, 2H), 3.82 (m, 1H).

Example 15

***N*-(3-((7-(3-((1,1-Dioxidothiomorpholino)methyl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-(3-bromobenzyl)thiomorpholine 1, 1-dioxide

[00541] To a solution of 1-bromo-3-(bromomethyl)benzene (500 mg, 2.0 mmol) in THF (10 mL) were added thiomorpholine 1,1-dioxide hydrochloride (513 mg, 2.99 mmol) and triethylamine (834.7 μL , 6.0 mmol) in turn. The mixture was stirred at 30 °C for 16 h and quenched with water

(20 mL). The resulting mixture was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (440 mg, 72.30%).

MS (ESI, pos.ion) m/z : 306.00[M+1]⁺.

Step 2) 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)thiomorpholine 1,1-dioxide

[00542] To a solution of 4-(3-bromobenzyl)thiomorpholine 1,1-dioxide (120 mg, 0.39 mmol) in 1,4-dioxane (5 mL) were added bis(pinacolato)diboron (120 mg, 0.47 mmol), potassium acetate (92.8 mg, 0.95 mmol) and Pd(dppf)Cl₂ (29 mg, 0.04 mmol). The mixture was stirred at 115 °C for 5 h and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (190 mg, 93.81%).

MS (ESI, pos.ion) m/z : 352.1[M+1]⁺.

Step 3) *N*-(3-((7-(3-((1,1-dioxidothiomorpholino)methyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00543] To a solution of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (157 mg, 0.29 mmol) in 1,4-dioxane (6 mL) were added 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)thiomorpholine 1,1-dioxide (130 mg, 0.35 mmol), potassium carbonate (60.6 mg, 0.44 mmol), Pd(dppf)Cl₂ (42.8 mg, 0.06 mmol) and water (1.5 mL) in turn. The mixture was stirred at 70 °C under N₂ for 2.5 h and diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a brown oily product (110 mg, 59.3%).

MS (ESI, pos.ion) m/z : 634.0[M+1]⁺.

Step 4) *N*-(3-((7-(3-((1,1-dioxidothiomorpholino)methyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00544] To a solution of *N*-(3-((7-(3-((1,1-dioxidothiomorpholino)methyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (130 mg, 0.26 mmol) in DCM (6 mL, 93.5 mmol) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The

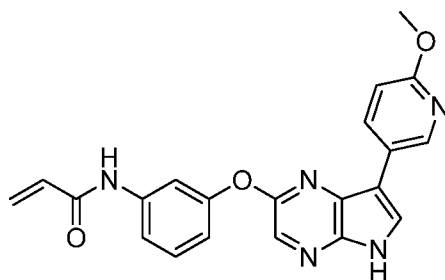
solution was adjusted with saturated aqueous NaHCO_3 to $\text{pH} > 7$ and stirred at rt for 2 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a yellow solid product (27 mg, 20.77%).

MS (ESI, pos.ion) m/z : 504.30 $[\text{M}+1]^+$; and

^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ (ppm) 12.36 (s, 1H), 10.31 (s, 1H), 8.38 (s, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.86 (t, $J = 17.2$ Hz, 1H), 7.66 (s, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 7.40 (t, $J = 8.1$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.14 (d, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.41 (m, 1H), 6.22 (m, 1H), 5.72 (dd, $J_1 = 18.2$ Hz, $J_2 = 16.6$ Hz, 1H), 3.56 (s, 2H), 3.05 (s, 4H), 2.80 (s, 4H).

Example 16

N-(3-((7-(6-Methoxypyridin-3-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *N*-(3-((7-(6-methoxypyridin-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00545] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (235 mg, 0.44 mmol), (6-methoxypyridin-3-yl)boronic acid (110 mg, 0.72 mmol), sodium carbonate (80 mg, 0.72 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mg, 0.03 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N_2 . The mixture was stirred at 65 °C for 4.5 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was diluted with water, and the resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a brown solid product (140 mg, 61.7%).

MS (ESI, pos.ion) m/z : 518.3 $[\text{M}+1]^+$.

Step 2) *N*-(3-((7-(6-methoxypyridin-3-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

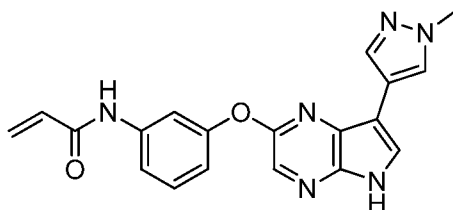
[00546] To a solution of *N*-(3-((7-(6-methoxypyridin-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (120 mg, 0.23 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 3.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/2 to give a white solid product (45 mg, 50.1%).

MS (ESI, pos.ion) *m/z*: 388.0[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.40 (s, 1H), 10.23 (s, 1H), 8.80 (d, *J* = 1.6 Hz, 1H), 8.38 (s, 1H), 8.28 (dd, *J*₁ = 8.6 Hz, *J*₂ = 2.1 Hz, 1H), 8.20 (s, 1H), 7.60 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.40 (dd, *J* = 17.1 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.75 (d, *J* = 11.2 Hz, 1H), 3.84 (s, 3H).

Example 17

N-(3-((7-(1-Methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 2,7-dibromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine

[00547] To a solution of 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (0.51 g, 1.53 mmol) in DCM (26 mL) was added NBS (0.29 g, 1.59 mmol) at rt. The mixture was stirred at rt for 30 h and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a white solid product (560 mg, 89.4%).

MS (ESI, pos. ion) *m/z*: 408.0[M+1]⁺.

Step 2) *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00548] To a mixture of 2,7-dibromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (0.30 g, 0.73 mmol), *N*-(3-hydroxyphenyl)acrylamide (0.15 g, 0.92 mmol), cesium carbonate (0.36 g, 1.10 mmol), cuprous iodide (0.16 g, 0.84 mmol) and *N,N*-dimethylglycine

(0.08 g, 0.81 mmol) was added 1,4-dioxane (5 mL). The mixture was stirred at 115 °C under N₂ for 5 h and cooled to rt, and then filtered through a Celite pad. The filter cake was washed with DCM. The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (260 mg, 72.59%).

MS (ESI, pos. ion) *m/z*: 491.1[M+1]⁺.

Step 3) *N*-(3-((7-(1-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00549] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (486 mg, 0.99 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (324 mg, 1.56 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/1 to give a brown solid product (320 mg, 55.8%).

MS (ESI, pos.ion) *m/z*: 491.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00550] To a solution of *N*-(3-((7-(1-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (300 mg, 0.52 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/5 to give a yellow solid product (75 mg, 40.0%).

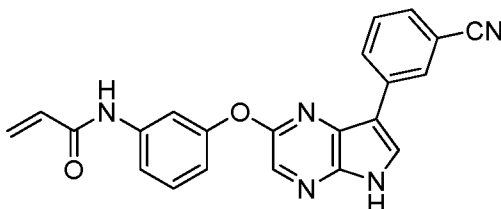
MS (ESI, pos.ion) *m/z*: 361.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.09 (s, 1H), 10.26 (s, 1H), 8.13 (s, 1H), 8.08 (d, *J* = 1.0 Hz, 1H), 8.02 (s, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.91 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.5 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24

(dd, $J_1 = 17.0$ Hz, $J_2 = 1.7$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.7$ Hz, 1H), 3.81 (s, 3H).

Example 18

N-(3-((7-(3-Cyanophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *N*-(3-((7-(3-cyanophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00551] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (240 mg, 0.45 mmol), (3-cyanophenyl)boronic acid (140 mg, 0.95 mmol), sodium carbonate (80 mg, 0.72 mmol) and Pd(dppf)Cl₂ (20 mg, 0.03 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N₂. The mixture was stirred at 65 °C for 5 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/2 to give a brown solid product (120 mg, 52.4%).

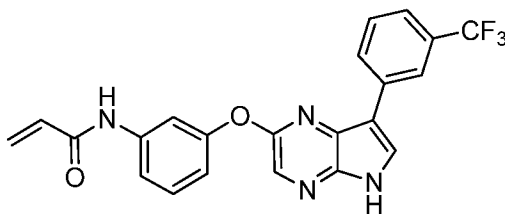
MS (ESI, pos.ion) *m/z*: 512.4[M+1]⁺.

Step 2) *N*-(3-((7-(3-cyanophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00552] To a solution of *N*-(3-((7-(3-cyanophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (102 mg, 0.20 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 3.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 20/1 to give a gray solid product (15 mg, 19.73%).

MS (ESI, pos.ion) *m/z*: 382.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.56 (s, 1H), 10.25 (s, 1H), 8.57 (s, 1H), 8.48 (s, 1H), 8.37 (d, $J = 7.9$ Hz, 1H), 8.22 (s, 1H), 7.72 (s, 1H), 7.60 (d, $J = 7.7$ Hz, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.41 (m, 2H), 6.98 (d, $J = 7.4$ Hz, 1H), 6.41 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.1$ Hz, 1H), 6.22 (dd, $J_1 = 16.9$ Hz, $J_2 = 1.8$ Hz, 1H), 5.74 (dd, $J_1 = 9.9$ Hz, $J_2 = 1.7$ Hz, 1H).

Example 19***N*-(3-((7-(3-(trifluoromethyl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide****Step 1) *N*-(3-((7-(3-(trifluoromethyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

[00553] To a mixture of (3-(trifluoromethyl)phenyl)boronic acid (63 mg, 0.33 mmol), *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (152 mg, 0.28 mmol), potassium carbonate (105 mg, 0.76 mmol) and Pd(dppf)Cl₂ (9 mg, 0.01 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N₂. The mixture was stirred at 110 °C for 12 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow oily product (115 mg, 73.2%).

MS (ESI, pos.ion) *m/z*: 555.0[M+1]⁺.

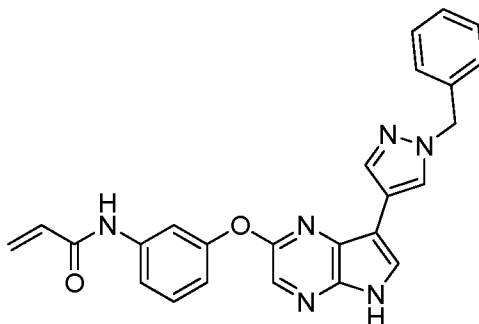
Step 2) *N*-(3-((7-(3-(trifluoromethyl)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00554] To a solution of *N*-(3-((7-(3-(trifluoromethyl)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (115 mg, 0.21 mmol) in DCM (6 mL) was added trifluoroacetic acid (6 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with THF (4 mL) and saturated aqueous sodium bicarbonate solution (4 mL). The resulting mixture was stirred at rt for 5 h and extracted with EtOAc (50 mL × 6). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a white solid product (16 mg, 18.2%).

MS (ESI, pos.ion) *m/z*: 425.0[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.52 (s, 1H), 10.23 (s, 1H), 8.58 (d, *J* = 1.8 Hz, 1H), 8.45 (s, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 7.71 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.51-7.43 (m, 2H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.98 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.7 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.74 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H).

Example 20

***N*-(3-((7-(1-Benzyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide****Step 1) 1-benzyl-4-iodo-1*H*-pyrazole**

[00555] To a solution of 4-iodo-1*H*-pyrazole (1.40 g, 7.20 mmol) in actone (20 mL) were added (bromomethyl)benzene (1.44 g, 8.42 mmol) and potassium carbonate (2.80 g, 20.00 mmol) at rt. The mixture was refluxed for 3 h. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a white solid product (1.40 g, 68.0%).

MS (ESI, pos.ion) *m/z*: 285.1[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.57 (s, 1H), 7.42 (s, 1H), 7.41-7.31 (m, 3H), 7.27-7.20 (m, 2H), 5.32 (s, 2H).

Step 2) 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00556] A mixture of 1-benzyl-4-iodo-1*H*-pyrazole (1.05 g, 3.70 mmol), bis(pinacolato)diboron (1.00 g, 3.94 mmol), potassium acetate (1.00 g, 9.88 mmol) and Pd(dppf)Cl₂ (130 mg, 0.18 mmol) in DMSO (20 mL) was stirred at 80 °C under N₂ for 7 h. The reaction mixture was cooled to rt and quenched with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (50 mL × 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a light yellow oily product (200 mg, 19.0%).

MS (ESI, pos.ion) *m/z*: 282.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ (ppm) 7.84 (s, 1H), 7.69 (s, 1H), 7.34 (m, 3H), 7.25 (m, 2H), 5.32 (s, 2H), 1.32 (s, 12H).

Step 3) *N*-(3-((7-(1-benzyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00557] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (235 mg, 0.41 mmol), 1-benzyl-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (200 mg, 0.70 mmol), sodium carbonate (80 mg, 0.72 mmol) and Pd(dppf)Cl₂ (20 mg, 0.03 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) under N₂. The mixture was stirred at 65°C for 2 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give an earthy yellow solid product (130 mg, 52.4%).

MS (ESI, pos.ion) *m/z*: 567.4[M+1]⁺.

Step 4) *N*-(3-((7-(1-benzyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

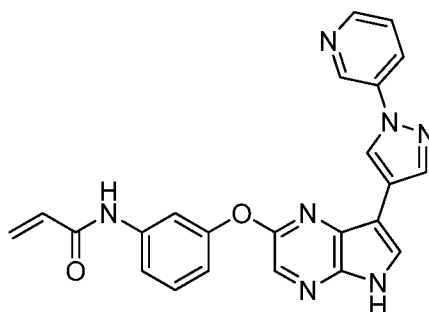
[00558] To a solution of *N*-(3-((7-(1-benzyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (122 mg, 0.21 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 4.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a light yellow solid product (55 mg, 58.5%).

MS (ESI, pos.ion) *m/z*: 437.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (s, 1H), 10.28 (s, 1H), 8.14 (s, 1H), 8.12 (s, 1H), 8.11 (d, *J* = 3.0 Hz, 1H), 7.87 (s, 1H), 7.64 (t, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.91 (dd, *J*₁ = 7.8 Hz, *J*₂ = 2.0 Hz, 1H), 6.41 (dd, *J*₁ = 17.4 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 16.8 Hz, *J*₂ = 1.8 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 5.28 (s, 2H).

Example 21

***N*-(3-((7-(1-(Pyridin-3-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 3-(4-bromo-1H-pyrazol-1-yl)pyridine

[00559] A mixture of cesium carbonate (15.47 g, 47.46 mmol), cuprous iodide (5.42 g, 28.48 mmol), *N,N*-dimethylglycine (2.94 g, 28.48 mmol), 3-bromopyridine (3.00 g, 18.98 mmol) and 4-bromo-1H-pyrazole (3.35 g, 22.78 mmol) in DMF (20 mL) was stirred at 100 °C under N₂ for 20 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a white solid product (3.42 g, 81.1%).

MS (ESI, pos.ion) *m/z*: 226.1[M+1]⁺.

Step 2) 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)pyridine

[00560] A mixture of potassium acetate (3.30 g, 33.12 mmol), Pd(dppf)Cl₂ (400 mg, 0.56 mmol), 3-(4-bromo-1H-pyrazol-1-yl)pyridine (2.50 g, 11.10 mmol) and bis(pinacolato)diboron (3.40 g, 13.02 mmol) in DMF (30 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow oily product (2.71 g, 90.1%).

MS (ESI, pos.ion) *m/z*: 272.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00561] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485mg, 0.99 mmol), 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)pyridine (900 mg, 1.66 mmol), potassium carbonate (220 mg, 1.59 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/3 to give a brown solid product (350 mg, 51.1%).

MS (ESI, pos.ion) *m/z*: 554.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00562] To a solution of *N*-(3-((7-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)

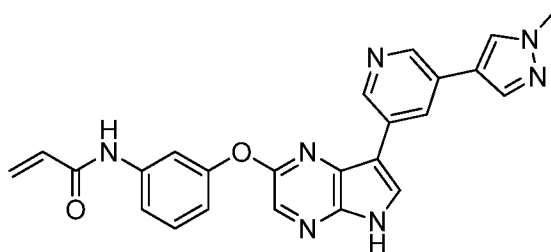
ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.46 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (100 mg, 51.1%).

MS (ESI, pos.ion) *m/z*: 423.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.24 (s, 1H), 10.29 (s, 1H), 9.00 (d, *J* = 2.5 Hz, 1H), 8.76 (s, 1H), 8.52 (dd, *J*₁ = 4.6 Hz, *J*₂ = 1.1 Hz, 1H), 8.23 (s, 1H), 8.21 (s, 2H), 8.10-8.01 (m, 1H), 7.76 (s, 1H), 7.54 (dd, *J*₁ = 8.3 Hz, *J*₂ = 4.7 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.00 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.5 Hz, 1H), 6.39 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.21 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.72 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H).

Example 22

N-(3-((7-(5-(1-Methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine

[00563] To a solution of 3, 5-dibromopyridine (244 mg, 1.03 mmol) in 1,4-dioxane (8 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (190 mg, 0.91 mmol), potassium acetate (200 mg, 1.45 mmol) and Pd(dppf)Cl₂ (70 mg, 0.09 mmol), and then water (2 mL) was added. The mixture was stirred at 90 °C under N₂ for 2 h and quenched with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a brown solid product (110 mg, 50.6%).

MS (ESI, pos.ion) *m/z*: 238.1, 240.1 [M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 8.83 (s, 1H), 8.49 (d, *J* = 1.5 Hz, 1H), 8.34 (s, 1H),

8.27 (s, 1H), 8.05 (s, 1H), 3.88 (s, 3H).

Step 2) *N*-(3-((7-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00564] To a solution of 3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine (30 mg, 0.13 mmol) in 1,4-dioxane (4 mL) were added potassium acetate (32 mg, 0.33 mmol), bis(pinacolato)diboron (40 mg, 0.16 mmol) and Pd(dppf)Cl₂ (10 mg, 0.01 mmol) in turn. The mixture was stirred at 110 °C under N₂ for 9 h, then cooled to rt. To the reaction mixture was added *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (55 mg, 0.10 mmol), potassium carbonate (28 mg, 0.20 mmol) and Pd(dppf)Cl₂ (10 mg, 0.01 mmol) in turn. The mixture was stirred at 65 °C under N₂ for 2 h, cooled to rt and quenched with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a brown solid product (27.5 mg, 38.4%).

MS (ESI, pos.ion) *m/z*: 568.2[M+1]⁺.

Step 3) *N*-(3-((7-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00565] To a solution of *N*-(3-((7-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.55 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 12 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a light red solid product (78 mg, 32.66%).

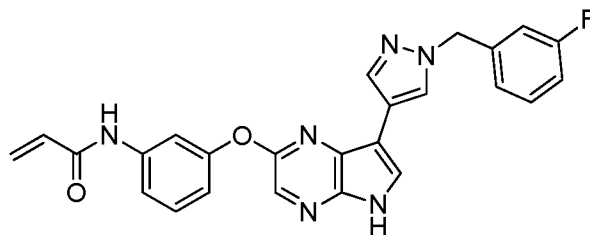
MS (ESI, pos.ion) *m/z*: 438.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.54 (s, 1H), 10.26 (s, 1H), 9.02 (d, *J* = 1.8 Hz, 1H), 8.60 (d, *J* = 1.9 Hz, 1H), 8.58 (d, *J* = 2.9 Hz, 1H), 8.50 (t, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.02 (dt, *J*₁ = 18.1 Hz, *J*₂ = 9.0 Hz, 1H), 6.39 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.22 (dd, *J*₁ = 17.0 Hz,

$J_2 = 1.7$ Hz, 1H), 5.73 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.6$ Hz, 1H), 3.90 (s, 3H).

Example 23

***N*-(3-((7-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(3-fluorobenzyl)-4-iodo-1*H*-pyrazole

[00566] To a solution of 4-iodo-1*H*-pyrazole (1.0 g, 5.2 mmol) in acetone (15 mL) were added potassium carbonate (1.1 g, 8.0 mmol) and 1-(bromomethyl)-3-fluorobenzene (760 μ L, 6.13 mmol). The mixture was stirred at 60 °C for 12 h and diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oily product (1.38 g, 89%).

MS (ESI, pos.ion) m/z : 303.0[M+1]⁺.

Step 2) 1-(3-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00567] To a solution of 1-(3-fluorobenzyl)-4-iodo-1*H*-pyrazole (3.6 g, 12 mmol) in DMSO (30 mL) were added potassium acetate (2.9 g, 30 mmol), bis(pinacolato)diboron (3.6 g, 14 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (700 mg, 0.95 mmol). The mixture was stirred at 100 °C under N_2 for 6 h, cooled to rt and quenched with saturated aqueous NaCl (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oily product (1.5 g, 42%).

MS (ESI, pos.ion) m/z : 303.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00568] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (400 mg, 0.82 mmol) in 1,4-dioxane (12 mL) were added 1-(3-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

(390 mg, 1.25 mmol), potassium carbonate (170 mg, 1.23 mmol) and Pd(dppf)Cl₂ (70 mg, 0.09 mmol) in turn. The mixture was stirred at 115 °C under N₂ for 15 h and cooled to rt, and then quenched with saturated aqueous NaCl (15 mL). The resulting mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a brown oily product (270 mg, 56.5%).

MS (ESI, pos.ion) *m/z*: 584.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

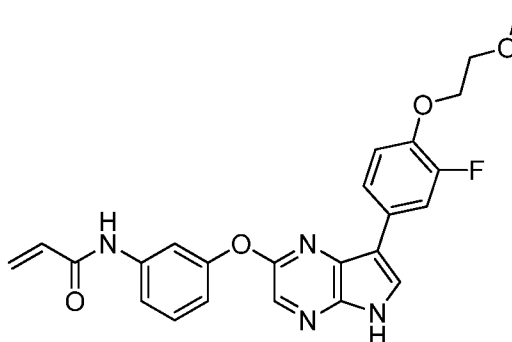
[00569] To a solution of *N*-(3-((7-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (270 mg, 0.46 mmol) in DCM (7 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 12 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a yellow solid product (25 mg, 11.91%).

MS (ESI, pos.ion) *m/z*: 455.80[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.24 (s, 1H), 8.16 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.90 (s, 1H), 7.64 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.35 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.01 (m, 2H), 6.90 (dd, *J*₁ = 16.2 Hz, *J*₂ = 8.6 Hz, 1H), 6.38 (dt, *J*₁ = 24.2 Hz, *J*₂ = 12.1 Hz, 1H), 6.21 (m, 1H), 5.72 (t, *J* = 15.6 Hz, 1H), 5.32 (s, 2H).

Example 24

***N*-(3-((7-(3-Fluoro-4-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 2-fluoro-4-iodo-1-(2-methoxyethoxy)benzene

[00570] A mixture of cesium carbonate (3.50 g, 10.50 mmol), potassium iodide (350 mg, 2.10 mmol), 2-fluoro-4-iodophenol (1.01 g, 4.20 mmol) and 1-bromo-2-methoxyethane (880 mg, 6.30 mmol) in DMF (15.00 mL) was stirred at 70 °C for 3 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a colorless oily product (982 mg, 75.3%).

MS (ESI, pos.ion) *m/z*: 297.0[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.49-7.31 (m, 2H), 6.74 (t, *J* = 8.5 Hz, 1H), 4.16 (t, *J* = 4.8 Hz, 2H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.44 (s, 3H).

Step 2) 2-(3-fluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00571] A mixture of potassium acetate (970 mg, 9.87 mmol), Pd(dppf)Cl₂ (118 mg, 0.16 mmol), 2-fluoro-4-iodo-1-(2-methoxyethoxy)benzene (974 mg, 3.30 mmol) and bis(pinacolato)diboron (1.25 g, 4.93 mmol) in DMSO (20 mL) was stirred at 90 °C under N₂ for 14 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a yellow oil product (560 mg, 57.5%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.53-7.45 (m, 2H), 6.96 (t, *J* = 8.2 Hz, 1H), 4.21 (t, *J* = 4.8 Hz, 2H), 3.78 (t, *J* = 4.8 Hz, 2H), 3.45 (s, 3H).

Step 3) *N*-(3-((7-(3-fluoro-4-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00572] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (360 mg, 0.74 mmol), 2-(3-fluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (325 mg, 1.10 mmol), potassium carbonate (130 mg, 1.27 mmol) and Pd(dppf)Cl₂ (31 mg, 0.04 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C for 10 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give an earthy yellow solid product (280 mg, 59.2%).

MS (ESI, pos.ion) *m/z*: 578.8[M+1]⁺.

Step 4) *N*-(3-((7-(3-fluoro-4-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

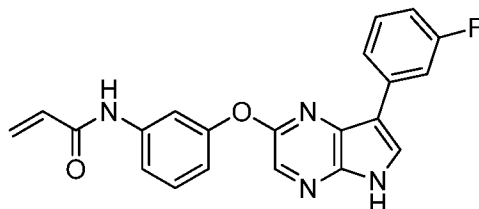
[00573] To a solution of *N*-(3-((7-(3-fluoro-4-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (270 mg, 0.37 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/6 to give a light yellow solid product (60 mg, 35.9%).

MS (ESI, pos.ion) *m/z*: 448.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.35 (s, 1H), 10.24 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 7.89 (d, *J* = 13.3 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 8.9 Hz, 1H), 6.93 (dd, *J*₁ = 8.1 Hz, *J*₂ = 2.2 Hz, 1H), 6.41 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (t, *J* = 16.9 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 4.15 (t, *J* = 4.8 Hz, 2H), 3.66 (t, *J* = 4.2 Hz, 2H), 3.31 (s, 3H).

Example 25

N-(3-((7-(3-Fluorophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *N*-(3-((7-(3-fluorophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00574] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (300 mg, 0.56 mmol), (3-fluorophenyl)boronic acid (160 mg, 1.14 mmol), sodium carbonate (95 mg, 0.85 mmol) and Pd(dppf)Cl₂ (20 mg, 0.03 mmol) were added 1,4-dioxane (12 mL) and water (3 mL) under N₂. The mixture was stirred at 65 °C for 5 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/2 to give an earthy yellow solid product (150 mg, 53.15%).

MS (ESI, pos.ion) *m/z*: 505.2[M+1]⁺.

Step 2) *N*-(3-((7-(3-fluorophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

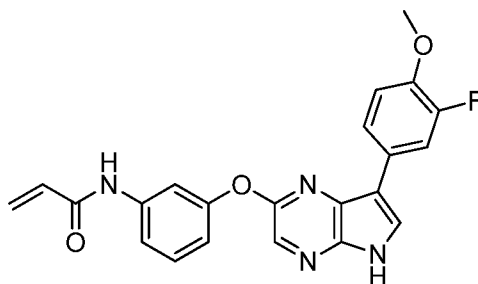
[00575] To a solution of *N*-(3-((7-(3-fluorophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (150 mg, 0.24 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a light yellow solid product (50 mg, 56.16%).

MS (ESI, pos.ion) *m/z*: 375.1[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.47 (s, 1H), 10.23 (s, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.93-7.88 (m, 1H), 7.87 (s, 1H), 7.66 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.42-7.31 (m, 2H), 7.03-6.90 (m, 2H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.1 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.74 (dd, *J*₁ = 10.1 Hz, *J*₂ = 1.8 Hz, 1H).

Example 26

***N*-(3-((7-(3-Fluoro-4-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N*-(3-((7-(3-fluoro-4-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00576] To a mixture of *N*-(3,5-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (350 mg, 0.72 mmol), (3-fluoro-4-methoxyphenyl)boronic acid (190 mg, 1.12 mmol), potassium carbonate (150 mg, 1.07 mmol) and Pd(dppf)Cl₂ (27 mg, 0.04 mmol) were added 1,4-dioxane (14 mL) and water (3 mL) under N₂. The mixture was stirred at 115 °C for 20 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/2 to give a light yellow solid product (220 mg, 57.5%).

MS (ESI, pos.ion) m/z : 534.7[M+1]⁺.

Step 2) *N*-(3-((7-(3-fluoro-4-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

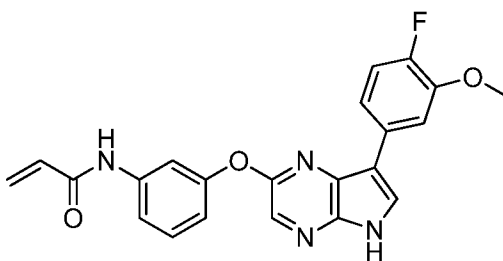
[00577] To a solution of *N*-(3-((7-(3-fluoro-4-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (215 mg, 0.32 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a light yellow solid product (90 mg, 69.2%).

MS (ESI, pos.ion) m/z : 404.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.35 (d, *J* = 2.4 Hz, 1H), 10.23 (s, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 8.18 (s, 1H), 7.89 (dd, *J*₁ = 13.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.83 (dd, *J*₁ = 8.5 Hz, *J*₂ = 1.1 Hz, 1H), 7.65 (t, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 8.9 Hz, 1H), 6.95-6.92 (m, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 3.82 (s, 3H).

Example 27

***N*-(3-((7-(4-fluoro-3-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N*-(3-((7-(4-fluoro-3-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00578] To a mixture of *N*-(3-5-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (397 mg, 0.74 mmol), (4-fluoro-3-methoxyphenyl)boronic acid (195 mg, 1.15 mmol), sodium carbonate (130 mg, 1.16 mmol) and Pd(dppf)Cl₂ (30 mg, 0.04 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 65 °C for 5 h. The mixture was cooled to rt and filtered through a Celite pad. The

filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/2 to give an earthy yellow solid product (180 mg, 45.5%).

MS (ESI, pos.ion) *m/z*: 535.2[M+1]⁺.

Step 2) *N*-(3-((7-(4-fluoro-3-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

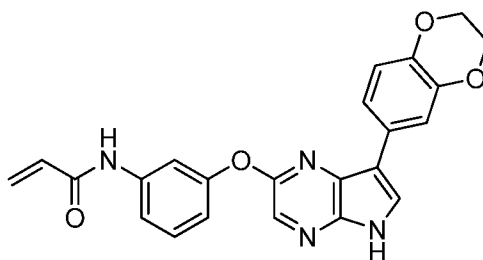
[00579] To a solution of *N*-(3-((7-(4-fluoro-3-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (178 mg, 0.30 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/3 to give a light yellow solid product (30 mg, 24.8%).

MS (ESI, pos.ion) *m/z*: 404.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.36 (s, 1H), 10.25 (s, 1H), 8.39 (s, 1H), 8.23 (s, 1H), 7.90 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.66 (s, 1H), 7.49 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 1H), 7.14 (dd, *J*₁ = 11.4 Hz, *J*₂ = 8.4 Hz, 1H), 6.97 (dd, *J*₁ = 7.8 Hz, *J*₂ = 1.2 Hz, 1H), 6.41 (dd, *J*₁ = 17.4 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 16.8 Hz, *J*₂ = 1.8 Hz, 1H), 5.76 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 3.52 (s, 3H).

Example 28

***N*-(3-((7-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N*-(3-((7-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00580] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.63 mmol), (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (170 mg, 0.95 mmol), potassium carbonate

(130 mg, 0.93 mmol) and Pd(dppf)Cl₂ (25 mg, 0.03 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C for 10 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/3 to give a brown yellow solid product (240 mg, 59.13%).

MS (ESI, pos.ion) *m/z*: 545.1[M+1]⁺.

Step 2) *N*-(3-((7-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

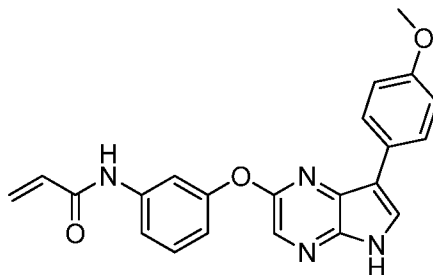
[00581] To a solution of *N*-(3-((7-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (240 mg, 0.37 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/6 to give a light yellow solid product (25 mg, 16.1%).

MS (ESI, pos.ion) *m/z*: 414.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.26 (s, 1H), 10.23 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.57 (d, *J* = 1.4 Hz, 2H), 7.48 (dd, *J*₁ = 8.5 Hz, *J*₂ = 1.7 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J*₁ = 8.1 Hz, *J*₂ = 2.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.39 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (d, *J* = 16.9 Hz, 1H), 5.75 (d, *J* = 10.1 Hz, 1H), 4.21 (s, 4H).

Example 29

***N*-(3-((7-(4-Methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00582] To a solution of 1-bromo-4-methoxybenzene (1.51 g, 8.07 mmol) in DMSO (20 mL)

were added bis(pinacolato)diboron (2.63 g, 10.4 mmol), potassium acetate (2.1 g, 21 mmol) and Pd(dppf)Cl₂ (550 mg, 0.74 mmol). The mixture was stirred at 100 °C under N₂ for 10 h, and then cooled to rt and quenched with saturated aqueous NaCl (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow solid product (1.5 g, 79%).

MS (ESI, pos.ion) *m/z*: 235.2[M+1]⁺.

Step 2) *N*-(3-((7-(4-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00583] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (30 mg, 0.06 mmol) in 1,4-dioxane (4 mL) were added 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18 mg, 0.07 mmol), potassium carbonate (15 mg, 0.11 mmol) and Pd(dppf)Cl₂ (7 mg, 0.01 mmol) in turn. The mixture was stirred at 110 °C under N₂ for 5 h and cooled to rt, and then quenched with saturated aqueous NaCl (15 mL). The resulting mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a brown oil product (30 mg, 94.72%).

MS (ESI, pos.ion) *m/z*: 517.3[M+1]⁺.

Step 3) *N*-(3-((7-(4-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00584] To a solution of *N*-(3-((7-(4-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (300 mg, 0.58 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 5 h and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 12 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (22 mg, 8.91%).

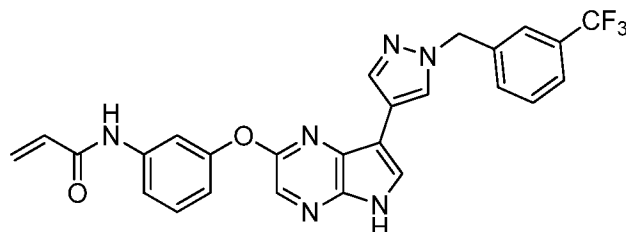
MS (ESI, pos.ion) *m/z*: 387.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.26 (s, 1H), 10.24 (s, 1H), 8.27 (s, 1H), 8.18 (d,

$J = 28.5$ Hz, 1H), 7.95 (d, $J = 8.6$ Hz, 2H), 7.61 (s, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.1$ Hz, 1H), 6.90 (m, 3H), 6.39 (dt, $J_1 = 26.7$ Hz, $J_2 = 13.4$ Hz, 1H), 6.23 (m, 1H), 5.75 (m, 1H), 3.74 (s, 3H).

Example 30

***N*-(3-((7-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-iodo-1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazole

[00585] A mixture of cesium carbonate (4.71 g, 14.01 mmol), 4-iodo-1*H*-pyrazole (1.41 g, 7.21 mmol) and 1-(bromomethyl)-3-(trifluoromethyl)benzene (2.61 g, 11.01 mmol) in DMF (20 mL) was stirred at rt for 4 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a colorless oily product (2.08 g, 82.1%).

MS (ESI, pos.ion) m/z : 352.8[M+1]⁺.

Step 2) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazole

[00586] A mixture of potassium acetate (1.80 g, 18.11 mmol), Pd(dppf)Cl₂ (220 mg, 0.31 mmol), bis(pinacolato)diboron (2.25 g, 8.86 mmol) and 4-iodo-1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazole (2.08 g, 5.90 mmol) in DMF (40.00 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with saturated aqueous ammonium chloride (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a yellow oily product (1.51 g, 72.1%).

MS (ESI, pos.ion) m/z : 353.2[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00587] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo

[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazole (530 mg, 1.21 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. To the filtrate was added appropriate amount of silica gel and the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/3 to give an earthy yellow solid (320 mg, 50.9%).

MS (ESI, pos.ion) *m/z*: 634.7[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

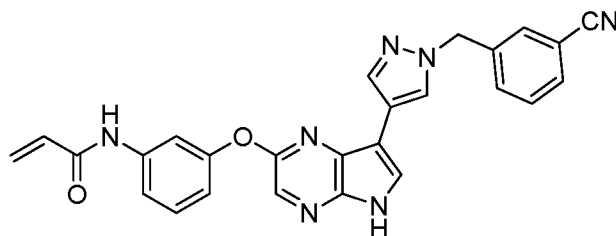
[00588] To a solution of *N*-(3-((7-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.50 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/5 to give a light yellow solid product (120 mg, 47.2%).

MS (ESI, pos.ion) *m/z*: 505.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (s, 1H), 10.25 (s, 1H), 8.21 (s, 1H), 8.13 (s, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 7.92 (s, 1H), 7.67-7.62 (m, 2H), 7.59-7.55 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 6.91 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.8 Hz, 1H), 6.39 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.21 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.72 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.5 Hz, 1H), 5.42 (s, 2H).

Example 31

***N*-(3-((7-(1-(3-Cyanobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 3-((4-iodo-1*H*-pyrazol-1-yl)methyl)benzonitrile

[00589] To a solution of 4-iodo-1*H*-pyrazole (1.54 g, 7.94 mmol) in acetonitrile (25 mL) were added 3-(bromomethyl)benzonitrile (1.70 g, 8.70 mmol) and potassium carbonate (2.80 g, 20.00 mmol) at rt. The mixture was refluxed overnight. The mixture was cooled to rt and filtered through a Celite pad. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a white solid product (2.20 g, 90.0%).

MS (ESI, pos.ion) m/z : 309.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 8.08 (s, 1H), 7.80-7.76 (m, 1H), 7.72 (s, 1H), 7.59-7.55 (m, 3H), 5.41 (s, 2H).

Step 2) 3-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl) benzonitrile

[00590] A mixture of 3-((4-iodo-1*H*-pyrazol-1-yl)methyl)benzonitrile (2.20 g, 7.10 mmol), bis(pinacolato)diboron (2.90 g, 11.00 mmol), potassium acetate (1.50 g, 15.00 mmol) and Pd(dppf)Cl₂ (265 mg, 0.05 mmol) in DMSO (35 mL) was stirred at 80 °C under N₂ overnight. The reaction mixture was cooled to rt and quenched with water (100 mL). The resulting mixture was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (100 mL × 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow solid product (1.50 g, 68.0%).

MS (ESI, pos.ion) m/z : 310.0[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.83 (s, 1H), 7.73 (s, 1H), 7.58 (m, 1H), 7.44 (m, 3H), 5.35 (s, 2H), 1.23 (s, 12H).

Step 3) *N*-(3-((7-(1-(3-cyanobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00591] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (408 mg, 0.83 mmol), 3-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)benzonitrile (400 mg, 1.29 mmol), potassium

carbonate (160 mg, 1.16 mmol) and Pd(dppf)Cl₂ (30 mg, 0.04 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C for 10 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give an earthy yellow solid product (140 mg, 28.4%).

MS (ESI, pos.ion) *m/z*: 591.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3-cyanobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

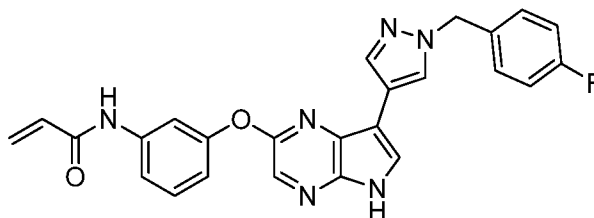
[00592] To a solution of *N*-(3-((7-(1-(3-cyanobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (140 mg, 0.24 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/7 to give a light yellow solid product (48 mg, 44.0%).

MS (ESI, pos.ion) *m/z*: 461.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (s, 1H), 10.24 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 11.5 Hz, 2H), 7.92 (s, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.64 (d, *J* = 10.1 Hz, 2H), 7.53 (q, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.39 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.21 (d, *J* = 16.9 Hz, 1H), 5.73 (d, *J* = 10.0 Hz, 1H), 5.38 (s, 2H).

Example 32

***N*-(3-((7-(1-(4-Fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-bromo-1-(4-fluorobenzyl)-1*H*-pyrazole

[00593] To a solution of 4-bromo-1*H*-pyrazole (1.5 g, 10 mmol) in acetone (30 mL) were added potassium carbonate (2.1 g, 15 mmol) and 1-(bromomethyl)-4-fluorobenzene (1.6 mL, 13 mmol).

The mixture was stirred at 60 °C for 12 h and diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 4). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oily product (2.5 g, 96%).

MS (ESI, pos.ion) *m/z*: 255.1, 257.1[M+1]⁺.

Step 2) 1-(4-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00594] To a solution of 4-bromo-1-(4-fluorobenzyl)-1*H*-pyrazole (2.5 g, 9.8 mmol) in DMSO (50 mL) was added bis(pinacolato)diboron (3.3 g, 13 mmol), potassium acetate (2.3 g, 23 mmol) and Pd(dppf)Cl₂ (700 mg, 0.94 mmol). The mixture was refluxed at 100 °C under N₂ for 11 h. The reaction mixture was cooled to rt and quenched with saturated aqueous NaCl (50 mL). The resulting mixture was extracted with DCM (60 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a yellow oily product (3.0 g, 99%).

MS (ESI, pos.ion) *m/z*: 303.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(4-fluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00595] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 1-(4-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (600 mg, 1.59 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1.5 to give an earthy yellow solid product (320 mg, 55.2%).

MS (ESI, pos.ion) *m/z*: 585.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(4-fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00596] To a solution of *N*-(3-((7-(1-(4-fluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.42 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt

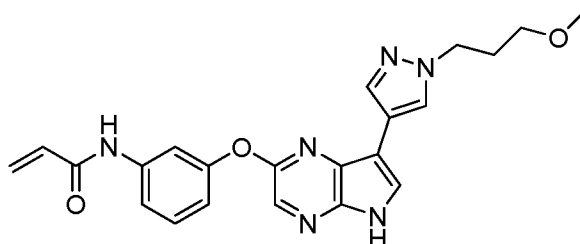
for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/8 to give a light yellow solid product (65 mg, 33.7%).

MS (ESI, pos.ion) *m/z*: 454.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.24 (s, 1H), 8.13 (d, *J* = 6.6 Hz, 2H), 8.10 (s, 1H), 7.88 (s, 1H), 7.63 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.27 (dd, *J*₁ = 8.4 Hz, *J*₂ = 5.6 Hz, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 6.91 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.9 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.6 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.6 Hz, 1H), 5.28 (s, 2H).

Example 33

***N*-(3-((7-(1-(3-Methoxypropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-bromo-1-(3-methoxypropyl)-1*H*-pyrazole

[00597] To a solution of 4-bromo-1*H*-pyrazole (1.5 g, 10 mmol) in DMF (15 mL) were added cesium carbonate (5.1 g, 16 mmol) and 1-bromo-3-methoxypropane (1.6 mL, 14 mmol). The mixture was stirred at rt for 8 h and diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oil product (2.1 g, 94%).

MS (ESI, pos.ion) *m/z*: 219.1, 221.1[M+1]⁺.

Step 2) 1-(3-methoxypropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00598] To a solution of 4-bromo-1-(3-methoxypropyl)-1*H*-pyrazole (2.1 g, 9.6 mmol) in DMSO (20 mL) were added bis(pinacolato)diboron (3.7 g, 15 mmol), potassium acetate (2.4 g, 24 mmol) and Pd(dppf)Cl₂ (900 mg, 1.22 mmol). The mixture was stirred at 100 °C under N₂ for

13 h, cooled to rt and quenched with saturated aqueous NaCl (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (1.3 g, 51%).

MS (ESI, pos.ion) *m/z*: 267.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-methoxypropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00599] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (501 mg, 1.02 mmol), 1-(3-methoxypropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (700 mg, 1.58 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (16 mL) and water (4 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/10 to give a brown oily product (300 mg, 53.4%).

MS (ESI, pos.ion) *m/z*: 548.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3-methoxypropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00600] To a solution of *N*-(3-((7-(1-(3-methoxypropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (290 mg, 0.53 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (70 mg, 31.7%).

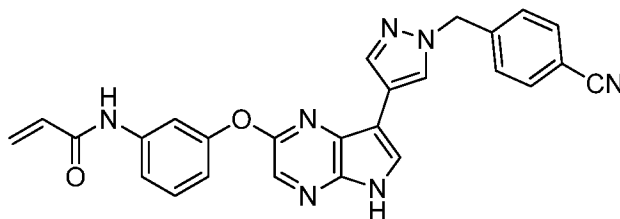
MS (ESI, pos.ion) *m/z*: 419.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.09 (s, 1H), 10.24 (s, 1H), 8.14 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.92 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.6 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ =

17.0 Hz, $J_2 = 1.8$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.8$ Hz, 1H), 4.11 (t, $J = 6.9$ Hz, 2H), 3.25 (t, $J = 6.2$ Hz, 2H), 3.19 (s, 3H), 1.96 (dd, $J_1 = 13.2$ Hz, $J_2 = 6.6$ Hz, 2H).

Example 34

***N*-(3-((7-(1-(4-Cyanobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-((4-iodo-1*H*-pyrazol-1-yl)methyl)benzonitrile

[00601] A mixture of cesium carbonate (2.36 g, 10.31 mmol), potassium iodide (450 mg, 2.58 mmol), 4-(bromomethyl)benzonitrile (1.50 g, 7.73 mmol) and 4-iodo-1*H*-pyrazole (3.35 g, 22.78 mmol) in DMF (20.00 mL) was stirred at rt for 8 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a white solid product (1.01 g, 62.8%).

MS (ESI, pos.ion) m/z : 309.8[M+1]⁺.

Step 2) 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)benzonitrile

[00602] A mixture of potassium acetate (960 mg, 9.78 mmol), Pd(dppf)Cl₂ (115 mg, 0.16 mmol), 4-((4-iodo-1*H*-pyrazol-1-yl)methyl)benzonitrile (1.01 g, 3.24 mmol) and bis(pinacolato)diboron (980 mg, 3.88 mmol) in DMF (15.00 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a yellow oil product (900 mg, 90.2%).

MS (ESI, pos.ion) m/z : 310.2[M+1]⁺.

Step 3) *N*-(3-((7-(1-(4-cyanobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00603] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)benzonitrile (600 mg, 1.55 mmol), potassium

carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1.5 to give a gray solid product (400 mg, 54.6%).

MS (ESI, pos.ion) *m/z*: 592.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(4-cyanobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

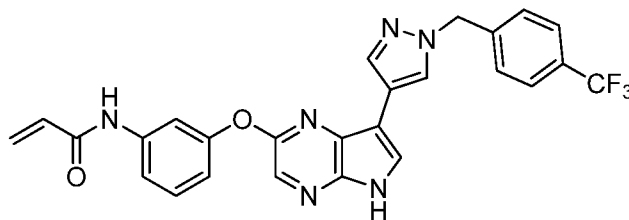
[00604] To a solution of *N*-(3-((7-(1-(4-cyanobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.43 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (70 mg, 35.0%).

MS (ESI, pos.ion) *m/z*: 461.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.13 (s, 1H), 10.22 (s, 1H), 8.20 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.93 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.39-7.31 (m, 3H), 6.91 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.9 Hz, 1H), 6.39 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.22 (dd, *J*₁ = 16.9 Hz, *J*₂ = 1.5 Hz, 1H), 5.74 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H), 5.43 (s, 2H).

Example 35

***N*-(3-((7-(1-(4-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-iodo-1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazole

[00605] A mixture of cesium carbonate (2.36 g, 10.31 mmol), potassium iodide (450 mg, 2.58 mmol), 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.85 g, 7.73 mmol) and

4-iodo-1*H*-pyrazole (1.15 g, 5.16 mmol) in DMF (15 mL) was stirred at rt for 4 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a yellow oily product (2.01 g, 95.8%).

MS (ESI, pos.ion) *m/z*: 352.7[M+1]⁺.

Step 2) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazole

[00606] A mixture of potassium acetate (1.70 g, 17.04 mmol), Pd(dppf)Cl₂ (200 mg, 0.28 mmol), 4-iodo-1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazole (2.01 g, 5.68 mmol) and bis(pinacolato)diboron (1.73 g, 6.82 mmol) in DMF (15 mL) was stirred at 85°C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a light yellow oily product (1.70 g, 85.1%).

MS (ESI, pos.ion) *m/z*: 353.3[M+1]⁺.

Step 3) *N*-(3-((7-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00607] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (491 mg, 1.00 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazole (578 mg, 1.31 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give an earthy yellow solid product (330 mg, 51.8%).

MS (ESI, pos.ion) *m/z*: 635.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00608] To a solution of *N*-(3-((7-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.50 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF

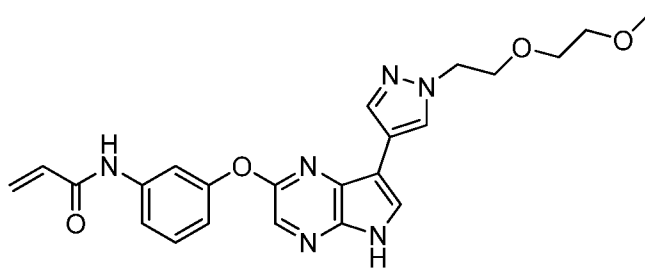
(6 mL). The solution was basified with saturated aqueous NaHCO_3 to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (100 mg, 39.3%).

MS (ESI, pos.ion) m/z : 505.1 $[\text{M}+1]^+$; and

^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ (ppm) 12.12 (s, 1H), 10.23 (s, 1H), 8.20 (s, 1H), 8.13 (d, $J = 9.0$ Hz, 2H), 7.92 (s, 1H), 7.69 (d, $J = 7.9$ Hz, 2H), 7.63 (s, 1H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.42-7.34 (m, 3H), 6.91 (d, $J = 7.8$ Hz, 1H), 6.40 (dd, $J_1 = 16.9$ Hz, $J_2 = 10.2$ Hz, 1H), 6.22 (d, $J = 16.9$ Hz, 1H), 5.73 (d, $J = 10.1$ Hz, 1H), 5.43 (s, 2H).

Example 36

***N*-(3-((7-(1-(2-(2-Methoxyethoxy)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-iodo-1-(2-(2-methoxyethoxy)ethyl)-1*H*-pyrazole

[00609] To a solution of 2-(2-methoxyethoxy)ethanol (3.72 g, 30.93 mmol) in CHCl_3 (20 mL) were added two drops of DMF and thionyl chloride (22.10 g, 185.60 mmol) in turn. After stirring at rt for 10 min, the mixture was warmed to 70 °C and refluxed for 6 h, and then concentrated *in vacuo*. To the residue was added 4-iodo-1*H*-pyrazole (2.0 g, 10.3 mmol), cesium carbonate (12.80 g, 39.30 mmol), potassium iodide (0.75 g, 4.50 mmol) and DMF (15 mL). The resulting mixture was stirred at 70 °C for 5 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a yellow oily product (2.01 g, 67.1%).

MS (ESI, pos.ion) m/z : 297.0 $[\text{M}+1]^+$.

Step 2) 1-(2-(2-methoxyethoxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00610] A mixture of potassium acetate (960 mg, 9.78 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (115 mg, 0.16 mmol),

4-iodo-1-(2-(2-methoxyethoxy)ethyl)-1*H*-pyrazole (980 mg, 3.24 mmol) and bis(pinacolato)diboron (980 mg, 3.88 mmol) in DMF (15.00 mL) was stirred at 85°C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a light yellow oily product (735 mg, 75.0%).

MS (ESI, pos.ion) *m/z*: 297.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(2-methoxyethoxy)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00611] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (490 mg, 1.01 mmol), 1-(2-(2-methoxyethoxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (530 mg, 1.43 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a brown solid product (400 mg, 55.2%).

MS (ESI, pos.ion) *m/z*: 578.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-(2-methoxyethoxy)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00612] To a solution of *N*-(3-((7-(1-(2-(2-methoxyethoxy)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (370 mg, 0.42 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow thick product (80 mg, 42.9%).

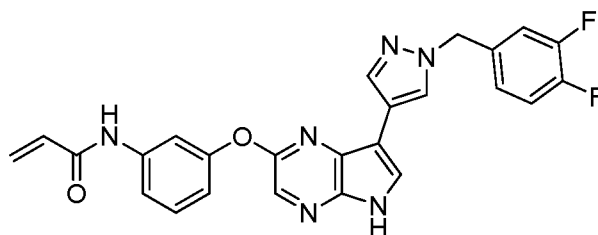
MS (ESI, pos.ion) *m/z*: 448.9[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ (ppm) 9.90 (s, 1H), 8.65 (s, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.75 (s, 1H), 7.60 (s, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.47 (s, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 6.97 (d,

$J = 7.6$ Hz, 1H), 6.45 (d, $J = 16.8$ Hz, 1H), 6.32 (dd, $J_1 = 16.8$ Hz, $J_2 = 10.2$ Hz, 1H), 5.72 (t, $J = 10.3$ Hz, 1H), 4.24 (t, $J = 5.2$ Hz, 2H), 3.82 (t, $J = 5.3$ Hz, 2H), 3.54 (m, 4H), 3.34 (s, 3H).

Example 37

***N*-(3-((7-(1-(3,4-Difluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-bromo-1-(3, 4-difluorobenzyl)-1*H*-pyrazole

[00613] To a solution of 4-bromo-1*H*-pyrazole (1.5 g, 10.0 mmol) in acetone (30 mL) were added potassium carbonate (2.1 g, 15 mmol) and 4-(bromomethyl)-1, 2-difluorobenzene (1.6 mL, 12 mmol) in turn. The mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oily product (1.9 g, 68%).

MS (ESI, pos.ion) m/z : 273.00, 275.05[M+1]⁺.

Step 2) 1-(3, 4-difluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00614] To a solution of 4-bromo-1-(3, 4-difluorobenzyl)-1*H*-pyrazole (1.9 g, 7.0 mmol) in DMSO (15 mL) were added bis(pinacolato)diboron (2.32 g, 9.14 mmol), potassium acetate (1.65 g, 16.8 mmol) and Pd(dppf)Cl₂ (500 mg, 0.68 mmol). The mixture was stirred at 100 °C under N₂ for 8 h, cooled to rt and quenched with saturated aqueous NaCl (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oil product (1.1 g, 49%).

MS (ESI, pos.ion) m/z : 321.00[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3,4-difluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00615] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (491 mg, 1.00 mmol),

1-(3,4-difluorobenzyl)4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.00 g, 1.56 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give an earthy yellow solid product (400 mg, 52.9%).

MS (ESI, pos.ion) *m/z*: 603.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3,4-difluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

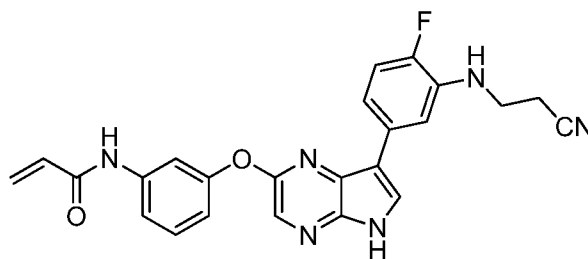
[00616] To a solution of *N*-(3-((7-(1-(3,4-difluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (400 mg, 0.66 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 4.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a beige solid product (100 mg, 31.9%).

MS (ESI, pos.ion) *m/z*: 472.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (s, 1H), 10.22 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.38 (m, 2H), 7.32-7.24 (m, 1H), 7.06 (s, 1H), 6.91 (dd, *J*₁ = 8.1 Hz, *J*₂ = 2.3 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.22 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.74 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H), 5.31 (s, 2H).

Example 38

***N*-(3-((7-(3-((2-Cyanoethyl)amino)-4-fluorophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 3-((5-bromo-2-fluorophenyl)amino)propanenitrile

[00617] To a solution of 4-bromo-1-fluoro-2-iodobenzene (500 mg, 1.66 mmol) in DMSO (10 mL) were added 3-aminopropanenitrile (0.15 mL, 2.0 mmol), cuprous iodide (320 mg, 1.68 mmol), cesium carbonate (800 mg, 2.45 mmol) and *N,N*-dimethylglycine (200 mg, 1.92 mmol) in turn. The mixture was stirred at 70 °C for 5 h and diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow oily product (60 mg, 14.85%).

MS (ESI, pos.ion) *m/z*: 243.0, 245.1[M+1]⁺.

Step 2) 3-((2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile

[00618] To a solution of 3-((5-bromophenyl)amino)propanenitrile (480 mg, 1.98 mmol) in 1,4-dioxane (10 mL) were added bis(pinacolato)diboron (680 mg, 2.68 mmol), potassium acetate (500 mg, 5.10 mmol) and Pd(dppf)Cl₂ (130 mg, 0.18 mmol). The mixture was stirred at 110 °C for 8 h and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a light yellow oily product (530 mg, 92.52%).

MS (ESI, pos.ion) *m/z*: 291.2[M+1]⁺.

Step 3) *N*-(3-((7-(3-((2-cyanoethyl)amino)-4-fluorophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00619] To a solution of 3-((2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)propanenitrile (520 mg, 1.79 mmol) in 1,4-dioxane (8 mL) were added *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (500 mg, 1.02 mmol), potassium carbonate (300 mg, 2.17 mmol), Pd(dppf)Cl₂ (130 mg, 0.18 mmol) and water (1.5 mL) in turn. The mixture was stirred at 110 °C under N₂ for 18 h, cooled to rt and quenched with saturated aqueous NaCl (25 mL). The resulting mixture was extracted with DCM (25 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give yellow oil (340 mg, 33.1%).

MS (ESI, pos.ion) *m/z*: 572.8[M+1]⁺.

Step 4) *N*-(3-((7-(3-((2-cyanoethyl)amino)-4-fluorophenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

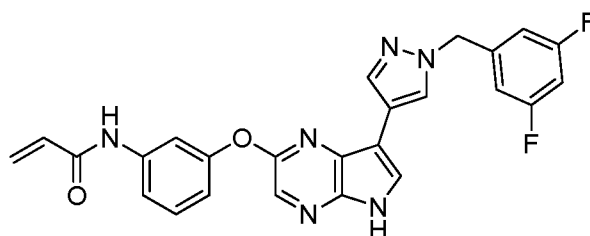
[00620] To a solution of *N*-(3-((7-(3-((2-cyanoethyl)amino)-4-fluorophenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (270 mg, 0.47 mmol) in DCM (5 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h and concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was adjusted with saturated aqueous NaHCO₃ to pH > 7 and stirred at rt for 12 h. The reaction mixture was diluted with saturated aqueous NaCl (10 mL). The resulting mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a light yellow solid (30 mg, 14.38%).

MS (ESI, pos.ion) *m/z*: 442.80[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.31 (s, 1H), 10.24 (s, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 8.18 (m, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.46 (m, 1H), 7.39 (dd, *J*₁ = 15.6 Hz, *J*₂ = 7.4 Hz, 1H), 7.22 (m, 1H), 6.99 (dd, *J*₁ = 11.7 Hz, *J*₂ = 8.4 Hz, 1H), 6.94 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.7 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (m, 1H), 5.75 (m, 1H), 5.64 (t, *J* = 5.2 Hz, 1H), 3.12 (dd, *J*₁ = 12.3 Hz, *J*₂ = 6.1 Hz, 2H), 2.64 (t, *J* = 6.3 Hz, 2H).

Example 39

N-(3-((7-(1-(3,5-Difluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 4-iodo-1-(3, 5-difluorobenzyl)-1*H*-pyrazole

[00621] A mixture of cesium carbonate (4.20 g, 12.88 mmol), potassium iodide (427 mg, 2.58 mmol), 1-(bromomethyl)-3,5-difluorobenzene (1.33 g, 6.44 mmol) and 4-iodo-1*H*-pyrazole (1.01 g, 5.16 mmol) in DMF (20 mL) was stirred at rt for 15 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a yellow oily product (1.54 g, 93.5%).

MS (ESI, pos.ion) *m/z*: 320.8[M+1]⁺.

Step 2) 1-(3, 5-difluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00622] A mixture of potassium acetate (1.50 g, 14.46 mmol), Pd(dppf)Cl₂ (170 mg, 0.24 mmol),

4-iodo-1-(3, 5-difluorobenzyl)-1*H*-pyrazole (1.54 g, 4.82 mmol) and bis(pinacolato)diboron (1.47 g, 5.78 mmol) in DMF (30 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 6/1 to give a light yellow oily product (1.01 g, 64.8%).

MS (ESI, pos.ion) *m/z*: 321.2[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3,5-difluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00623] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 1-(3,5-difluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (600 mg, 1.50 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1.5 to give an earthy yellow solid product (350 mg, 58.6%).

MS (ESI, pos.ion) *m/z*: 602.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(3,5-difluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00624] To a solution of *N*-(3-((7-(1-(3,5-difluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.42 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/8 to give a light yellow solid product (100 mg, 49.84%).

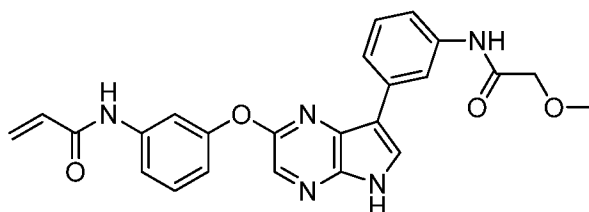
MS (ESI, pos.ion) *m/z*: 472.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.14 (s, 1H), 10.22 (s, 1H), 8.20 (s, 1H), 8.14 (s, 2H), 7.93 (s, 1H), 7.64 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 9.2

Hz, 1H), 6.94-6.86 (m, 3H), 6.39 (dd, $J_1 = 16.9$ Hz, $J_2 = 10.2$ Hz, 1H), 6.22 (d, $J = 16.9$ Hz, 1H), 5.73 (d, $J = 10.2$ Hz, 1H), 5.36 (s, 2H).

Example 40

N-(3-((7-(3-(2-Methoxyacetamido)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *N*-(3-bromophenyl)-2-chloroacetamide

[00625] To a mixture of triethylamine (1.75 g, 17.44 mmol) and 3-bromoaniline (2.01 g, 11.63 mmol) in DCM (20 mL) was added 2-chloroacetyl chloride (1.51 g, 13.37 mmol). The mixture was stirred at rt for 5 h. To the mixture was added silica gel. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v = 4/1) to give a light yellow solid product (2.85 g, 98.6%).

MS (ESI, pos.ion) m/z : 248.0[M+1]⁺.

Step 2) *N*-(3-bromophenyl)-2-methoxyacetamide

[00626] To a methanol (10 mL) was added sodium (444 mg, 19.32 mmol) slowly followed by addition of *N*-(3-bromophenyl)-2-chloroacetamide (2.40 g, 9.66 mmol). The mixture was stirred at 60 °C for 2 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a white solid product (1.83 g, 77.5%).

MS (ESI, pos.ion) m/z : 244.1[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.25 (s, 1H), 7.82 (t, $J = 1.7$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 6.4$ Hz, 1H), 7.19 (t, $J = 8.0$ Hz, 1H), 4.01 (s, 2H), 3.50 (s, 3H).

Step 3) 2-methoxy-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide

[00627] A mixture of potassium acetate (2.21 g, 22.52 mmol), Pd(dppf)Cl₂ (267 mg, 0.38 mmol), *N*-(3-bromophenyl)-2-methoxyacetamide (1.83 g, 7.51 mmol) and bis(pinacolato)diboron (2.29 g, 9.01 mmol) in DMF (15 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a light

yellow oily product (1.78 g, 81.4%).

MS (ESI, pos.ion) m/z : 292.2[M+1]⁺.

Step 4) *N*-(3-((7-(3-(2-methoxyacetamido)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00628] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (495 mg, 0.86 mmol), 2-methoxy-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (520 mg, 1.52 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was refluxed at 110 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/4 to give a brown solid product (320 mg, 55.2%).

MS (ESI, pos.ion) m/z : 573.8[M+1]⁺.

Step 5) *N*-(3-((7-(3-(2-methoxyacetamido)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

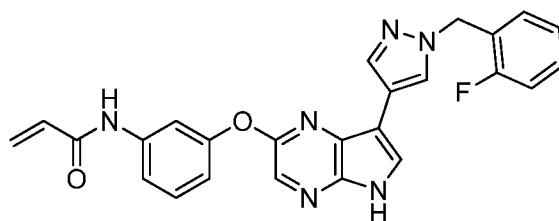
[00629] To a solution of *N*-(3-((7-(3-(2-methoxyacetamido)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.46 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (80 mg, 39.3%).

MS (ESI, pos.ion) m/z : 444.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.40 (s, 1H), 10.21 (s, 1H), 9.60 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 12.4 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 12.0 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.40 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (d, *J* = 16.9 Hz, 1H), 5.75 (d, *J* = 10.3 Hz, 1H), 4.00 (s, 2H), 3.39 (s, 3H).

Example 41

***N*-(3-((7-(1-(2-Fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-fluorobenzyl)-4-iodo-1H-pyrazole

[00630] A mixture of cesium carbonate (4.21 g, 12.88 mmol), potassium iodide (430 mg, 2.58 mmol), 1-(bromomethyl)-2-fluorobenzene (1.46 g, 7.73 mmol) and 4-iodo-1H-pyrazole (1.01 g, 5.16 mmol) in DMF (20 mL) was stirred at rt for 5 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a light yellow oily product (1.52 g, 97.2%).

MS (ESI, pos.ion) m/z : 302.8[M+1]⁺.

Step 2) 1-(2-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00631] A mixture of potassium acetate (1.61 g, 16.04 mmol), Pd(dppf)Cl₂ (200 mg, 0.27 mmol), 1-(2-fluorobenzyl)-4-iodo-1H-pyrazole (1.62 g, 5.35 mmol) and bis(pinacolato)diboron (1.63 g, 6.42 mmol) in DMF (30 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a light yellow oily product (1.12 g, 69.3%).

MS (ESI, pos.ion) m/z : 303.0[M+1]⁺.

Step 3) N-(3-((7-(1-(2-fluorobenzyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide

[00632] To a mixture of N-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 1-(2-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (600 mg, 1.59 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (35 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1.5 to give an earthy yellow solid product (320 mg, 55.2%).

MS (ESI, pos.ion) m/z : 585.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-fluorobenzyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

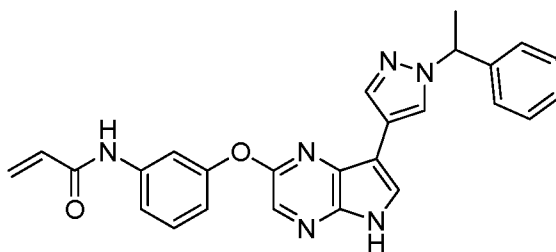
[00633] To a solution of *N*-(3-((7-(1-(2-fluorobenzyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (310 mg, 0.53 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/9 to give a light yellow solid product (115 mg, 47.7%).

MS (ESI, pos.ion) *m/z*: 455.2 [M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.11 (s, 1H), 10.23 (s, 1H), 8.14 (s, 1H), 8.13 (d, *J* = 3.2 Hz, 2H), 7.88 (s, 1H), 7.63 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.42-7.31 (m, 2H), 7.23-7.12 (m, 3H), 6.92 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.8 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.74 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 5.35 (s, 2H).

Example 42

***N*-(3-((7-(1-(1-Phenylethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(1-phenylethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00634] To a mixture of cesium carbonate (3.50 g, 12.38 mmol), potassium iodide (342 mg, 2.06 mmol) and (1-bromoethyl)benzene (1.10 g, 6.19 mmol) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (800 mg, 4.12 mmol) and DMF (15 mL). The mixture was warmed to 60 °C and stirred for 4 h, and then cooled to rt and diluted with water (50 mL). The resulting mixture was extracted with EtOAc (60 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a colorless oil product (600 mg, 48.8%).

MS (ESI, pos.ion) m/z : 299.3[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (s, 1H), 7.73 (s, 1H), 7.41-7.27 (m, 3H), 7.21 (d, J = 7.1 Hz, 2H), 5.54 (q, J = 7.1 Hz, 1H), 1.89 (d, J = 7.1 Hz, 3H), 1.31 (s, 12H).

Step 2) *N*-(3-((7-(1-(1-phenylethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00635] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.99 mmol), 1-(1-phenylethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol (500 mg, 1.51 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (35 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115°C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc(v/v) = 1/1.5 to give a hoary solid product (350 mg, 48.7%).

MS (ESI, pos.ion) m/z : 580.8[M+1]⁺.

Step 3) *N*-(3-((7-(1-(1-phenylethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

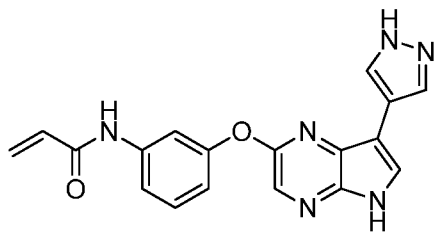
[00636] To a solution of *N*-(3-((7-(1-(1-phenylethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.55 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (80 mg, 32.2%).

MS (ESI, pos.ion) m/z : 451.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.07 (s, 1H), 10.27 (s, 1H), 8.15 (s, 1H), 8.11 (s, 1H), 8.08 (s, 1H), 7.86 (s, 1H), 7.67 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 6.94 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 6.41 (dd, J_1 = 16.9 Hz, J_2 = 10.2 Hz, 1H), 6.24 (d, J = 16.9 Hz, 1H), 5.75 (dd, J_1 = 10.1 Hz, J_2 = 1.7 Hz, 1H), 5.54 (q, J = 7.0 Hz, 1H), 1.74 (d, J = 7.1 Hz, 3H).

Example 43

***N*-(3-((7-(1*H*-Pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 2-(3-(4-iodo-1*H*-pyrazol-1-yl)oxetan-3-yl)acetonitrile

[00637] To a mixture of 4-iodo-1*H*-pyrazole (1 g, 5.15 mmol) and 2-(oxetan-3-ylidene)acetonitrile (0.6 g, 6.31 mmol) in acetonitrile (40 mL) was added DBU (0.8 g, 5 mmol) at rt. The mixture was stirred at 55 °C for 12 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was quenched with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a brown oily product (1.1 g, 74%).

MS (ESI, pos.ion) *m/z*: 290.1[M+1]⁺.

Step 2) 2-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)oxetan-3-yl)acetonitrile

[00638] A mixture of 2-(3-(4-iodo-1*H*-pyrazol-1-yl)oxetan-3-yl)acetonitrile (0.02 g, 0.07 mmol), bis(pinacolato)diboron (0.026 g, 0.10 mmol), potassium acetate (0.021 g, 0.20 mmol) and Pd(dppf)Cl₂ (0.002 g, 0.0027 mmol) in DMSO (35 mL) was stirred at 80 °C under N₂ for 22 h. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a brown oily product (15 mg, 75%).

MS (ESI, pos.ion) *m/z*: 290.1[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-(cyanomethyl)oxetan-3-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00639] To a solution of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.22 g, 0.41 mmol), 2-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)oxetan-3-yl)acetonitrile (0.32 g, 1.11 mmol), sodium carbonate (0.1 g, 0.89 mmol) and Pd(dppf)Cl₂ (0.016 g, 0.02 mmol) were added 1,4-dioxane (16

mL) and water (4 mL). The mixture was stirred at 65°C under N₂ for 3 h and cooled to rt, and then filtered through a Celite pad. The filter cake was washed with DCM. The filtrate was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a brown solid product (200 mg, 68.24%).

MS (ESI, pos.ion) *m/z*: 572.0[M+1]⁺.

Step 4) *N*-(3-((7-(1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

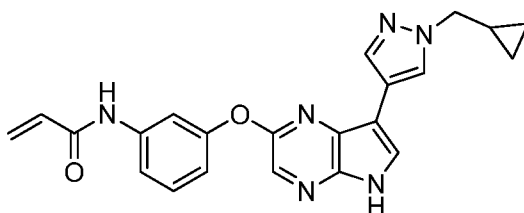
[00640] To a solution of *N*-(3-((7-(1-(3-(cyanomethyl)oxetan-3-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.16 g, 0.22 mmol) in DCM (6 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with CH₂Cl₂/MeOH (v/v) = 20/1 to give a light yellow solid product (25 mg, 32.24%).

MS (ESI, pos.ion) *m/z*: 347.05[M+1]⁺; and

¹H NMR (600 MHz, CD₃OD): δ (ppm) 8.07 (s, 1H), 8.03 (br, 2H), 7.93 (s, 1H), 7.76 (br, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 8.2 Hz, 1H), 6.99 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.6 Hz, 1H), 6.43 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.0 Hz, 1H), 6.35 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.77 (dd, *J*₁ = 10.0 Hz, *J*₂ = 1.7 Hz, 1H).

Example 44

***N*-(3-((7-(1-(Cyclopropylmethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(cyclopropylmethyl)-4-iodo-1*H*-pyrazole

[00641] A mixture of cesium carbonate (4.62 g, 14.18 mmol), potassium iodide (470 mg, 2.84 mmol), (bromomethyl)cyclopropane (1.03 g, 6.81 mmol) and 4-iodo-1*H*-pyrazole (1.10 g, 5.67 mmol) in DMF (20.00 mL) was stirred at 70 °C for 2.5 h and diluted with water (50 mL), and

then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a light yellow oily product (1.31 g, 93.1%).

MS (ESI, pos.ion) *m/z*: 248.9[M+1]⁺.

Step 2) 1-(cyclopropylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00642] A mixture of potassium acetate (1.56 g, 15.91 mmol), Pd(dppf)Cl₂ (190 mg, 0.27 mmol), 1-(cyclopropylmethyl)-4-iodo-1*H*-pyrazole (1.31 g, 5.30 mmol) and bis(pinacolato)diboron (1.62 g, 6.36 mmol) in DMF (25.00 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow oily product (1.11 g, 84.9%).

MS (ESI, pos.ion) *m/z*: 249.1[M+1]⁺.

Step 3) *N*-(3-((7-(1-(cyclopropylmethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00643] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.89 mmol), 1-(cyclopropylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (550 mg, 1.55 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 110 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a brown solid product (350 mg, 59.1%).

MS (ESI, pos.ion) *m/z*: 530.8[M+1]⁺.

Step 4) *N*-(3-((7-(1-(cyclopropylmethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00644] To a solution of *N*-(3-((7-(1-(cyclopropylmethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.51 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted

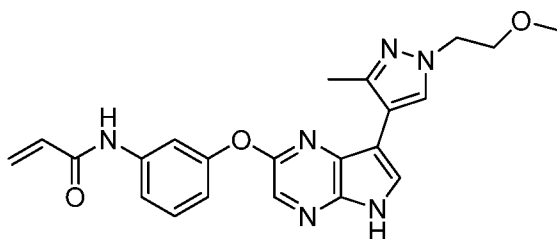
with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (75 mg, 36.6%).

MS (ESI, pos.ion) m/z : 401.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.09 (s, 1H), 10.24 (s, 1H), 8.15 (s, 1H), 8.08 (d, J = 8.9 Hz, 2H), 7.82 (s, 1H), 7.67 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.41 (dd, J_1 = 16.9 Hz, J_2 = 10.1 Hz, 1H), 6.24 (d, J = 16.9 Hz, 1H), 5.75 (d, J = 10.1 Hz, 1H), 3.91 (d, J = 7.0 Hz, 2H), 2.10-1.87 (m, 1H), 0.48 (d, J = 7.1 Hz, 2H), 0.29 (d, J = 4.4 Hz, 2H).

Example 45

***N*-(3-((7-(1-(2-Methoxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-bromo-1-(2-methoxyethyl)-3-methyl-1*H*-pyrazole

[00645] To a mixture of cesium carbonate (14.52 g, 46.58 mmol), potassium iodide (1.62 g, 9.32 mmol) and 4-bromo-3-methyl-1*H*-pyrazole (3.02 g, 18.64 mmol) were added 1-bromo-2-methoxyethane (3.92 g, 27.95 mmol) and DMF (30 mL). The mixture was warmed to 70 °C and stirred for 4 h and cooled to rt, and then diluted with water (100 mL). The resulting mixture was extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a colorless oily product (1.23 g, 30.1%).

MS (ESI, pos.ion) m/z : 219.0[M+1]⁺; and

¹H NMR (400 MHz, CDCl_3): δ (ppm) 7.42 (s, 1H), 4.18 (d, J = 5.2 Hz, 2H), 3.69 (d, J = 5.2 Hz, 2H), 3.33 (s, 3H), 2.23 (s, 3H).

Step 2) 1-(2-methoxyethyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00646] A mixture of potassium acetate (1.72 g, 17.01 mmol), bis(pinacolato)diboron (1.73 g, 6.72 mmol) and 4-bromo-1-(2-methoxyethyl)-3-methyl-1*H*-pyrazole (1.22 g, 5.58 mmol) and

Pd(dppf)Cl₂ (210 mg, 0.29 mmol) in DMF (35 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt. The reaction mixture was filtered through a Celite pad. The filtrate was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow oily product (1.41 g, 94.5%).

MS (ESI, pos.ion) *m/z*: 267.0[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-methoxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00647] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (480 mg, 0.98 mmol), 1-(2-methoxyethyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (800 mg, 1.50 mmol), potassium carbonate (220 mg, 1.52 mmol) and Pd(dppf)Cl₂ (40 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C for 30 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a brown oily product (150 mg, 27.9%).

MS (ESI, pos.ion) *m/z*: 549.3[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-methoxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00648] To a solution of *N*-(3-((7-(1-(2-methoxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (140 mg, 0.25 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (28 mg, 26.2%).

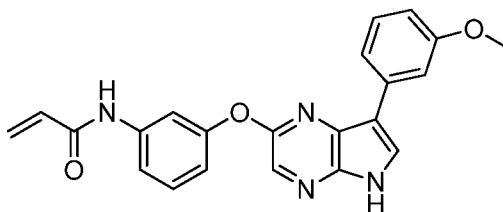
MS (ESI, pos.ion) *m/z*: 419.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.13 (s, 1H), 10.23 (s, 1H), 8.16 (s, 1H), 7.94 (s, 1H), 7.89 (s, 1H), 7.63 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.91 (dd, *J*₁ =

8.0 Hz, $J_2 = 2.1$ Hz, 1H), 6.41 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, 1H), 6.24 (d, $J = 16.9$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.8$ Hz, 1H), 4.11 (t, $J = 5.4$ Hz, 2H), 3.61 (t, $J = 5.4$ Hz, 2H), 3.17 (s, 3H), 2.28 (s, 3H).

Example 46

N-(3-((7-(3-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) *N*-(3-((7-(3-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00649] To a mixture of *N*-(3-((7-iodo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (530 mg, 0.99 mmol), (3-methoxyphenyl)boronic acid (250 mg, 1.67 mmol), sodium carbonate (160 mg, 1.53 mmol) and Pd(dppf)Cl₂ (35 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 115 °C for 20 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a brown solid product (120 mg, 16.5%).

MS (ESI, pos.ion) m/z : 517.3[M+1]⁺.

Step 2) *N*-(3-((7-(3-methoxyphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00650] To a solution of *N*-(3-((7-(3-methoxyphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (120 mg, 0.16 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a beige solid product (20 mg, 31.8%).

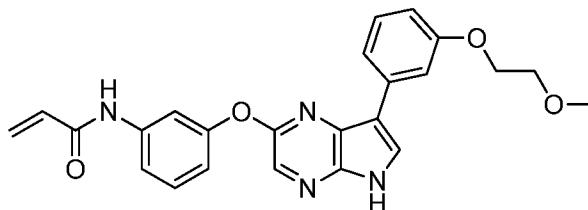
MS (ESI, pos.ion) m/z : 386.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 10.26 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 7.77-7.67 (m, 1H), 7.62 (t, $J = 2.0$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.47 (d, $J = 8.1$ Hz, 1H), 7.38 (t, $J =$

8.1 Hz, 1H), 7.21 (t, $J = 7.9$ Hz, 1H), 6.95 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 6.70 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.3$ Hz, 1H), 6.41 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, 1H), 6.24 (dd, $J_1 = 17.0$ Hz, $J_2 = 1.8$ Hz, 1H), 5.75 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.8$ Hz, 1H), 3.54 (s, 3H).

Example 47

***N*-(3-((7-(3-(2-Methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-bromo-3-(2-methoxyethoxy)benzene

[00651] A mixture of cesium carbonate (4.51 g, 14.45 mmol), potassium iodide (560 mg, 2.89 mmol), 3-bromophenol (1.01 g, 7.73 mmol) and 1-bromo-2-methoxyethane (1.21 g, 8.67 mmol) in DMF (20 mL) was stirred at 70 °C for 12 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a white solid product (1.08 g, 80.7%).

MS (ESI, pos.ion) m/z : 231.1[M+1]⁺.

Step 2) 2-(3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00652] A mixture of potassium acetate (1.50 g, 13.99 mmol), Pd(dppf)Cl₂ (190 mg, 0.23 mmol), 1-bromo-3-(2-methoxyethoxy)benzene (1.08 g, 4.67 mmol) and bis(pinacolato)diboron (1.42 g, 5.60 mmol) in dioxane (20 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt. The reaction mixture was concentrated *in vacuo* with silica gel. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a light yellow oily product (944 mg, 72.7%).

MS (ESI, pos.ion) m/z : 279.3[M+1]⁺.

Step 3) *N*-(3-((7-(3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00653] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.88 mmol), 2-(3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (450 mg, 1.29 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 110 °C overnight.

The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a brown solid product (220 mg, 37.8%).

MS (ESI, pos.ion) m/z : 561.3[M+1]⁺.

Step 4) *N*-(3-((7-(3-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

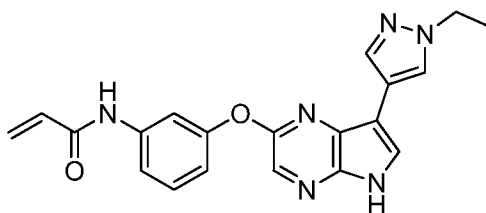
[00654] To a solution of *N*-(3-((7-(3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (210 mg, 0.37 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (20 mg, 12.4%).

MS (ESI, pos.ion) m/z : 431.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.36 (s, 1H), 10.23 (s, 1H), 8.41 (d, J = 2.8 Hz, 1H), 8.20 (s, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.95 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 6.71 (dd, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H), 6.41 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 1H), 6.24 (dd, J_1 = 17.0 Hz, J_2 = 1.7 Hz, 1H), 5.75 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.86-3.80 (m, 2H), 3.63-3.57 (m, 2H), 3.29 (s, 3H).

Example 48

***N*-(3-((7-(1-Ethyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00655] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.0 g, 5.2 mmol) in DMF (10 mL) were added cesium carbonate (2.5 g, 7.7 mmol) and iodoethane (1.2 mL, 15 mmol). The mixture was stirred at rt for 12 h and diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over

anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a colorless oily product (880 mg, 77%).

MS (ESI, pos.ion) *m/z*: 223.25[M+1]⁺.

Step 2) *N*-(3-((7-(1-ethyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00656] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.88 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (350 mg, 1.58 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 110 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a brown solid product (350 mg, 66.8%).

MS (ESI, pos.ion) *m/z*: 504.9[M+1]⁺.

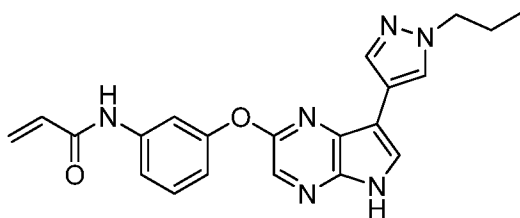
Step 3) *N*-(3-((7-(1-ethyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00657] To a solution of *N*-(3-((7-(1-ethyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (320 mg, 0.50 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (65 mg, 34.2%).

MS (ESI, pos.ion) *m/z*: 375.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.08 (s, 1H), 10.25 (s, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.25 (d, *J* = 16.9 Hz, 1H), 5.75 (d, *J* = 10.5 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

Example 49

***N*-(3-((7-(1-propyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide****Step 1) *N*-(3-((7-(1-propyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

[00658] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.88 mmol), 1-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (350 mg, 1.48 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 110 °C overnight. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a brown solid product (350 mg, 65.0%).

MS (ESI, pos.ion) *m/z*: 518.9[M+1]⁺.

Step 2) *N*-(3-((7-(1-propyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

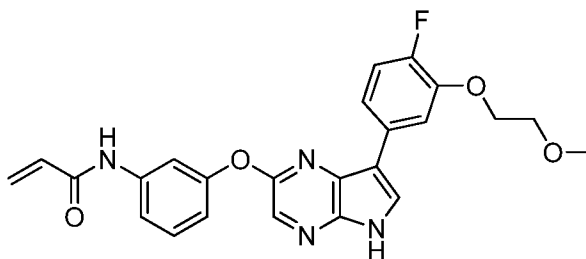
[00659] To a solution of *N*-(3-((7-(1-propyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (340 mg, 0.52 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with EtOAc to give a light yellow solid product (80 mg, 39.3%).

MS (ESI, pos.ion) *m/z*: 389.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.07 (s, 1H), 10.25 (s, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 6.93 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.4 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 16.9 Hz, *J*₂ = 1.1 Hz, 1H), 5.76 (dd, *J*₁ = 10.1 Hz, *J*₂ = 1.3 Hz, 1H), 4.01 (t, *J* = 6.9 Hz, 2H), 1.74 (d, *J* = 7.2 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

Example 50

***N*-(3-((7-(4-fluoro-3-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

**Step 1) 4-bromo-1-fluoro-2-(2-methoxyethoxy)benzene**

[00660] A mixture of cesium carbonate (3.41 g, 10.47 mmol), potassium iodide (453 mg, 2.62 mmol), 5-bromo-2-fluorophenol (1.10 g, 5.24 mmol) and 1-bromo-2-methoxyethane (1.10 g, 7.85 mmol) in DMF (15 mL) was stirred at 100 °C for 5 h and diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a colorless oily product (1.20 g, 92.3%).

MS (ESI, pos.ion) *m/z*: 251.1[M+1]⁺.

Step 2) 2-(4-fluoro-3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00661] A mixture of potassium acetate (1.79 g, 18.08 mmol), Pd(dppf)Cl₂ (214 mg, 0.30 mmol), 4-bromo-1-fluoro-2-(2-methoxyethoxy)benzene (1.50 g, 6.02 mmol) and bis(pinacolato)diboron (1.80 g, 7.23 mmol) in DMF (20.00 mL) was stirred at 85 °C under N₂ for 24 h and cooled to rt, and then filtered through a Celite pad. The filtrate was diluted with water (50 mL), and then extracted with EtOAc (50 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a yellow oily product (1.70 g, 95.3%).

MS (ESI, pos.ion) *m/z*: 297.3[M+1]⁺.

Step 3) *N*-(3-((7-(4-fluoro-3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00662] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (485 mg, 0.88 mmol), 2-(4-fluoro-3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (600 mg, 1.62 mmol), potassium carbonate (210 mg, 1.52 mmol) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) were added 1,4-dioxane (14 mL) and water (3.5 mL) under N₂. The mixture was stirred at 110 °C overnight.

The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/4 to give a brown solid product (300 mg, 52.3%).

MS (ESI, pos.ion) m/z : 578.8[M+1]⁺.

Step 4) *N*-(3-((7-(4-fluoro-3-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

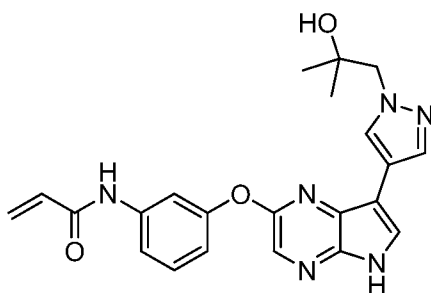
[00663] To a solution of *N*-(3-((7-(4-fluoro-3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (300 mg, 0.52 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (6 mL). The solution was basified with saturated aqueous NaHCO₃ to pH 8-9, and stirred at rt overnight. The mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/10 to give a light yellow solid product (40 mg, 17.2%).

MS (ESI, pos.ion) m/z : 448.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.37 (s, 1H), 10.25 (s, 1H), 8.40 (s, 1H), 8.23 (s, 1H), 7.94-7.83 (m, 1H), 7.64 (s, 1H), 7.55-7.47 (m, 2H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.15 (dd, *J*₁ = 11.4 Hz, *J*₂ = 8.5 Hz, 1H), 6.96 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.8 Hz, 1H), 6.41 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.25 (dd, *J*₁ = 16.9 Hz, *J*₂ = 1.2 Hz, 1H), 5.76 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H), 3.88-3.72 (m, 2H), 3.59 (dd, *J*₁ = 5.1 Hz, *J*₂ = 3.2 Hz, 2H), 3.29 (s, 3H).

Example 51

***N*-(3-((7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propan-2-ol

[00664] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.01 g, 5.2 mmol), 1-chloro-2-methylpropan-2-ol (1.1 mL, 11 mmol) and Cs₂CO₃ (4.2 g, 13 mmol) in DMF

(15 mL) was stirred under a microwave condition at 160 °C for 2.5 h. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a light yellow oily product (1.30 g, 94%).

MS (ESI, pos.ion) *m/z*: 267.1[M+1]⁺.

Step 2) *N*-(3-((7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00665] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.61 g, 1.2 mmol), 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propan-2-ol (0.61 g, 1.8 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.25 g, 1.8 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.2 g, 29%).

MS (ESI, pos.ion) *m/z*: 549.3[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

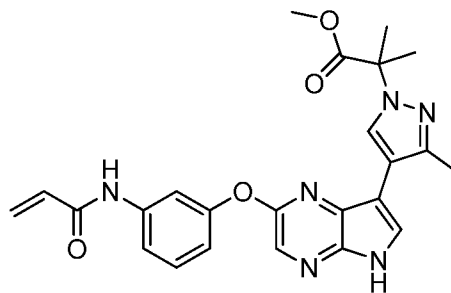
[00666] To a solution of *N*-(3-((7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.2 g, 0.38 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a brown solid product (0.01 g, 6.2%).

MS (ESI, pos.ion) m/z : 419.1[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.22 (s, 1H), 9.03 (s, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.59 (s, 1H), 7.41-7.32 (m, 1H), 7.19 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.40 (dd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, 1H), 5.75 (d, J = 9.2 Hz, 1H), 5.37-5.29 (m, 1H), 4.66 (s, 1H), 3.98 (s, 2H), 1.25 (s, 6H).

Example 52

Methyl 2-(4-(2-(3-acrylamidophenoxy)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate



Step 1) methyl 2-methyl-2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanoate

[00667] A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 g, 7.2 mmol), methyl 2-bromo-2-methylpropanoate (1.4 mL, 10.8 mmol) and Cs₂CO₃ (4.5 g, 14 mmol) in DMF (15 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 9/1 to give a colorless oily product (1.3 g, 58%).

MS (ESI, pos.ion) m/z : 309.3[M+1]⁺.

Step 2) methyl 2-(4-(2-(3-acrylamidophenoxy)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate

[00668] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.50 g, 1.0 mmol), methyl 2-methyl-2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanoate (0.5 g, 2 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over

anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/3 to give a yellow solid product (0.2 g, 30%).

MS (ESI, pos.ion) m/z : 591.4[M+1]⁺.

Step 3) methyl 2-(4-(2-(3-acrylamidophenoxy)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate

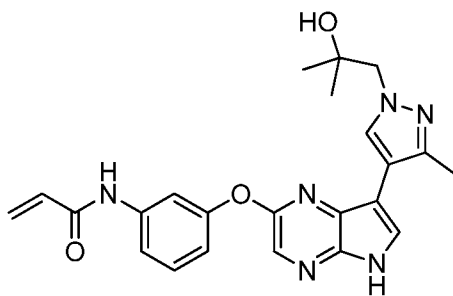
[00669] To a solution of methyl 2-(4-(2-(3-acrylamidophenoxy)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate (0.14 g, 0.24 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.03 g, 27%).

MS (ESI, pos.ion) m/z : 460.8[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.11 (s, 1H), 10.24 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.40 (dd, J_1 = 16.8 Hz, J_2 = 10.4 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 5.74 (d, J = 8.0 Hz, 1H), 3.57 (s, 3H), 2.29 (s, 3H), 1.61 (s, 6H).

Example 53

***N*-(3-((7-(1-(2-Hydroxy-2-methylpropyl)-3-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(4-bromo-3-methyl-1H-pyrazol-1-yl)-2-methylpropan-2-ol

[00670] A mixture of 4-bromo-3-methyl-1H-pyrazole (2.00 g, 12.4 mmol), 1-chloro-2-methylpropan-2-ol (2.5 mL, 24 mmol) and cesium carbonate (10.1 g, 31 mmol) in DMF (40 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated *in vacuo*

to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (40 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oily product (1 g, 34.5%).

MS (ESI, pos.ion) *m/z*: 233.1[M+1]⁺.

Step 2) 2-methyl-1-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol

[00671] A mixture of 1-(4-bromo-3-methyl-1H-pyrazol-1-yl)-2-methylpropan-2-ol (0.75 g, 3.25 mmol), bis(pinacolato)diboron (1.3 g, 5 mmol), potassium acetate (1 g, 10 mmol) and Pd(dppf)Cl₂ (0.13 g, 0.18 mmol) in DMSO (10 mL) was stirred at 90 °C under N₂ overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow oily product (0.4 g, 40%).

MS (ESI, pos.ion) *m/z*: 281.1[M+1]⁺.

Step 3) N-(3-((7-(1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00672] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.41 g, 0.84 mmol), 2-methyl-1-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol (0.41 g, 1.2 mmol), Pd(dppf)Cl₂ (0.03 g, 0.04 mmol) and potassium carbonate (0.20 g, 1.4 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.2 g, 42%).

MS (ESI, pos.ion) *m/z*: 563.8[M+1]⁺.

Step 4) N-(3-((7-(1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00673] To a solution of *N*-(3-((7-(1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)ac

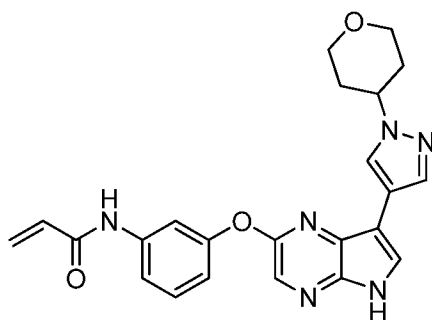
rylamide (0.21 g, 0.37 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a brown solid product (0.03 g, 18.6%).

MS (ESI, pos.ion) *m/z*: 433.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 10.23 (s, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.59 (t, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.95-6.89 (m, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.76 (d, *J* = 2.1 Hz, 1H), 4.62 (s, 1H), 3.88 (s, 2H), 2.30 (s, 3H), 1.02 (s, 6H).

Example 54

***N*-(3-((7-(1-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) tetrahydro-2*H*-pyran-4-yl methanesulfonate

[00674] To a solution of tetrahydro-2*H*-pyran-4-ol (4 mL, 41.11 mmol) in DCM (60 mL) was added TEA (9 mL, 63.9 mmol) at 0°C. After stirring 5 min, methanesulfonyl chloride (3.5 mL, 45 mmol) was added slowly to the mixture. The resulting mixture was stirred for 1 h and warmed to rt, and then further stirred overnight. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with DCM (100 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give a light yellow solid product (7 g, 94.5%).

MS (ESI, pos.ion) *m/z*: no response.

Step 2) 1-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00675] A mixture of tetrahydro-2*H*-pyran-4-yl methanesulfonate (2.8 g, 16 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.01 g, 10.4 mmol) and cesium carbonate (5.4 g, 17 mmol) in DMF (30 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oily product (1.1 g, 38%).

MS (ESI, pos.ion) *m/z*: 279.3[M+1]⁺.

Step 3) *N*-(3-((7-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00676] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.50 g, 1.0 mmol), 1-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.40 g, 1.4 mmol), Pd(dppf)Cl₂ (0.04 g, 0.05 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.21 g, 36%).

MS (ESI, pos.ion) *m/z*: 561.2[M+1]⁺.

Step 4) *N*-(3-((7-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

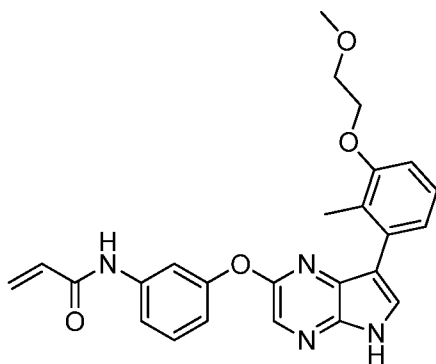
[00677] To a solution of *N*-(3-((7-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.21 g, 0.37 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.02 g, 12%).

MS (ESI, pos.ion) m/z : 431.9[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.07 (s, 1H), 10.27 (s, 1H), 8.16 (s, 1H), 8.07 (d, J = 2.8 Hz, 1H), 8.06 (s, 1H), 7.84 (s, 1H), 7.70 (t, J = 1.9 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 6.94 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.42 (dd, J_1 = 17.0 Hz, J_2 = 10.1 Hz, 1H), 6.24 (dd, J_1 = 17.0 Hz, J_2 = 1.9 Hz, 1H), 5.75 (dd, J_1 = 10.0 Hz, J_2 = 1.9 Hz, 1H), 4.32 (m, 1H), 3.94 (m, 2H), 3.42 (m, 2H), 1.94 (m, 2H), 1.83 (m, 2H).

Example 55

***N*-(3-((7-(3-(2-Methoxyethoxy)-2-methylphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-bromo-3-(2-methoxyethoxy)-2-methylbenzene

[00678] A mixture of 3-bromo-2-methylphenol (1 g, 5.40 mmol), 1-bromo-2-methoxyethane (0.75 g, 5.40 mmol) and cesium carbonate (3.5 g, 11.00 mmol) in DMF (15 mL) was stirred at 50°C for 6 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a light yellow liquid product (1.31 g, 83.00%).

MS (ESI, pos.ion) m/z : 245.10[M+1]⁺.

Step 2) 2-(3-(2-methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00679] A mixture of 1-bromo-3-(2-methoxyethoxy)-2-methylbenzene (0.98 g, 4.00 mmol), potassium acetate (1.2 g, 12.00 mmol), bis(pinacolato)diboron (1.24 g, 4.88 mmol) and Pd(dppf)Cl₂ (170 mg, 0.21 mmol) in DMSO (20 mL) was stirred at 100°C under N₂ for 8 h. The reaction mixture was cooled to rt and diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a

light yellow liquid product (1.19 g, 52.33%).

MS (ESI, pos.ion) m/z : 293.1[M+1]⁺.

Step 3) *N*-(3-((7-(3-(2-methoxyethoxy)-2-methylphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00680] A mixture of 2-(3-(2-methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (111 mg, 0.38 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (185 mg, 0.38 mmol), potassium carbonate (155 g, 1.12 mmol) and Pd(dppf)Cl₂ (30 mg, 0.037 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 120 °C under N₂ for 8 h. The reaction mixture was cooled to rt and diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a puce liquid product (92 mg, 42.14%).

MS (ESI, pos.ion) m/z : 575.30[M+1]⁺.

Step 4) *N*-(3-((7-(3-(2-methoxyethoxy)-2-methylphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00681] To a solution of *N*-(3-((7-(3-(2-methoxyethoxy)-2-methylphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (53 mg, 0.09 mmol) in DCM (5.0 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (11 mg, 26.83%).

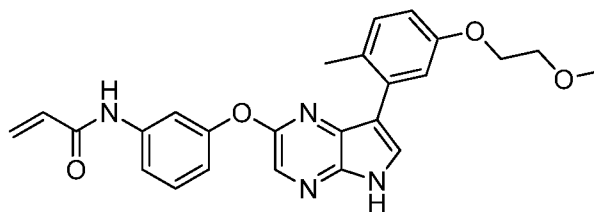
MS (ESI, pos.ion) m/z : 444.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.36 (s, 1H), 10.20 (s, 1H), 8.17 (s, 1H), 7.93 (d, *J* = 2.6 Hz, 1H), 7.51 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 5.6 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.39 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (d, *J* = 16.9 Hz, 1H), 5.75 (dd, *J*₁ = 5.9 Hz, *J*₂ = 4.1 Hz, 1H),

4.11-4.04 (m, 2H), 3.70-3.66 (m, 2H), 3.32 (s, 3H), 2.08 (s, 3H).

Example 56

NN-(3-((7-(5-(2-Methoxyethoxy)-2-methylphenyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 2-bromo-4-(2-methoxyethoxy)-1-methylbenzene

[00682] A mixture of 3-bromo-4-methylphenol (1.66 g, 8.87 mmol), 1-bromo-2-methoxyethane (0.85 mL, 9.00 mmol) and cesium carbonate (3.5 g, 11.00 mmol) in DMF (15 mL) was stirred at rt for 8 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a light yellow liquid product (2.10 g, 96.60%).

MS (ESI, pos.ion) *m/z*: 246.90[M+1]⁺.

Step 2) 2-(5-(2-methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00683] A mixture of 2-bromo-4-(2-methoxyethoxy)-1-methylbenzene (2.71 g, 11.04 mmol), potassium acetate (3.20 g, 33.00 mmol), bis(pinacolato)diboron (4.20 g, 17.00 mmol) and Pd(dppf)Cl₂ (450 mg, 0.55 mmol) in DMSO (20 mL) was stirred at 100 °C under N₂ for 12 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 8/1 to give a light yellow liquid product (1.79 g, 55.5%).

MS (ESI, pos.ion) *m/z*: 293.30[M+1]⁺.

Step 3) N-(3-((7-(5-(2-methoxyethoxy)-2-methylphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide

[00684] A mixture of 2-(5-(2-methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 g, 1.54 mmol), N-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide (0.51 g, 1.03 mmol), potassium carbonate

(0.36 g, 2.60 mmol) and Pd(dppf)Cl₂ (85 mg, 0.10 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 120 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a puce liquid product (322 mg, 54.41%).

MS (ESI, pos.ion) *m/z*: 575.30 [M+1]⁺.

Step 4) *N*-(3-((7-(5-(2-methoxyethoxy)-2-methylphenyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

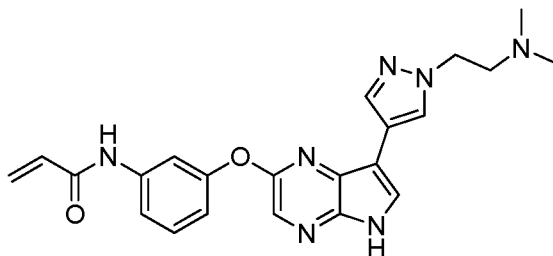
[00685] To a solution of *N*-(3-((7-(5-(2-methoxyethoxy)-2-methylphenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (76 mg, 1.32 mmol) in DCM (4.9 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (26 mg, 44.23%).

MS (ESI, pos.ion) *m/z*: 445.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.38 (s, 1H), 10.21 (s, 1H), 8.21 (s, 1H), 8.02 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.33 (s, 1H), 7.14 (d, *J* = 28.0 Hz, 2H), 6.87 (s, 1H), 6.73 (s, 1H), 6.39 (s, 1H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.75 (s, 1H), 3.88 (s, 2H), 3.57 (s, 2H), 3.27 (s, 3H), 2.25 (s, 3H).

Example 57

***N*-(3-((7-(1-(2-(Dimethylamino)ethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N,N*-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)

ethanamine

[00686] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.5 g, 7.7 mmol), 2-bromo-*N,N*-dimethylethanamine hydrobromide (4 g, 20 mmol) and Cs₂CO₃ (9 g, 17.6 mmol) in DMF (15 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 25/1 to give a white solid product (0.5 g, 20%).

MS (ESI, pos.ion) *m/z*: 266.1[M+1]⁺.

Step 2) *N*-(3-((7-(1-(2-(dimethylamino)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00687] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.20 g, 0.41 mmol) in 1,4-dioxane (20 mL) were added *N,N*-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanamine (0.13 g, 0.49 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.25 g, 1.8 mmol) followed by addition of water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.1 g, 40%).

MS (ESI, pos.ion) *m/z*: 548.9[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(dimethylamino)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00688] To a solution of *N*-(3-((7-(1-(2-(dimethylamino)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.1 g, 0.2 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.

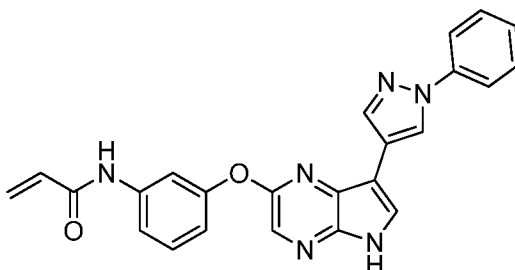
The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.015 g, 18%).

MS (ESI, pos.ion) m/z : 418.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.11 (s, 1H), 10.31 (s, 1H), 8.14 (s, 1H), 8.09 (d, J = 2.8 Hz, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.64 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 8.2 Hz, 1H), 6.92 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 6.43 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 1H), 6.24 (dd, J_1 = 17.0 Hz, J_2 = 1.8 Hz, 1H), 5.75 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 4.16 (t, J = 6.2 Hz, 2H), 2.15 (s, 6H).

Example 58

***N*-(3-((7-(1-Phenyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-iodo-1-phenyl-1*H*-pyrazole

[00689] A mixture of 4-iodo-1*H*-pyrazole (1.01 g, 5.21 mmol), phenylboronic acid (1.26 g, 10.3 mmol), copper acetate (1.87 g, 10.3 mmol) and pyridine (1.3 mL, 16 mmol) in DCM (15 mL) was stirred at rt under O₂ for 12 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a yellow solid product (982 mg, 69.8%).

MS (ESI, pos.ion) m/z : 271.05[M+1]⁺.

Step 2) 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00690] A mixture of 4-iodo-1-phenyl-1*H*-pyrazole (706 mg, 2.59 mmol), potassium acetate (762 mg, 7.76 mmol), bis(pinacolato)diboron (860 mg, 3.37 mmol) and Pd(dppf)Cl₂ (212 mg, 0.26 mmol) was suspended in DMSO (15 mL). The system was exchanged with N₂. The mixture was stirred at 80 °C for 8 h. The reaction mixture was diluted with water (60 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to

give a yellow solid product (340 mg, 48.15%).

MS (ESI, pos.ion) m/z : 271.05[M+1]⁺.

Step 3) *N*-(3-((7-(1-phenyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00691] A mixture of 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (250 mg, 0.93 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (296 mg, 0.61 mmol), potassium carbonate (214 mg, 1.55 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (50 mg, 0.06 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 100 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a puce oily product (201 mg, 60.13%).

MS (ESI, pos.ion) m/z : 553.2[M+1]⁺.

Step 4) *N*-(3-((7-(1-phenyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

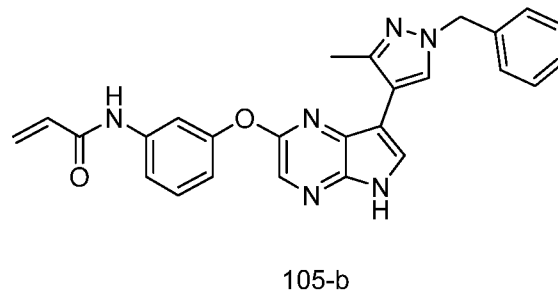
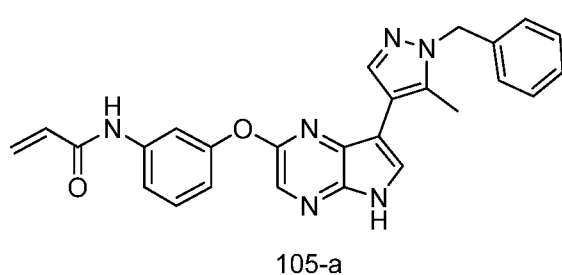
[00692] To a solution of *N*-(3-((7-(1-phenyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (203 mg, 0.37 mmol) in DCM (5 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (12 mg, 7.74%).

MS (ESI, pos.ion) m/z : 423.2[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.20 (s, 1H), 10.35 (s, 1H), 8.65 (s, 1H), 8.21 (s, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.76 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 3H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.1 Hz, 1H), 6.22 (d, *J* = 16.7 Hz, 1H), 5.73 (d, *J* = 9.8 Hz, 1H).

Example 59

N-(3-((7-(1-Benzyl-5-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide and *N*-(3-((7-(1-Benzyl-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 1-benzyl-4-bromo-3-methyl-1*H*-pyrazole and 1-benzyl-4-bromo-5-methyl-1*H*-pyrazole

[00693] A mixture of (bromomethyl)benzene (1.3 g, 7.6 mmol), 4-bromo-3-methyl-1*H*-pyrazole (1.01 g, 6.27 mmol) and potassium carbonate (2.1 g, 15 mmol) in DMF (15 mL) was stirred at 50 °C for 6 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a light yellow mixture of isomerides (806 mg, 51.2%).

MS (ESI, pos.ion) *m/z*: 251.10[M+1]⁺.

Step 2) 1-benzyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole and 1-benzyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00694] A mixture of 1-benzyl-4-bromo-3-methyl-1*H*-pyrazole and 1-benzyl-4-bromo-5-methyl-1*H*-pyrazole (1.247 g, 4.97 mmol), and potassium acetate (1.5 g, 15 mmol), bis(pinacolato)diboron (1.6 g, 6.3 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (200 mg, 0.25 mmol) in DMSO (20 mL) was stirred at 100 °C for 12 h. The reaction mixture was diluted with water (60 mL). The resulting mixture was extracted with EtOAc (60 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a puce mixture of isomerides (321 mg, 21.68%). The mixture of isomerides was purified by pre-HPLC to give compound 105-1: 1-benzyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (47 mg); compound 105-2: 1-benzyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-

pyrazole (200 mg).

Compound 105-1:MS (ESI, pos.ion) m/z : 299.05 $[M+1]^+$; and

Compound 105-2:MS (ESI, pos.ion) m/z : 299.00 $[M+1]^+$.

Step 3) *N*-(3-((7-(1-benzyl-5-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide and *N*-(3-((7-(1-benzyl-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00695] A mixture of 1-benzyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (47 mg, 0.16 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (80 mg, 0.16 mmol), potassium carbonate (70 mg, 0.51 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (10 mg, 0.012 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 110 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a black oily product (6 mg, 6.55%).

Compound 105-3: MS (ESI, pos.ion) m/z : 581.38 $[M+1]^+$.

[00696] A mixture of 1-benzyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (201 mg, 0.67 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (275 mg, 0.56 mmol), potassium carbonate (280 mg, 2.02 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (54 mg, 0.06 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 110 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a black oily product (92 mg, 23.50%).

Compound 105-4:MS (ESI, pos.ion) m/z : 581.3 $[M+1]^+$.

Step 4) *N*-(3-((7-(1-benzyl-5-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide and *N*-(3-((7-(1-benzyl-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00697] To a solution of *N*-(3-((7-(1-benzyl-5-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (12 mg,

0.021 mmol) in DCM (6 mL) was added trifluoroacetic acid (3.1 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (5 mg, 53.72%).

Compound 105-a: MS (ESI, pos.ion) *m/z*: 451.30[M+1]⁺;

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.15 (s, 1H), 10.28 (s, 1H), 8.16 (s, 1H), 8.05 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.65 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.90 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.9 Hz, 1H), 6.42-6.38 (m, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.6 Hz, 1H), 5.75-5.73 (m, 1H), 5.15 (s, 2H), 2.28 (s, 3H).

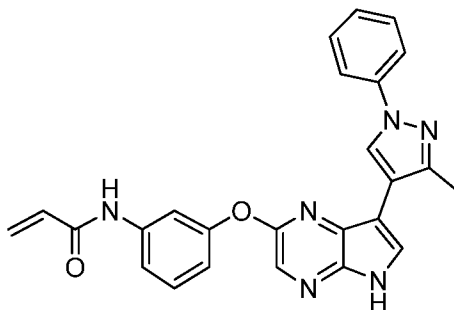
[00698] To a solution of *N*-(3-((7-(1-benzyl-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (51 mg, 0.088 mmol) in DCM (6 mL) was added trifluoroacetic acid (4.9 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (14 mg, 35.39%).

Compound 105-b: MS (ESI, pos.ion) *m/z*: 450.9[M+1]⁺;

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.18 (s, 1H), 10.21 (s, 1H), 8.16 (s, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.71 (s, 1H), 7.55 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.36-7.29 (m, 3H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.15-7.09 (m, 2H), 6.89 (d, *J* = 10.4 Hz, 1H), 6.42-6.36 (m, 1H), 6.23 (d, *J* = 15.2 Hz, 1H), 5.73 (s, 1H), 5.31 (s, 2H), 2.27 (s, 3H).

Example 60

N-(3-((7-(3-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 4-bromo-3-methyl-1-phenyl-1H-pyrazole

[00699] A mixture of phenylboronic acid (2.3 g, 19 mmol), pyridine (2.3 mL, 28 mmol), copper acetate (3.4 g, 19 mmol) and 4-bromo-3-methyl-1H-pyrazole (1.49 g, 9.25 mmol) in DCM (15 mL) was stirred at rt under O₂ for 24 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 5/1 to give a yellow liquid product (1.8 g, 82%).

MS (ESI, pos.ion) *m/z*: 237.10[M+1]⁺.

Step 2) 3-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00700] A mixture of 4-bromo-3-methyl-1-phenyl-1H-pyrazole (701 mg, 2.96 mmol) potassium acetate (870 mg, 8.88 mmol), bis(pinacolato)diboron (1.12 g, 6.3 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (120 mg, 0.15 mmol) in DMSO (15 mL) was stirred at 100 °C under N₂ for 6 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oily product (320 mg, 38.08%).

MS (ESI, pos.ion) *m/z*: 285.05[M+1]⁺.

Step 3) N-(3-((7-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide

[00701] A mixture of 3-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (290 mg, 1.02 mmol), N-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide (501 mg, 1.02 mmol), potassium carbonate (420 mg, 3.04 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (80 mg, 0.098 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 100 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30

mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a black oily product (230 mg, 39.65%).

MS (ESI, pos.ion) *m/z*: 567.80[M+1]⁺.

Step 4) *N*-(3-((7-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

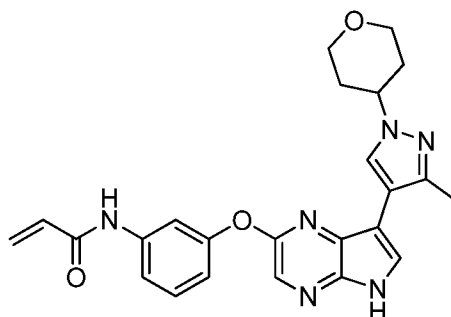
[00702] To a solution of *N*-(3-((7-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (64 mg, 0.094 mmol) in DCM (6 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (22 mg, 53.61%).

MS (ESI, pos.ion) *m/z*: 436.85[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.25 (s, 1H), 10.40 (s, 1H), 8.53 (s, 1H), 8.24 (s, 1H), 8.01 (s, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.48-7.42 (m, 3H), 7.25 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.21 (d, *J* = 16.8 Hz, 1H), 5.73 (d, *J* = 10.2 Hz, 1H), 2.42 (s, 3H).

Example 61

***N*-(3-((7-(3-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-bromo-3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole

[00703] A mixture of tetrahydro-2*H*-pyran-4-yl methanesulfonate (2.9 g, 11 mmol),

4-bromo-3-methyl-1*H*-pyrazole (1.20 g, 7.45 mmol) and cesium carbonate (3.9 g, 12 mmol) in DMF (40 mL) was stirred at 100°C for 10 h. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (40 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oily product (1.6 g, 88%).

MS (ESI, pos.ion) *m/z*: 246.9[M+1]⁺.

Step 2) 3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00704] A mixture of 4-bromo-3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole (2.01 g, 6.56 mmol), bis(pinacolato)diboron (1.3 g, 5 mmol), potassium acetate (1 g, 10 mmol) and Pd(dppf)Cl₂ (0.25 g, 0.34 mmol) in DMSO (20 mL) was stirred at 90 °C under N₂ overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow oily product (0.6 g, 30%).

MS (ESI, pos.ion) *m/z*: 293.1[M+1]⁺.

[00705] **Step 3) *N*-(3-((7-(3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.35 g, 0.72 mmol), 3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.30 g, 1.0 mmol), Pd(dppf)Cl₂ (0.04 g, 0.05 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (0.15 g, 36%).

MS (ESI, pos.ion) *m/z*: 575.3[M+1]⁺.

Step 4) *N*-(3-((7-(3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

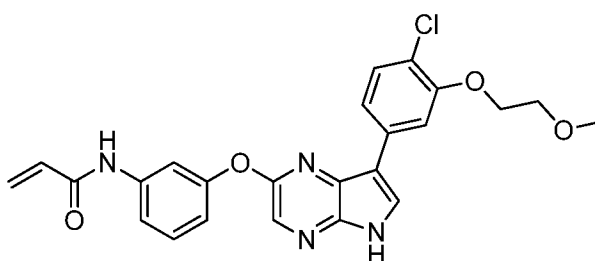
[00706] To a solution of *N*-(3-((7-(3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.15 g, 0.26 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.02 g, 17%).

MS (ESI, pos.ion) *m/z*: 444.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (d, *J* = 2.4 Hz, 1H), 10.27 (s, 1H), 8.18 (s, 1H), 7.95 (s, 1H), 7.87 (d, *J* = 2.8 Hz, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.48 (m, 1H), 7.40 (dd, *J*₁ = 9.5 Hz, *J*₂ = 6.7 Hz, 1H), 6.93 (m, 1H), 6.42 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.75 (m, 1H), 4.19 (m, 1H), 3.92 (m, 2H), 3.41 (m, 2H), 2.29 (s, 3H), 1.88 (m, 2H), 1.74 (m, *J*₁ = 12.2 Hz, *J*₂ = 4.4 Hz, 2H).

Example 62

N-(3-((7-(4-Chloro-3-(2-methoxyethoxy)phenyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 1-chloro-4-iodo-2-(2-methoxyethoxy)benzene

[00707] To a solution of 2-chloro-5-iodophenol (4 g, 15.720 mmol) in DMF (100 mL) was added K₂CO₃ (13 g, 39 mmol) at 0 °C under N₂. After stirring 10 min, 1-bromo-2-methoxyethane (3 mL, 31.92 mmol) and potassium iodide (1.3 g, 7.8 mmol) were added to the mixture. The resulting mixture was stirred at 70 °C for 12 h. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and

concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 20/1 to give a yellow oily product (4.8 g, 98%).

MS (ESI, pos.ion) m/z : 314.8[M+1]⁺.

Step 2) 2-(4-chloro-3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A mixture of 1-chloro-4-iodo-2-(2-methoxyethoxy)benzene (1.00 g, 3.20 mmol), bis(pinacolato)diboron (1.3 g, 5.1 mmol), potassium acetate (0.95 g, 9.7 mmol) and Pd(dppf)Cl₂ (0.12 g, 0.16 mmol) in DMSO (20 mL) was stirred at 90 °C under N₂ overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a light yellow solid product (0.25 g, 25%).

MS (ESI, pos.ion) m/z : 313.0[M+1]⁺.

Step 3) N-(3-((7-(4-chloro-3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide

[00708] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide (0.31 g, 0.63 mmol), 2-(4-chloro-3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.25 g, 0.80 mmol), Pd(dppf)Cl₂ (0.03 g, 0.04 mmol) and potassium carbonate (0.13 g, 0.94 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/3 to give a yellow solid product (0.15 g, 40%).

MS (ESI, pos.ion) m/z : 595.3[M+1]⁺.

Step 4) N-(3-((7-(4-chloro-3-(2-methoxyethoxy)phenyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide

[00709] To a solution of *N*-(3-((7-(4-chloro-3-(2-methoxyethoxy)phenyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)phenyl)acrylamide (0.14 g, 0.24 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated

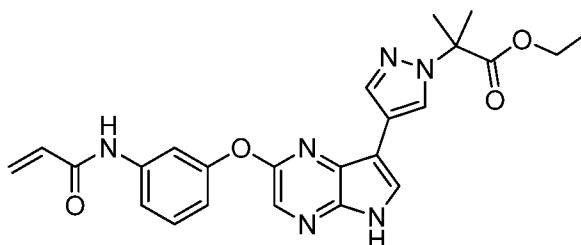
aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (0.02 g, 18.3%).

MS (ESI, pos.ion) *m/z*: 464.8[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.43 (s, 1H), 10.26 (s, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.64 (s, 1H), 7.53 (dd, *J*₁ = 13.5 Hz, *J*₂ = 5.2 Hz, 2H), 7.37 (m, 2H), 6.96 (dd, *J*₁ = 8.0 Hz, *J*₂ = 2.0 Hz, 1H), 6.41 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.1 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.8 Hz, 1H), 5.75 (dd, *J*₁ = 10.1 Hz, *J*₂ = 1.8 Hz, 1H), 3.76 (m, 2H), 3.58 (m, 2H), 3.30 (s, 3H).

Example 63

Ethyl 2-(4-(2-(3-acrylamidophenoxy)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)-2-methylpropanoate



Step 1) ethyl 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propanoate

[00710] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.00 g, 10.3 mmol), ethyl 2-bromo-2-methylpropanoate (4.1 g, 21 mmol) and cesium carbonate (8.4 g, 26 mmol) in DMF (40 mL) was stirred at 70 °C for 10 h. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a white solid product (2.1 g, 66%).

MS (ESI, pos.ion) *m/z*: 309.0[M+1]⁺.

Step 2) ethyl 2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)-2-methylpropanoate

[00711] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.61 g, 1.2 mmol), ethyl 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propanoate (0.6 g, 2 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.3 g, 2 mmol) were added 1,4-dioxane (20 mL)

and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.15 g, 20%).

MS (ESI, pos.ion) *m/z*: 591.7[M+1]⁺.

Step 3) ethyl 2-(4-(2-(3-acrylamidophenoxy)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)-2-methylpropanoate

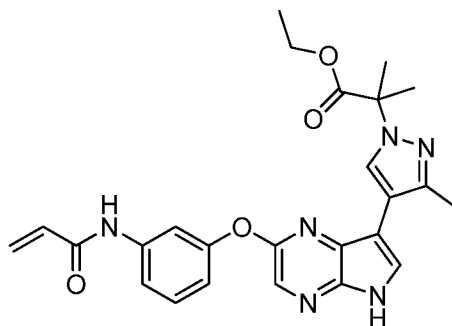
[00712] To a solution of ethyl 2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)-2-methylpropanoate (0.14 g, 0.24 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (0.03 g, 27.5%).

MS (ESI, pos.ion) *m/z*: 460.9[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.08 (d, *J* = 2.3 Hz, 1H), 10.28 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 8.11 (d, *J* = 2.8 Hz, 1H), 7.88 (s, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 6.97 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.8 Hz, 1H), 6.42 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.1 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.75 (dd, *J*₁ = 10.0 Hz, *J*₂ = 2.0 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.68 (s, 6H), 1.08 (t, *J* = 7.1 Hz, 3H).

Example 64

Ethyl 2-(4-(2-(3-acrylamidophenoxy)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1*H*-pyrazol-1-yl)-2-methylpropanoate



Step 1) ethyl 2-methyl-2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanoate

[00713] A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 g, 7.2 mmol), ethyl 2-bromo-2-methylpropanoate (1.7 mL, 11 mmol) and Cs₂CO₃ (4.5 g, 14 mmol) in DMF (15 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 9/1 to give a colorless oily product (1.4 g, 60%).

MS (ESI, pos.ion) *m/z*: 323.3[M+1]⁺.

Step 2) ethyl 2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate

[00714] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.51 g, 1.0 mmol), ethyl 2-methyl-2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanoate (0.5 g, 2 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120°C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/3 to give a yellow solid product (0.2 g, 30%).

MS (ESI, pos.ion) *m/z*: 604.8[M+1]⁺.

Step 3) ethyl 2-(4-(2-(3-acrylamidophenoxy)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate

[00715] To a solution of ethyl 2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-7-yl)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanoate

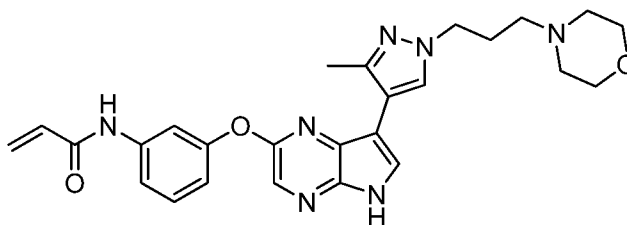
(0.08 g, 0.13 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.01 g, 20%).

MS (ESI, pos.ion) m/z : 475.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.11 (s, 1H), 10.24 (s, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.90 (d, J = 2.7 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 6.96 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 6.40 (dd, J_1 = 17.0 Hz, J_2 = 10.1 Hz, 1H), 6.23 (dd, J_1 = 17.0 Hz, J_2 = 1.8 Hz, 1H), 5.74 (m, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.60 (s, 6H), 1.08 (t, J = 7.1 Hz, 3H).

Example 65

***N*-(3-((7-(3-Methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-(3-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propyl)morpholine

[00716] A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.5 g, 7.2 mmol), 4-(3-chloropropyl)morpholine (1.7 mL, 2.7 mmol), potassium iodide (0.5 g, 2.7 mmol) and Cs₂CO₃ (4.5 g, 14 mmol) in DMF (30 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oily product (0.9 g, 50%).

MS (ESI, pos.ion) m/z : 336.0[M+1]⁺.

Step 2) *N*-(3-((7-(3-methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)

ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00717] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.3 g, 0.61 mmol), 4-(3-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propyl)morpholine (0.33 g, 0.99 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.20 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 25/1 to give a yellow solid product (0.11 g, 29%).

MS (ESI, pos.ion) *m/z*: 618.4[M+1]⁺.

Step 3) *N*-(3-((7-(3-methyl-1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

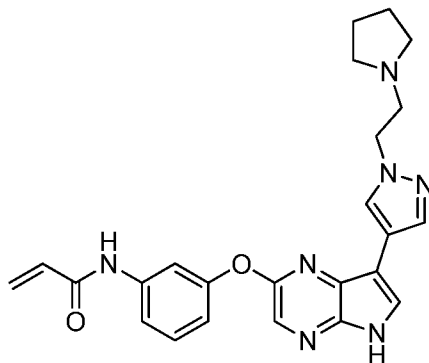
[00718] To a solution of *N*-(3-((7-(3-methyl-1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.11 g, 0.18 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.02 g, 23%).

MS (ESI, pos.ion) *m/z*: 487.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.14 (s, 1H), 10.25 (s, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.90 (d, *J* = 2.7 Hz, 1H), 7.64 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.90 (dd, *J*₁ = 7.9 Hz, *J*₂ = 1.8 Hz, 1H), 6.41 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.76 (dd, *J*₁ = 9.5 Hz, *J*₂ = 2.3 Hz, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.53 (m, 4H), 2.27 (m, 9H), 1.83 (m, 2H).

Example 66

***N*-(3-((7-(1-(2-(Pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)p**

henyl)acrylamide**Step 1) 1-(2-(pyrrolidin-1-yl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole**

[00719] A mixture of 1-(2-chloroethyl)pyrrolidine hydrochloride (1.48 g, 8.70 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.7 g, 8.8 mmol) and potassium carbonate (3.7 g, 27.00 mmol) in DMF (15 mL) was stirred at 80 °C for 6 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/EtOAc (v/v) = 20/1 to give a light yellow liquid product (1.27 g, 50.10%).

MS (ESI, pos.ion) *m/z*: 292.10[M+1]⁺.

Step 2) N-(3-((7-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00720] A mixture of 1-(2-(pyrrolidin-1-yl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (182 mg, 0.63 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (201 mg, 0.41 mmol), potassium carbonate (170 mg, 1.23 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (33 mg, 0.04 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 100 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a puce liquid product (121 mg, 51.34%).

MS (ESI, pos.ion) *m/z*: 574.35[M+1]⁺.

Step 3) N-(3-((7-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin

-2-yl)oxy)phenyl)acrylamide

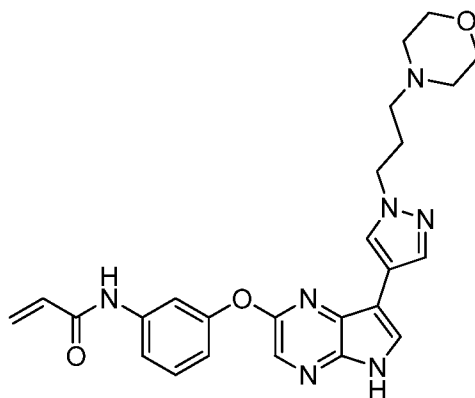
[00721] To a solution of *N*-(3-((7-(1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (124 mg, 0.22 mmol) in DCM (5.0 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (10 mg, 10.43%).

MS (ESI, pos.ion) *m/z*: 444.30[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.25 (s, 1H), 8.15 (s, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 6.93 (dd, *J*₁ = 8.1 Hz, *J*₂ = 1.6 Hz, 1H), 6.41 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.9 Hz, 1H), 5.75 (dd, *J*₁ = 10.1 Hz, *J*₂ = 1.8 Hz, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 2.79-2.74 (m, 2H), 2.41 (m, 4H), 1.61 (m, 4H).

Example 67

***N*-(3-((7-(1-(3-Morpholinopropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

**Step 1) 4-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propyl)morpholine**

[00722] A mixture of 4-(3-chloropropyl)morpholine (1.01 g, 6.17 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.19 g, 6.13 mmol) and potassium carbonate (1.7 g, 12.00 mmol) in DMF (15 mL) was stirred at 80 °C for 6 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with DCM (50 mL

× 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a light yellow liquid product (789 mg, 39.8%).

MS (ESI, pos.ion) *m/z*: 322.10[M+1]⁺.

Step 2) *N*-(3-((7-(1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00723] A mixture of 4-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propyl)morpholine (220 mg, 0.68 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (304 mg, 0.62 mmol), potassium carbonate (255 mg, 1.85 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (45 mg, 0.06 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 100 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a puce liquid product (89 mg, 23.73%).

MS (ESI, pos.ion) *m/z*: 603.9[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00724] To a solution of *N*-(3-((7-(1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (112 mg, 0.19 mmol) in DCM (6 mL) was added trifluoroacetic acid (6 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concetracted *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (13 mg, 14.80%).

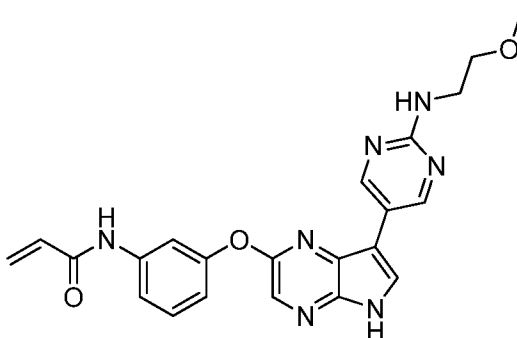
MS (ESI, pos.ion) *m/z*: 474.30[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.25 (s, 1H), 8.14 (s, 1H), 8.10 (d,

$J = 1.7$ Hz, 1H), 8.05 (s, 1H), 7.83 (s, 1H), 7.64 (t, $J = 1.9$ Hz, 1H), 7.46 (d, $J = 8.2$ Hz, 1H), 7.38 (t, $J = 8.1$ Hz, 1H), 6.92 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.6$ Hz, 1H), 6.43-6.38 (m, 1H), 6.24 (dd, $J_1 = 17.0$ Hz, $J_2 = 1.8$ Hz, 1H), 5.76 (dd, $J_1 = 10.1$ Hz, $J_2 = 1.8$ Hz, 1H), 4.09 (t, $J = 6.9$ Hz, 2H), 3.53 (m, 4H), 2.28 (m, 4H), 2.19 (t, $J = 6.9$ Hz, 2H), 1.90-1.85 (m, 2H).

Example 68

N-(3-((7-(2-((2-Methoxyethyl)amino)pyrimidin-5-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 5-bromo-*N*-(2-methoxyethyl)pyrimidin-2-amine

[00725] To a solution of 5-bromo-2-chloropyrimidine (4 g, 20.68 mmol) in acetonitrile (40 mL) was added 2-methoxyethanamine (5.5 mL, 63 mmol) and potassium carbonate (14 g, 100 mmol). The mixture was heated at 100 °C and stirred for 6 h. The reaction mixture was concentrated to remove solvent. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 9/1 to give a colorless oily product (4.43 g, 92.3%).

MS (ESI, pos.ion) m/z : 233.2[M+1]⁺.

Step 2) *N*-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine

[00726] A mixture of 5-bromo-*N*-(2-methoxyethyl)pyrimidin-2-amine (2.55 g, 11.0 mmol), bis(pinacolato)diboron (5 g, 19.69 mmol), potassium acetate (3.2 g, 33 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.8 g, 1 mmol) in 1,4-dioxane (40 mL) was stirred at 90 °C under N_2 overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/3 to give a yellow oily product (9.0 g, 82%).

MS (ESI, pos.ion) m/z : 280.1[M+1]⁺.

Step 3) *N*-(3-((7-(2-((2-methoxyethyl)amino)pyrimidin-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00727] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.40 g, 0.82 mmol) in 1,4-dioxane (8 mL) were added *N*-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (0.8 g, 3 mmol), Pd(dppf)Cl₂ (0.1 g, 0.1 mmol) and potassium carbonate (0.2 g, 1 mmol) followed by addition of water (2 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with saturated aqueous NaCl (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 40/1 to give a yellow solid product (0.31 g, 68%).

MS (ESI, positive) *m/z*: 562.3[M+1]⁺.

Step 4) *N*-(3-((7-(2-((2-methoxyethyl)amino)pyrimidin-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

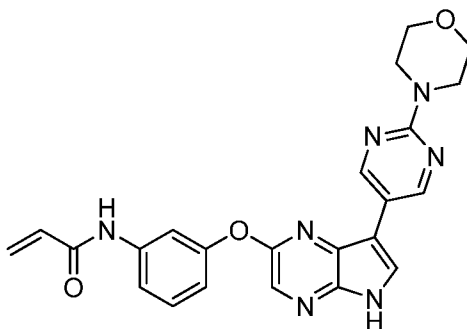
[00728] To a solution of *N*-(3-((7-(2-((2-methoxyethyl)amino)pyrimidin-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.31 g, 0.55 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a brown solid product (0.05 g, 21%).

MS (ESI, positive) *m/z*: 432.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.34 (d, *J* = 2.2 Hz, 1H), 10.24 (s, 1H), 8.84 (s, 2H), 8.31 (d, *J* = 2.9 Hz, 1H), 8.19 (s, 1H), 7.58 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.08 (s, 1H), 6.92 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.8 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.5 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.6 Hz, 1H), 3.48-3.41 (m, 4H), 3.25 (s, 3H).

Example 69

***N*-(3-((7-(2-Morpholinopyrimidin-5-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-(5-bromopyrimidin-2-yl)morpholine

[00729] To a solution of 5-bromo-2-chloropyrimidine (3 g, 15.50 mmol) in acetonitrile (40 mL) was added morpholine (4.1 mL, 47 mmol) and potassium carbonate (11 g, 78.80 mmol). The mixture was heated at 85 °C and stirred for 10 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (40 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give a white solid product (3.6 g, 95%).

MS (ESI, pos.ion) *m/z*: 245.9[M+1]⁺.

Step 2) 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)morpholine

[00730] A mixture of 4-(5-bromopyrimidin-2-yl)morpholine (2.01 g, 8.23 mmol), bis(pinacolato)diboron (3.8 g, 15 mmol), potassium acetate (2.5 g, 25 mmol) and Pd(dppf)Cl₂ (0.61 g, 0.83 mmol) in 1,4-dioxane (30 mL) was stirred at 90 °C under N₂ overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 7/3 to give a white solid product (0.4 g, 88%).

MS (ESI, pos.ion) *m/z*: 292.0[M+1]⁺.

Step 3) *N*-(3-((7-(2-morpholinopyrimidin-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00731] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.41 g, 0.84 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)morpholine (0.5 g, 2 mmol), Pd(dppf)Cl₂ (0.1 g, 0.1 mmol) and potassium carbonate (0.20 g, 1.4 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 90 °C overnight. The reaction mixture was

cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.24 g, 51%).

MS (ESI, pos.ion) *m/z*: 574.8[M+1]⁺.

Step 4) *N*-(3-((7-(2-morpholinopyrimidin-5-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

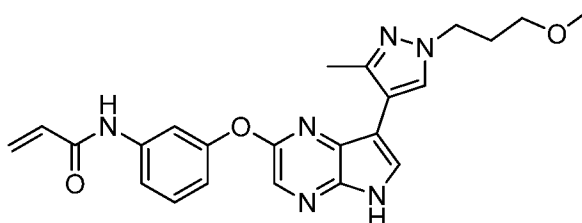
[00732] To a solution of *N*-(3-((7-(2-morpholinopyrimidin-5-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.34 g, 0.59 mmol) in DCM (15 mL) was added trifluoroacetic acid (3 mL, 64.6 mmol). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a brown solid product (0.1 g, 40%).

MS (ESI, pos.ion) *m/z*: 444.3[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.39 (s, 1H), 10.23 (s, 1H), 8.94 (d, *J* = 6.3 Hz, 2H), 8.35 (s, 1H), 8.20 (s, 1H), 7.60 (s, 1H), 7.42 (dd, *J*₁ = 27.3 Hz, *J*₂ = 8.1 Hz, 2H), 6.92 (d, *J* = 6.3 Hz, 1H), 6.40 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.1 Hz, 1H), 6.23 (dd, *J*₁ = 16.9 Hz, *J*₂ = 1.5 Hz, 1H), 5.81-5.69 (m, 1H), 3.76-3.56 (m, 8H).

Example 70

***N*-(3-((7-(1-(3-Methoxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(3-methoxypropyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00733] To a solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

(1.5 g, 7.2 mmol) in DMF (30 mL) were added 1-bromo-3-methoxypropane (4.5 g, 29 mmol), potassium iodide (1.2 g, 7.2 mmol) and Cs₂CO₃ (12 g, 36.8 mmol). The mixture was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a colorless oily product (1.2 g, 30%).

MS (ESI, pos.ion) *m/z*: 281.3[M+1]⁺.

Step 2) *N*-(3-((7-(1-(3-methoxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00734] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.5 g, 1.0 mmol), 1-(3-methoxypropyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.5 g, 2 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.35 g, 61%).

MS (ESI, pos.ion) *m/z*: 563.8[M+1]⁺.

Step 3) *N*-(3-((7-(1-(3-methoxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

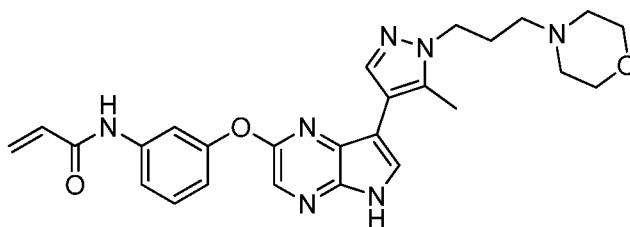
[00735] To a solution of *N*-(3-((7-(1-(3-methoxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.34 g, 0.61 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.1 g, 40%).

MS (ESI, pos.ion) m/z : 433.9[M+1]⁺; and

¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.13 (s, 1H), 10.24 (s, 1H), 8.16 (s, 1H), 7.92 (s, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.65 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 6.90 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 6.41 (dd, J_1 = 16.9 Hz, J_2 = 10.1 Hz, 1H), 6.24 (dd, J_1 = 16.9 Hz, J_2 = 1.7 Hz, 1H), 5.75 (dd, J_1 = 10.1 Hz, J_2 = 1.7 Hz, 1H), 3.99 (t, J = 6.9 Hz, 2H), 3.23 (t, J = 6.1 Hz, 2H), 3.17 (s, 3H), 2.28 (s, 3H), 1.95-1.85 (m, 2H).

Example 71

***N*-(3-((7-(5-Methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 4-(3-(5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propyl)morpholine

[00736] A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.5 g, 7.2 mmol), 4-(3-chloropropyl)morpholine (1.8 mL, 11 mmol), potassium iodide (0.5 g, 2.7 mmol) and Cs₂CO₃ (4.5 g, 14 mmol) in DMF (30 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated *in vacuo* to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by pre-HPLC to give a light yellow oil product (0.9 g, 50%).

MS (ESI, pos.ion) m/z : 336.0[M+1]⁺.

Step 2) *N*-(3-((7-(5-methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00737] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.3 g, 0.61 mmol), 4-(3-(5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propyl)morpholine (0.33 g, 0.99 mmol), Pd(dppf)Cl₂ (0.05 g, 0.07 mmol) and potassium carbonate (0.20 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column

chromatography eluted with DCM/MeOH (v/v) = 25/1 to give a yellow solid product (0.11 g, 29%).

MS (ESI, pos.ion) m/z : 618.4[M+1]⁺.

Step 3) *N*-(3-((7-(5-methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

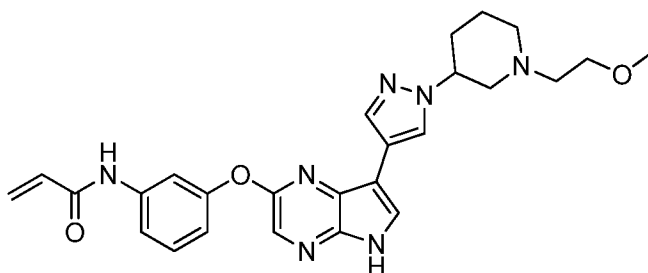
[00738] To a solution of *N*-(3-((7-(5-methyl-1-(3-morpholinopropyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.11 g, 0.18 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.02 g, 23%).

MS (ESI, pos.ion) m/z : 487.9[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.17 (d, J = 2.1 Hz, 1H), 10.22 (s, 1H), 8.17 (s, 1H), 7.90 (d, J = 2.8 Hz, 1H), 7.64 (s, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 8.1 Hz, 1H), 6.89 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 6.40 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 1H), 6.23 (dd, J_1 = 17.0 Hz, J_2 = 1.8 Hz, 1H), 5.75 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 4.05 (t, J = 6.8 Hz, 2H), 3.55 (m, 4H), 2.27 (m, 9H), 1.86 (m, 2H).

Example 72

***N*-(3-((7-(1-(1-(2-Methoxyethyl)piperidin-3-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *tert*-butyl 3-((methylsulfonyl)oxy)piperidine-1-carboxylate

[00739] *tert*-Butyl 3-hydroxypiperidine-1-carboxylate (1.01 g, 4.97 mmol), methylsulfonyl chloride (0.77 mL, 9.94 mmol) and triethylamine (1.4 mL, 9.94 mmol) were mixed in DCM (15 mL) at 0 °C. The mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted

with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/1 to give a yellow liquid product (1.3 g, 93%).

MS (ESI, pos.ion) *m/z*: 224.0[M-*t*-Bu+2]⁺.

Step 2) *tert*-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[00740] A mixture of *tert*-butyl 3-((methylsulfonyl)oxy)piperidine-1-carboxylate (1.30 g, 4.66 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (901 mg, 4.64 mmol) and cesium carbonate (3.76 g, 11.5 mmol) in DMF (15 mL) was stirred at 100 °C for 12 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 10/1 to give a colorless oily product (630 mg, 35.83%).

MS (ESI, pos.ion) *m/z*: 378.3[M+1]⁺.

Step 3) 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine

[00741] A mixture of *tert*-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (296 mg, 0.78 mmol) and a solution of HCl in EtOAc (4 M, 1.98 mL) in DCM was stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo* to give a colorless oily product (181 mg, 83.23%), which was used directly in the next step.

MS (ESI, pos.ion) *m/z*: 278.10[M+1]⁺.

Step 4) 1-(2-methoxyethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine

[00742] A mixture of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine (206 mg, 0.74 mmol), 1-bromo-2-methoxyethane (155 mg, 1.12 mmol) and potassium carbonate (250 mg, 1.81 mmol) in DMF (15 mL) was stirred at 90 °C for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow oily product (86 mg, 34.52%).

MS (ESI, pos.ion) m/z : 336.30[M+1]⁺.

Step 5) *N*-(3-((7-(1-(1-(2-methoxyethyl)piperidin-3-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00743] A mixture of 1-(2-methoxyethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine (61 mg, 0.18 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (95 mg, 0.19 mmol), potassium carbonate (65 mg, 0.47 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (15 mg, 0.018 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred under a microwave condition at 120 °C under N₂ for 1.5 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a black oily product (36 mg, 32.02%).

MS (ESI, pos.ion) m/z : 617.8[M+1]⁺.

Step 6) *N*-(3-((7-(1-(1-(2-methoxyethyl)piperidin-3-yl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00744] To a solution of *N*-(3-((7-(1-(1-(2-methoxyethyl)piperidin-3-yl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (35 mg, 0.057 mmol) in DCM (6 mL) was added trifluoroacetic acid (2.5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (6 mg, 21.72%).

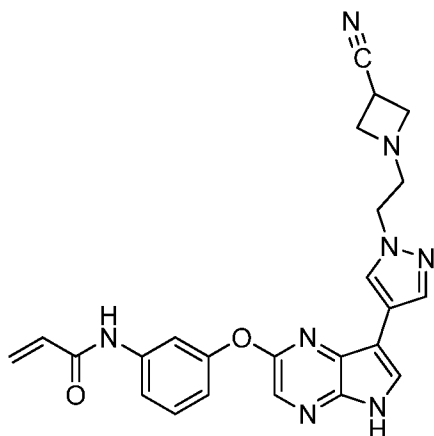
MS (ESI, pos.ion) m/z : 488.35[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.07 (s, 1H), 10.27 (s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.43-7.38 (m, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.75 (dd, *J*₁ = 10.1 Hz, *J*₂ = 1.6 Hz, 1H), 5.36-5.31 (m, 1H), 4.19 (s, 2H), 4.04 (s, 1H), 3.22 (s, 3H), 3.06 (s, 1H), 2.80 (s, 1H), 2.19 (s, 2H), 2.02-1.93 (m, 2H), 1.71 (s, 1H), 1.58 (s, 2H), 1.47 (d, *J* = 7.0 Hz,

1H).

Example 73

***N*-(3-((7-(1-(2-(3-Cyanoazetidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-bromoethyl)azetidine-3-carbonitrile

[00745] A mixture of azetidine-3-carbonitrile hydrochloride (1.51 g, 12.7 mmol), 1,2-dibromoethane (9 mL, 8.20 mmol) and cesium carbonate (8 g, 104 mmol) in acetonitrile (15 mL) was stirred at rt for 18 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 40/1 to give a light yellow liquid product (1.16 g, 48.2%).

MS (ESI, pos.ion) *m/z*: 189.05[M+1]⁺.

Step 2) 1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethyl)azetidine-3-carbonitrile

[00746] A mixture of 1-(2-bromoethyl)azetidine-3-carbonitrile (804 mg, 4.25 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (825 mg, 4.25 mmol) and cesium carbonate (2.8 g, 8.6 mmol) in DMF (15 mL) was stirred at 100 °C for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a light yellow liquid product (78 mg, 6.07%).

MS (ESI, pos.ion) *m/z*: 303.05[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(3-cyanoazetidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)

ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00747] A mixture of 1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethyl)azetidine-3-carbonitrile (97 mg, 0.32 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (160 mg, 0.33 mmol), potassium carbonate (137 mg, 0.99 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (30 mg, 0.037 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred under a microwave condition at 120 °C under N₂ for 1 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a puce oily product (62 mg, 33.04%).

MS (ESI, pos.ion) *m/z*: 584.80[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-(3-cyanoazetidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

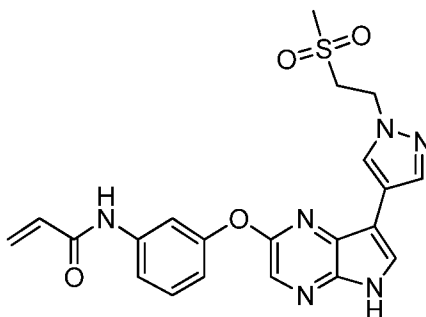
[00748] To a solution of *N*-(3-((7-(1-(2-(3-cyanoazetidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (60 mg, 0.10 mmol) in DCM (5 mL) was added trifluoroacetic acid (2.1 mL). The mixture was stirred at rt for 10 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (10 mg, 21.44%).

MS (ESI, pos.ion) *m/z*: 455.30[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.11 (s, 1H), 10.31 (s, 1H), 8.14 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 6.9 Hz, 1H), 6.43 (dd, *J*₁ = 16.3 Hz, *J*₂ = 9.9 Hz, 1H), 6.25 (d, *J* = 16.6 Hz, 1H), 5.76 (m, 2H), 5.31 (m, 1H), 4.04 (m, 6H), 3.16 (m, 1H).

Example 74

***N*-(3-((7-(1-(2-(Methylsulfonyl)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-(methylsulfonyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00749] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.01 g, 10.4 mmol), methyl vinyl sulfone (1.4 mL, 16 mmol) and DBU (0.8 mL, 5 mmol) in dry acetonitrile (15 mL) was stirred at 90 °C for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a yellow liquid product (2.1 g, 68%).

MS (ESI, pos.ion) *m/z*: 301.2[M+1]⁺.

Step 2) N-(3-((7-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00750] A mixture of 1-(2-(methylsulfonyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (140 mg, 0.47 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (101 mg, 0.21 mmol), potassium carbonate (70 mg, 0.51 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (20 mg, 0.025 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred under a microwave condition at 120 °C under N₂ for 1.5 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a black oily product (65 mg, 54.04%).

MS (ESI, pos.ion) *m/z*: 583.3[M+1]⁺.

Step 3) N-(3-((7-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00751] To a solution of *N*-(3-((7-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-4-yl)-5-

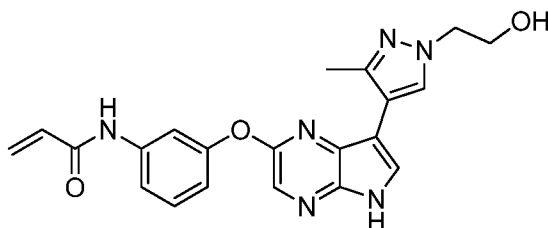
((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (210 mg, 0.36 mmol) in DCM (6 mL) was added trifluoroacetic acid (1.97 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (12 mg, 7.36%).

MS (ESI, pos.ion) *m/z*: 452.80[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.17 (s, 1H), 10.28 (s, 1H), 8.18 (s, 1H), 8.14 (s, 2H), 7.93 (s, 1H), 7.60 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.42 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (d, *J* = 16.9 Hz, 1H), 5.75 (d, *J* = 10.3 Hz, 1H), 4.53 (t, *J* = 6.7 Hz, 2H), 3.68 (t, *J* = 6.6 Hz, 2H), 2.85 (s, 3H).

Example 75

N-(3-((7-(1-(2-Hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide



Step 1) 2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanol

[00752] A mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2 g, 9.7 mmol), 2-bromoethanol (2.5 mL, 28.8 mmol), KI (0.8 g, 4.8 mmol) and Cs₂CO₃ (7.9 g, 24 mmol) in DMF (30 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 9/1 to give a white solid product (1.5 g, 62%).

MS (ESI, pos.ion) *m/z*: 253.1[M+1]⁺.

Step 2) *N*-(3-((7-(1-(2-hydroxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00753] To a mixture of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.51 g, 1.0 mmol), 2-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanol (0.5 g, 2 mmol), Pd(dppf)Cl₂ (0.1 g, 0.1 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added 1,4-dioxane (20 mL) and water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.1 g, 20%).

MS (ESI, pos.ion) *m/z*: 535.3[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-hydroxypropyl)-3-methyl-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

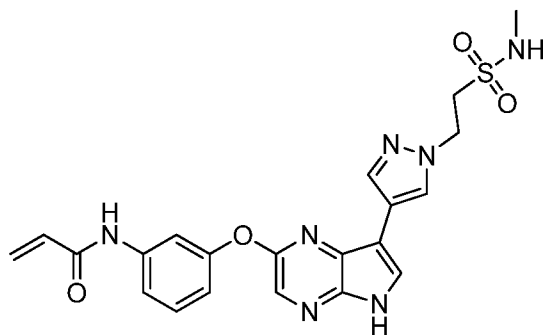
[00754] To a solution of *N*-(3-((7-(1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.11 g, 0.20 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.02 g, 20%).

MS (ESI, pos.ion) *m/z*: 404.2[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.15 (d, *J* = 1.9 Hz, 1H), 10.23 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.89 (d, *J* = 2.8 Hz, 1H), 7.60 (s, 1H), 7.50-7.33 (m, 2H), 6.90 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.6 Hz, 1H), 6.40 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.7 Hz, 1H), 4.82 (t, *J* = 5.3 Hz, 1H), 4.01 (t, 2H), 3.72-3.64 (m, 2H), 2.27 (s, 3H).

Example 76

***N*-(3-((7-(1-(2-(*N*-Methylsulfamoyl)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *N*-methylethanesulfonamide

[00755] To a mixture of methanamine hydrochloride (2.12 g, 31.40 mmol) and 2-chloroethanesulfonyl chloride (1.21 g, 7.42 mmol) in DCM (15 mL) was added a solution of K_2CO_3 (4.54 g, 32.90 mmol) in water (5 mL) at 0 °C dropwise slowly. The mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a yellow liquid product (240 mg, 26.72%).

MS (ESI, pos.ion) m/z : 122.25[M+1]⁺.

Step 2) *N*-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanesulfonamide

[00756] A mixture of *N*-methylethanesulfonamide (243 mg, 2.01 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (380 mg, 1.99 mmol) and cesium carbonate (155 mg, 1.02 mmol) in dry DMF (15 mL) was stirred at 90 °C for 8 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a light yellow oily product (126 mg, 19.93%).

MS (ESI, pos.ion) m/z : 316.00[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(*N*-methylsulfamoyl)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00757] A mixture of *N*-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanesulfonamide (58 mg, 0.18 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (100 mg, 0.20 mmol),

potassium carbonate (80 mg, 0.58 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (16 mg, 0.02 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 110 °C under N₂ for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a black oily product (46 mg, 41.82%).

MS (ESI, pos.ion) *m/z*: 598.40[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-(*N*-methylsulfamoyl)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

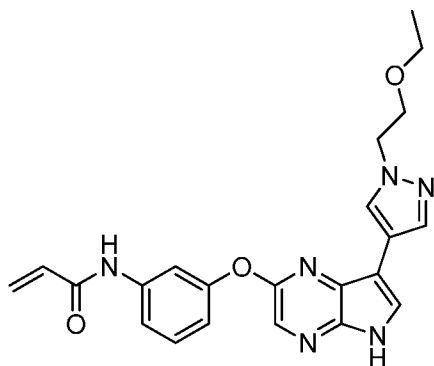
[00758] To a solution of *N*-(3-((7-(1-(2-(*N*-methylsulfamoyl)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (44 mg, 0.074 mmol) in DCM (6 mL) was added trifluoroacetic acid (2.1 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (8 mg, 23.25%).

MS (ESI, pos.ion) *m/z*: 468.85[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.02 (s, 1H), 10.32 (s, 1H), 8.32 (s, 1H), 8.19 (s, 2H), 8.08 (s, 1H), 7.85 (s, 1H), 7.45-7.30 (m, 3H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.65 (s, 1H), 5.60 (s, 1H), 5.33 (s, 1H), 4.30-4.25 (m, 2H), 3.64-3.58 (m, 2H), 2.85 (s, 3H).

Example 77

***N*-(3-((7-(1-(2-Ethoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00759] A mixture of 1-bromo-2-ethoxyethane (1.51 g, 9.87 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.11 g, 10.90 mmol) and cesium carbonate (4.8 g, 15 mmol) in DMF (15 mL) was stirred at 90 °C for 6 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a light yellow liquid product (1.6 g, 61%).

MS (ESI, pos.ion) *m/z*: 267.30[M+1]⁺.

Step 2) N-(3-((7-(1-(2-ethoxyethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00760] A mixture of 1-(2-ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (220 mg, 0.83 mmol), N-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (411 mg, 0.84 mmol), potassium carbonate (312 mg, 2.26 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (70 mg, 0.08 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred under a microwave condition at 120 °C under N₂ for 1.5 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a puce liquid product (156 mg, 33.85%).

MS (ESI, pos.ion) *m/z*: 548.80[M+1]⁺.

Step 3) N-(3-((7-(1-(2-ethoxyethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

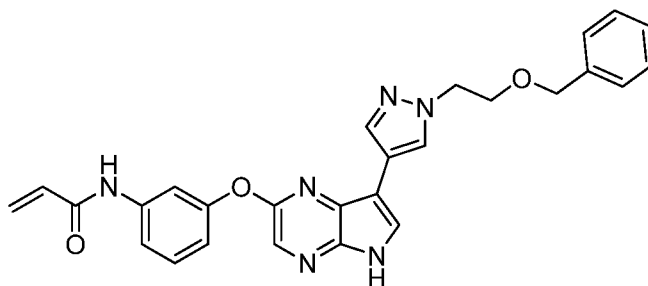
[00761] To a solution of *N*-(3-((7-(1-(2-ethoxyethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (66 mg, 0.12 mmol) in DCM (6 mL) was added trifluoroacetic acid (2.3 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 20/1 to give a yellow solid product (6 mg, 11.92%).

MS (ESI, pos.ion) *m/z*: 418.90[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.10 (s, 1H), 10.23 (s, 1H), 8.16-8.08 (m, 2H), 8.05 (s, 1H), 7.84 (s, 1H), 7.61 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 6.4 Hz, 1H), 6.41 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 5.75 (d, *J* = 11.5 Hz, 1H), 4.21 (t, *J* = 5.3 Hz, 2H), 3.68 (t, *J* = 5.3 Hz, 2H), 3.10 (dd, *J*₁ = 7.2 Hz, *J*₂ = 4.6 Hz, 2H), 1.36 (s, 3H).

Example 78

***N*-(3-((7-(1-(2-Benzoyloxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-(benzyloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00762] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.01 g, 5.2 mmol), ((2-bromoethoxy)methyl)benzene (3.4 g, 16 mmol), KI (0.65 mL, 3.87 mmol) and Cs₂CO₃ (4.2 g, 13 mmol) in DMF (30 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/2 to give a light yellow oily product (1.1 g,

43%).

MS (ESI, pos.ion) m/z : 329.3[M+1]⁺.

Step 2) *N*-(3-((7-(1-(2-(benzyloxy)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00763] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.40 g, 0.82 mmol) in 1,4-dioxane (20 mL) were added 1-(2-(benzyloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.0 g, 1.83 mmol), Pd(dppf)Cl₂ (0.1 g, 0.1 mmol) and potassium carbonate (0.2 g, 1 mmol) followed by addition of water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a yellow oil product (0.25 g, 50%).

MS (ESI, pos.ion) m/z : 611.8[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(benzyloxy)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

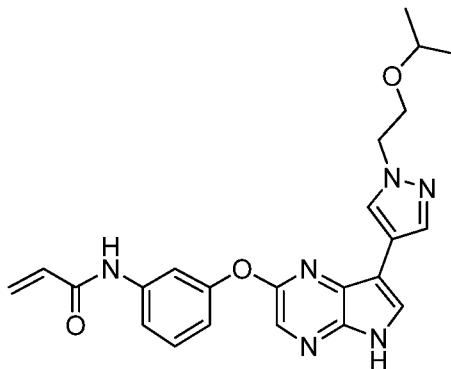
[00764] To a solution of *N*-(3-((7-(1-(2-(benzyloxy)ethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.24 g, 0.39 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 9/1 to give a yellow solid product (0.1 g, 50%).

MS (ESI, pos.ion) m/z : 481.1[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.16 (s, 1H), 10.47 (s, 1H), 8.14 (s, 1H), 8.12 (s, 2H), 7.86 (s, 1H), 7.67 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.30-7.25 (m, 2H), 7.25-7.17 (m, 3H), 6.95-6.86 (m, 1H), 6.48 (dd, *J*₁ = 16.9 Hz, *J*₂ = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.1 Hz, 1H), 5.76-5.68 (m, 1H), 4.42 (s, 2H), 4.28 (t, *J* = 5.2 Hz, 2H), 3.75 (t, *J* = 5.3 Hz, 2H).

Example 79

***N*-(3-((7-(1-(2-Isopropoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**

**Step 1) 2-isopropoxyethyl methanesulfonate**

[00765] 2-Isopropoxyethanol (3.01 g, 28.92 mmol), triethylamine (10 mL, 72.10 mmol) and methylsulfonyl chloride (5.6 mL, 72 mmol) were mixed in DCM (15 mL) at 0 °C. The mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 2/1 to give a yellow liquid product (4.2 g, 80%).

MS (ESI, pos.ion) *m/z*: no response.

Step 2) 1-(2-isopropoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

[00766] A mixture of 2-isopropoxyethyl methanesulfonate (1.51 g, 8.30 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.61 g, 8.32 mmol) and cesium carbonate (5.42 g, 16.63 mmol) in DMF (15 mL) was stirred at 100 °C for 12 h. The reaction mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 1/1 to give a colorless oily product (1.16 g, 49.9%).

MS (ESI, pos.ion) *m/z*: 281.10[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-isopropoxyethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00767] A mixture of 1-(2-isopropoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (150 mg, 0.54 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (101 mg, 0.21 mmol), potassium carbonate (85 mg, 0.62 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (18 mg, 0.02 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred under a microwave condition at 120 °C under N₂ for 1.5 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a black oily product (65 mg, 55.97%).

MS (ESI, pos.ion) *m/z*: 562.90[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-isopropoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

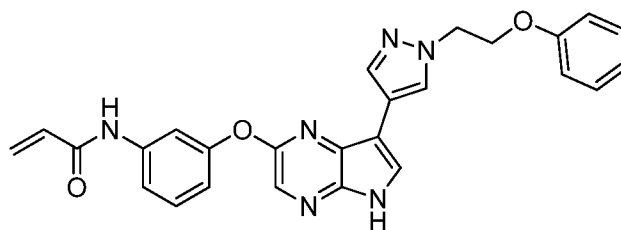
[00768] To a solution of *N*-(3-((7-(1-(2-isopropoxyethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (96 mg, 0.17 mmol) in DCM (6 mL) was added trifluoroacetic acid (2.1 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (5 mL). To the solution was added saturated aqueous sodium bicarbonate solution (10 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 10/1 to give a yellow solid product (23 mg, 31.17%).

MS (ESI, pos.ion) *m/z*: 433.30[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (s, 1H), 10.28 (s, 1H), 8.14 (s, 1H), 8.11 (d, *J* = 2.6 Hz, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.61 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.90 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.6 Hz, 1H), 6.42 (dd, *J*₁ = 17.0 Hz, *J*₂ = 10.2 Hz, 1H), 6.24 (dd, *J*₁ = 16.9 Hz, *J*₂ = 1.4 Hz, 1H), 5.75 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.3 Hz, 1H), 4.18 (t, *J* = 5.4 Hz, 2H), 3.67 (t, *J* = 5.4 Hz, 2H), 3.44 (m, 1H), 0.98 (d, *J* = 6.1 Hz, 6H).

Example 80

***N*-(3-((7-(1-(2-Phenoxyethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 1-(2-phenoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[00769] A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 g, 7.7 mmol), (2-bromoethoxy)benzene (3.2 g, 16 mmol), KI (0.65 g, 3.85 mmol) and Cs₂CO₃ (9 g, 27.6 mmol) in DMF (30 mL) was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 3/2 to give a yellow oily product (1.24 g, 51%).

MS (ESI, pos.ion) *m/z*: 315.3[M+1]⁺.

Step 2) N-(3-((7-(1-(2-phenoxyethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00770] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.40 g, 0.82 mmol) in 1,4-dioxane (20 mL) were added 1-(2-phenoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.5 g, 1 mmol), Pd(dppf)Cl₂ (0.1 g, 0.1 mmol) and potassium carbonate (0.2 g, 1 mmol) followed by addition of water (5 mL). The system was exchanged with N₂ and stirred at 120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 4/1 to give a yellow oily product (0.3 g, 60%).

MS (ESI, pos.ion) *m/z*: 597.4[M+1]⁺.

Step 3) N-(3-((7-(1-(2-phenoxyethyl)-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00771] To a solution of *N*-(3-((7-(1-(2-phenoxyethyl)-1H-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.29 g, 0.49 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (2 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and

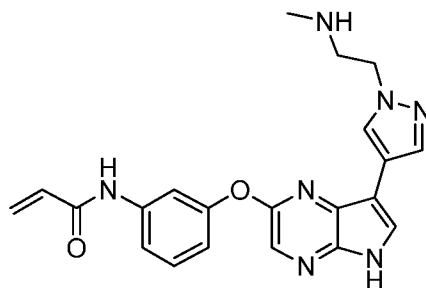
the residue was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.08 g, 33%).

MS (ESI, pos.ion) m/z : 467.1[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.12 (d, J = 2.1 Hz, 1H), 10.26 (s, 1H), 8.16 (d, J = 10.6 Hz, 2H), 8.12 (d, J = 2.8 Hz, 1H), 7.88 (s, 1H), 7.64 (s, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.24 (t, J = 8.0 Hz, 2H), 6.97-6.88 (m, 2H), 6.86 (d, J = 8.0 Hz, 2H), 6.40 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 1H), 6.24 (dd, J_1 = 17.0 Hz, J_2 = 1.7 Hz, 1H), 5.74 (dd, J_1 = 10.2 Hz, J_2 = 1.7 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 4.29 (t, J = 5.1 Hz, 2H).

Example 81

***N*-(3-((7-(1-(2-(Methylamino)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) *tert*-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethyl)carbamate

[00772] A mixture of *tert*-butyl (2-chloroethyl)(methyl)carbamate (1.62 g, 8.34 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.59 g, 8.22 mmol) and potassium carbonate (2.32 g, 16.78 mmol) in DMF (15 mL) was stirred at 80 °C for 8 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a light yellow liquid product (36 mg, 14.89%).

MS (ESI, pos.ion) m/z : 352.05[M+1]⁺.

Step 2) *tert*-butyl (2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate

[00773] A mixture of *tert*-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

1*H*-pyrazol-1-yl)ethyl)carbamate (140 mg, 0.40 mmol), *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (101 mg, 0.21 mmol), potassium carbonate (85 mg, 0.62 mmol) and Pd(dppf)Cl₂CH₂Cl₂ (20 mg, 0.02 mmol) in a mixture of dioxane and water (v/v = 4/1, 15 mL) was stirred at 110 °C under N₂ for 18 h. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 25/1 to give a black oily product (42 mg, 31.80%).

MS (ESI, pos.ion) *m/z*: 634.80[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(methylamino)ethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

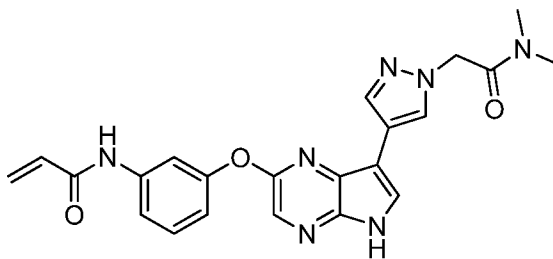
[00774] To a solution of *tert*-butyl (2-(4-(2-(3-acrylamidophenoxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-7-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (56 mg, 0.088 mmol) in DCM (5 mL) was added trifluoroacetic acid (2.9 mL). The mixture was stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (10 mL). To the solution was added saturated aqueous sodium bicarbonate solution (15 mL), the resulting mixture was stirred at rt for 8 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 8/1 to give a yellow solid product (8 mg, 22.44%).

MS (ESI, pos.ion) *m/z*: 404.3[M+1]⁺; and

¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.01 (d, *J* = 2.1 Hz, 1H), 10.13 (s, 1H), 8.58 (t, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.07-8.02 (m, 2H), 7.82 (s, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.91 (dd, *J*₁ = 8.0 Hz, *J*₂ = 1.7 Hz, 1H), 6.87 (s, 2H), 6.65 (s, 1H), 5.35-5.30 (m, 1H), 4.11-4.07 (m, 2H), 2.76-2.72 (m, 2H), 2.19 (s, 3H).

Example 82

***N*-(3-((7-(1-(2-(Methylamino)-2-oxoethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide**



Step 1) 2-chloro-*N,N*-dimethylacetamide

[00775] To a mixture of K_2CO_3 (17 g, 121.8 mmol) and DCM (150 mL) was added chloroacetyl chloride (4.7 mL, 59 mmol) in an ice bath, and then a solution of DIEA (3 mL, 59 mmol) in DCM (20 mL) was added dropwise slowly. The mixture was stirred in the ice bath for 2 h. The reaction mixture was diluted with water (20 mL). The resulting mixture was extracted with DCM (200 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow oily product (2 g, 28%).

Step 2) *N,N*-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetamine

[00776] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.00 g, 5.15 mmol) in DMF (40 mL) were added 2-chloro-*N,N*-dimethylacetamide (1 g, 8.2 mmol) and Cs_2CO_3 (4.7 g, 14 mmol) and KI (0.5 g, 3 mmol). The mixture was stirred at 70 °C overnight. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (30 mL). The resulting mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE/EtOAc (v/v) = 9/1 to give a yellow oily product (1.3 g, 90%).

MS (ESI, pos. ion) m/z : 280.3[M+1]⁺.

Step 3) *N*-(3-((7-(1-(2-(dimethylamino)2-oxoethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00777] To a solution of *N*-(3-((7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.50 g, 1.0 mmol) in 1,4-dioxane (20 mL) were added *N,N*-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetamine (0.5 g, 2 mmol), $Pd(dppf)Cl_2$ (0.1 g, 0.1 mmol) and potassium carbonate (0.21 g, 1.5 mmol) followed by addition of water (5 mL). The system was exchanged with N_2 and stirred at

120 °C overnight. The reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 40/1 to give a yellow oily product (0.04 g, 7%).

MS-ESI: (ESI, pos.ion) *m/z*: 562.1[M+1]⁺.

Step 4) *N*-(3-((7-(1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide

[00778] To a solution of *N*-(3-((7-(1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazol-4-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)oxy)phenyl)acrylamide (0.04 g, 0.07 mmol) in DCM (15 mL) was added trifluoroacetic acid (3 mL, 38.7 mmol) at 0 °C. The mixture was stirred at rt for 8 h. The reaction mixture was concentrated and diluted with THF (15 mL) and triethylamine (3 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (v/v) = 30/1 to give a yellow solid product (0.01 g, 30%).

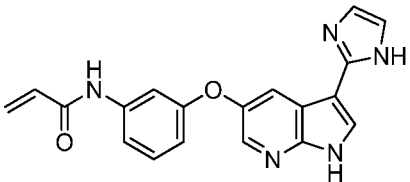
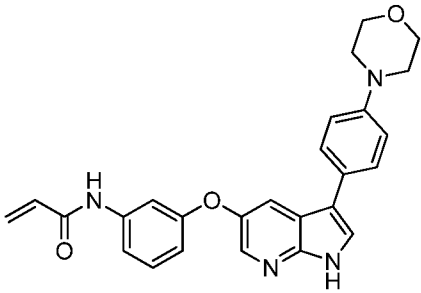
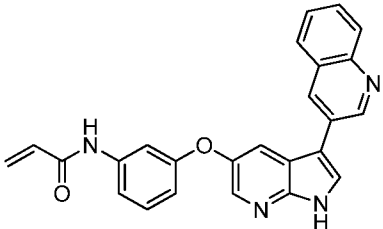
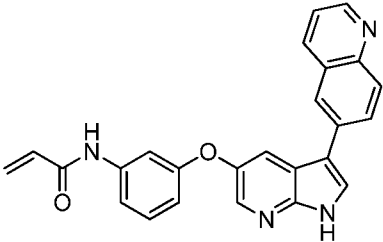
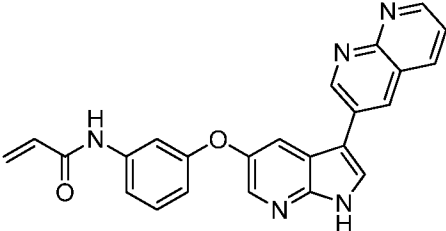
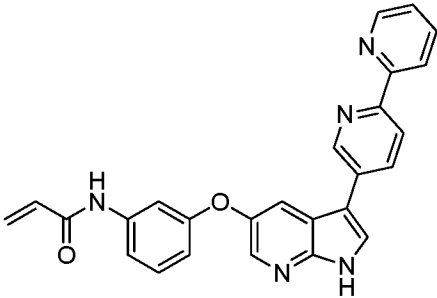
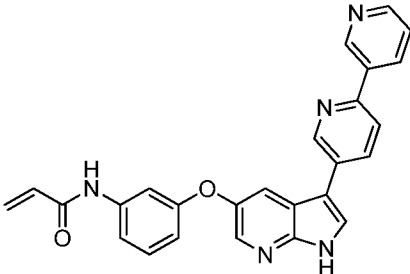
MS-ESI: (ESI, pos.ion) *m/z*: 432.3[M+1]⁺; and

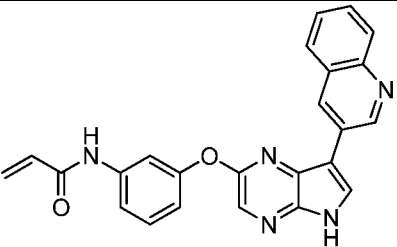
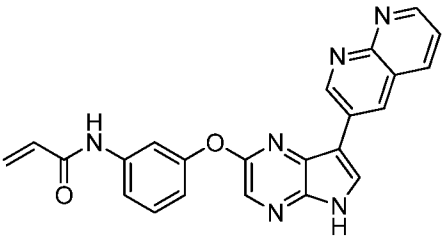
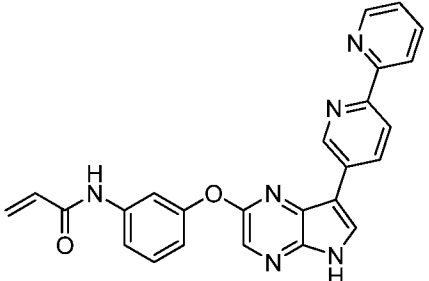
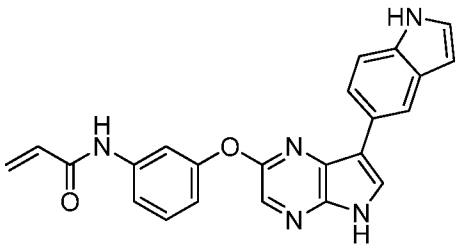
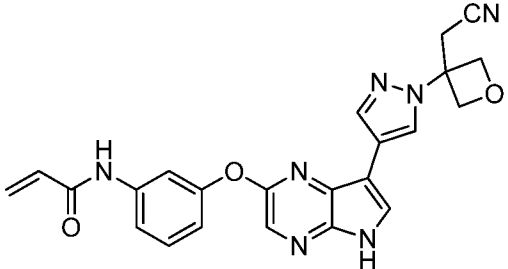
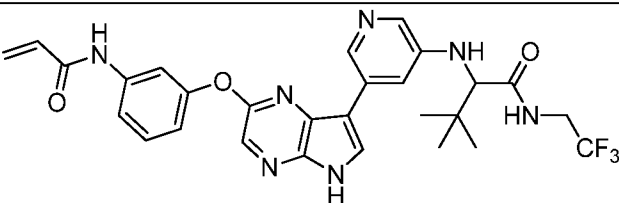
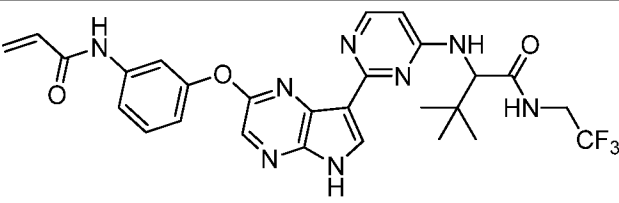
¹H NMR (600 MHz, DMSO-*d*₆): δ (ppm) 12.15 (s, 1H), 10.26 (s, 1H), 8.14 (d, *J* = 2.6 Hz, 1H), 8.15-8.12 (m, 1H), 8.03 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J*₁ = 8.1 Hz, *J*₂ = 2.1 Hz, 1H), 6.39 (d, *J* = 10.2 Hz, 1H), 6.23 (dd, *J*₁ = 17.0 Hz, *J*₂ = 1.7 Hz, 1H), 5.75 (s, 2H), 5.08 (s, 1H), 3.40 (s, 6H).

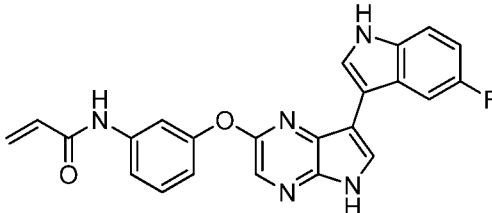
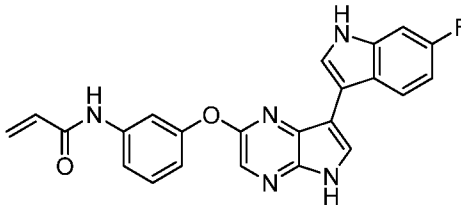
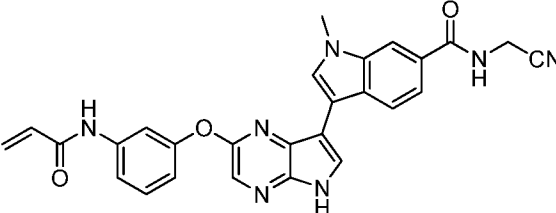
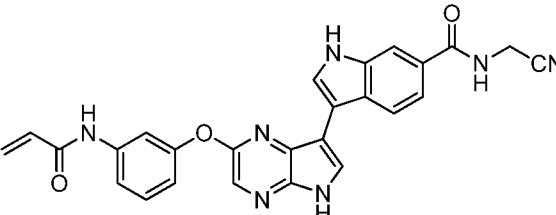
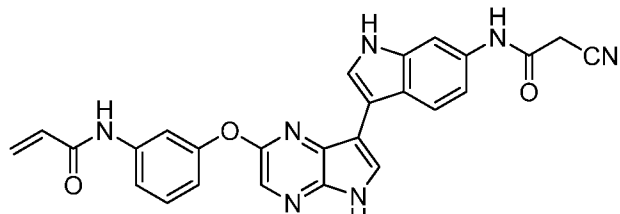
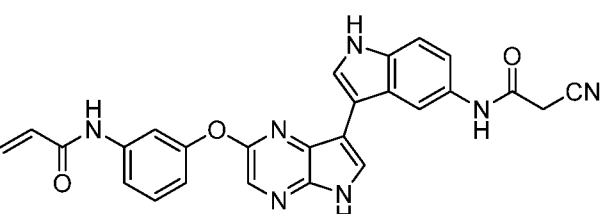
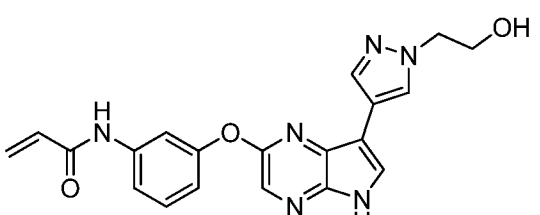
[00779] The compounds listed in table 1 were prepared by a similar method to that described in example 2:

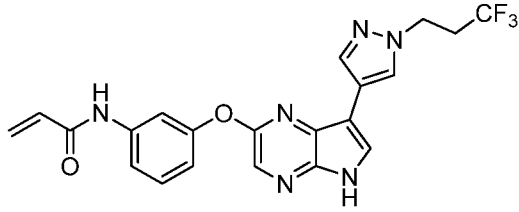
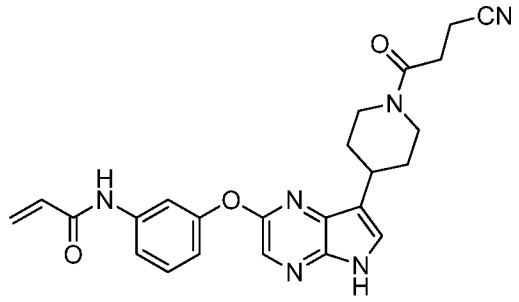
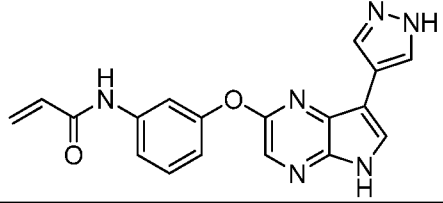
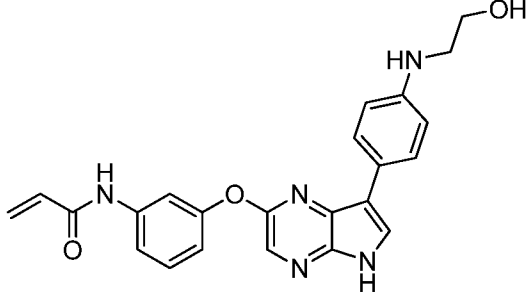
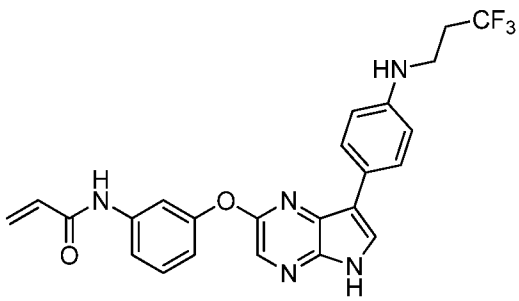
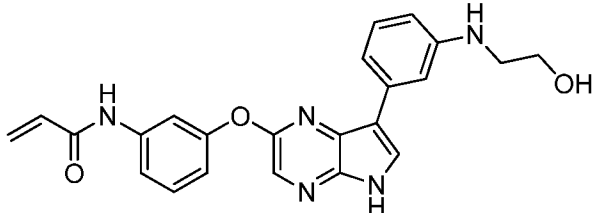
Table 1 Structures and MS data

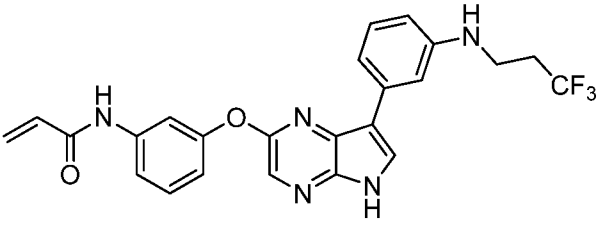
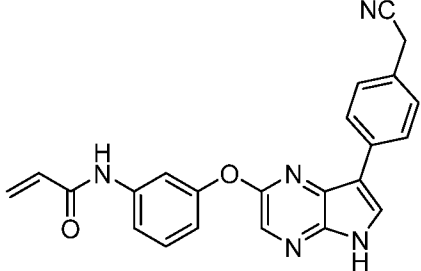
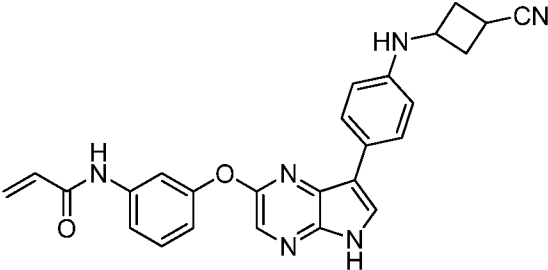
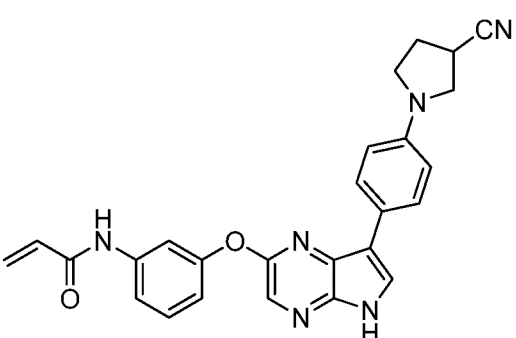
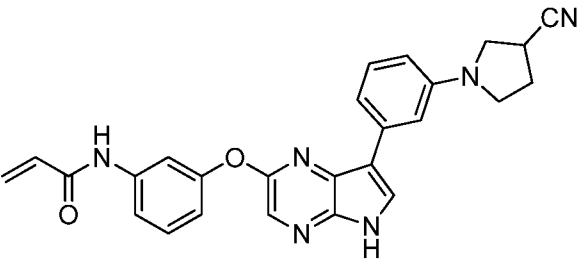
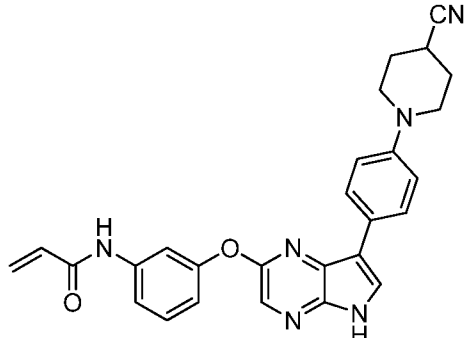
Example	Structure	MS [M+1] ⁺
Example 83		347.10

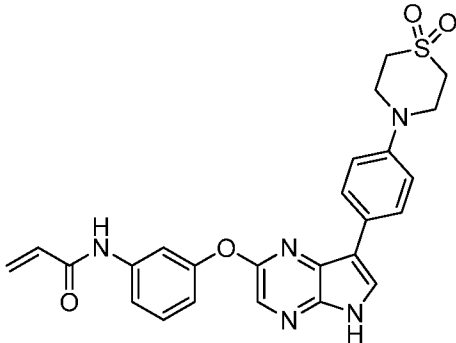
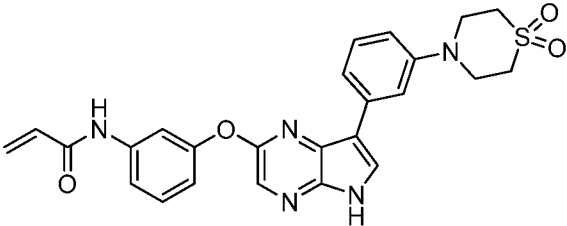
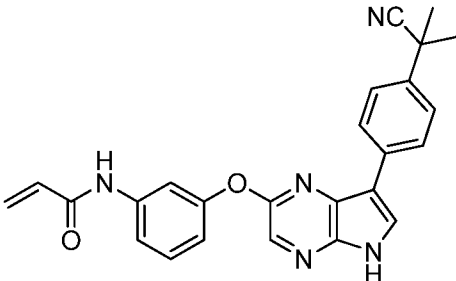
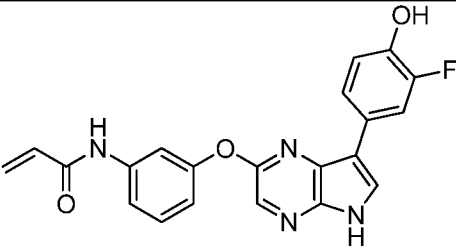
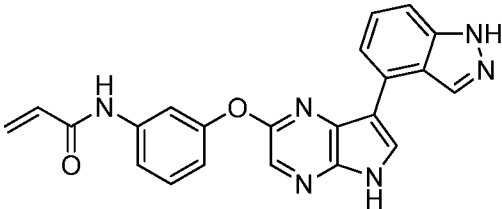
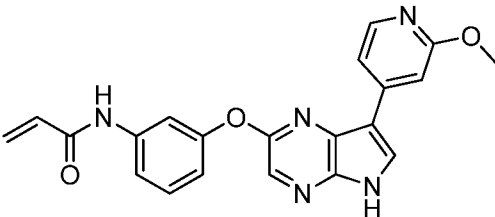
Example 84		346.10
Example 85		441.20
Example 86		407.10
Example 87		407.10
Example 88		408.10
Example 89		434.20
Example 90		434.20

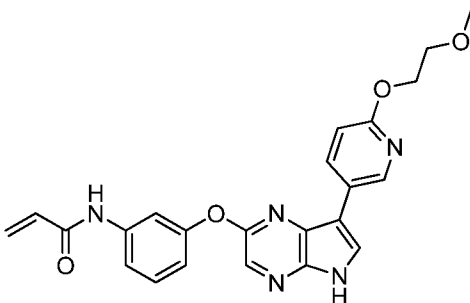
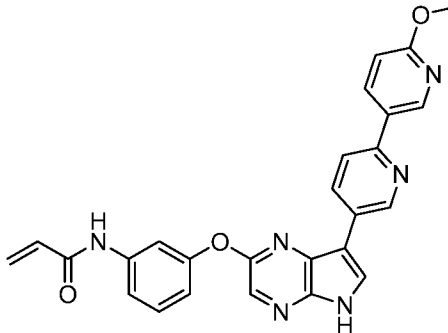
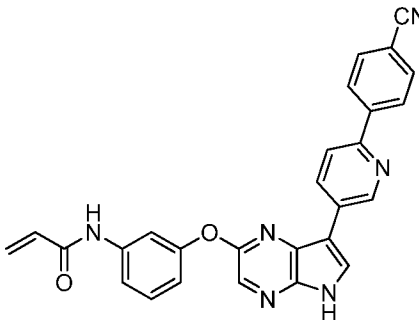
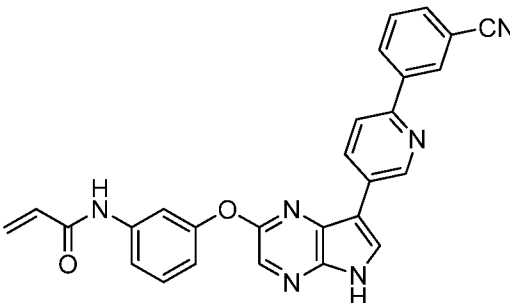
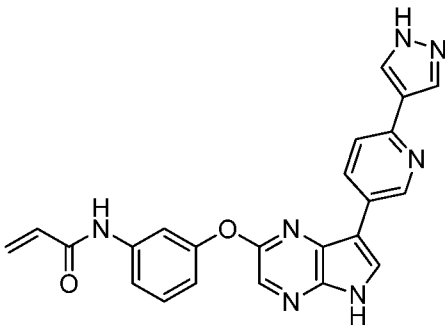
Example 91		408.10
Example 92		409.10
Example 93		435.10
Example 94		396.10
Example 95		442.20
Example 96		568.20
Example 97		569.20

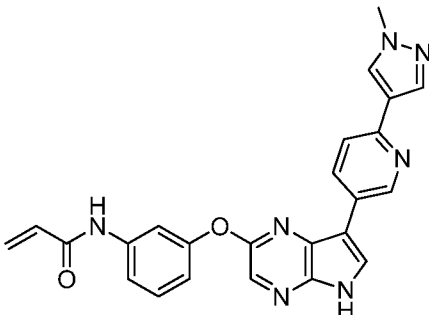
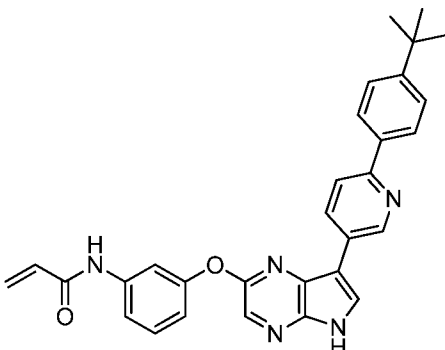
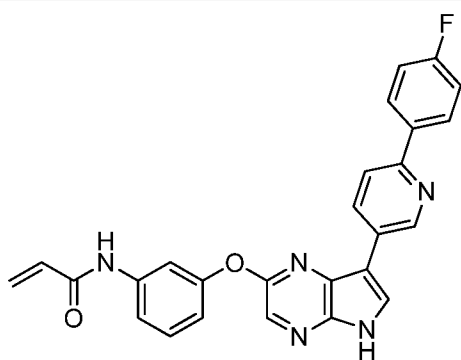
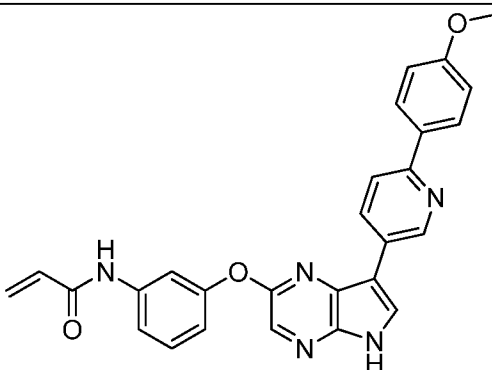
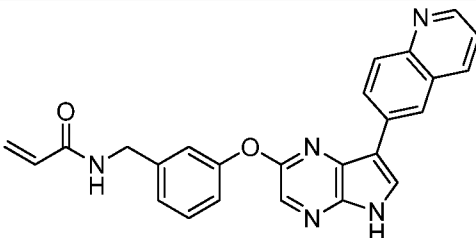
Example 98		414.10
Example 99		414.10
Example 100		492.20
Example 101		478.20
Example 102		478.20
Example 103		478.20
Example 104		391.10

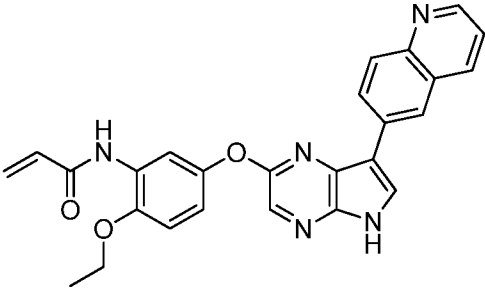
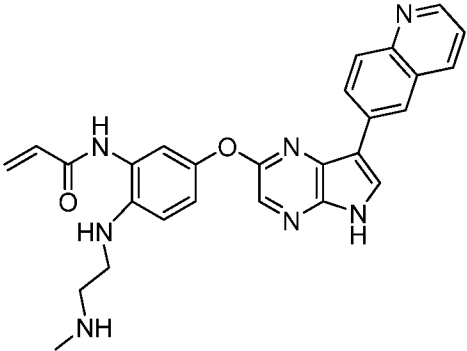
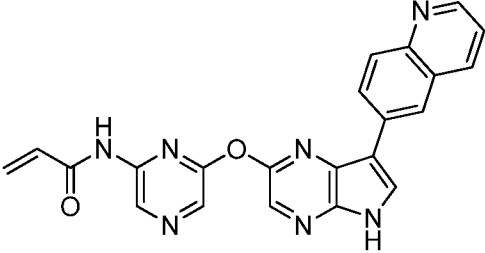
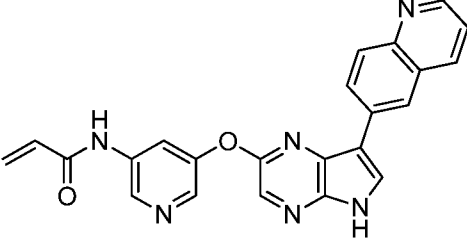
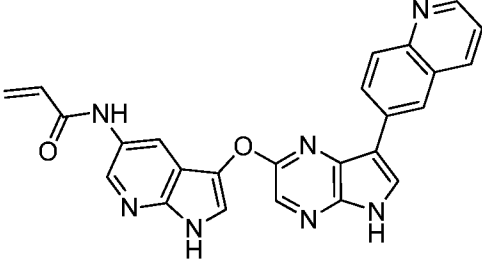
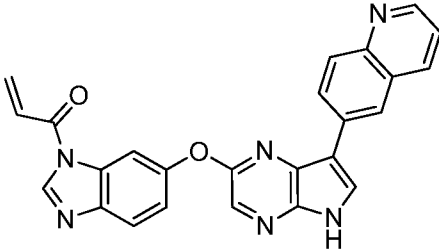
Example 105		443.10
Example 106		445.20
Example 107		347.10
Example 108		416.20
Example 109		468.20
Example 110		416.20

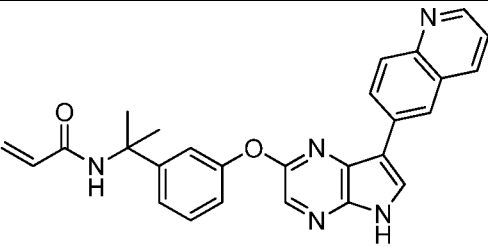
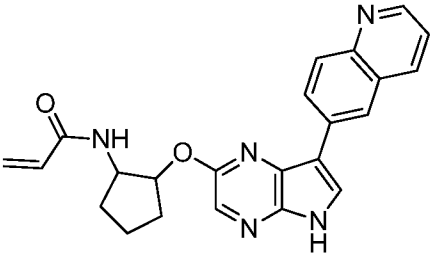
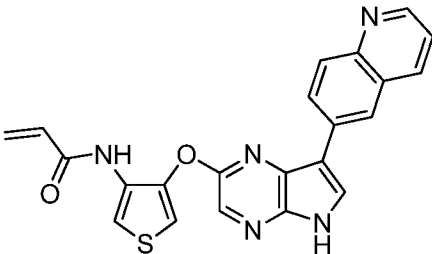
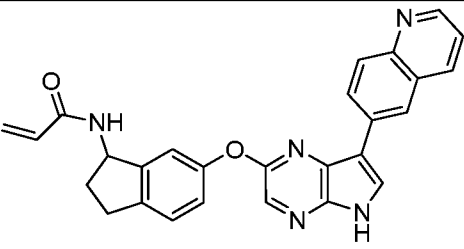
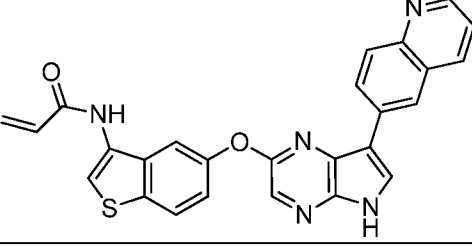
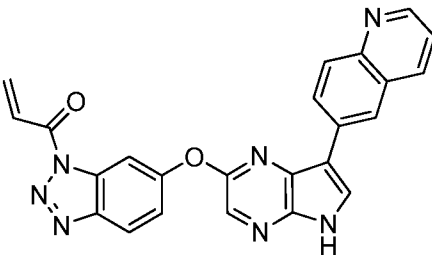
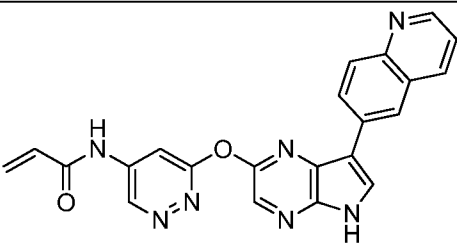
Example 111		468.20
Example 112		396.10
Example 113		451.20
Example 114		451.20
Example 115		451.20
Example 116		465.20

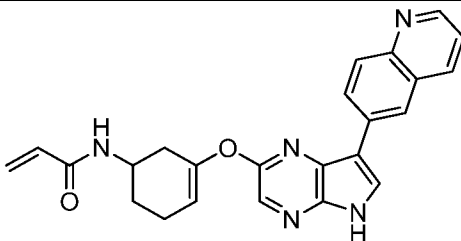
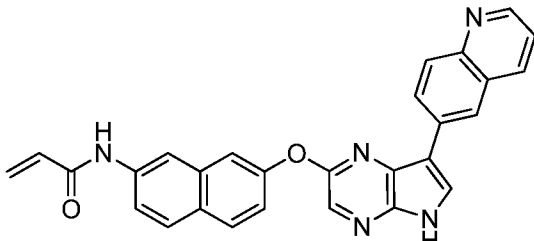
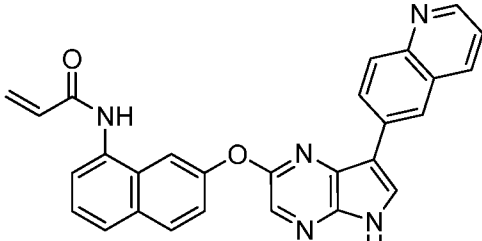
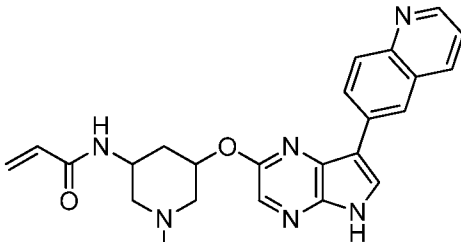
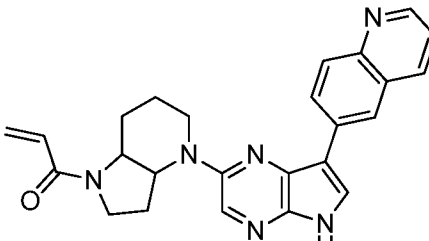
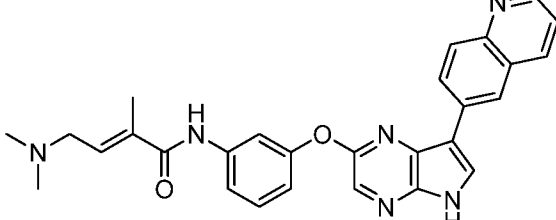
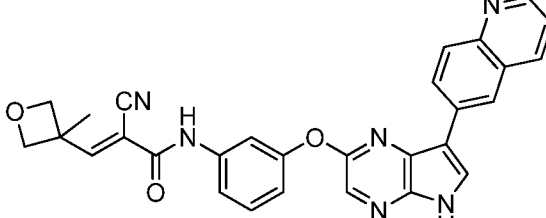
Example 117		490.20
Example 118		490.20
Example 119		424.30
Example 120		391.10
Example 121		397.10
Example 122		388.10

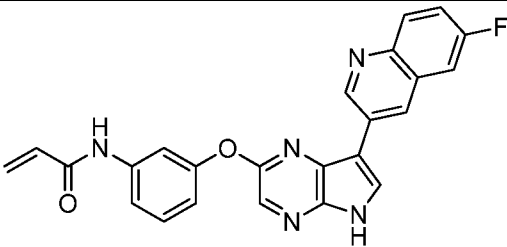
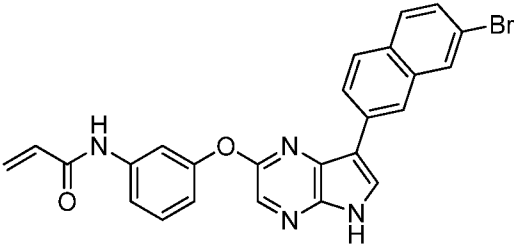
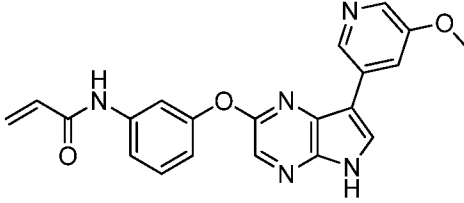
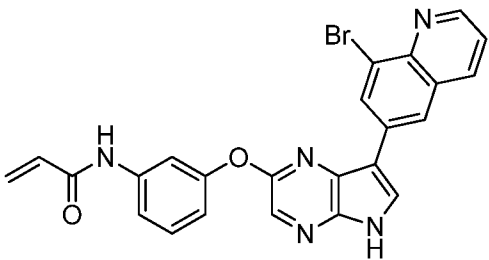
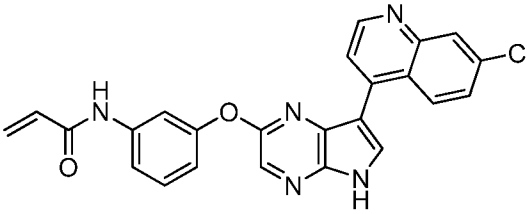
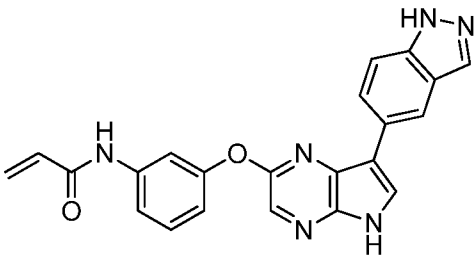
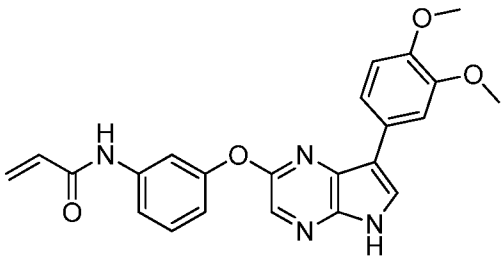
Example 123		432.20
Example 124		465.20
Example 125		459.20
Example 126		459.20
Example 127		424.10

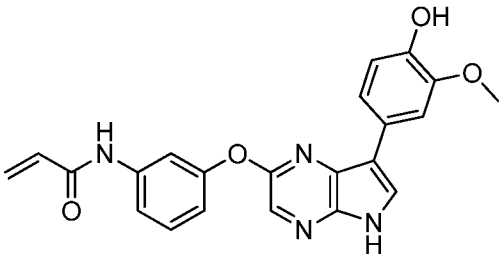
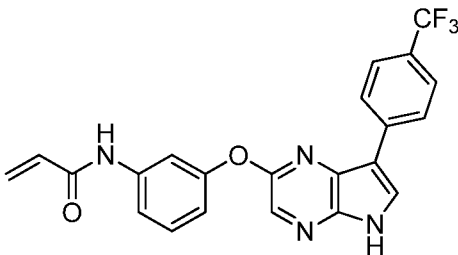
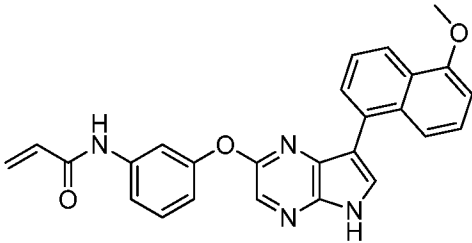
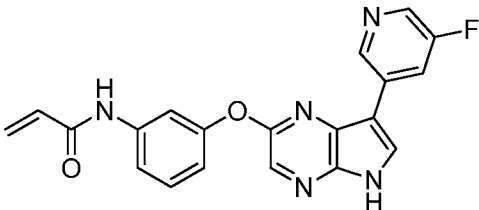
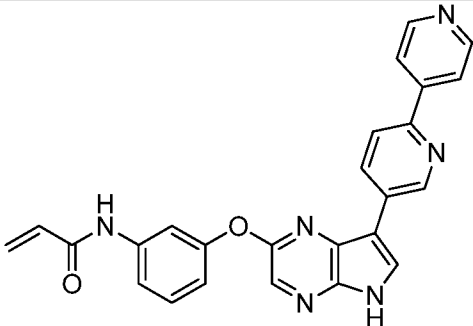
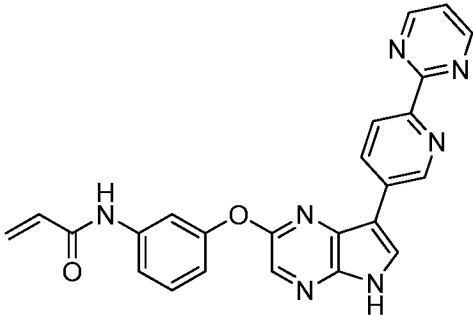
Example 128		438.20
Example 129		490.30
Example 130		452.10
Example 131		464.20
Example 132		422.10

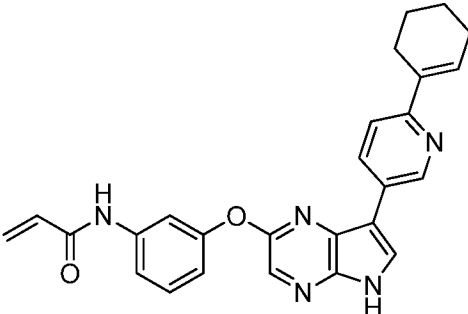
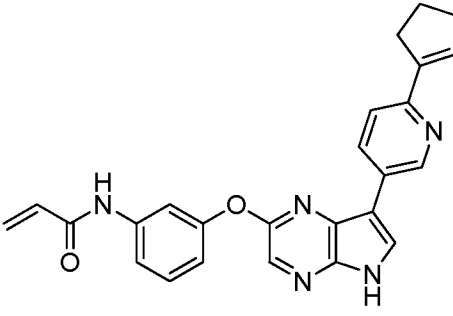
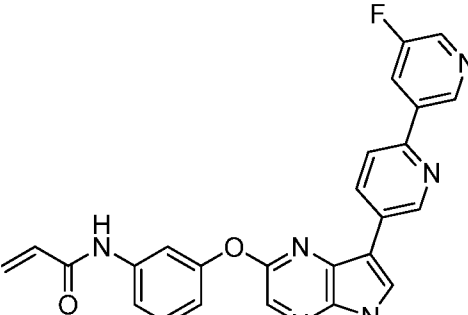
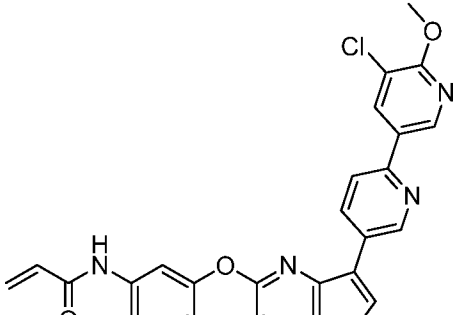
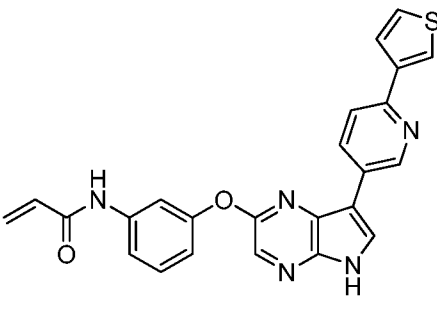
Example 133		452.20
Example 134		480.20
Example 135		410.10
Example 136		409.10
Example 137		448.10
Example 138		433.10

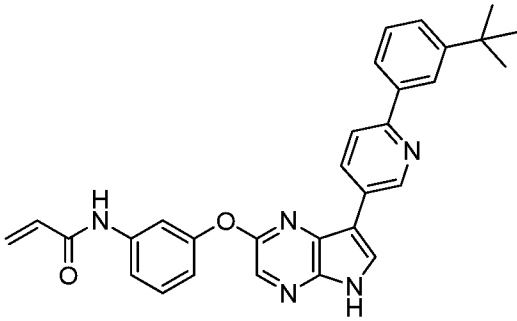
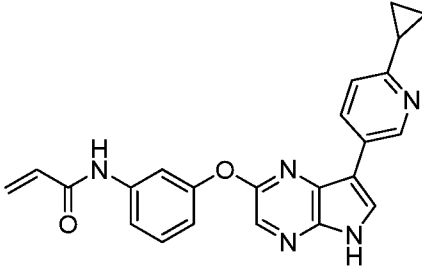
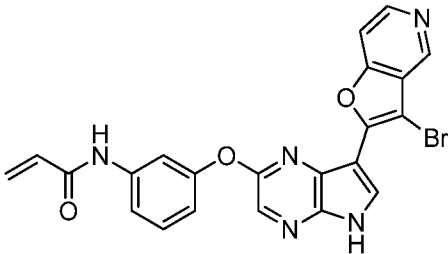
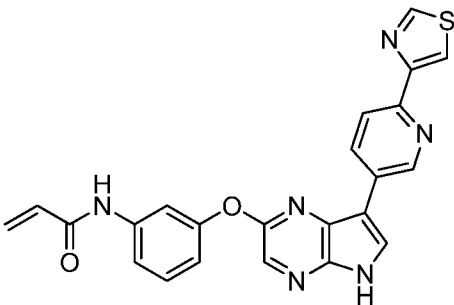
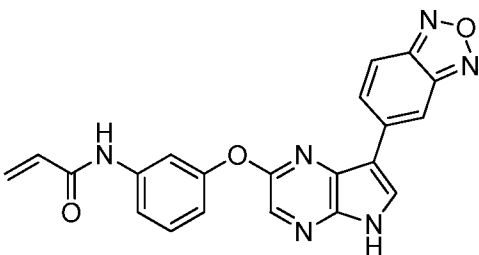
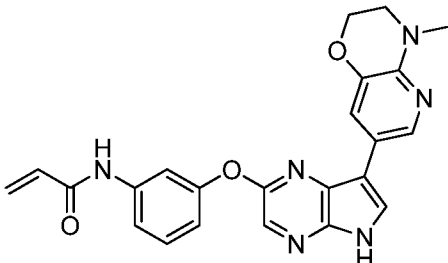
Example 139		450.20
Example 140		400.20
Example 141		414.10
Example 142		448.20
Example 143		464.10
Example 144		434.10
Example 145		410.10

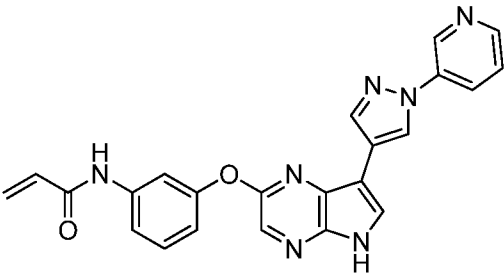
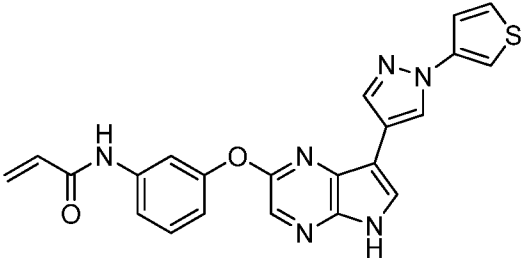
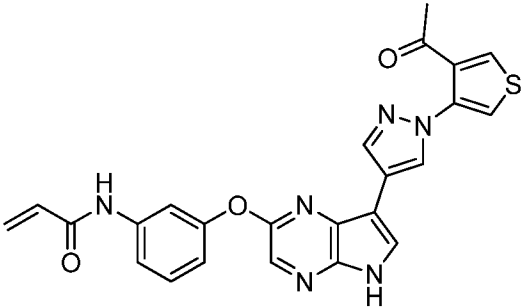
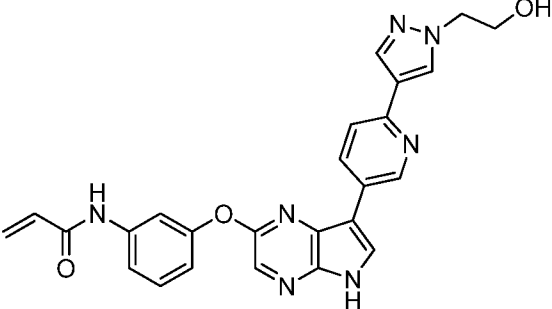
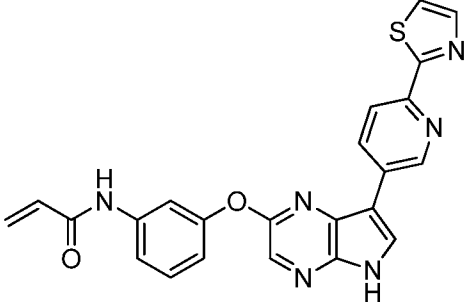
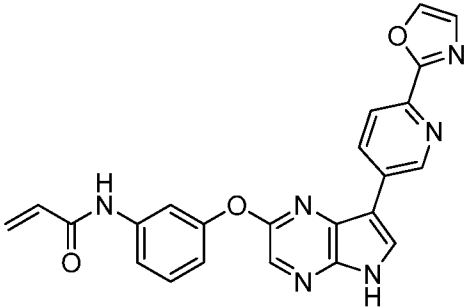
Example 146		412.20
Example 147		458.20
Example 148		458.20
Example 149		429.20
Example 150		425.20
Example 151		479.20
Example 152		503.20

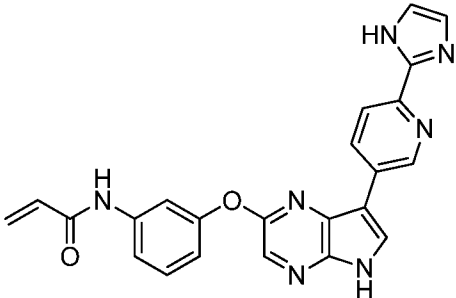
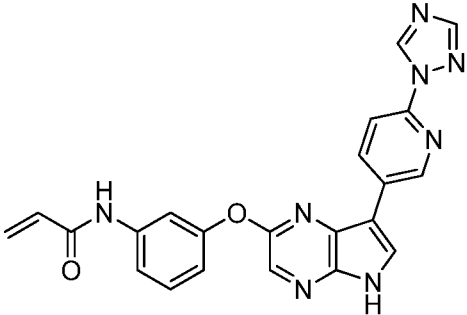
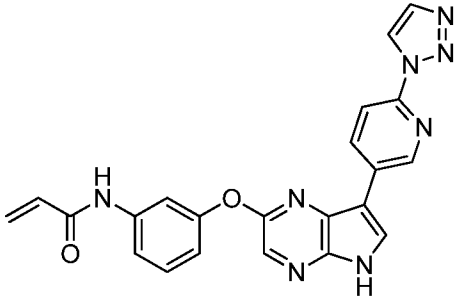
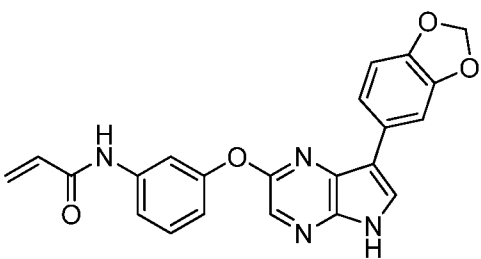
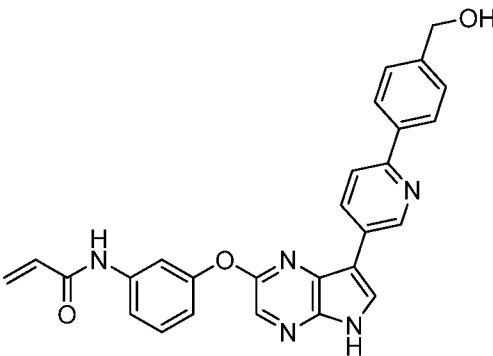
Example 153		426.10
Example 154		485.00
Example 155		388.10
Example 156		486.00
Example 157		442.10
Example 158		397.10
Example 159		417.10

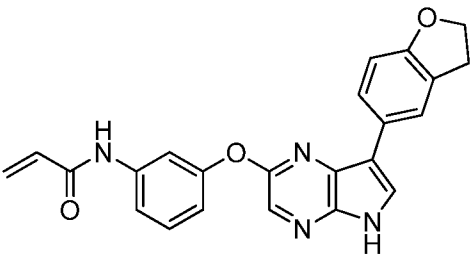
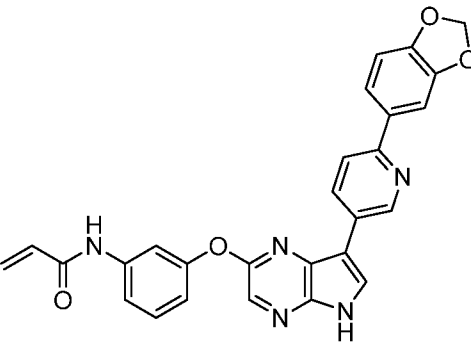
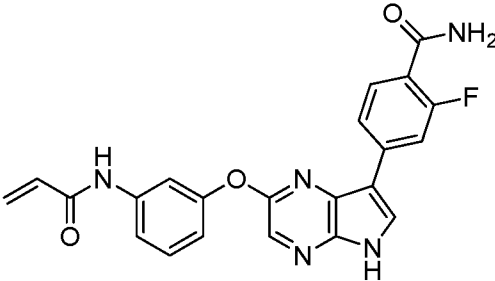
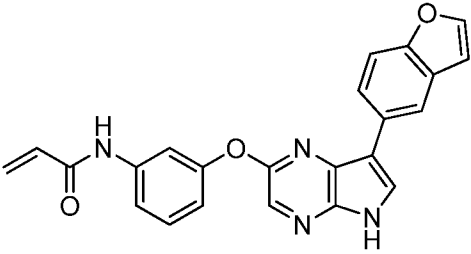
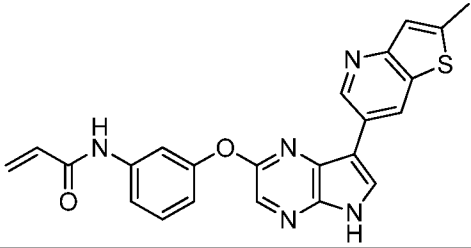
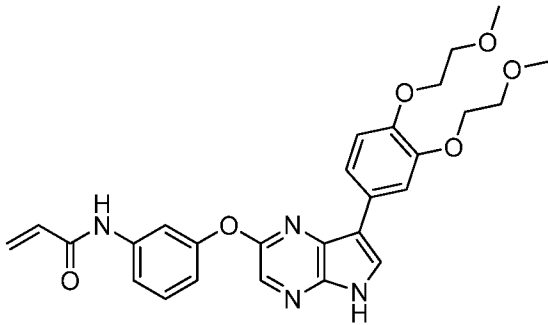
Example 160		403.10
Example 161		425.10
Example 162		437.10
Example 163		376.10
Example 164		435.10
Example 165		436.10

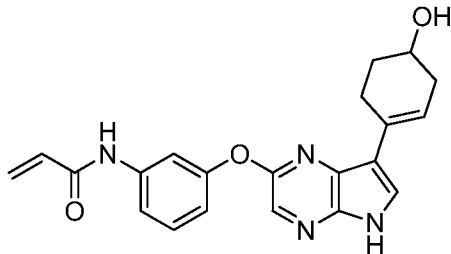
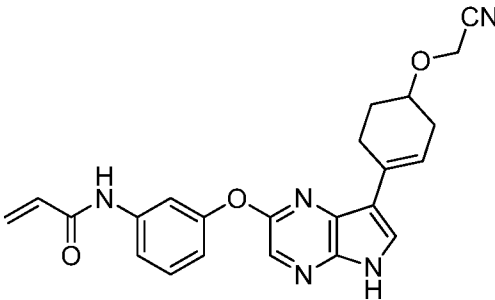
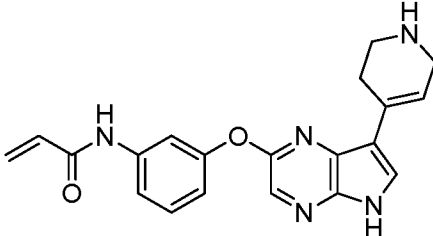
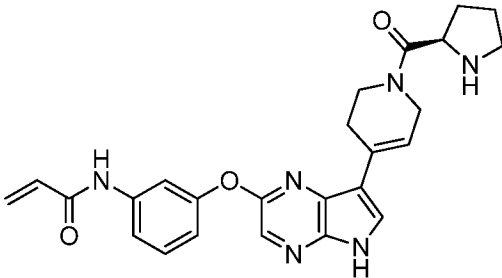
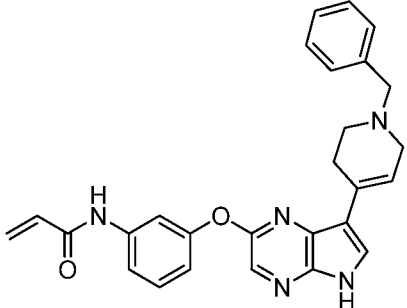
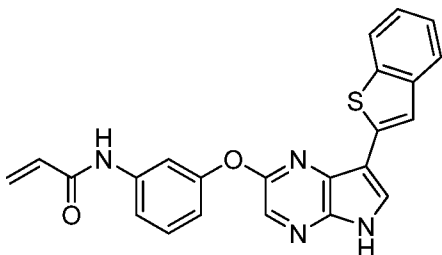
Example 166		438.20
Example 167		424.20
Example 168		453.10
Example 169		499.10
Example 170		440.10

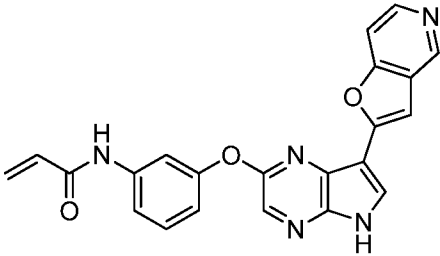
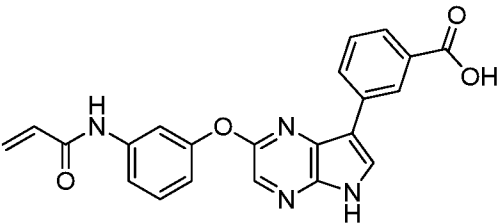
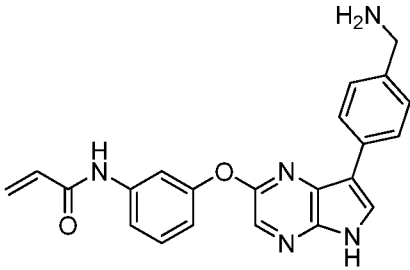
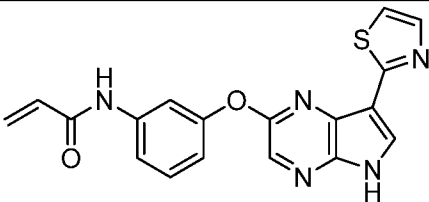
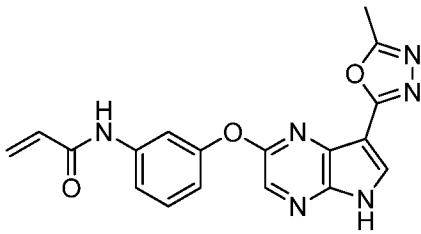
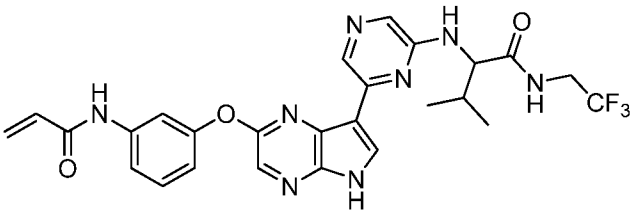
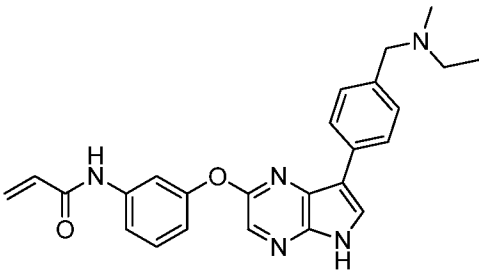
Example 171		490.20
Example 172		398.10
Example 173		476.10
Example 174		441.10
Example 175		399.10
Example 176		429.20

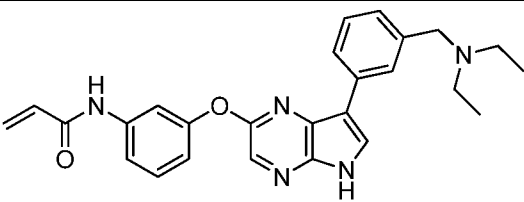
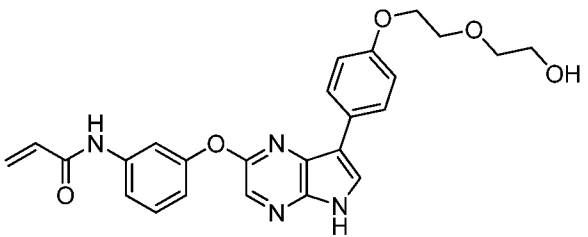
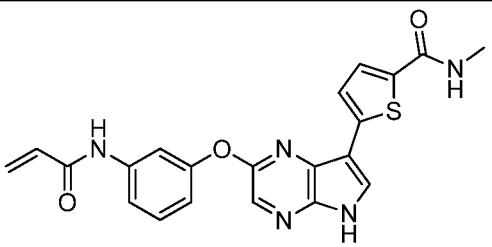
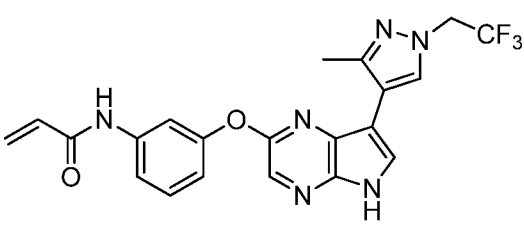
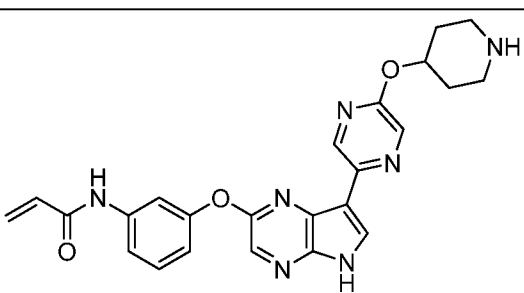
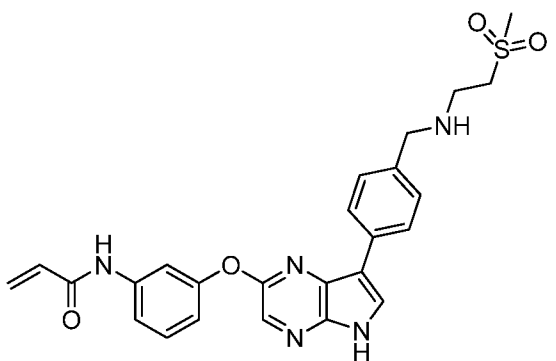
Example 177		424.10
Example 178		429.10
Example 179		471.10
Example 180		468.20
Example 181		441.10
Example 182		425.10

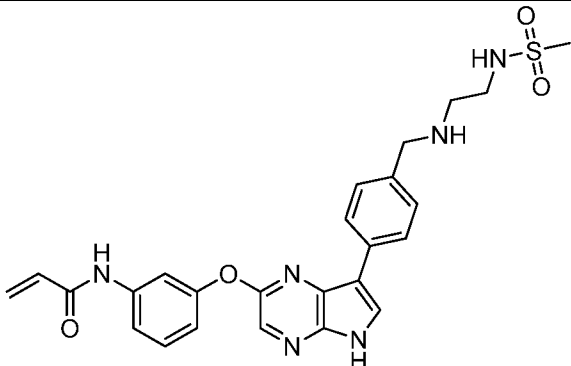
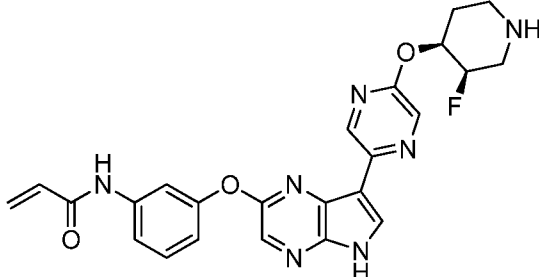
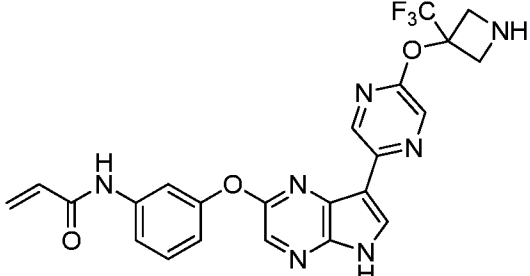
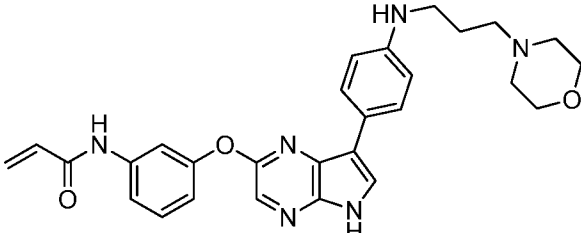
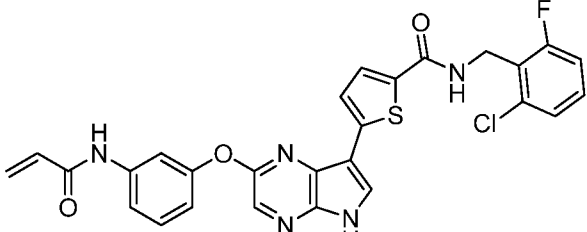
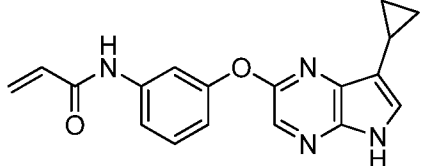
Example 183		424.10
Example 184		425.10
Example 185		425.10
Example 186		401.10
Example 187		464.10

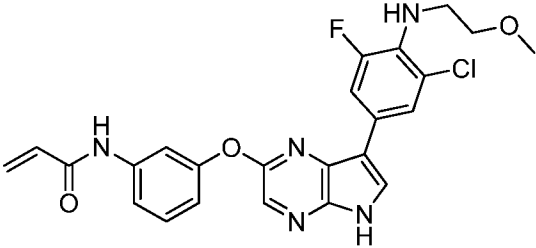
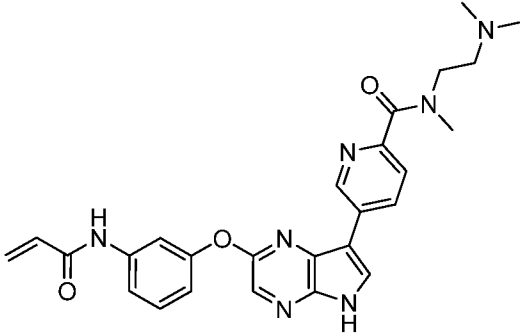
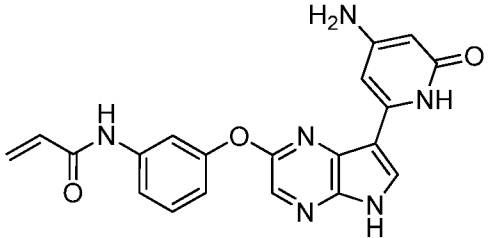
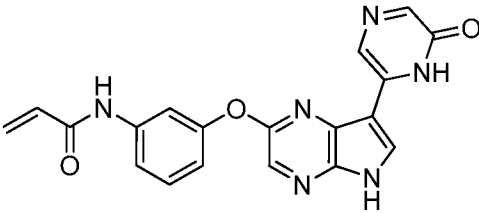
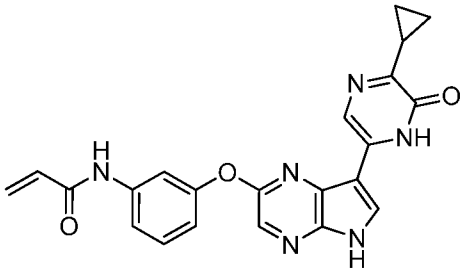
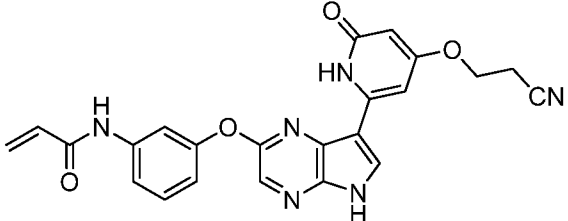
Example 188		399.10
Example 189		478.10
Example 190		418.10
Example 191		397.10
Example 192		428.10
Example 193		505.20

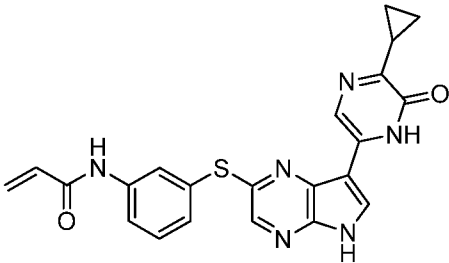
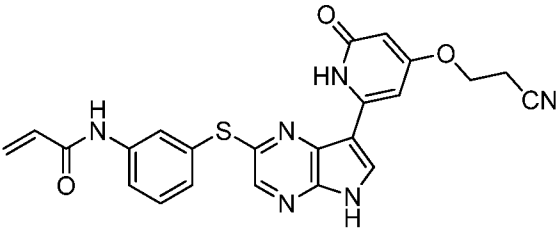
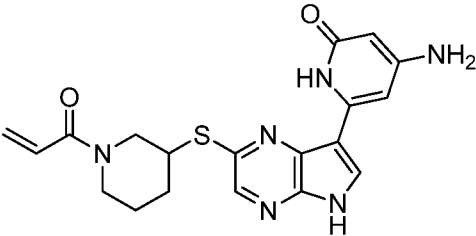
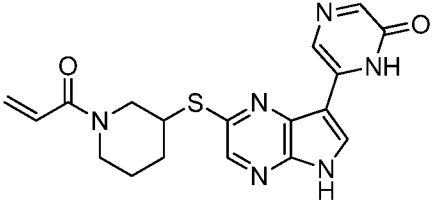
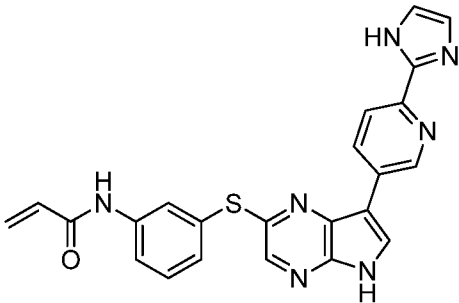
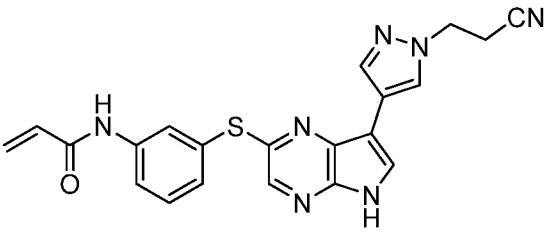
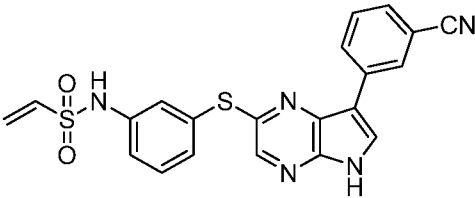
Example 194		377.10
Example 195		416.20
Example 196		362.20
Example 197		459.20
Example 198		452.20
Example 199		413.10

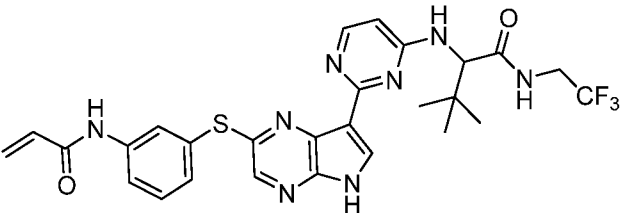
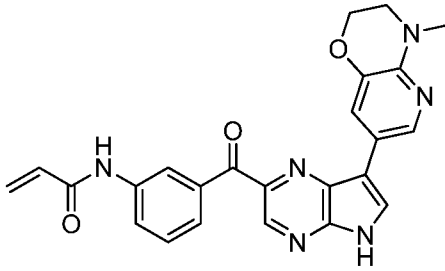
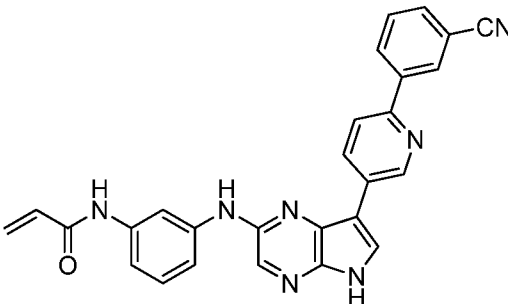
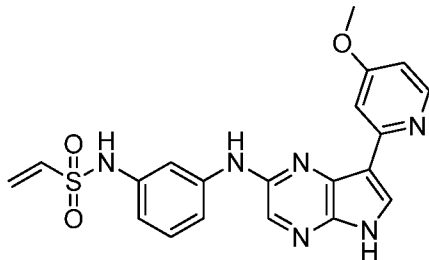
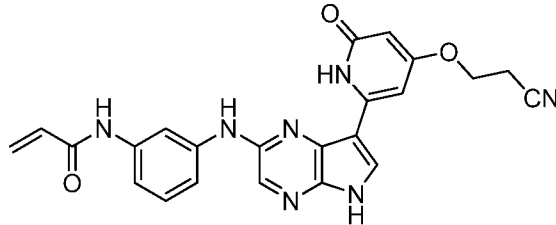
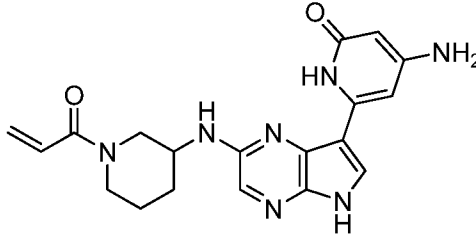
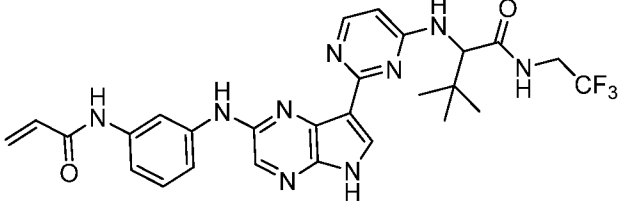
Example 200		398.10
Example 201		401.10
Example 202		386.20
Example 203		364.10
Example 204		363.10
Example 205		555.20
Example 206		428.20

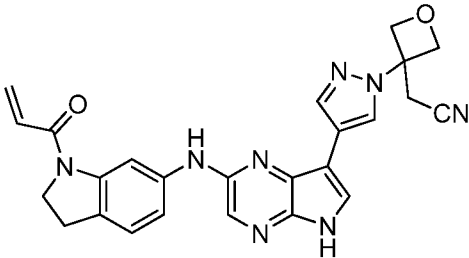
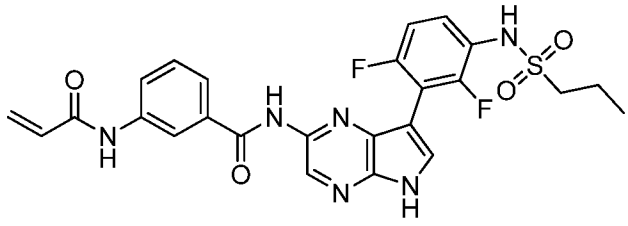
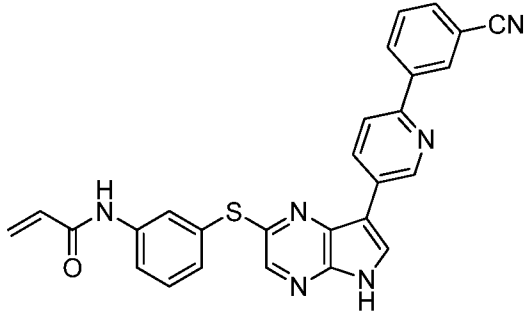
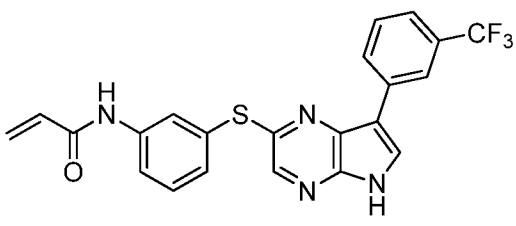
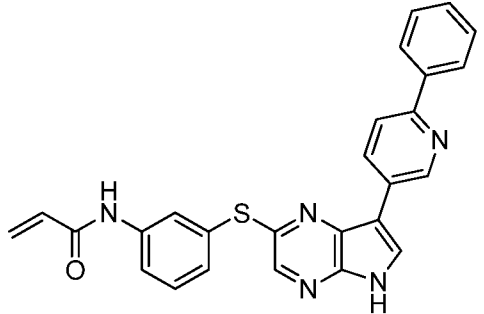
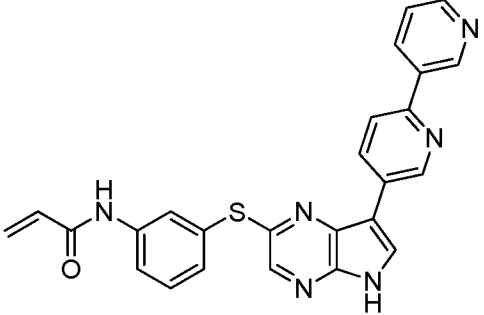
Example 207		442.20
Example 208		461.20
Example 209		420.10
Example 210		443.10
Example 211		458.20
Example 212		492.20

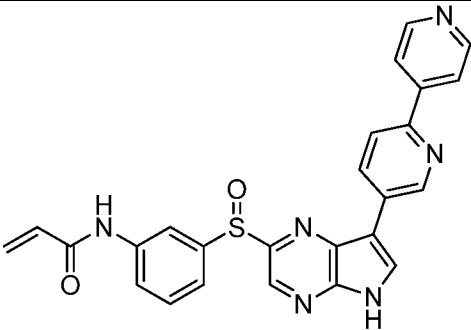
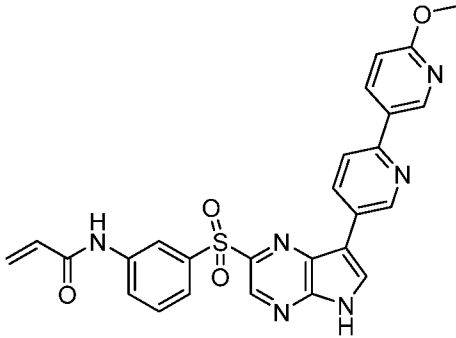
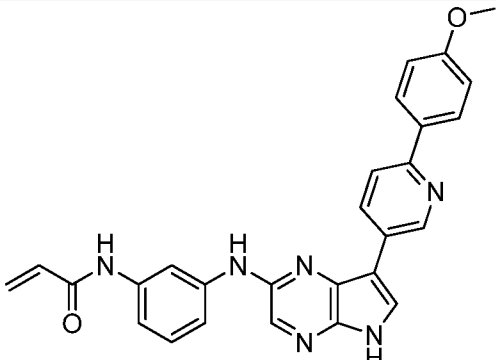
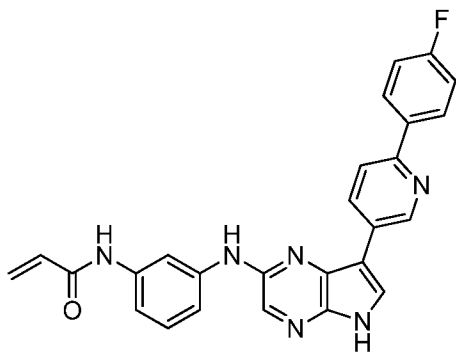
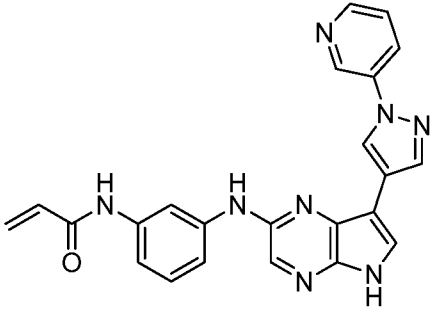
Example 213		507.20
Example 214		476.20
Example 215		498.10
Example 216		499.20
Example 217		548.10
Example 218		321.10

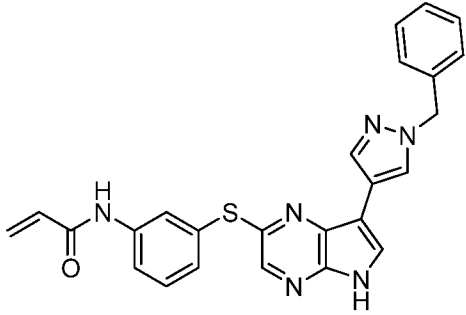
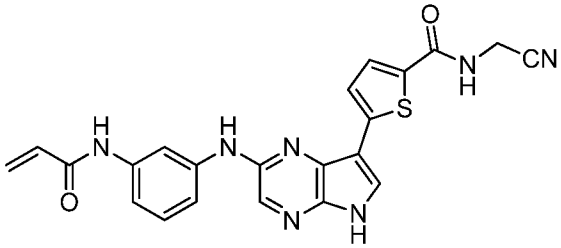
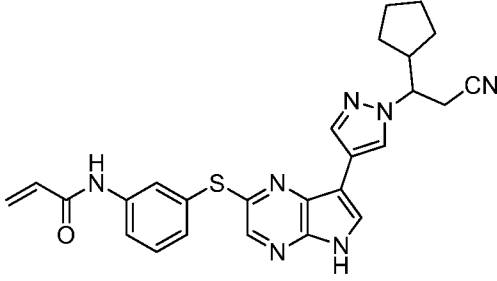
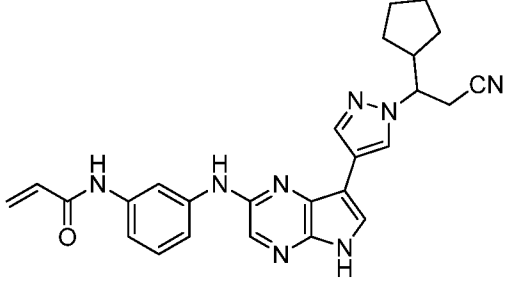
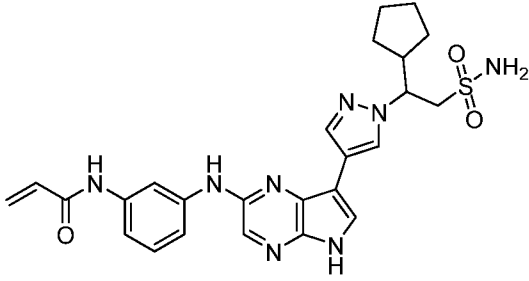
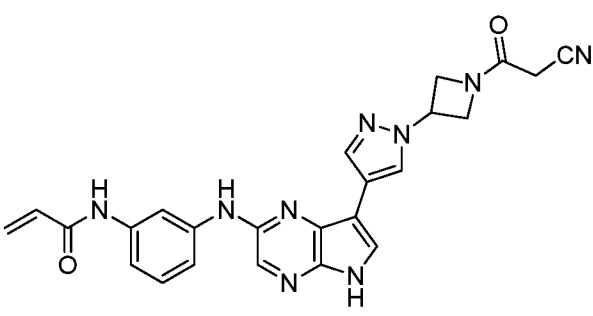
Example 219		482.10
Example 220		486.20
Example 221		389.10
Example 222		375.10
Example 223		415.10
Example 224		443.10

Example 225		431.10
Example 226		459.10
Example 227		397.10
Example 228		383.10
Example 229		440.10
Example 230		416.10
Example 231		434.10

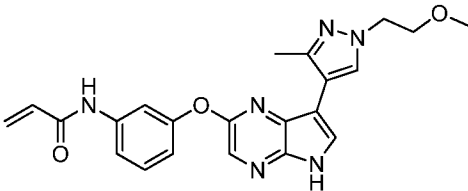
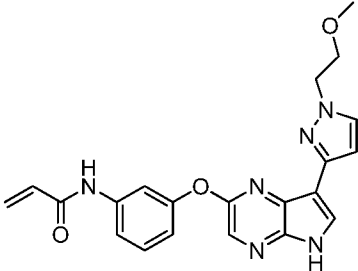
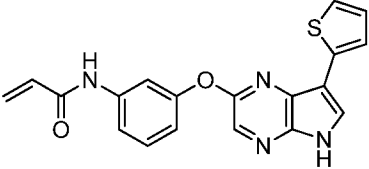
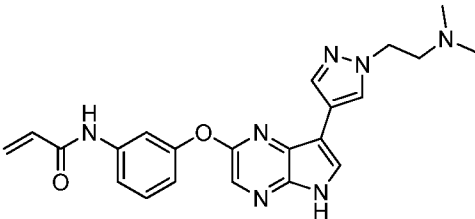
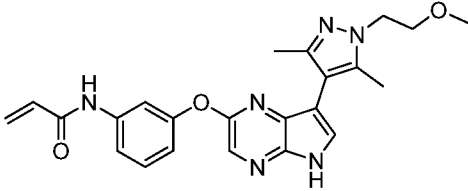
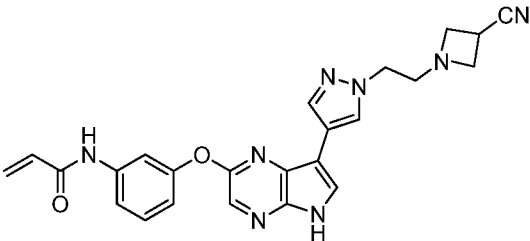
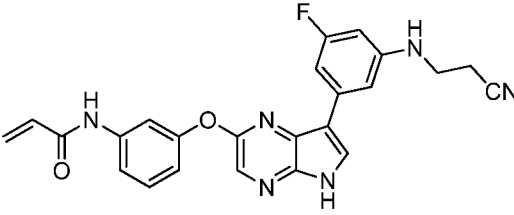
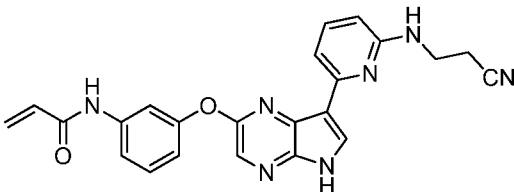
Example 232		585.20
Example 233		441.20
Example 234		458.20
Example 235		423.10
Example 236		442.10
Example 237		380.20
Example 238		568.20

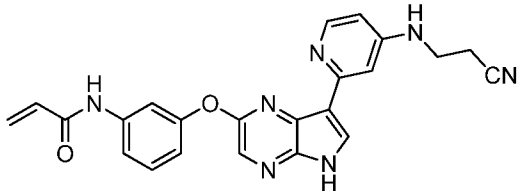
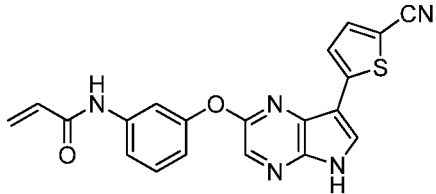
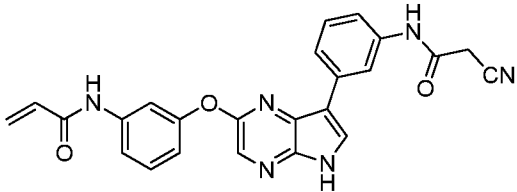
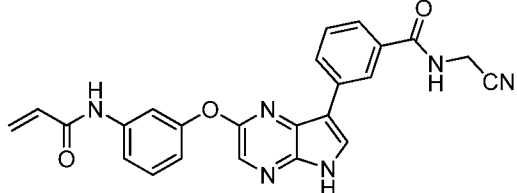
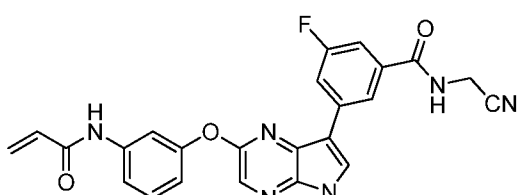
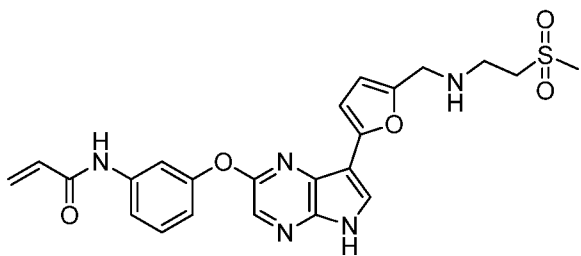
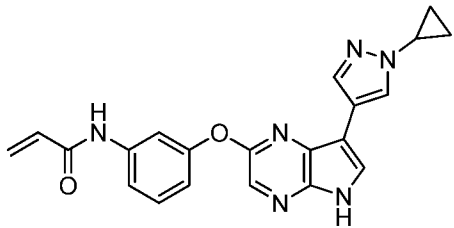
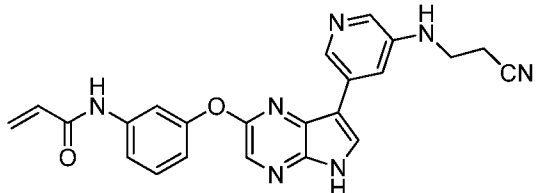
Example 239		467.20
Example 240		541.10
Example 241		475.10
Example 242		441.10
Example 243		450.10
Example 244		451.10

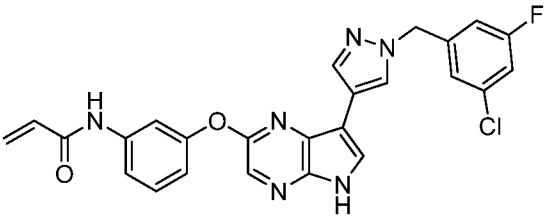
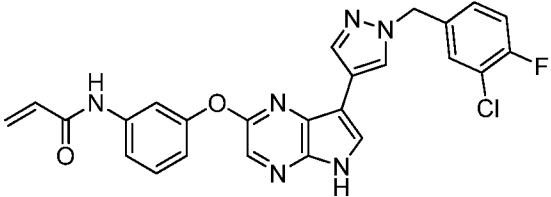
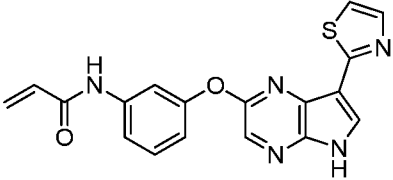
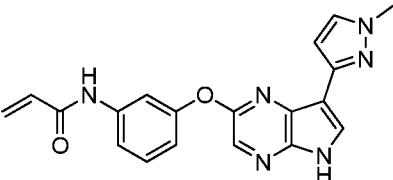
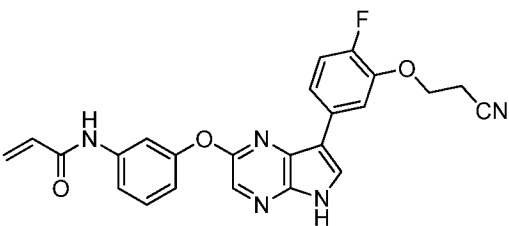
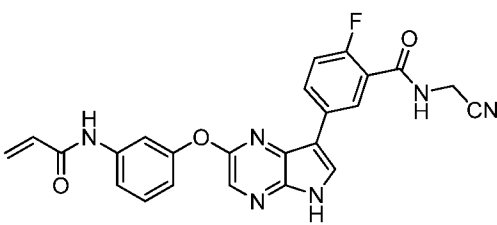
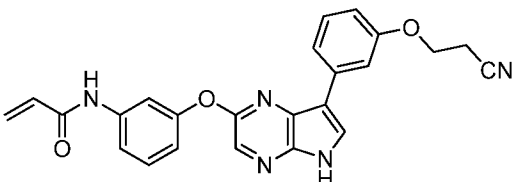
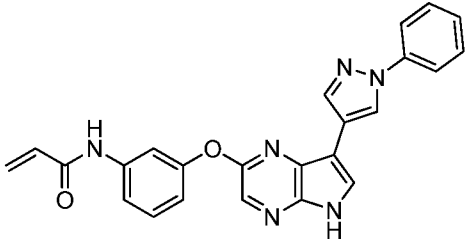
Example 245		467.10
Example 246		513.10
Example 247		463.20
Example 248		451.20
Example 249		423.20

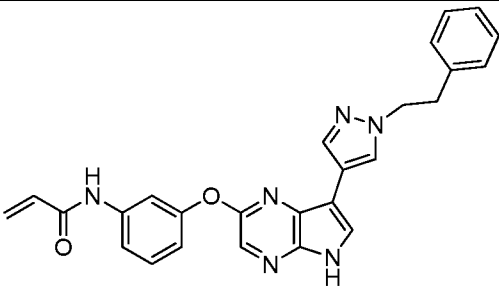
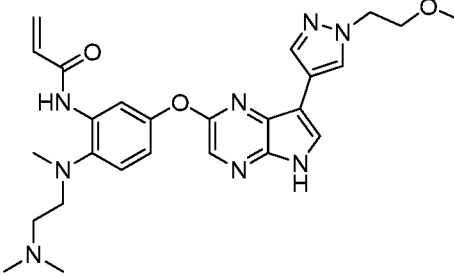
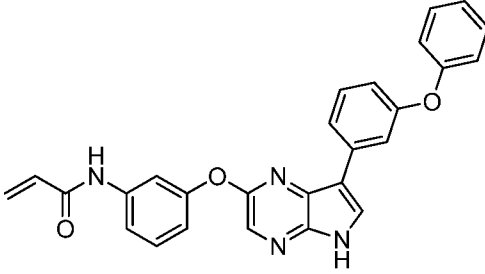
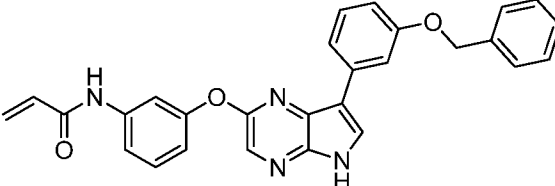
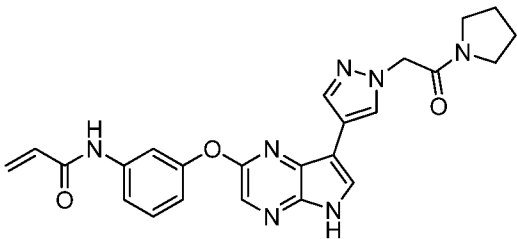
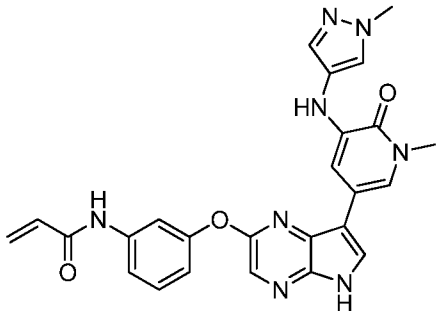
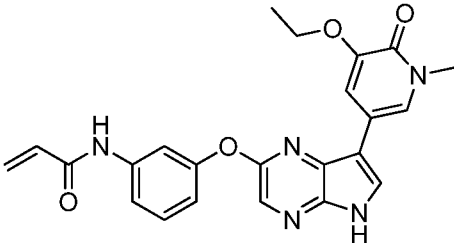
Example 250		453.10
Example 251		444.10
Example 252		484.20
Example 253		467.20
Example 254		521.20
Example 255		468.20

Example 256		443.20
Example 257		440.10
Example 258		478.10
Example 259		444.10
Example 260		397.13
Example 261		437.16
Example 262		397.19
Example 263		390.16

Example 264		419.18
Example 265		405.16
Example 266		363.08
Example 267		418.19
Example 268		433.19
Example 269		455.19
Example 270		443.16
Example 271		426.16

Example 272		426.16
Example 273		388.08
Example 274		439.14
Example 275		439.14
Example 276		457.13
Example 277		482.14
Example 278		387.15
Example 279		426.16

Example 280		489.12
Example 281		489.12
Example 282		364.08
Example 283		361.13
Example 284		444.14
Example 285		457.13
Example 286		426.15
Example 287		423.15

Example 288		451.18
Example 289		505.26
Example 290		449.15
Example 291		463.17
Example 292		458.19
Example 293		483.18
Example 294		432.16

BIOLOGICAL ACTIVITIES

Biological example 1: *In vitro* Activity of JAK1/2/3 test method

[00780] Biological assay of the compound disclosed herein was performed by using the following method:

[00781] 1. detecting the inhibitory activity of the compound to JAK1/2/3 by Caliper Mobility Shift Assay.

[00782] 2. preparing 1 × kinase base buffer for JAK1/2/3 by using 50 mM HEPES (pH 7.5), 0.0015% Brij-35, 10 mM MgCl₂, 2 mM DTT. JAK1: 25 mM HEPES, pH 7.5; 0.001% Brij-35; 0.01% Triton; 0.5 mM EGTA; 10 mM MgCl₂.

[00783] 3. preparing stop buffer by using 100 mM HEPES (pH 7.5), 0.0015% Brij-35, 0.2% Coating Reagent #3 (Caliper, Article No. 760050) and 50 mM EDTA.

[00784] 4. preparing enzyme (JAK1/2/3) by diluting enzyme solution with 1× kinase base buffer to a final concentration of 30 nM (JAK1), 2 nM (JAK2) or 4 nM (JAK 3);

[00785] 5. preparing substrate by diluting substrate solution with 1× kinase base buffer to a final concentration of that listed in table 2.

Table 2 The final concentrations of substrate

	ATP μ M	Peptide	
JAK1	90 μ M	3 μ M	PeptideD
JAK2	20 μ M	3 μ M	Peptide22
JAK3	6.2 μ M	3 μ M	Peptide22

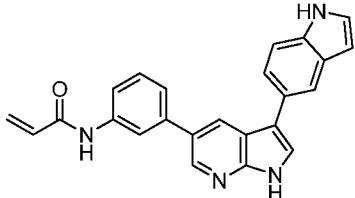
[00786] According to the results of assay method optimization, a 384-well plate was adopted (Corning, Cat. No. 3573, Lot. No. 12608008) in the assay for detection. For JAK1/2/3, preparing JAK1, JAK2, JAK3 respectively in a concentration of 75 nM, 5 nM, 10 nM, and the final concentration of JAK1, JAK2, JAK3 was respectively 30 nM, 2 nM, 4 nM; preparing Peptide FAM-P22 in a concentration of 7.5 μ M, the final concentration of which was 3 μ M; preparing ATP in a concentration of JAK1 (225 μ M), JAK2 (50 μ M), JAK3 (15.5 μ M), the final concentration of which was JAK1 (90 μ M), JAK2 (20 μ M), JAK3 (6.2 μ M); preparing Peptide D (sequence 5-FAM-C6-KKHTDDGYMPMSPGVA-NH₂) in a concentration of 7.5 μ M, the final concentration of which was 3 μ M; 1× kinase base buffer was used in preparation of enzyme and substrate. Reaction system was shown as Table 3:

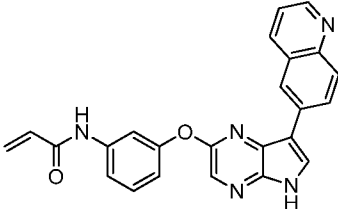
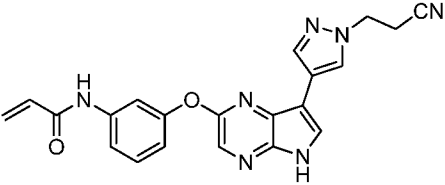
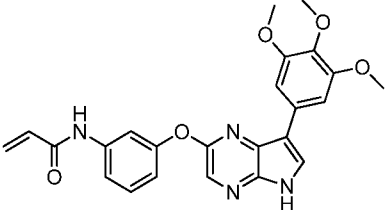
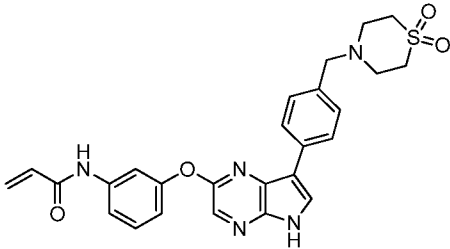
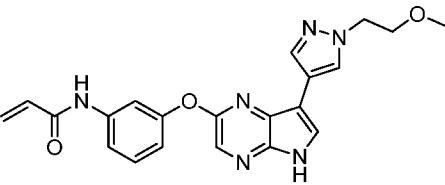
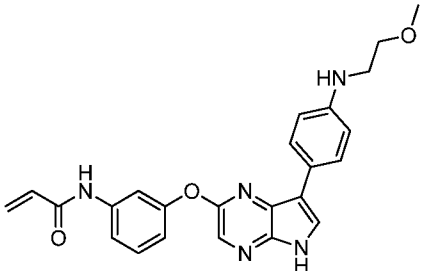
Table 3 IC₅₀ detection system of test compound against JAK1/2/3

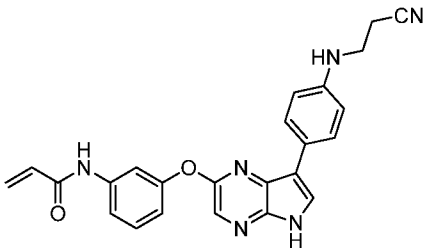
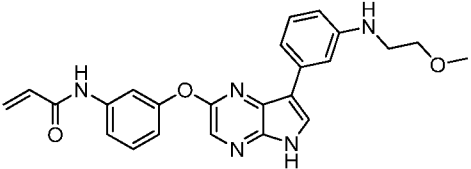
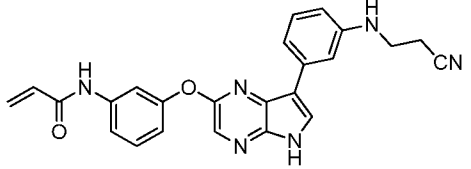
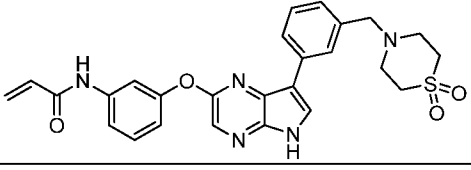
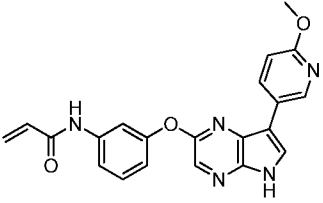
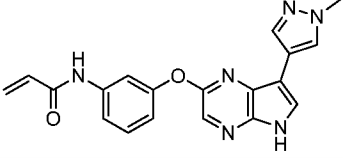
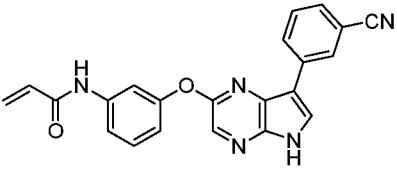
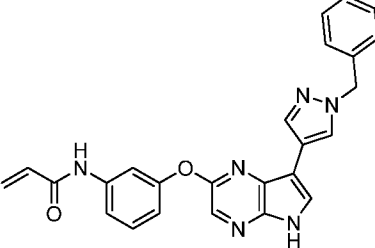
Test sample well		Positive control well	Negative control well
Test sample	5 μ L	5 μ L 10%DMSO	5 μ L 10%DMSO
1 $\times$ kinase base buffer			10 μ L
JAK1/2/3	10 μ L	10 μ L	
25 °C, incubated for 10 min			
Peptide solution (comprising			
ATP, Peptide FAM-P22,	10 μ L	10 μ L	10 μ L
Peptide D)			
28 °C, incubated for 60 min			
Stop buffer	25 μ L	25 μ L	25 μ L

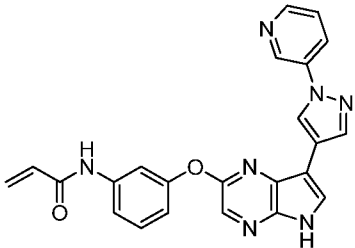
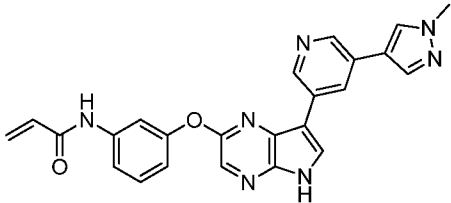
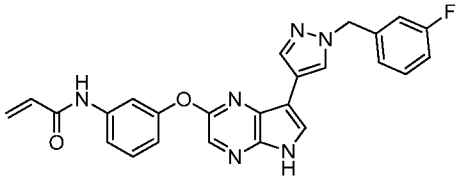
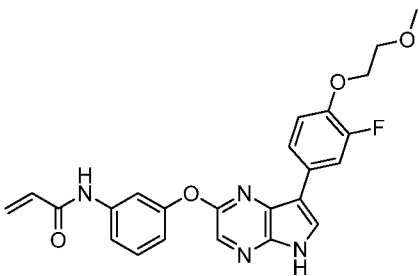
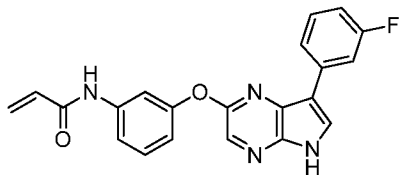
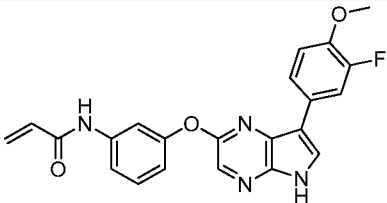
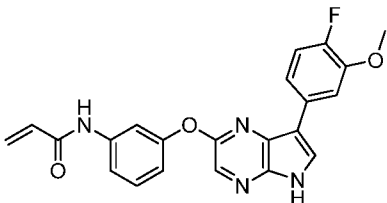
[00787] A 384-well plate was adopted for detection; and test sample well, positive control well and negative control well were built, inhibition of compound in 8 concentrations against JAK1/2/3 was detected by using duplicates in each test sample, the reaction well of enzyme and substrate was as positive control well, and no enzyme well was as negative control well. After adding the corresponding sample, buffer and enzyme to each well in order of table 3, the wells were incubated in incubator at 25 °C (RT) for 10 min, the prepared Peptide solution was added into each well, and then the 384-well plate was incubated in incubator at 28 °C for 60 min. After adding stop buffer, the wells were detected under FP485 nM excitation or 525 nM emission wavelength by using Caliper EZ Reader, percent conversions were read. Curve of various concentrations of compound to inhibition of which against JAK1/2/3 was plotted by Graph Pad Prism 5 software, the values of IC₅₀ were calculated. Results were listed in Table 4:

Table 4 Data of inhibitory activity of the compound Inhibition to JAK1/2/3

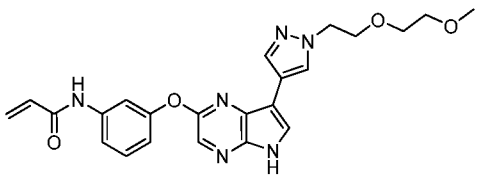
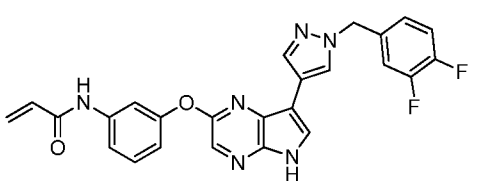
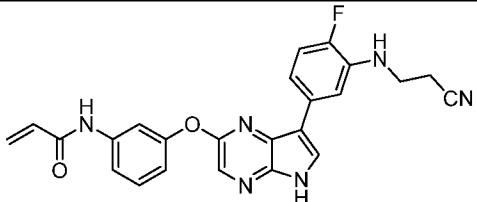
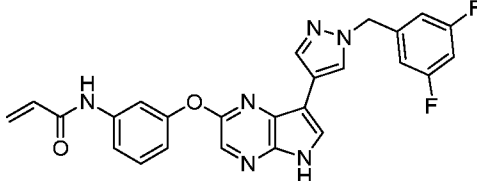
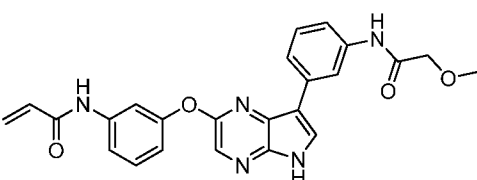
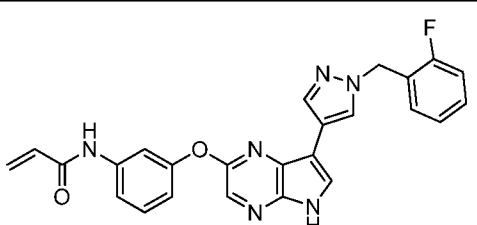
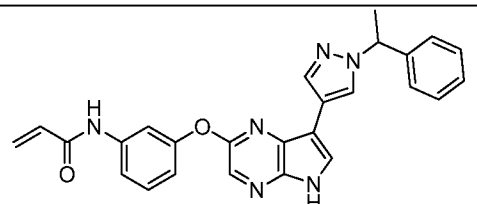
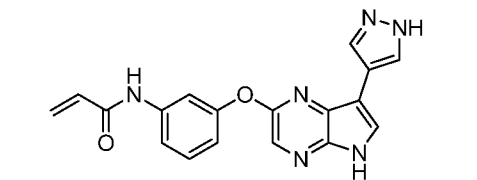
Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 1		>1000	>1000	3.0

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 3		>1000	>1000	2.6
Example 4		>1000	>1000	4.6
Example 5		>1000	>1000	11
Example 7		>1000	>1000	156
Example 9		>1000	>1000	0.89
Example 10		>1000	>1000	18.1

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 11		>1000	>1000	9.7
Example 12		>1000	>1000	1.4
Example 13		>1000	698.5	0.39
Example 15		>1000	>1000	23
Example 16		>1000	>1000	8.6
Example 17		>1000	>1000	1.1
Example 18		>1000	>1000	11.7
Example 20		>1000	>1000	0.28

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 21		>1000	>1000	1.1
Example 22		>1000	>1000	1.8
Example 23		>1000	>1000	1.5
Example 24		>1000	>1000	8.4
Example 25		>1000	>1000	25
Example 26		>1000	>1000	25
Example 27		>1000	>1000	13

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 28		>1000	>1000	5.5
Example 29		>1000	>1000	8.5
Example 30		>1000	>1000	14
Example 31		>1000	>1000	0.87
Example 32		>1000	>1000	1.8
Example 33		>1000	>1000	1.5
Example 34		>1000	>1000	84
Example 35		>1000	>1000	25

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 36		>1000	>1000	25
Example 37		>1000	>1000	13
Example 38		>1000	>1000	5.5
Example 39		>1000	>1000	8.5
Example 40		>1000	>1000	3.3
Example 41		>1000	>1000	14
Example 42		>1000	>1000	0.87
Example 43		>1000	>1000	6.2

Example	Compound	IC ₅₀ (nM)		
		JAK1	JAK2	JAK3
Example 44		>1000	361. 1	0. 15
Example 45		>1000	>1000	23
Example 46		>1000	849. 5	5. 1
Example 47		>1000	>1000	2. 5
Example 48		>1000	625. 3	0. 35
Example 49		>1000	567. 1	0. 18
Example 50		>1000	>1000	2. 1

[00788] The data listed in table 4 indicated that the compounds disclosed herein have strong inhibitory effects on JAK3 kinase, and have good selectivity for JAK3.

Biological example 2: *In vitro* Activity of BTK and EGFR^{T790M} test method

Experimental methods:

[00789] 1. Preparing 1× kinase base buffer and stop buffer for testing kinases

[00790] (1) 1× kinase base buffer (50 mM HEPES, pH 7.5, 0.01% Brij-35, 10 mM MgCl₂, 2 mM DTT);

[00791] (2) stop buffer (100 mM HEPES, pH 7.5, 0.01% Brij-35, 0.2% Coating Reagent #3, 50 mM EDTA).

[00792] 2. Preparing compound for kinase assay by diluting the compound serially

[00793] (1) Diluting the compound to 50 fold of the final desired highest inhibitor concentration with 100% DMSO. Transferring 100 μL of the compound in this concentration to one well of a 96-well plate; if compound was detected in a concentration of 10000 nM, a solution of compound in DMSO in a concentration of 500 μM was prepared in this step;

[00794] (2) Diluting the compound with DMSO serially by 4-fold per dilution to produce 10 concentrations;

[00795] (3) Adding 100 μL of 100% DMSO to two empty wells to prepare a no compound control and a no enzyme control; labeling this plate as source plate;

[00796] (4) Preparing intermediate plate by transfer 10 μL of the compound in various concentrations from source plate to a new 96-well plate as the intermediate plate, adding 90 μL of 1× kinase buffer to each well of the intermediate plate and mixing the compounds in intermediate plate for 10 min on shaker.

[00797] 3. Preparing assay plate by transferring 5 μL of the compound in each well from the 96-well intermediate plate to a 384-well plate; for example, A1 of the 96-well plate is transferred to A1 and A2 of the 384-well plate. A2 of the 96-well plate is transferred to A3 and A4 of the 384-well plate, and so on.

[00798] 4. Kinase reaction

[00799] (1) Preparing 2.5× enzyme solution by adding kinase in 1× kinase base buffer;

[00800] (2) Preparing 2.5× peptide solution by adding FAM-labeled peptide and ATP in the 1× kinase base buffer;

[00801] (3) the 384-well assay plate had contained 5 μL of compound in 10% DMSO

[00802] (4) Adding 10 μL of 2.5 × enzyme solution to each well of the 384-well assay plate containing 5 μL of compound in 10% DMSO ;

[00803] (5) Incubating at room temperature for 10 min;

[00804] (6) Adding 10 μ L of $2.5 \times$ peptide solution to each well of the 384-well assay plate;

[00805] (7) Kinase reaction and stop: Incubating at 28 °C for 1 hour and Adding 25 μ L of stop buffer to stop reaction.

[00806] 5. Caliper reading

[00807] Collecting data on Caliper.

[00808] 6. Curve fitting

[00809] (1) Copying conversion data from Caliper program;

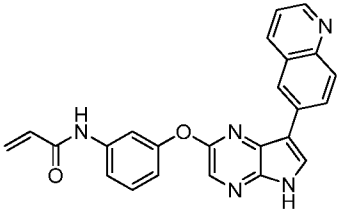
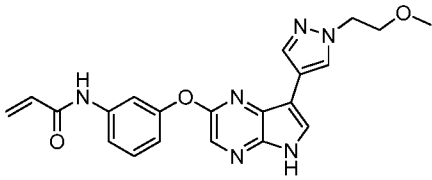
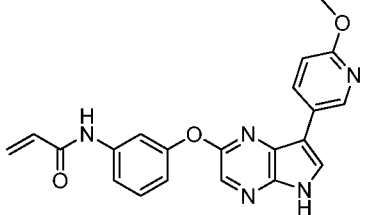
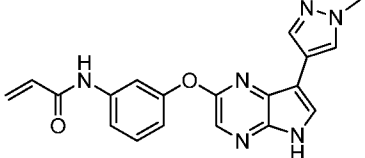
[00810] (2) Converting conversion values to inhibition values:

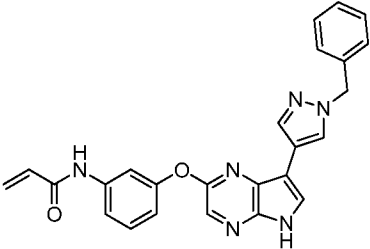
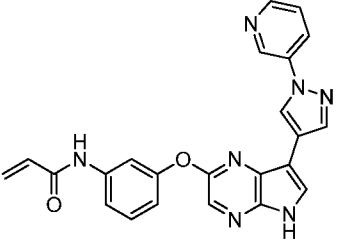
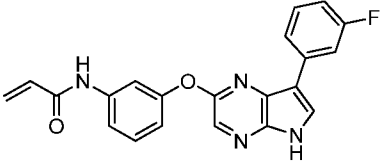
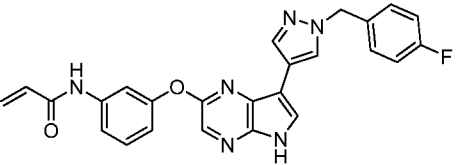
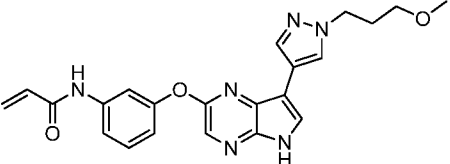
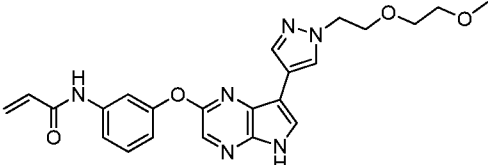
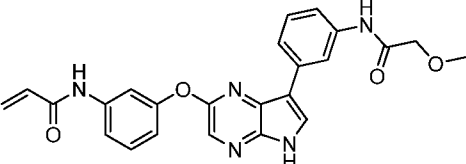
$$\text{Percent inhibition} = (\text{max-conversion})/(\text{max-min}) \times 100.$$

“max” stands for value of DMSO control; “min” stands for value of no kinase control.

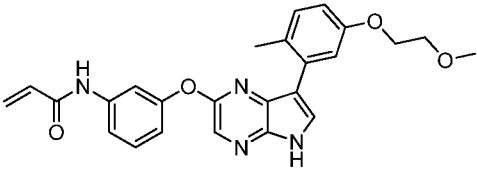
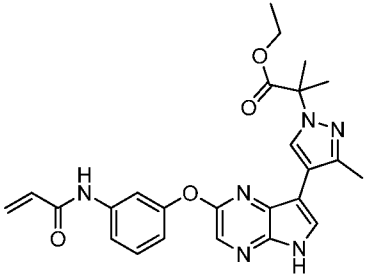
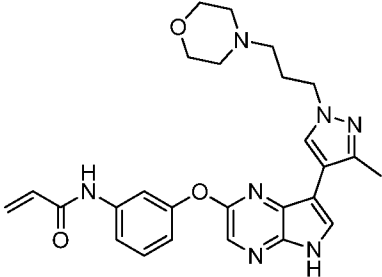
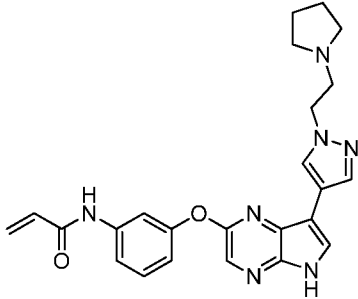
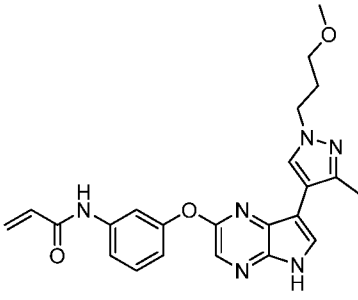
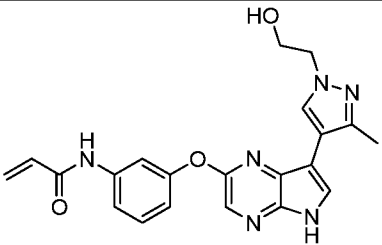
[00811] (3) Fitting the data in XLFit excel to obtain IC₅₀ values, the results were as shown in table 5:

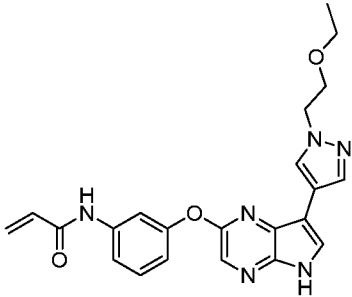
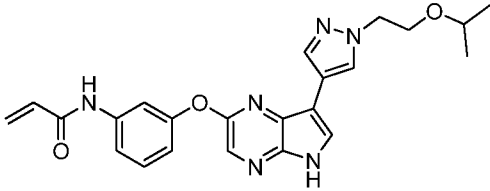
Table 5 Data of inhibitory activity of the compound to BTK/EGFR^{T790M}

Example	Compound	IC ₅₀ (nM)	
		BTK	EGFR ^{T790M}
Example 3		N/A	1.6
Example 9		31	7.5
Example 16		N/A	40
Example 17		N/A	9.1

Example	Compound	IC ₅₀ (nM)	
		BTK	EGFR ^{T790M}
Example 20		93	N/A
Example 21		N/A	24
Example 25		N/A	94
Example 32		N/A	19
Example 33		18	N/A
Example 36		76	N/A
Example 40		270	19

Example	Compound	IC ₅₀ (nM)	
		BTK	EGFR ^{T790M}
Example 44		N/A	3.2
Example 45		6.6	N/A
Example 46		133	32
Example 47		71	N/A
Example 50		54	44
Example 52		44.90	N/A
Example 53		42.72	N/A

Example	Compound	IC ₅₀ (nM)	
		BTK	EGFR ^{T790M}
Example 56		54.01	N/A
Example 64		62.44	N/A
Example 65		26	N/A
Example 66		55	N/A
Example 70		23	N/A
Example 75		93	N/A

Example	Compound	IC ₅₀ (nM)	
		BTK	EGFR ^{T790M}
Example 77		79.14	N/A
Example 79		39.34	N/A

(Note: N/A means no detection)

[00812] The data listed in table 5 indicated that the compounds disclosed herein have strong inhibitory effects on BTK and EGFR^{T790M} kinases.

Biological example 3: PK assay of the compound *in vivo* of rats

[00813] The test compound was administered by oral gavage at a dose of 5 mg/kg or by injection from caudal vein at a dose of 1 mg/kg. After administering, blood samples were collected at time points (0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h and 24 h) from orbital venous in anticoagulative tubes containing K₂EDTA. After liquid-liquid extraction, the plasma samples were quantitative analyzed using multiple reactive ion monitoring (MOM) on a triple quadrupole tandem mass spectrometer. The pharmacokinetic parameters were calculated using a noncompartmental method by WinNonlin 6.1 software.

[00814] Conclusion: The compounds of the present invention have a better advantage in clearance rate. After administering orally to SD rats at dose of 5 mg/kg, the compounds of the present invention show a higher AUC and a suitable half-life, which have a higher druggability.

[00815] The table 6 listed comparison data of the compound of example 24 disclosed herein to the JAK inhibitor (*i.e.* the comparison compound) disclosed in PCT patent application WO 2014081732A1. The comparison compound is example 2 of WO 2014081732A1: 2-(3-acrylamidophenyl)-*N*-(*tert*-butyl)-5*H*-pyrrolo[2,3-*b*]pyrazine-7-carboxamide).

Table 6 Comparison data

Example	Experimental animal	Administration route	Dose	t _{1/2}	AUC _{last}	CL	V _{ss}
			mg/kg	h	h* ng/mL	mL/min/kg	L/Kg
The comparison compound	Rat	iv	1	0.492	157	109	1.41
		po	5	1.3	39.8	/±/	/±/
Example 24	Rat	iv	1	2.94	1030	15.8	1.12
		po	5	2.78	1700	/±/	/±/

[00816] Conclusion: The value of orally AUC of the compound of example 24 disclosed herein is 42.7 times to that of the comparison compound, the clearance rate of which is 6.8 times slower than that of the comparison compound, and half-life is 2 times to that of the comparison compound, all of these data indicated that the compound of example 24 disclosed herein shows a better stability *in vivo*, and the value of V_{ss} is in a suitable range, which have obvious advantages compared with the comparison compound.

[00817] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

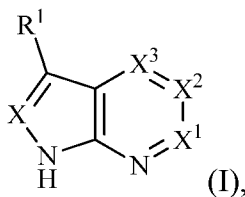
[00818] Reference throughout this specification to “an embodiment”, “some embodiments”, “one embodiment”, “another example”, “an example”, “a specific examples”, or “some examples”, means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as “in some embodiments”, “in one embodiment”, “in an embodiment”, “in another example”, “in an example”, “in a specific examples”, or “in some examples”, in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure.

[00819] Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the

embodiments without departing from spirit, principles and scope of the present disclosure.

What is claimed is:

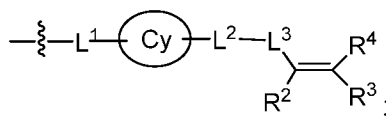
1. A compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

X is N or CR^x;

each of X¹ and X² is independently N, CR⁰ or CR^{x1} with the proviso of at least one of X¹ and X² is CR^{x1};



each R^{x1} is independently

X³ is CR or N, wherein R is H, deuterium, F, Cl, Br, I, CN, OH, NO₂, COOH, alkyl, alkoxy, alkenyl or alkynyl;

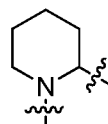
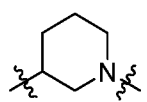
each R^x and R⁰ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

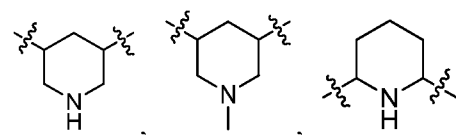
R¹ is cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, fused bicycyl, fused heterobicycyl, spiro bicycyl or spiro heterobicycyl;

each L¹ is independently -O-, -N(R^{1a})-, -S(=O)_p-, -C(=O)-, -C(=O)-N(R^{1a})-, -S(=O)_p-N(R^{1a})-, -(CR^mR^w)_g- or -(CR^mR^w)_n-CR^{1a}=CR^{1a}-(CR^mR^w)_n-;

each L² is independently a bond, -O-, -N(R^{1a})-, -CH₂-N(R^{1a})-, -CH(CH₃)-N(R^{1a})-, -C(CH₃)₂-N(R^{1a})-, -C(=O)-N(R^{1a})- or -S(=O)_p-N(R^{1a})-;

each L³ is independently -C(=O)- or -S(=O)₂-;

each Cy is independently cycloalkyl, cycloalkenyl, C₂₋₄ heterocyclyl, , ,



, C₆₋₁₀ heterocyclyl, aryl, heteroaryl, fused bicycyl, fused heterobicycyl, spiro bicycyl or spiro heterobicycyl;

each R^2 is independently H, deuterium, F, Cl, Br, I, CN, alkyl, alkenyl or alkynyl;

each R^3 and R^4 is independently H, deuterium, F, Cl, Br, I, CN, COOH, $-(CR^mR^w)_n-NR^mR^w$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, fused bicyclyl, fused bicyclalkyl, fused heterobicyclyl, fused heterobicyclalkyl, spiro bicyclyl, spiro bicyclalkyl, spiro heterobicyclyl or spiro heterobicyclalkyl;

each n is independently 0, 1, 2, 3, or 4;

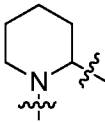
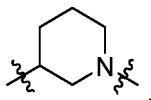
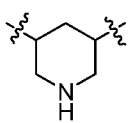
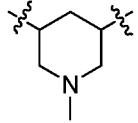
g is 1, 2, 3, or 4;

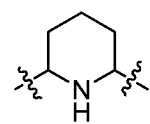
each p is independently 0, 1, or 2;

each R^{1a} is independently H, deuterium, alkyl, alkenyl or alkynyl;

each R^m and R^w is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclalkyl; or R^m and R^w , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each alkyl, haloalkyl, cyano-substituted alkyl, alkoxy, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, carbocyclyl,

heterocycle, heterocyclyl, C_{2-4} heterocyclyl, , , , ,



, C_{6-10} heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, fused bicyclyl, fused bicyclalkyl, fused heterobicyclyl, fused heterobicyclalkyl, spiro bicyclyl, spiro bicyclalkyl, spiro heterobicyclyl, spiro heterobicyclalkyl, $-N(R^{1a})-$, $-C(=O)-N(R^{1a})-$, $-S(=O)_p-N(R^{1a})-$, $-(CR^mR^w)_g-$ or $-(CR^mR^w)_n-CR^{1a}=CR^{1a}-(CR^mR^w)_n-$ described in R, R^x , R^{x1} , R^0 , R^1 , L^1 , L^2 , Cy, R^2 , R^3 , R^4 , R^{1a} , R^m and/or R^w is optionally and independently substituted with one or more R^5 ;

each R^5 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aryloxy, heteroaryloxy, heterocyclyloxy, arylalkoxy, heteroarylalkoxy, heterocyclalkoxy, alkylamino, alkylaminoalkyl, alkylaminoalkylamino, cycloalkylamino, alkylthio, haloalkyl, haloalkoxy, hydroxy-substituted alkyl, hydroxy-substituted alkylamino, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted alkylamino, amino-substituted alkyl, alkylacyl, heteroalkyl, cycloalkyl,

cycloalkenyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkylamino, heterocyclylacyl, aryl, arylalkyl, arylamino, heteroaryl, heteroarylamino, $\text{NH}_2\text{-C(=O)-}$, $\text{alkyl-N(R}^6\text{)-C(=O)-}$, $\text{NH}_2\text{-S(=O)}_2\text{-}$, $\text{alkyl-N(R}^6\text{)-S(=O)}_2\text{-}$, $\text{NH}_2\text{-S(=O)}_2\text{-alkyl-}$, $\text{alkyl-N(R}^6\text{)-S(=O)}_2\text{-alkyl-}$, $\text{alkyl-S(=O)}_2\text{-N(R}^6\text{)-alkyl-}$, $\text{aryl-alkyl-N(R}^6\text{)-C(=O)-}$, $\text{alkyl-C(=O)-N(R}^6\text{)-}$, $\text{alkyl-N(R}^6\text{)-C(=O)-alkyl-N(R}^6\text{)-}$, $\text{alkyl-S(=O)}_2\text{-}$, $\text{alkyl-S(=O)}_2\text{-alkyl-}$, $\text{-(CH}_2\text{)}_n\text{-N(R}^6\text{)-(CH}_2\text{)}_n\text{-S(=O)}_p\text{-R}^7$, $\text{-(CH}_2\text{)}_n\text{-N(R}^6\text{)-(CH}_2\text{)}_n\text{-N(R}^6\text{)-S(=O)}_p\text{-R}^7$, $\text{-(CR}^8\text{R}^9\text{)}_n\text{-COOR}^{10}$ or $\text{R}^{11}\text{R}^{12}\text{N-C(=O)-alkyl-}$;

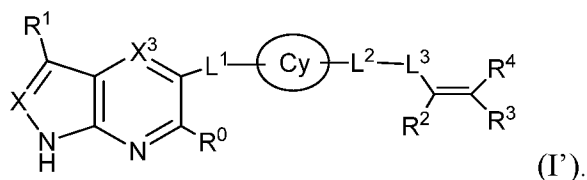
each R^6 , R^7 , R^8 , R^9 and R^{10} is independently H, deuterium, alkyl, alkenyl or alkynyl;

each R^{11} and R^{12} is independently H, deuterium, alkyl, cyano-substituted alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclylalkyl; or R^{11} and R^{12} , together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

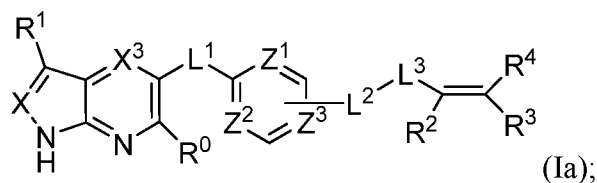
each R^5 is optionally and independently substituted with one or more substituents selected from H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH , alkyl, alkoxy, alkoxyalkyl, alkyl-C(=O)- , cyano-substituted alkyl-C(=O)- , alkylamino, $\text{NH}_2\text{-S(=O)}_2\text{-}$, $\text{alkyl-N(R}^{13}\text{)-S(=O)}_2\text{-}$, $\text{NH}_2\text{-S(=O)}_2\text{-alkyl-}$, $\text{alkyl-N(R}^{13}\text{)-S(=O)}_2\text{-alkyl-}$, $\text{alkyl-S(=O)}_2\text{-N(R}^{13}\text{)-alkyl-}$, haloalkyl, hydroxy-substituted alkyl, cyano-substituted alkyl, cycloalkyl, heterocyclyl, aryl, aryloxy or arylalkoxy; and

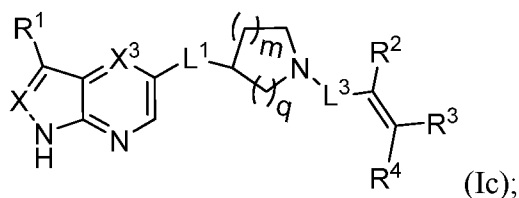
each R^{13} is independently H, deuterium, alkyl, alkenyl or alkynyl.

2. The compound of claim 1 having Formula (I') or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



3. The compound of claim 1 or 2 having Formula (Ia) or Formula (Ic) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,





wherein

each of Z^1 , Z^2 and Z^3 is independently N or CR^y ;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylamino- C_{1-6} -alkylamino or halo- C_{1-6} -alkyl;

m is 0, 1 or 2; and

q is 1, 2 or 3.

4. The compound of claim 1, 2 or 3, wherein each R^x and R^0 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl or C_{1-9} heteroaryl.

5. The compound of claim 4, wherein each R^x and R^0 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl or C_{1-5} heteroaryl.

6. The compound of claim 5, wherein each R^x and R^0 is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, phenyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, triazolyl, tetrazolyl, oxazolyl, pyridyl, pyrimidinyl or pyrazinyl.

7. The compound of any one of claims 1-6, wherein R^1 is C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{5-12} fused bicyclyl, C_{5-12} fused heterobicyclyl, C_{5-12} spiro bicyclyl or C_{5-12} spiro heterobicyclyl; and R^1 is optionally substituted with one or more R^5 .

8. The compound of claim 7, wherein R^1 is C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{2-6} heterocyclyl, C_{6-10} aryl or C_{1-9} heteroaryl; and R^1 is optionally substituted with one or more R^5 .

9. The compound of claim 8, wherein R^1 is pyrrolidinyl, piperazinyl, piperidyl, morpholinyl, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydropyridyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexdienyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolinyl, pteridinyl, naphthyridinyl, benzotriazolyl, benzofuranyl,

isobenzofuranyl, furo[3,2-*c*]pyridyl, furo[3,2-*b*]pyridyl, furo[2,3-*b*]pyridyl, furo[2,3-*c*]pyridyl, benzothienyl, benzothiazolyl, 1,2-benzoisothiazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyridyl, 3,4-dihydro-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridyl, thieno[2,3-*c*]pyridyl, thieno[2,3-*b*]pyridyl, 1,4-benzodioxinyl, pyridin-2(1*H*)-one-3-yl, pyridin-2(1*H*)-one-4-yl, pyridin-2(1*H*)-one-5-yl, pyridin-2(1*H*)-one-6-yl, pyrazin-2(1*H*)-one-3-yl, pyrazin-2(1*H*)-one-5-yl or pyrazin-2(1*H*)-one-6-yl; R¹ is optionally substituted with one or more R⁵.

10. The compound of any one of claims 1-9, wherein each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkylamino-C₁₋₆-alkyl, C₁₋₆ alkylthio-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₅₋₁₂ fused bicyclyl, C₅₋₁₂ fused bicyclyl-C₁₋₆-alkyl, C₅₋₁₂ fused heterobicyclyl, C₅₋₁₂ fused heterobicyclyl-C₁₋₆-alkyl, C₅₋₁₂ spiro bicyclyl, C₅₋₁₂ spiro bicyclyl-C₁₋₆-alkyl, C₅₋₁₂ spiro heterobicyclyl or C₅₋₁₂ spiro heterobicyclyl-C₁₋₆-alkyl;

each n is independently 0, 1, 2, 3, or 4; and

each R^m and R^w is independently H, deuterium, C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

11. The compound of claim 10, wherein each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₃ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₃ alkylthio-C₁₋₃-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₃-alkyl, C₂₋₈

heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₃-alkyl, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-C₁₋₃-alkyl, C₅₋₁₂ fused bicyclyl, C₅₋₁₂ fused bicyclyl-C₁₋₃-alkyl, C₅₋₁₂ fused heterobicyclyl, C₅₋₁₂ fused heterobicyclyl-C₁₋₃-alkyl, C₅₋₁₂ spiro bicyclyl, C₅₋₁₂ spiro bicyclyl-C₁₋₃-alkyl, C₅₋₁₂ spiro heterobicyclyl or C₅₋₁₂ spiro heterobicyclyl-C₁₋₃-alkyl;

each n is independently 0, 1, 2, 3, or 4; and

each R^m and R^w is independently H, deuterium, C₁₋₅ alkyl, cyano-substituted C₁₋₄ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

12. The compound of claim 11, wherein each R² is independently H, deuterium, F, Cl, Br, I, CN, C₁₋₃ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl;

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, -(CR^mR^w)_n-NR^mR^w, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₃ alkylthio-C₁₋₃-alkyl, C₂₋₆ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl, C₅₋₁₂ fused bicyclyl, C₅₋₁₂ fused bicyclyl-C₁₋₃-alkyl, C₅₋₁₂ fused heterobicyclyl, C₅₋₁₂ fused heterobicyclyl-C₁₋₃-alkyl, C₅₋₁₂ spiro bicyclyl, C₅₋₁₂ spiro bicyclyl-C₁₋₃-alkyl, C₅₋₁₂ spiro heterobicyclyl or C₅₋₁₂ spiro heterobicyclyl-C₁₋₃-alkyl;

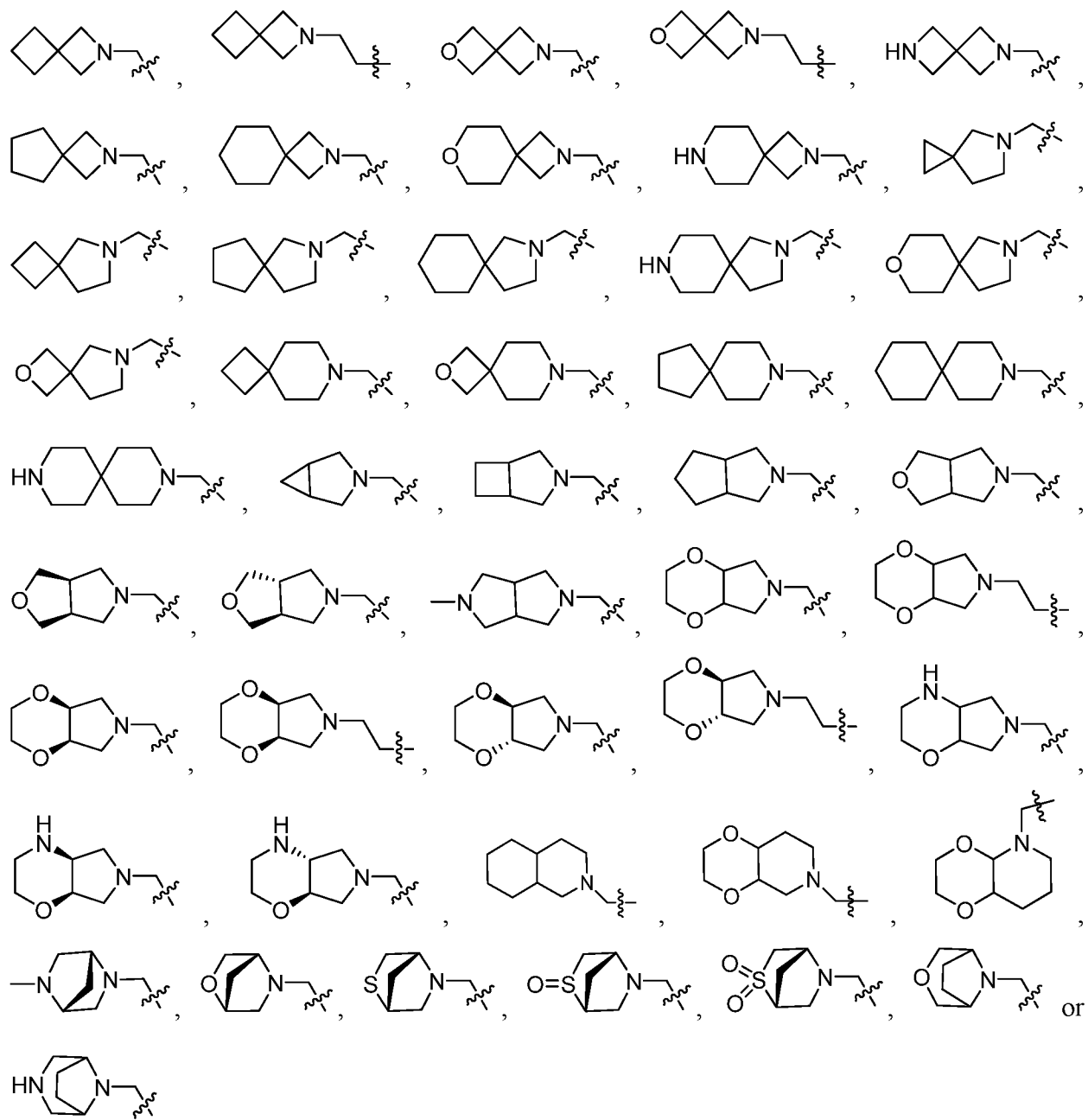
each n is independently 0, 1, 2, 3, or 4; and

each R^m and R^w is independently H, deuterium, C₁₋₄ alkyl, cyano-substituted C₁₋₄ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₃-alkyl; or R^m and R^w, together with the N atom to which they are attached, form a 3- to 12-membered heterocycle.

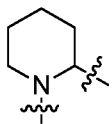
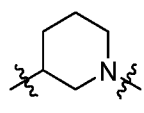
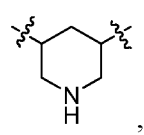
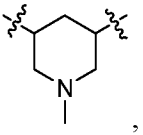
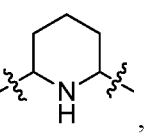
13. The compound of claim 12, wherein each R² is independently H, deuterium, F, Cl, Br, I, CN, methyl, ethyl, propyl or isopropyl; and

each R³ and R⁴ is independently H, deuterium, F, Cl, Br, I, CN, COOH, C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, -CH₂-NHMe, -CH₂-NMe₂, -(CH₂)₂-NMe₂, -(CH₂)₃-NMe₂, -CH₂-NEt, -CH₂-NEt₂, -(CH₂)₂-NEt₂, -(CH₂)₃-NEt₂, oxacyclobutyl, azacyclobutyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1-oxidothiomorpholinyl, 1,1-dioxidothiomorpholinyl, piperazinyl, piperidyl, morpholinylmethyl, thiomorpholinylmethyl, 1-oxidothiomorpholinyl methyl, 1,1-dioxidothiomorpholinyl methyl, morpholinylethyl, thiomorpholinylethyl, 1-oxidothiomorpholinylethyl, 1,1-dioxidothiomorpholinylethyl,

morpholinylpropyl, thiomorpholinylpropyl, 1-oxidithiomorpholinylpropyl, 1,1-dioxidithiomorpholinylpropyl, piperazinylmethyl, piperazinyethyl, piperazinypropyl, piperidylmethyl, piperidylethyl, piperidylpropyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydropyranylpropyl, pyrrolidinylmethyl, pyrrolidinylethyl or pyrrolidinylpropyl; or each R³ and R⁴ is independently

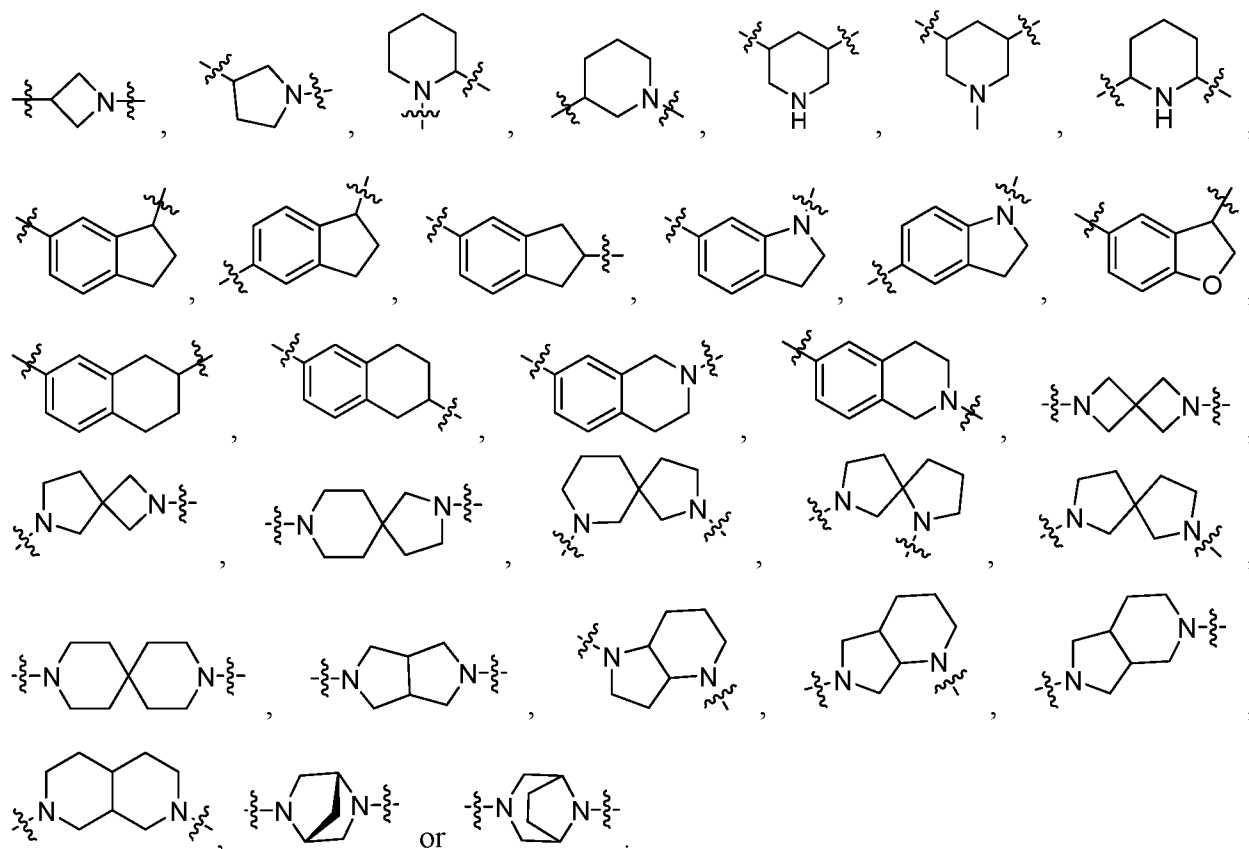


14. The compound of any one of claims 1-13, wherein each Cy is independently C₃₋₈ cycloalkyl,

C₃₋₈ cycloalkenyl, C₂₋₄ heterocyclyl, , , , , , C₆₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₅₋₁₂ fused bicycyl, C₅₋₁₂ fused heterobicycyl,

C₅₋₁₂ spiro bicycyl or C₅₋₁₂ spiro heterobicycyl.

15. The compound of claim 14, wherein each Cy is cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, indenyl, naphthyl, furyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pentazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolinyl, pteridinyl, naphthyridinyl, benzotriazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzothiazolyl, 1,2-benzisothiazolyl, benzoxazolyl, benzoisoxazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzopyrazinyl, pyridopyrazinyl, purinyl, 1*H*-pyrrolo[2,3-*b*]pyridyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, pyrrolo[2,3-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridyl, 1*H*-imidazo[4,5-*b*]pyridyl, 1*H*-imidazo[4,5-*c*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl or [1,2,4]triazolo[1,5-*a*]pyridyl; or each Cy is one of the following groups:



16. The compound of any one of claims 1-15, wherein each R⁵ is independently H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkylamino, C₆₋₁₀ aryloxy, C₁₋₉ heteroaryloxy, C₂₋₁₀ heterocycloxy, C₆₋₁₀ aryl-C₁₋₆-alkoxy, C₁₋₉ heteroaryl-C₁₋₆-alkoxy, C₂₋₁₀

heterocyclyl-C₁₋₆-alkoxy, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₆-alkyl, C₁₋₆ alkylamino-C₁₋₆-alkylamino, C₃₋₈ cycloalkylamino, C₁₋₆ alkylthio, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkylamino, cyano-substituted C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkoxy, cyano-substituted C₁₋₆ alkylamino, amino-substituted C₁₋₆ alkyl, C₁₋₆ alkylacyl, C₁₋₈ heteroalkyl, C₃₋₆ cycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkylamino, C₂₋₁₀ heterocyclylacyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₆₋₁₀ arylamino, C₁₋₉ heteroaryl, C₁₋₉ heteroarylamino, NH₂-C(=O)-, C₁₋₆ alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, C₁₋₆ alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-N(R⁶)-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-N(R⁶)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-C₁₋₆-alkyl-N(R⁶)-C(=O)-, C₁₋₆ alkyl-C(=O)-N(R⁶)-, C₁₋₆ alkyl-N(R⁶)-C(=O)-C₁₋₆-alkyl-N(R⁶)-, C₁₋₆ alkyl-S(=O)₂-, C₁₋₆ alkyl-S(=O)₂-C₁₋₆-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-C₁₋₆-alkyl-;

each n is independently 0, 1, 2, 3, or 4;

each p is independently 0, 1, or 2;

each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;

each R¹¹ and R¹² is independently H, deuterium, C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, halo-C₁₋₆-alkyl, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₂₋₁₀ heterocyclyl or C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl; or R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 12-membered heterocycle;

each R⁵ is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₆ alkyl-C(=O)-, cyano-substituted C₁₋₆ alkyl-C(=O)-, C₁₋₆ alkylamino, NH₂-S(=O)₂-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-N(R¹³)-S(=O)₂-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-N(R¹³)-C₁₋₆ alkyl-, halo-C₁₋₆-alkyl, hydroxy-substituted C₁₋₆ alkyl, cyano-substituted C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy or C₆₋₁₀ aryl-C₁₋₆-alkoxy; and

each R¹³ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl.

17. The compound of claim 1 or 16, wherein each R⁵ is independently H, deuterium, F, Cl, Br, I,

CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy-C₁₋₄-alkyl, C₁₋₄ alkoxy-C₁₋₄-alkoxy, C₁₋₃ alkoxy-C₁₋₄-alkylamino, C₆₋₁₀ aryloxy, C₁₋₉ heteroaryloxy, C₂₋₁₀ heterocycloxy, C₆₋₁₀ aryl-C₁₋₃-alkoxy, C₁₋₉ heteroaryl-C₁₋₃-alkoxy, C₂₋₁₀ heterocyclyl-C₁₋₆-alkoxy, C₁₋₄ alkylamino, C₁₋₃ alkylamino-C₁₋₃-alkyl, C₁₋₄ alkylamino-C₁₋₄-alkylamino, C₃₋₆ cycloalkylamino, C₁₋₄ alkylthio, halo-C₁₋₄-alkyl, halo-C₁₋₄-alkoxy, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkylamino, cyano-substituted C₁₋₄ alkyl, cyano-substituted C₁₋₄ alkoxy, cyano-substituted C₁₋₄ alkylamino, amino-substituted C₁₋₄ alkyl, C₁₋₄ alkylacyl, C₁₋₈ heteroalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₄-alkyl, C₂₋₆ heterocyclyl-C₁₋₄-alkylamino, C₂₋₁₀ heterocyclylacyl, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₆₋₁₀ arylamino, C₁₋₉ heteroaryl, C₁₋₉ heteroarylamino, NH₂-C(=O)-, C₁₋₄ alkyl-N(R⁶)-C(=O)-, NH₂-S(=O)₂-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-N(R⁶)-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-S(=O)₂-N(R⁶)-C₁₋₃-alkyl-, C₆₋₁₀ aryl-C₁₋₃ alkyl-N(R⁶)-C(=O)-, C₁₋₄ alkyl-C(=O)-N(R⁶)-, C₁₋₃ alkyl-N(R⁶)-C(=O)-C₁₋₆ alkyl-N(R⁶)-, C₁₋₄ alkyl-S(=O)₂-, C₁₋₃ alkyl-S(=O)₂-C₁₋₄-alkyl-, -(CH₂)_n-N(R⁶)-(CH₂)_n-S(=O)_p-R⁷, -(CH₂)_n-N(R⁶)-(CH₂)_n-N(R⁶)-S(=O)_p-R⁷, -(CR⁸R⁹)_n-COOR¹⁰ or R¹¹R¹²N-C(=O)-C₁₋₃-alkyl-;

each n is independently 0, 1, 2, 3, or 4;

each p is independently 0, 1, or 2;

each R⁶, R⁷, R⁸, R⁹ and R¹⁰ is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl;

each R¹¹ and R¹² is independently H, deuterium, C₁₋₃ alkyl, cyano-substituted C₁₋₃ alkyl, halo-C₁₋₃-alkyl, C₁₋₃ alkoxy-C₁₋₃-alkyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₂₋₆ heterocyclyl or C₂₋₆ heterocyclyl-C₁₋₃-alkyl; or R¹¹ and R¹², together with the N atom to which they are attached, form a 3- to 8-membered heterocycle;

each R⁵ is optionally and independently substituted with one or more H, deuterium, F, Cl, Br, I, CN, OH, NO₂, NH₂, COOH, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkoxy-C₁₋₄-alkyl, C₁₋₃ alkyl-C(=O)-, cyano-substituted C₁₋₃ alkyl-C(=O)-, C₁₋₃ alkylamino, NH₂-S(=O)₂-, C₁₋₃ alkyl-N(R¹³)-S(=O)₂-, NH₂-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-N(R¹³)-S(=O)₂-C₁₋₃-alkyl-, C₁₋₃ alkyl-S(=O)₂-N(R¹³)-C₁₋₃-alkyl-, halo-C₁₋₃-alkyl, hydroxy-substituted C₁₋₃ alkyl, cyano-substituted C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy or C₆₋₁₀ aryl-C₁₋₃-alkoxy; and

each R^{13} is independently H, deuterium, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *tert*-butyl.

18. The compound of claim 3, wherein X is N or CR^x ;

X^3 is CR or N;

each of Z^1 , Z^2 and Z^3 is independently N or CR^y ;

wherein R is H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , COOH, C_{1-3} alkyl or C_{1-3} alkoxy;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} alkylamino- C_{1-4} -alkylamino or halo- C_{1-3} -alkyl;

L^1 is -O-, $-N(R^{1a})$ -, $-S(=O)_p$ -, $-C(=O)$ -, $-C(=O)-NH$ - or $-S(=O)_p-NH$ -;

L^2 is a bond, -O-, $-N(R^{1a})$ -, $-CH_2-N(R^{1a})$ -, $-CH(CH_3)-N(R^{1a})$ -, $-C(CH_3)_2-N(R^{1a})$ -, $-C(=O)-NH$ - or $-S(=O)_p-NH$ -;

L^3 is $-C(=O)$ - or $-S(=O)_2$ -;

m is 0, 1 or 2;

q is 1, 2 or 3;

each p is independently 0, 1, or 2; and

each R^{1a} is independently H, deuterium, C_{1-3} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

19. The compound of claim 18, wherein X is N or CH;

X^3 is CH or N;

each of Z^1 , Z^2 and Z^3 is independently N or CR^y ;

each R^y is independently H, deuterium, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , COOH, methyl, ethyl, propyl, $-CF_3$, $-CH_2Cl$, $-CCl_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CH_2CCl_3$, methoxy, ethoxy, propoxy, isopropoxy, $-NH-CH_3$, $-NH-CH_2-CH_3$, $-NH-CH_2-NH-CH_3$, $-N(CH_3)-CH_2-NH-CH_3$, $-NH-(CH_2)_2-NH-CH_3$ or $-N(CH_3)-(CH_2)_2-N(CH_3)_2$;

L^1 is -O-, $-NH$ -, $-S(=O)_p$ -, $-C(=O)$ -, $-C(=O)-NH$ - or $-S(=O)_p-NH$ -;

L^2 is a bond, -O-, $-NH$ -, $-CH_2-NH$ -, $-CH(CH_3)-NH$ - or $-C(CH_3)_2-NH$ -;

L^3 is $-C(=O)$ - or $-S(=O)_2$ -;

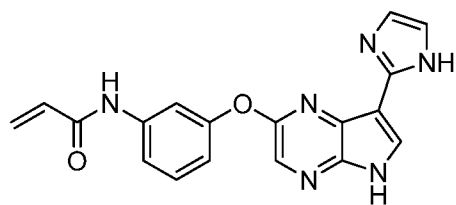
m is 0, 1 or 2;

q is 1, 2 or 3; and

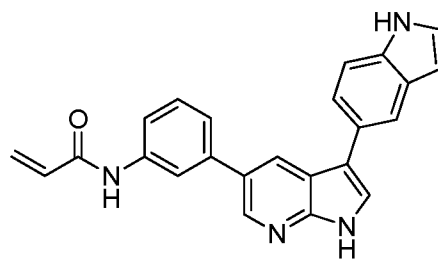
each p is independently 0, 1, or 2.

20. The compound of claim 1 having one of the following structures or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically

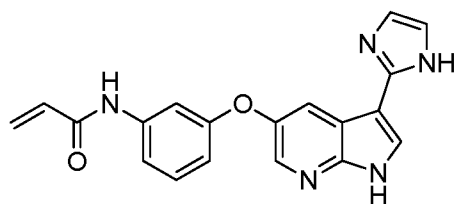
acceptable salt or a prodrug thereof,



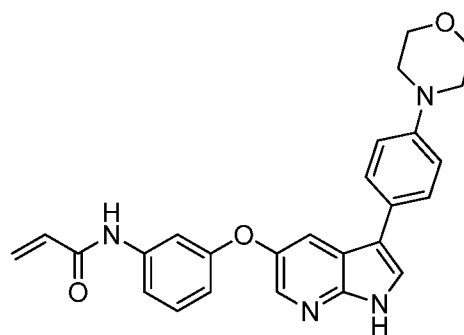
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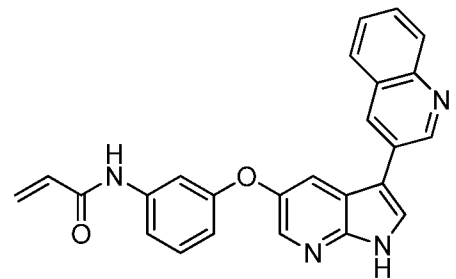
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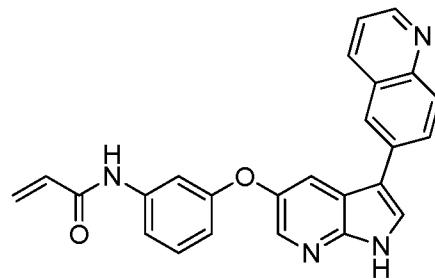
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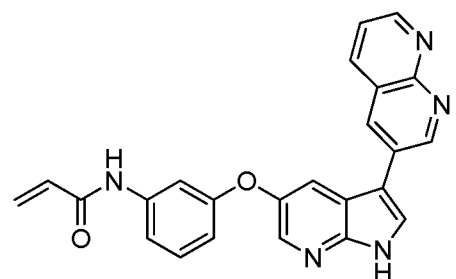
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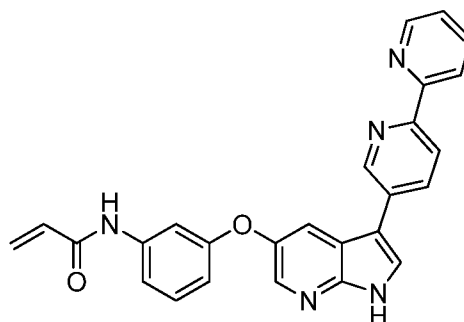
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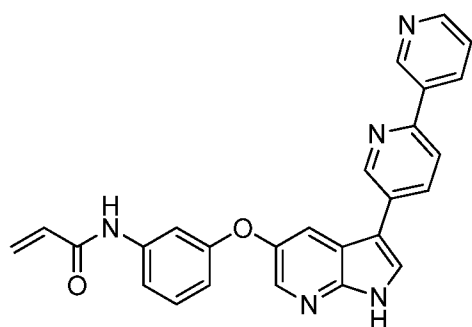
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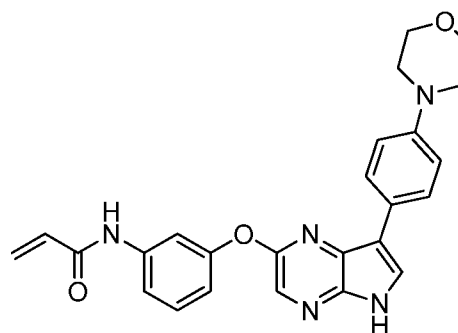
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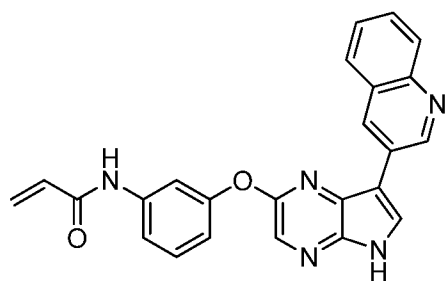
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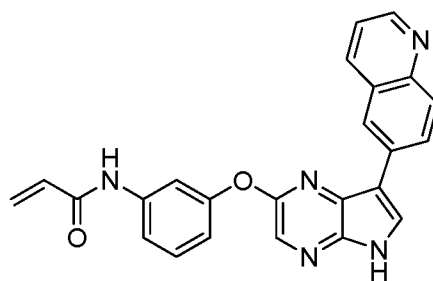
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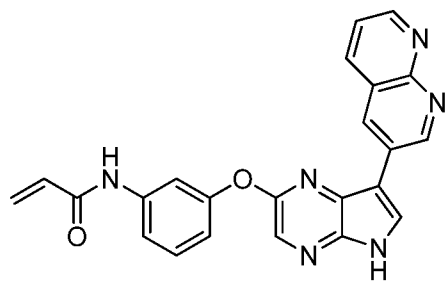
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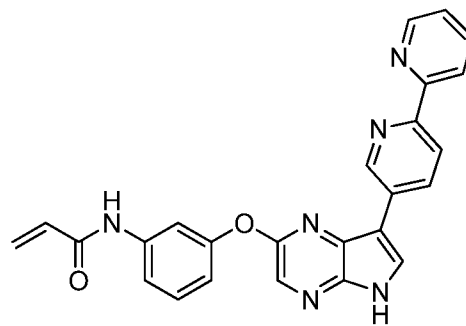
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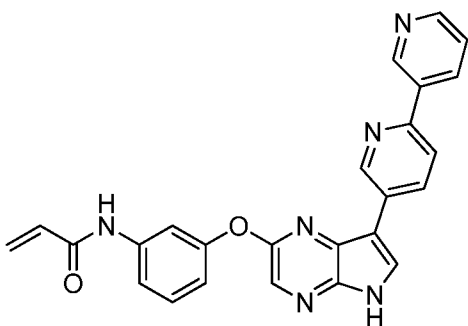
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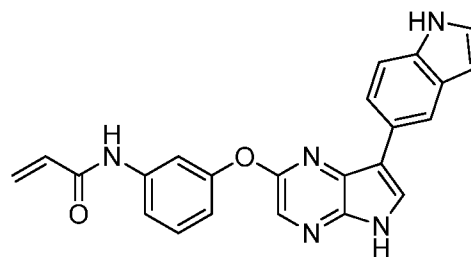
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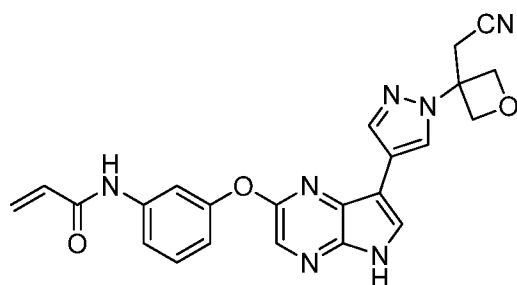
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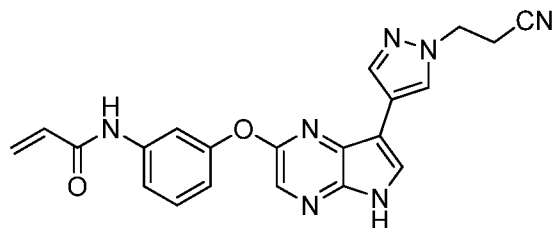
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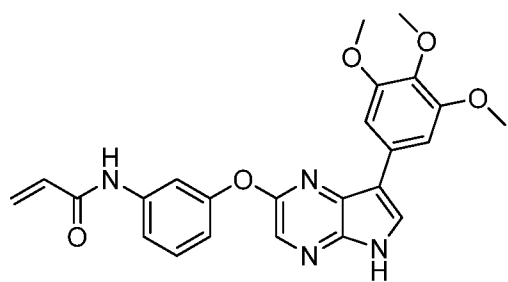
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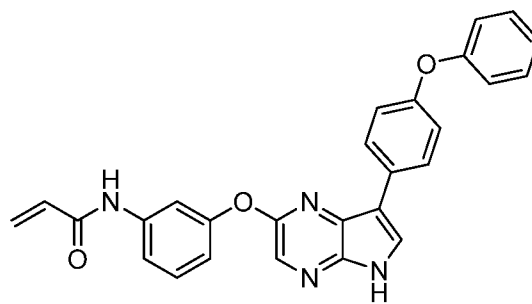
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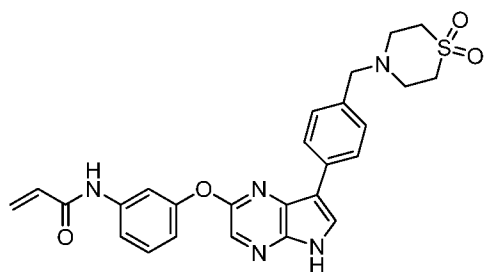
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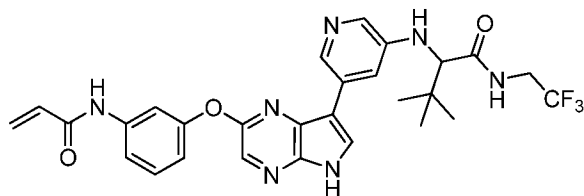
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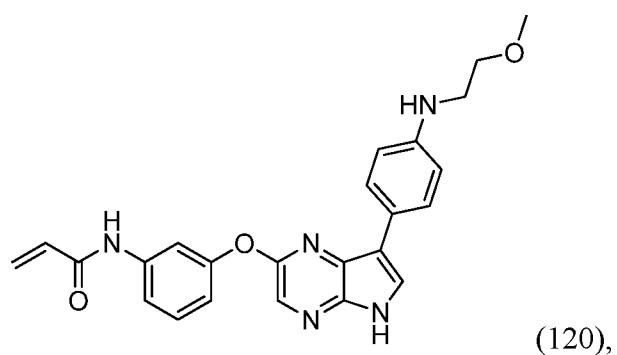
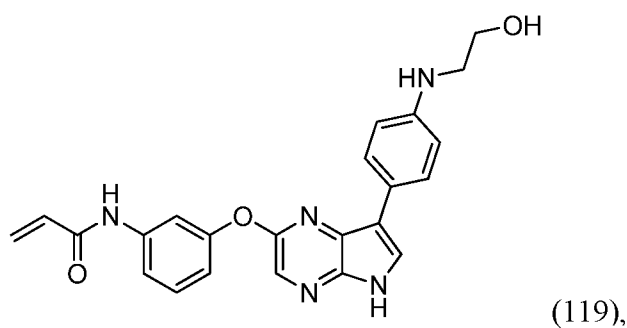
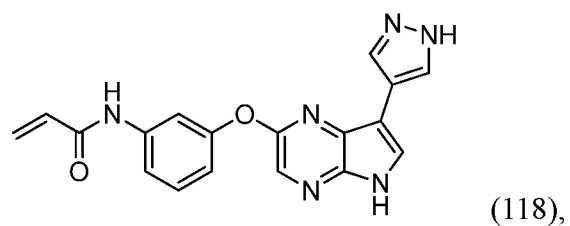
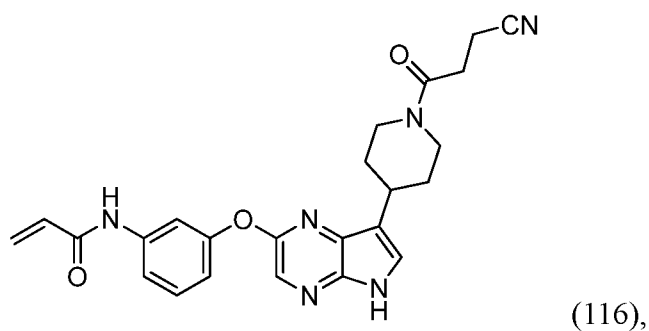
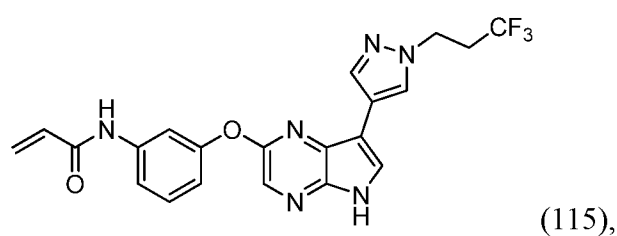
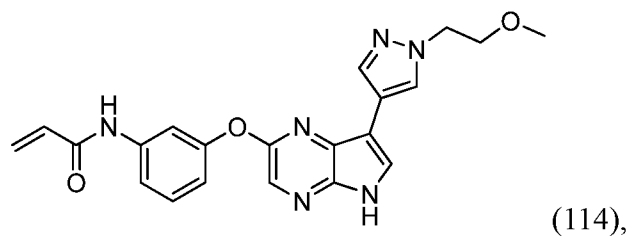
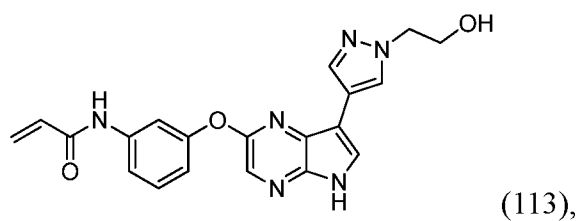
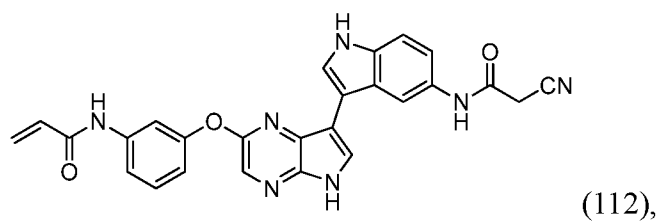
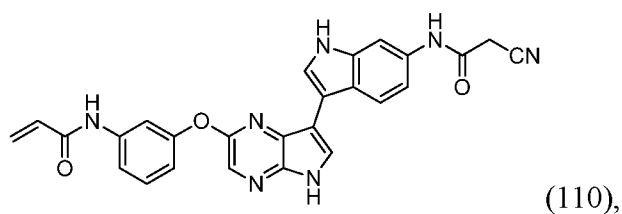
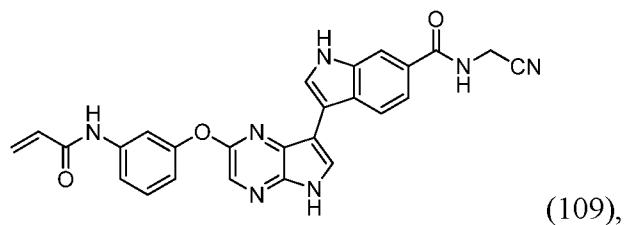
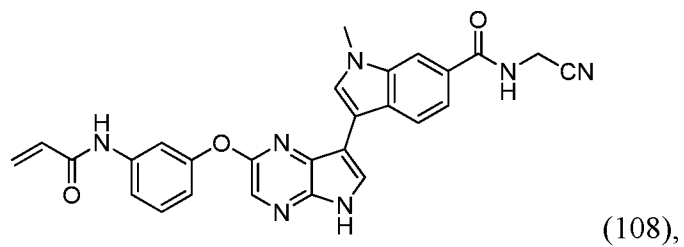
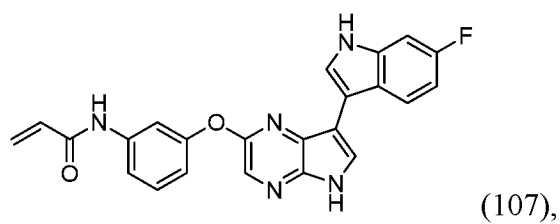
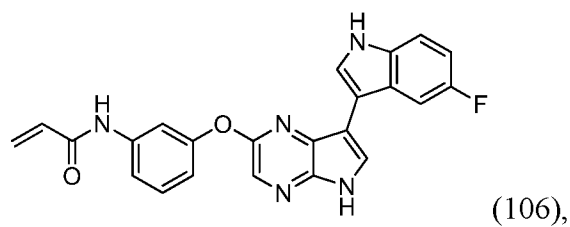
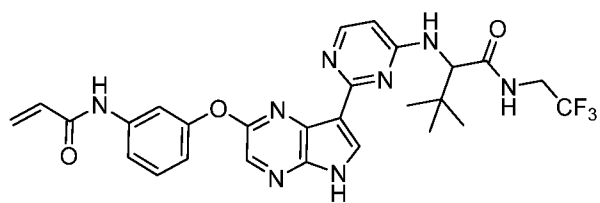
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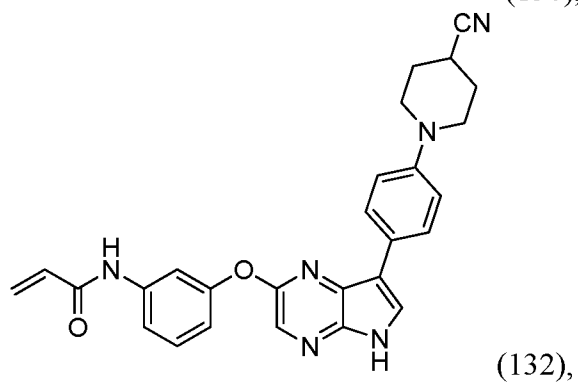
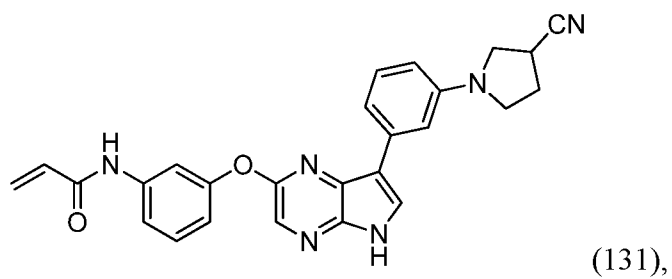
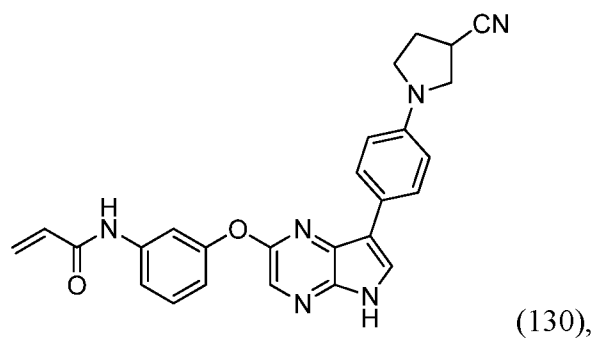
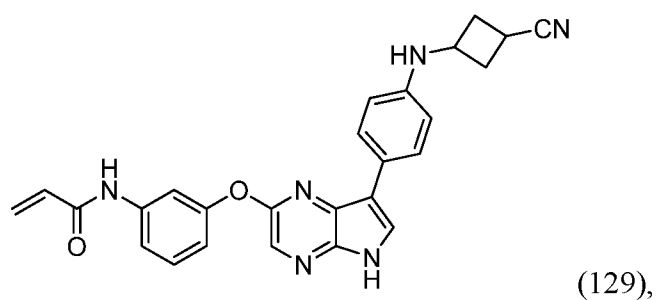
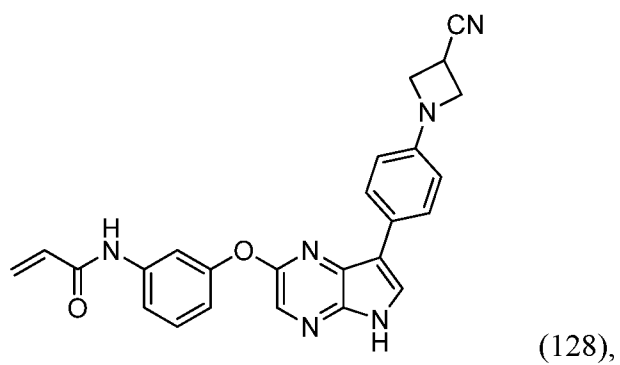
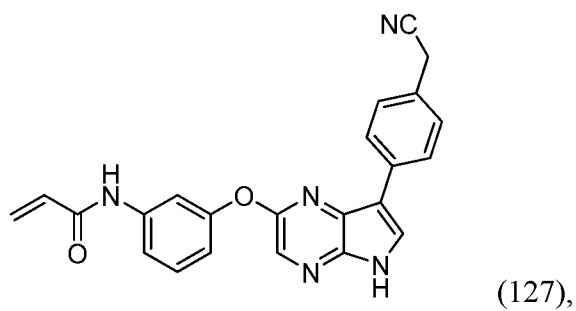
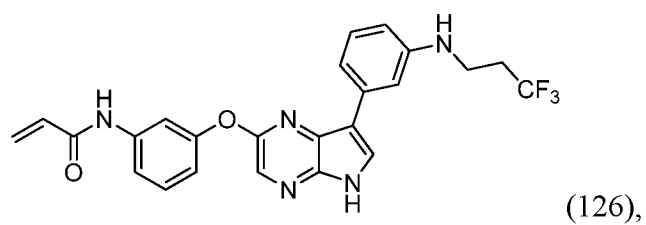
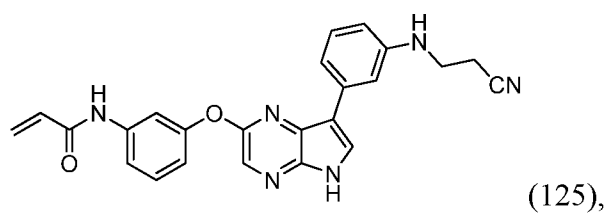
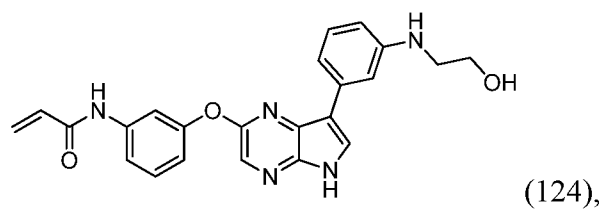
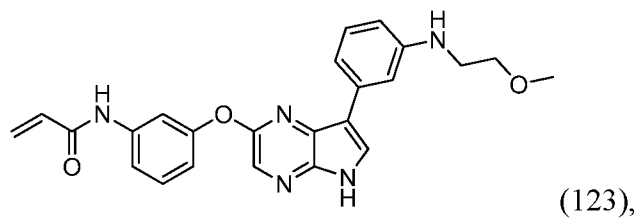
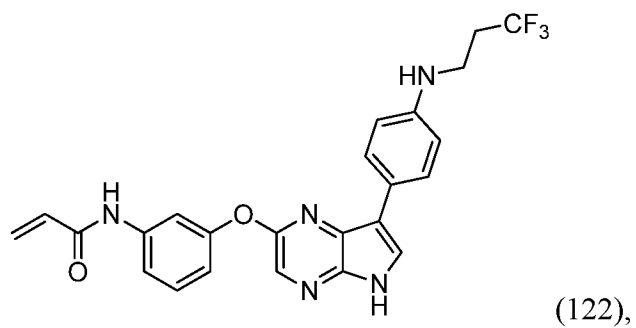
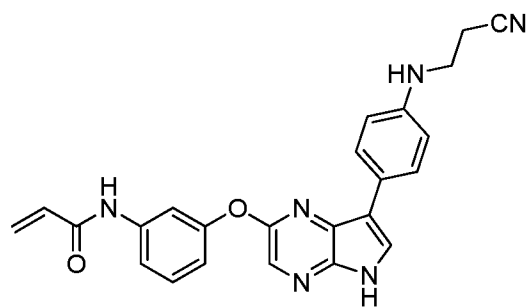


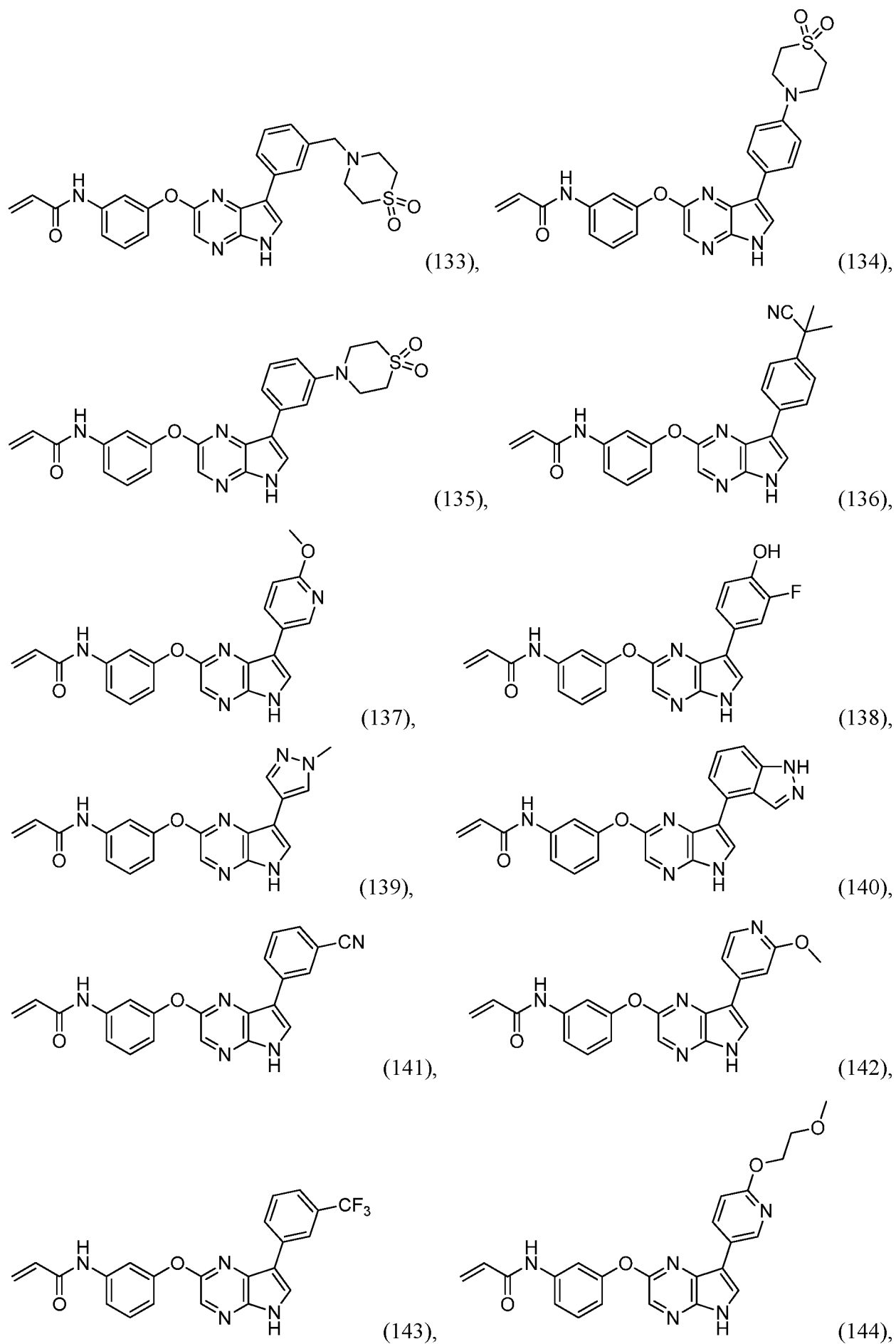
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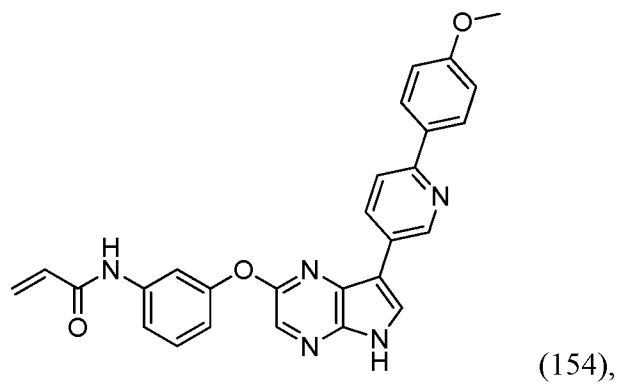
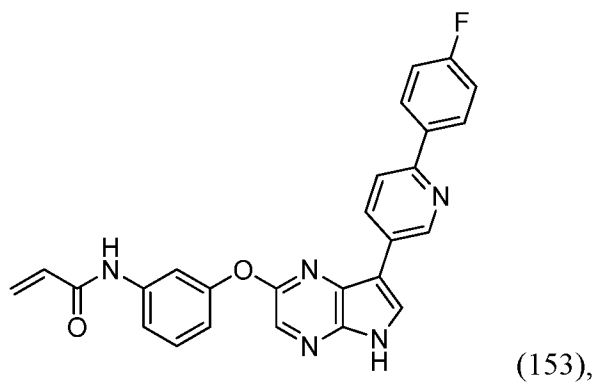
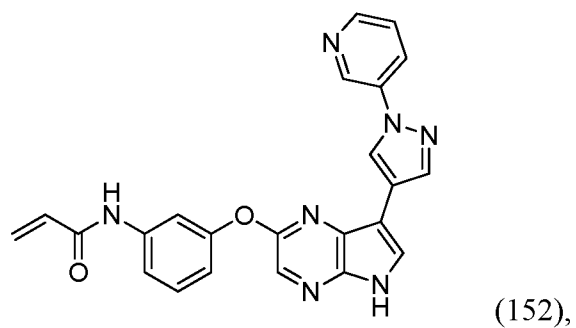
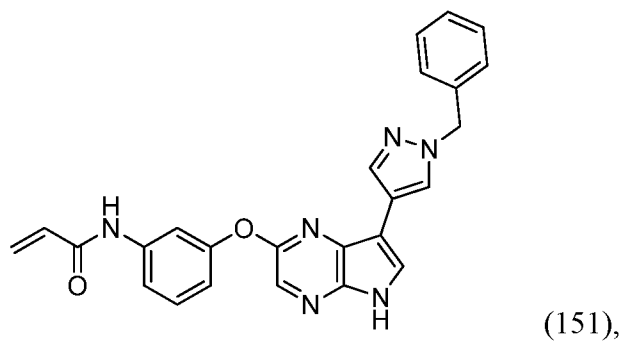
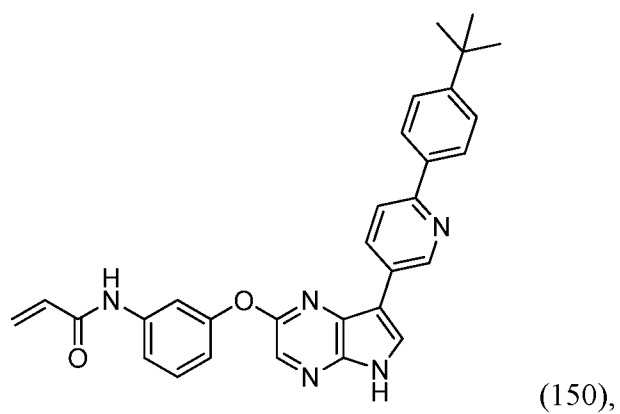
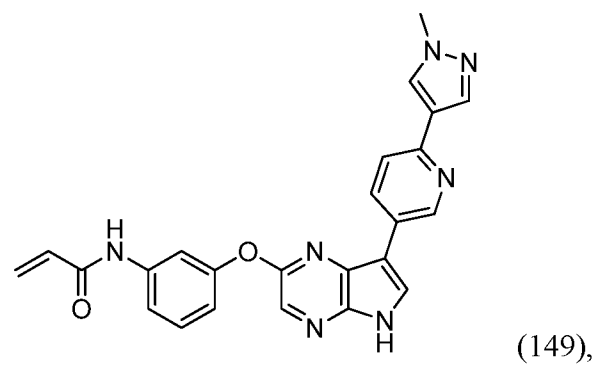
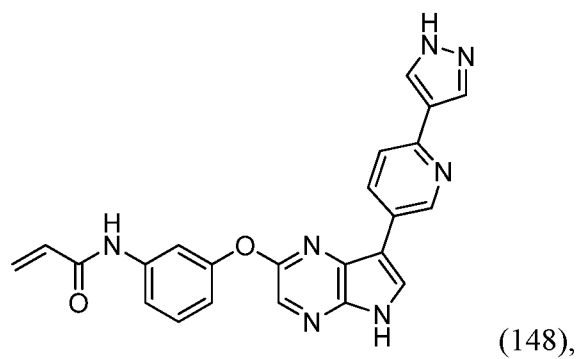
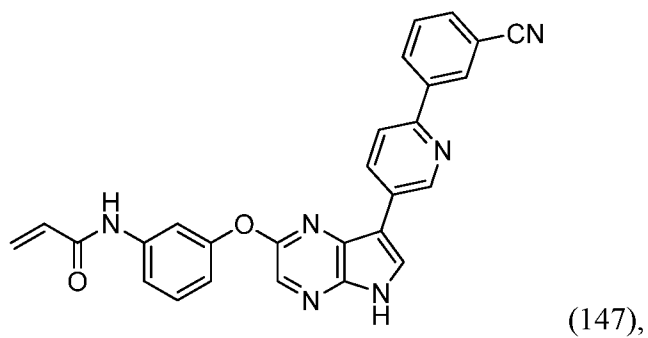
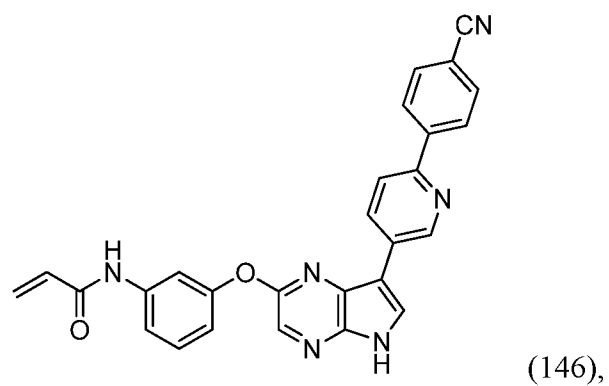
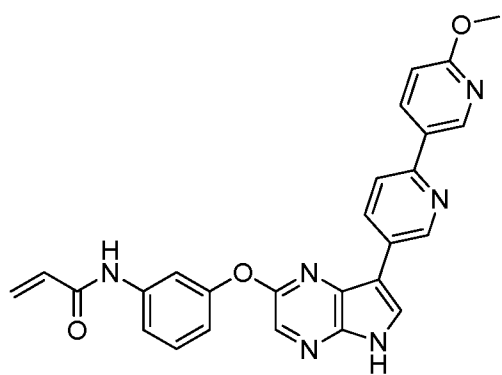


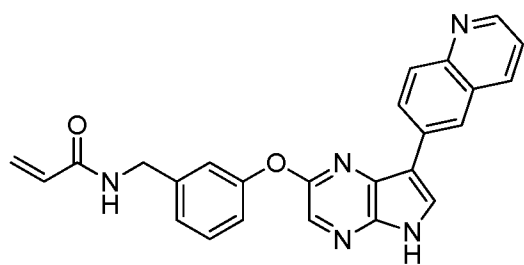
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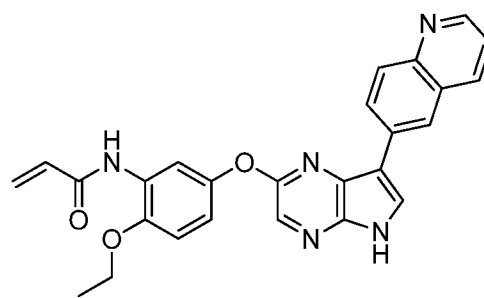




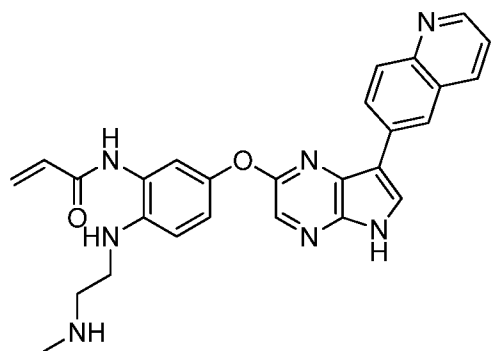




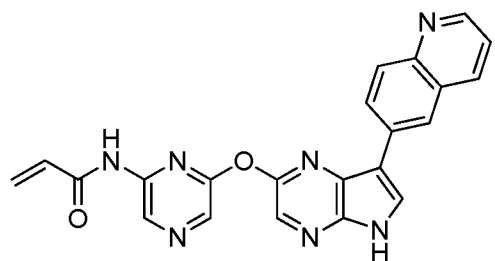
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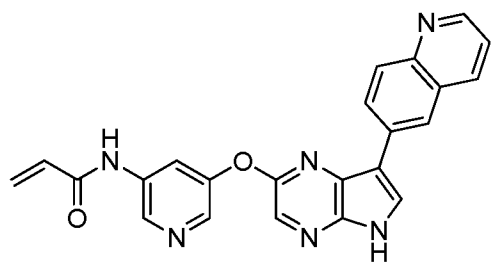
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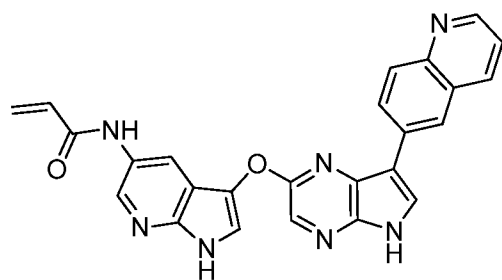
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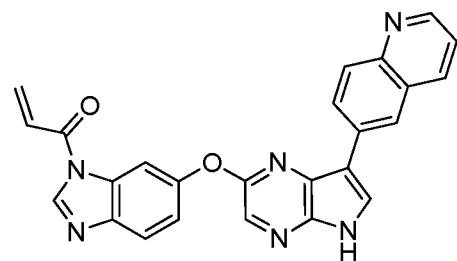
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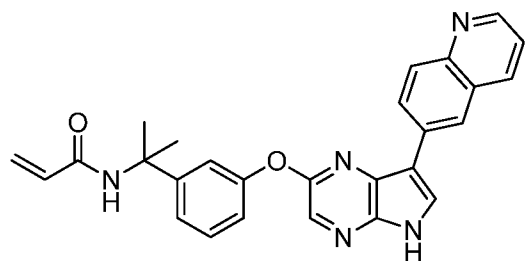
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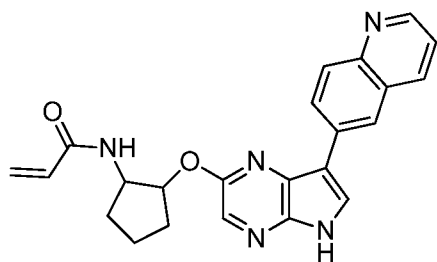
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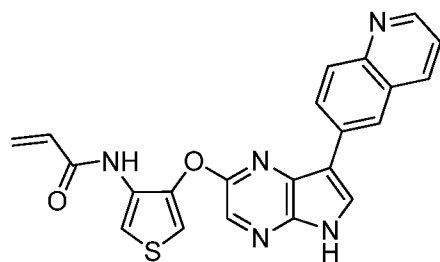
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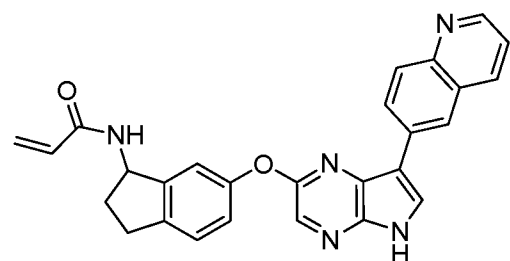
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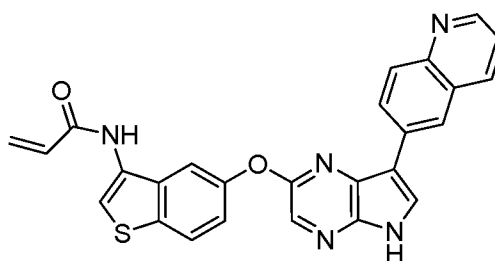
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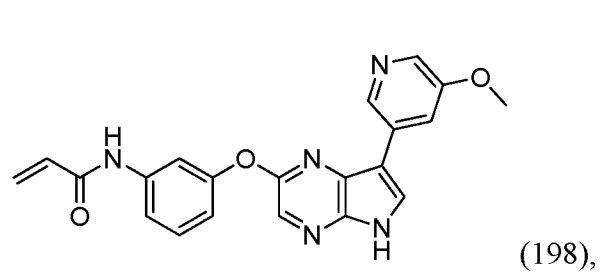
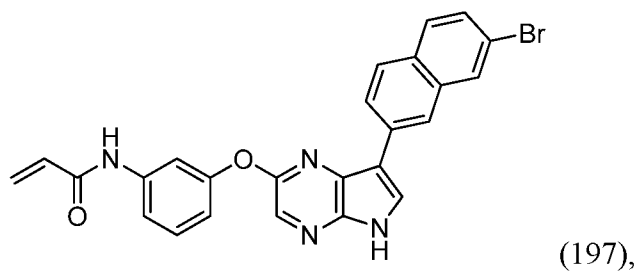
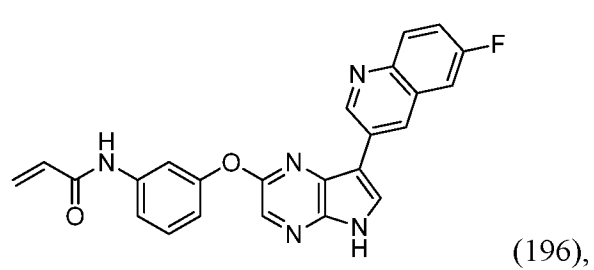
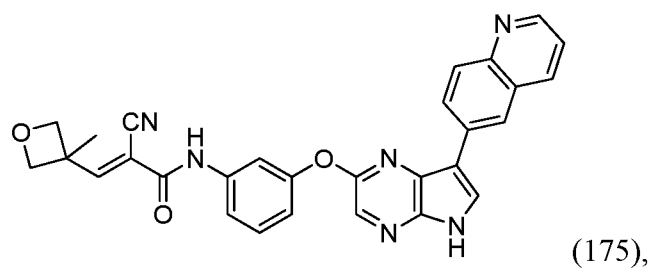
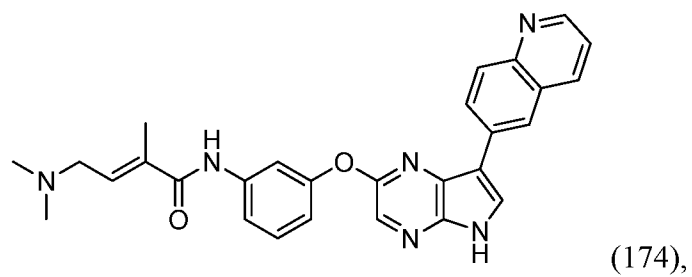
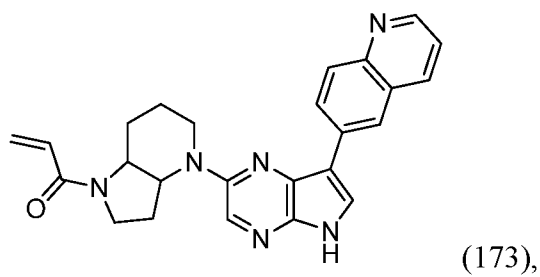
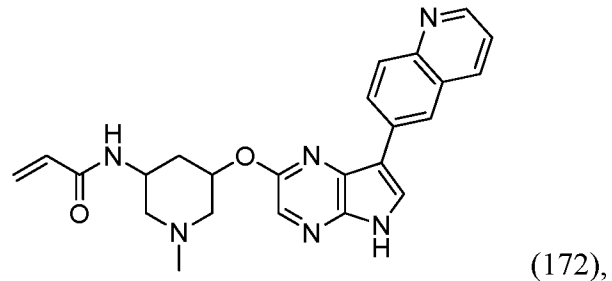
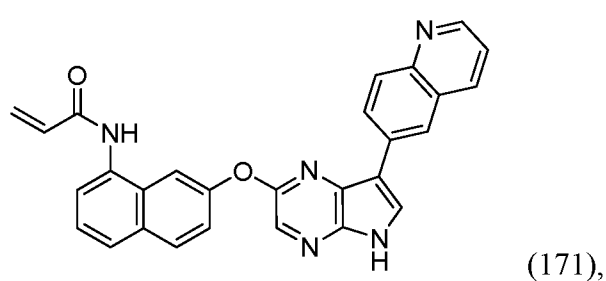
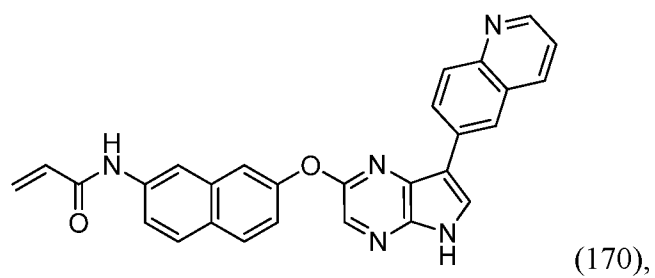
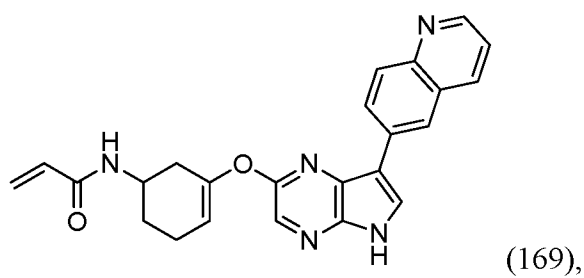
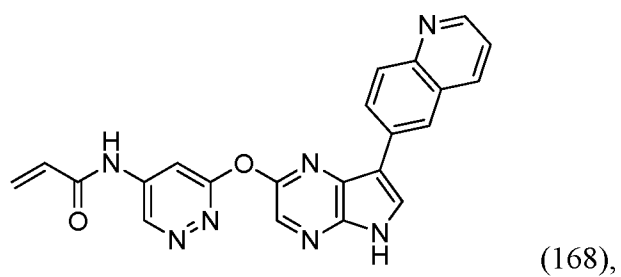
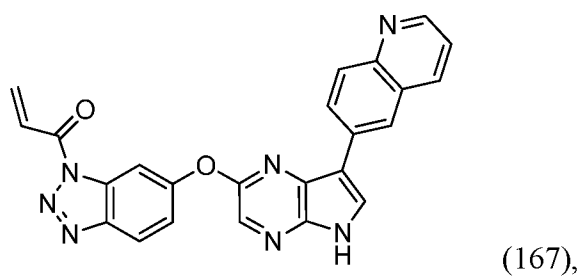
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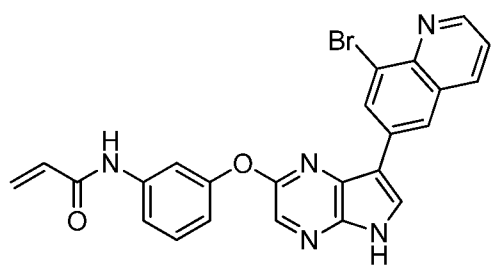


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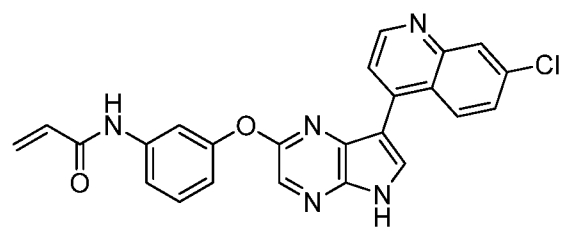


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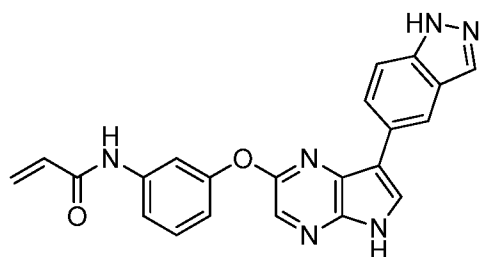




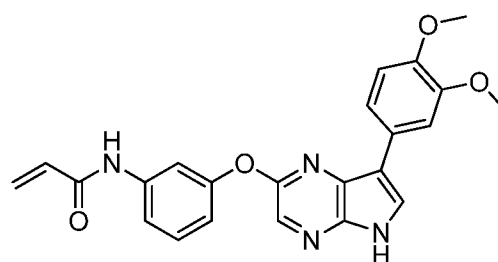
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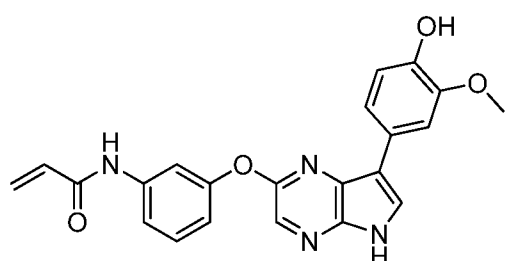
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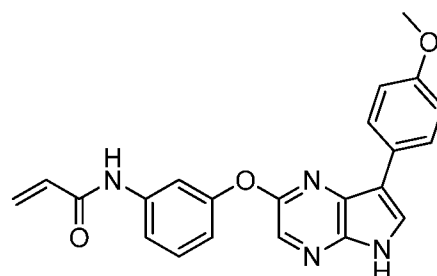
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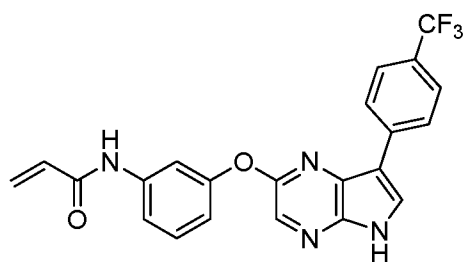
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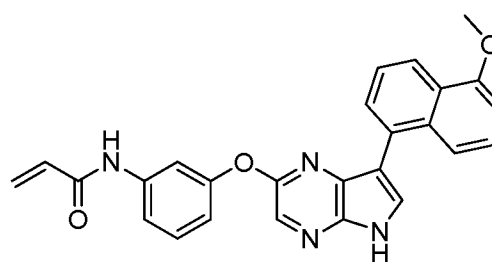
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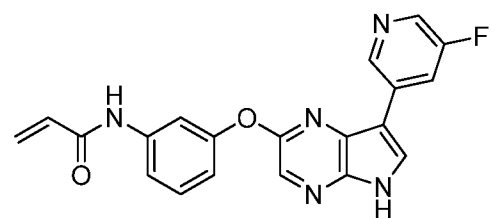
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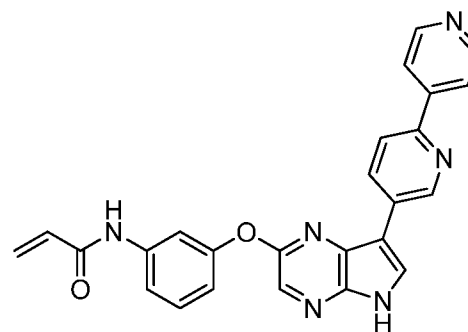
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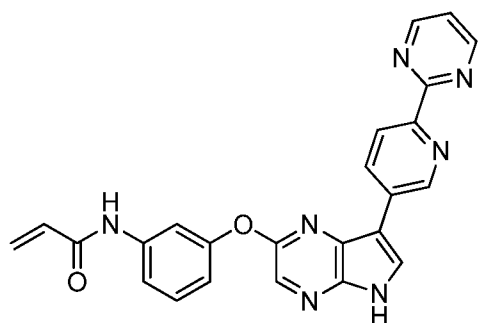
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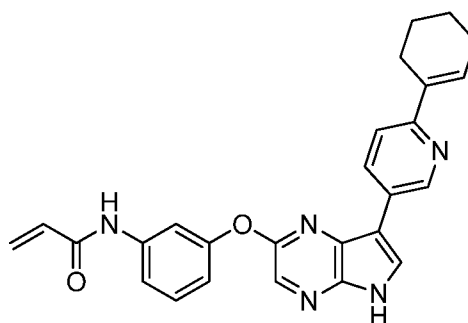
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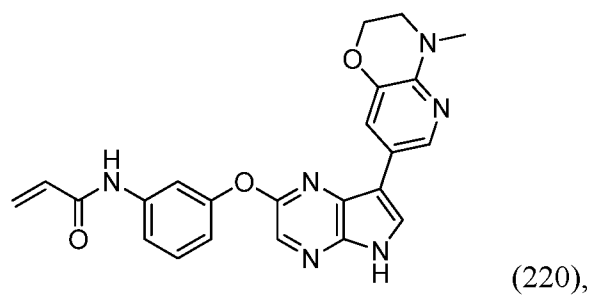
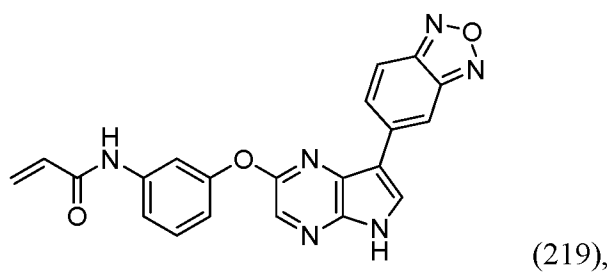
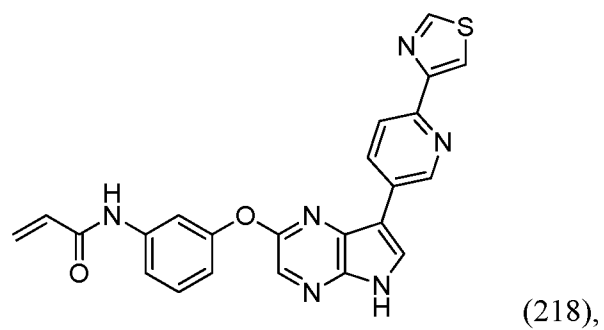
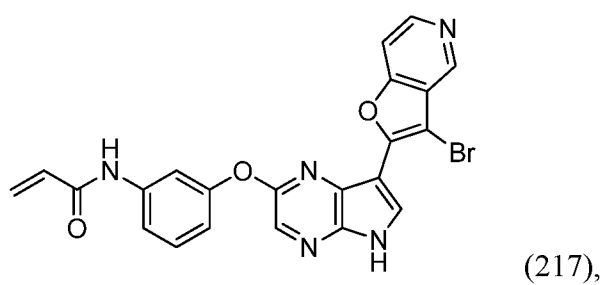
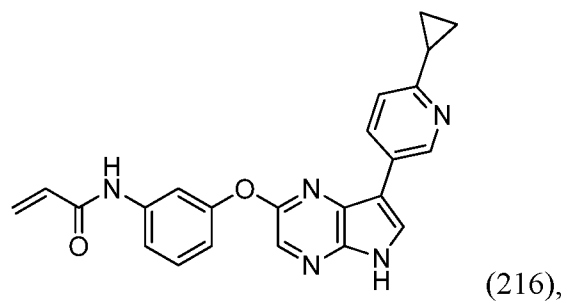
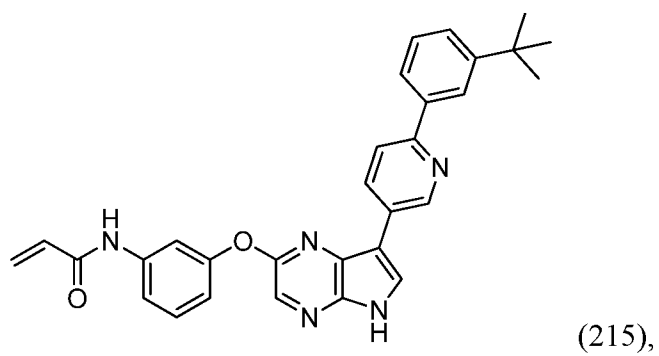
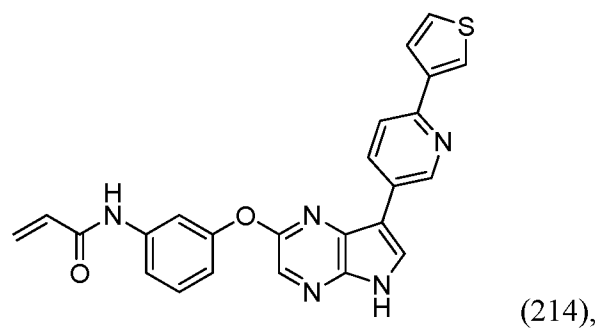
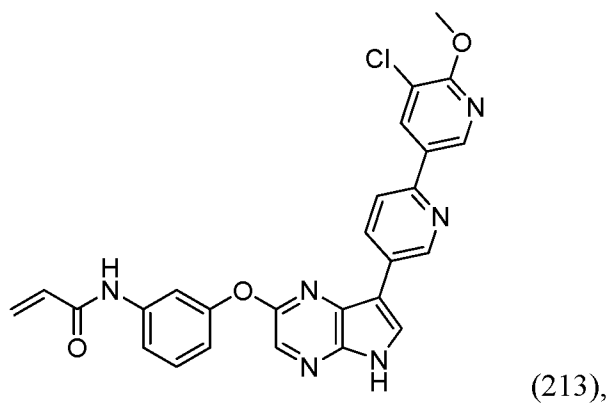
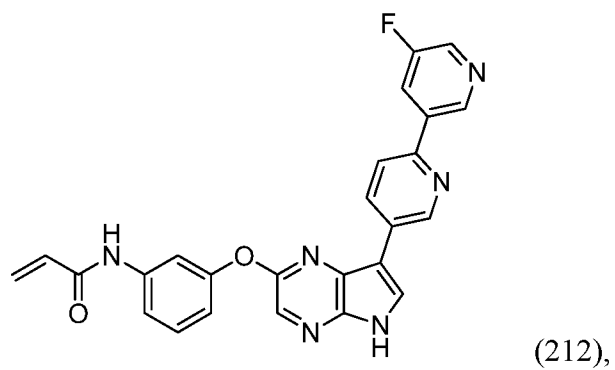
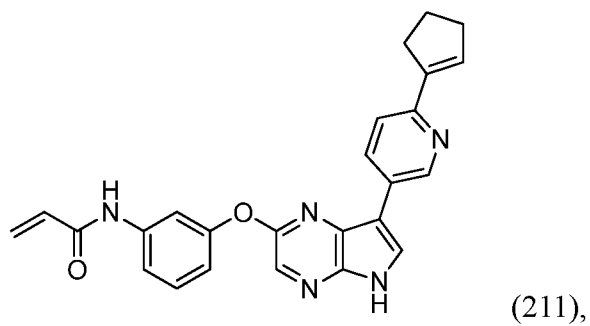
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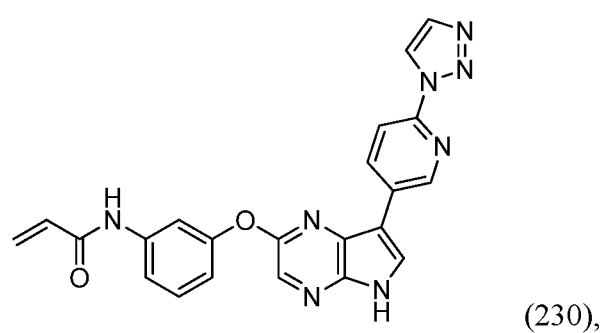
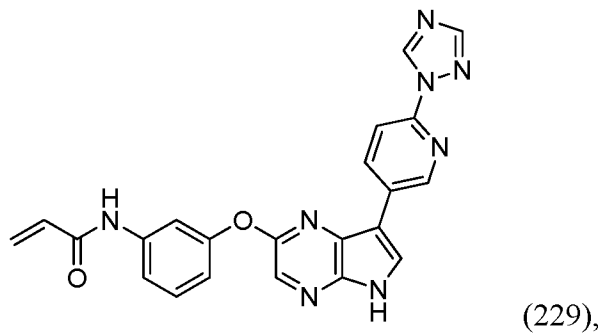
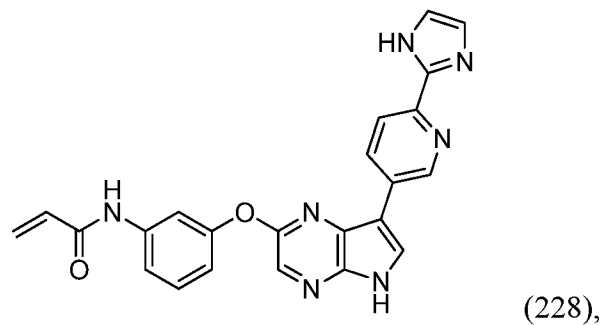
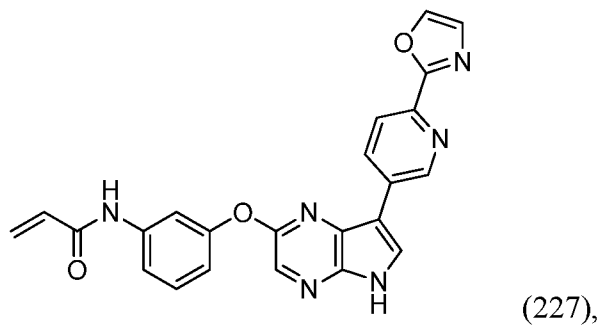
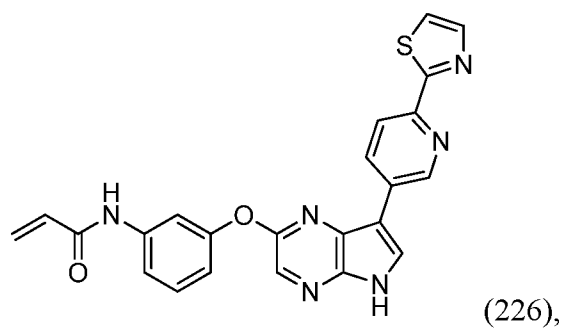
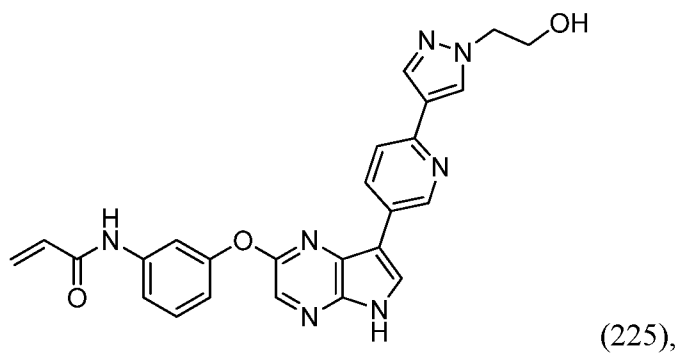
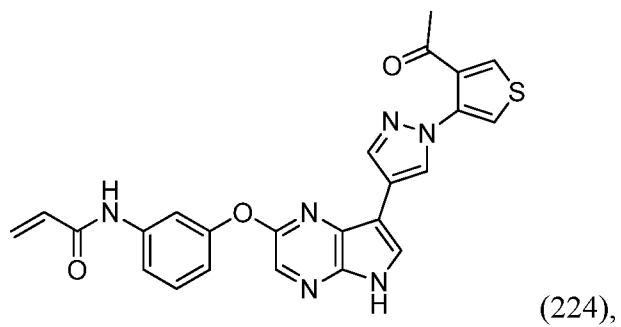
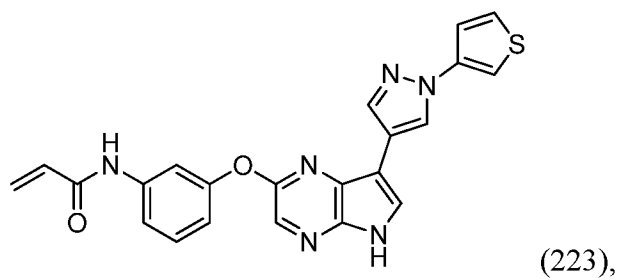
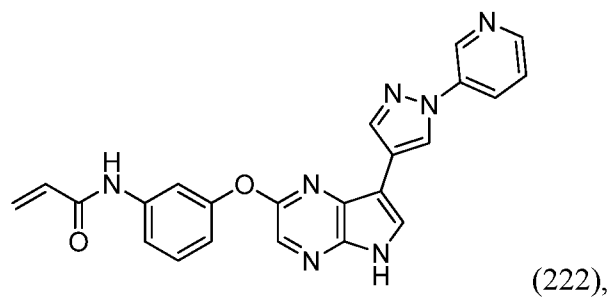
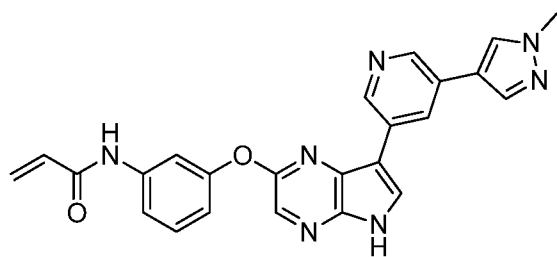


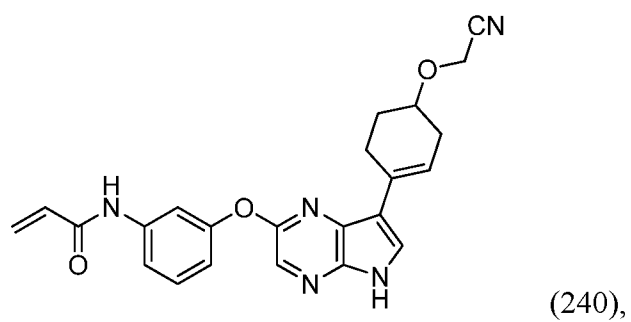
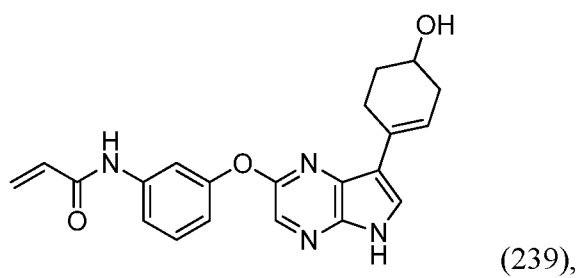
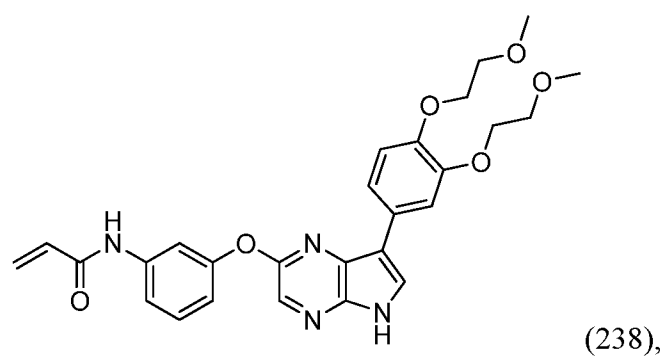
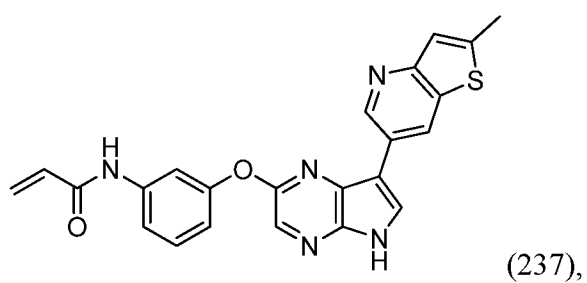
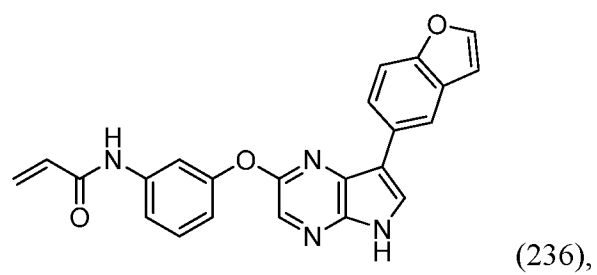
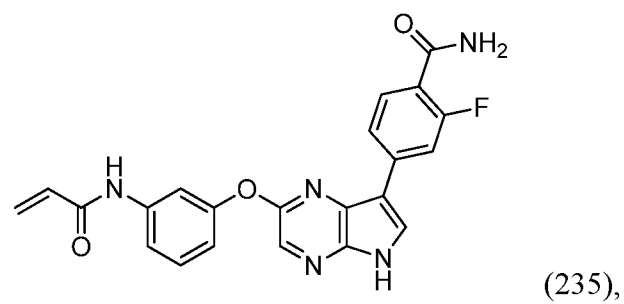
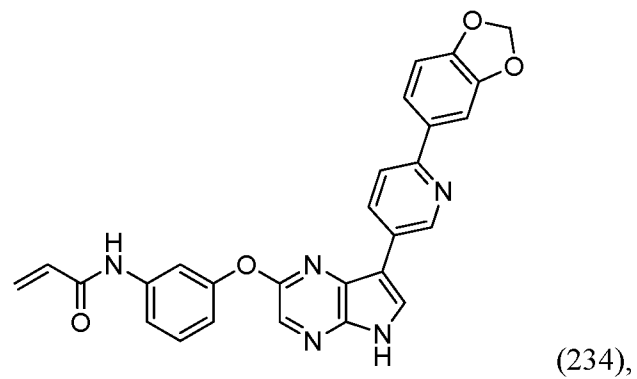
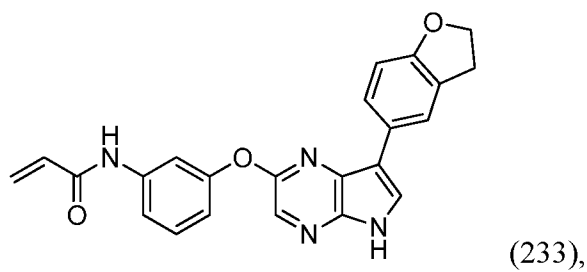
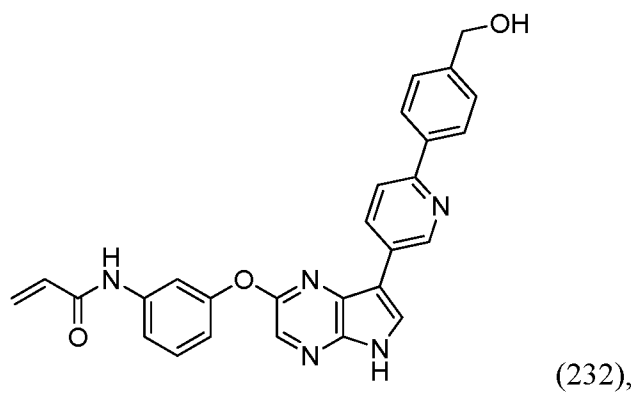
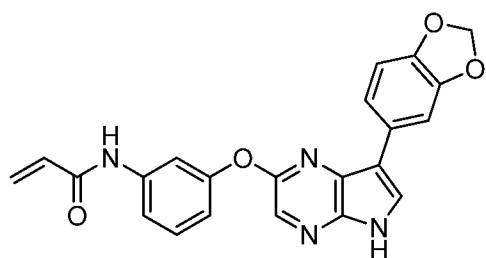
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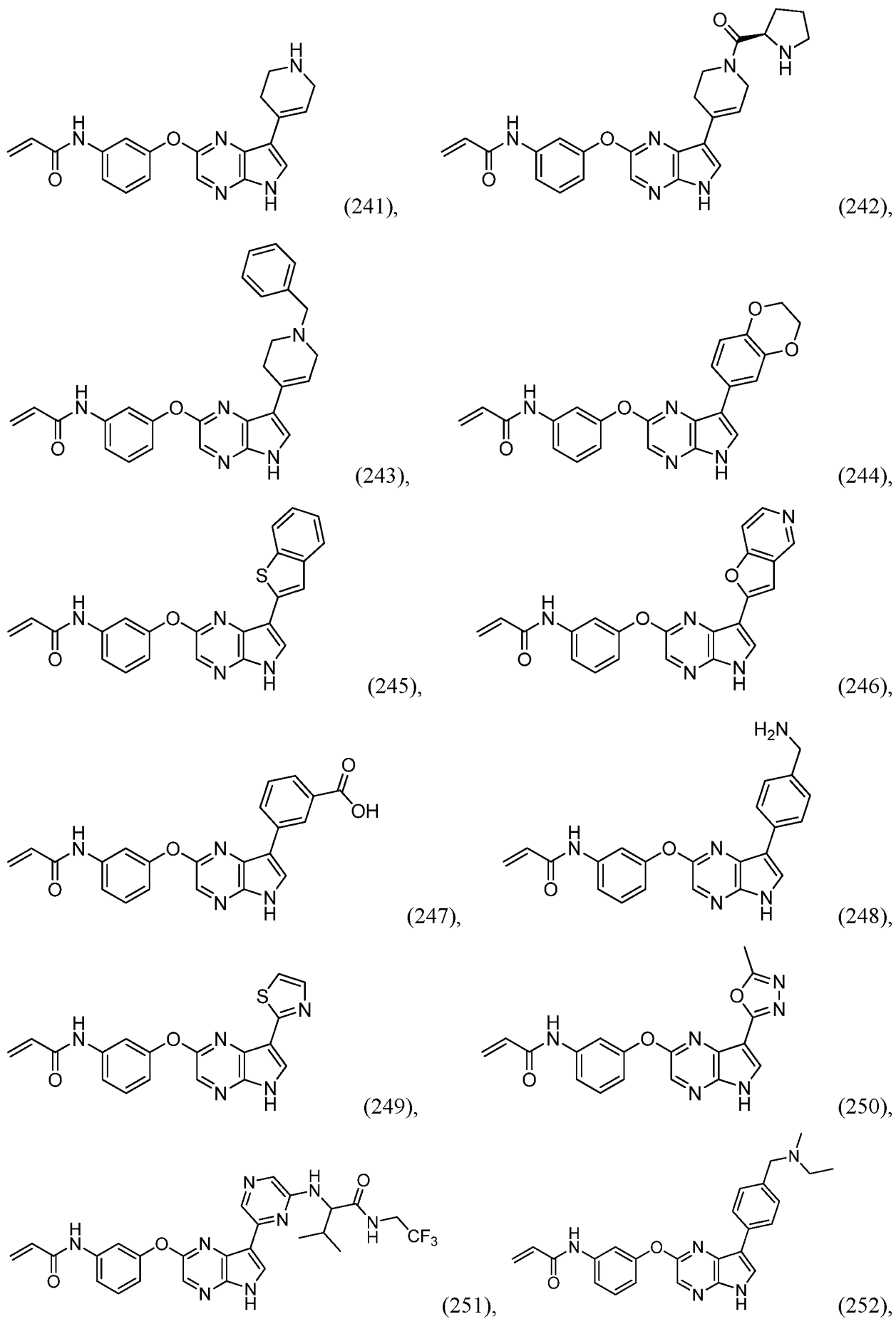


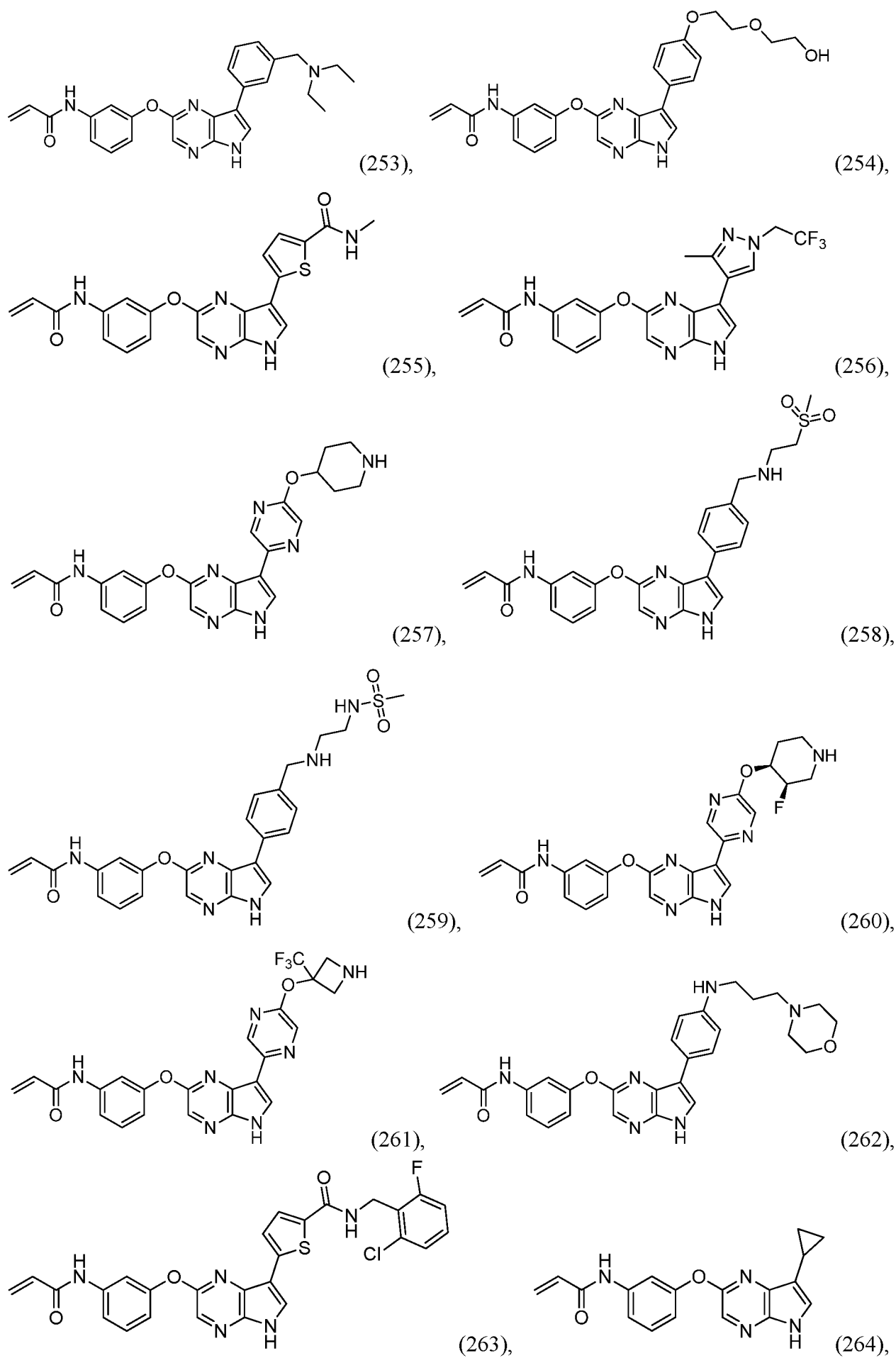
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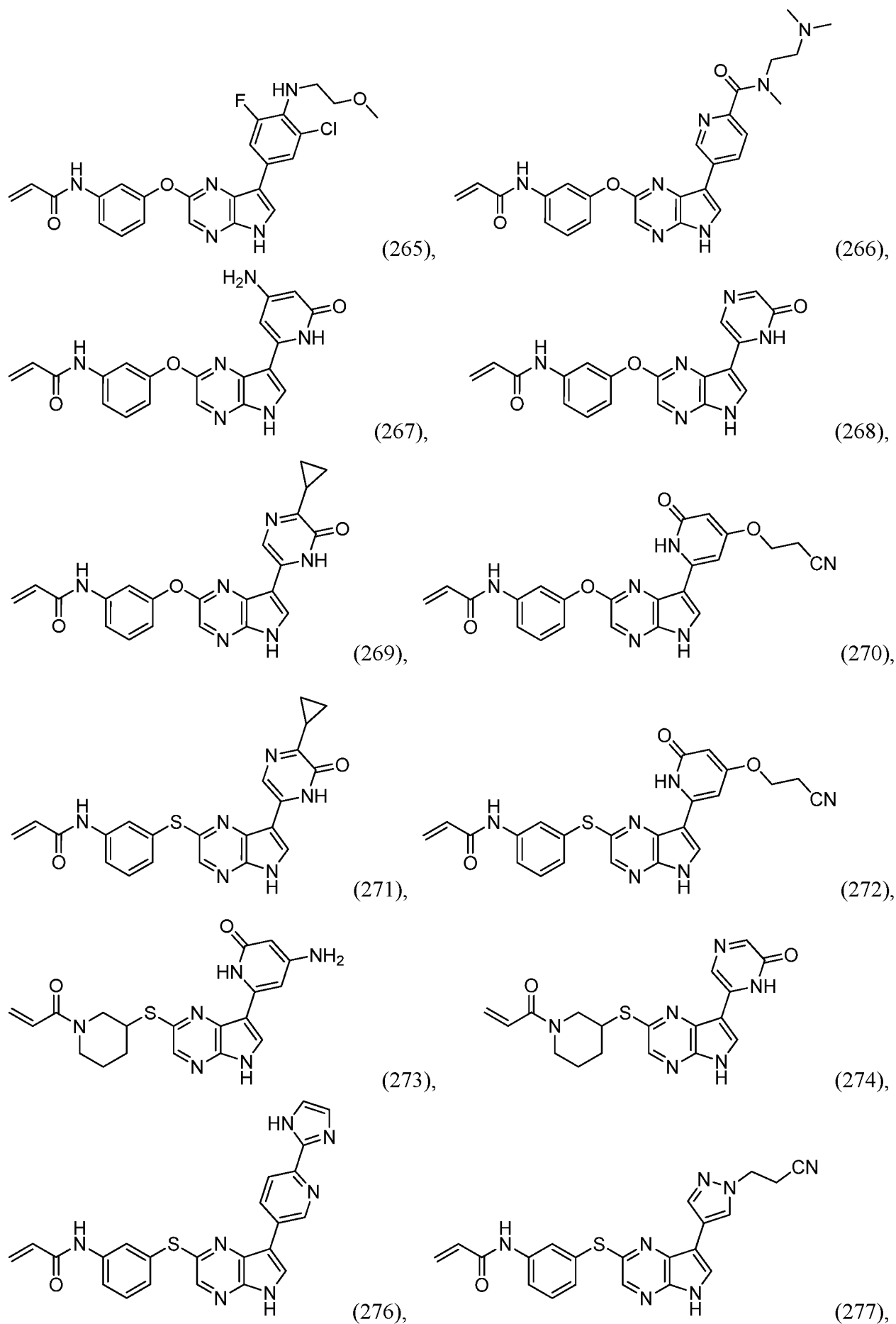


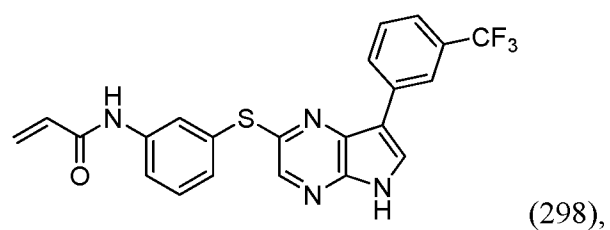
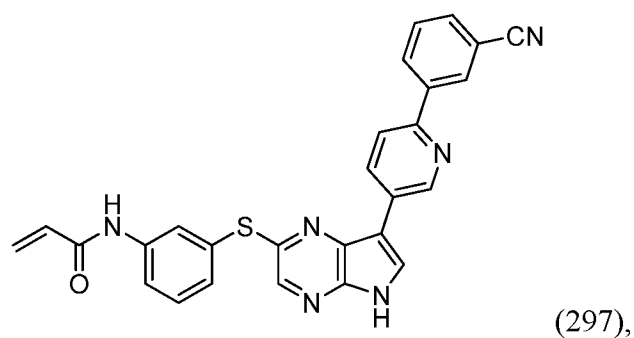
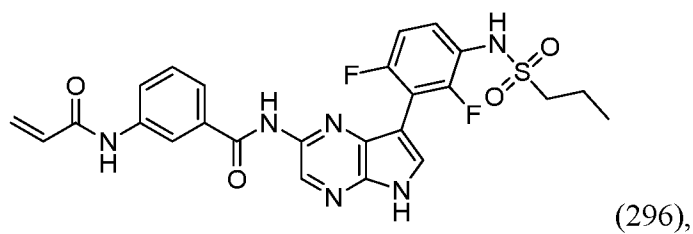
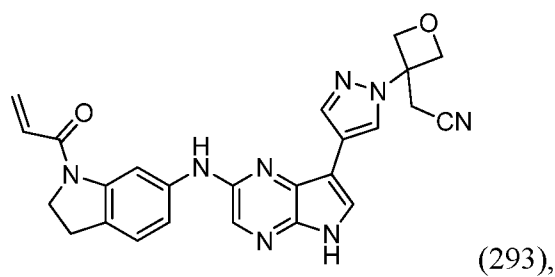
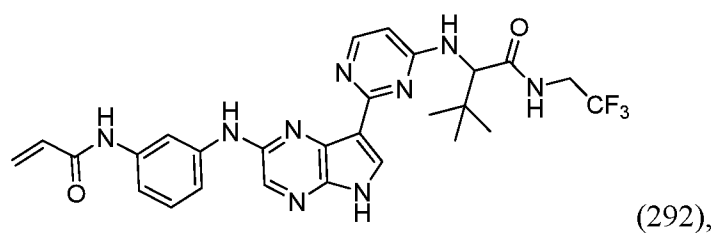
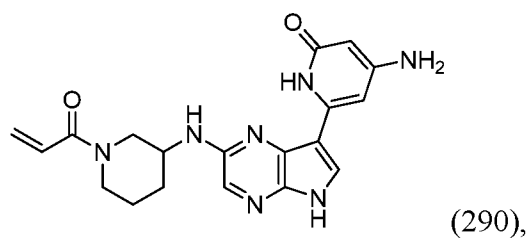
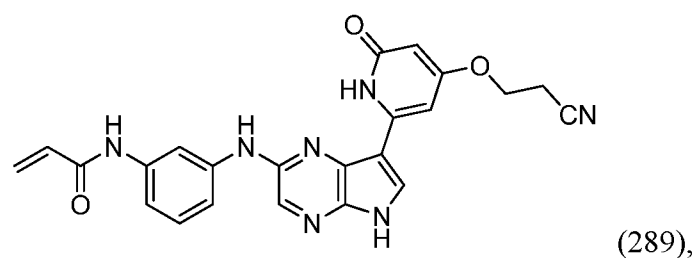
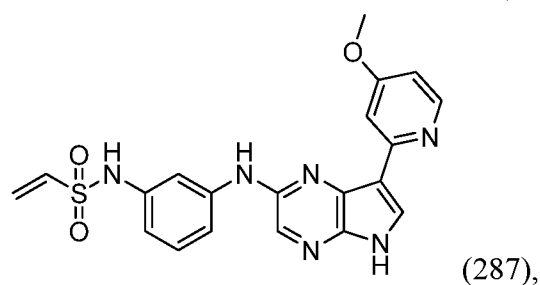
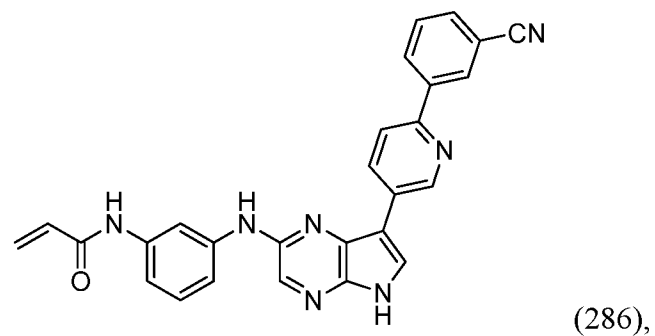
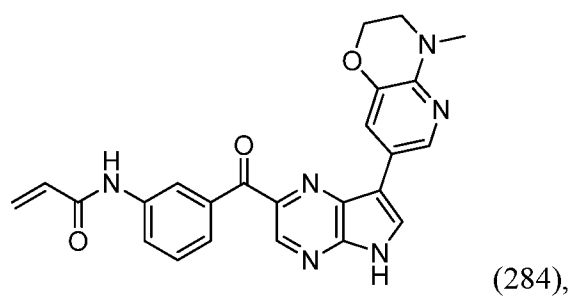
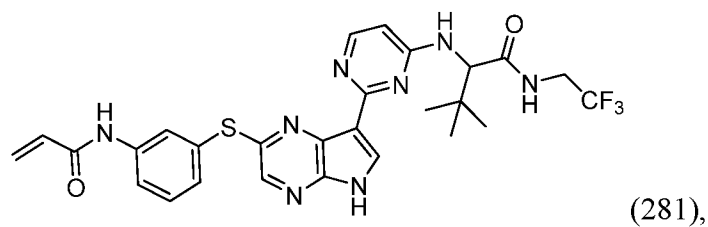
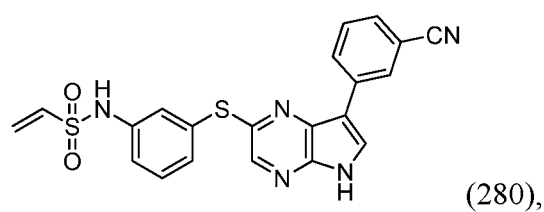


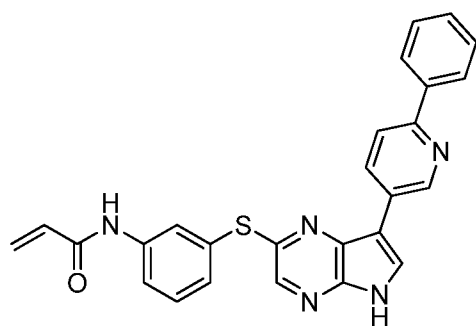




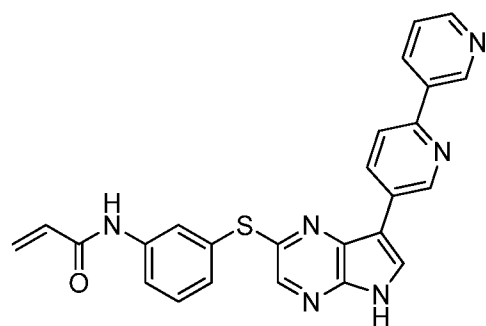




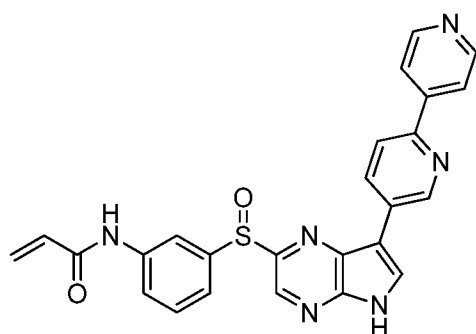




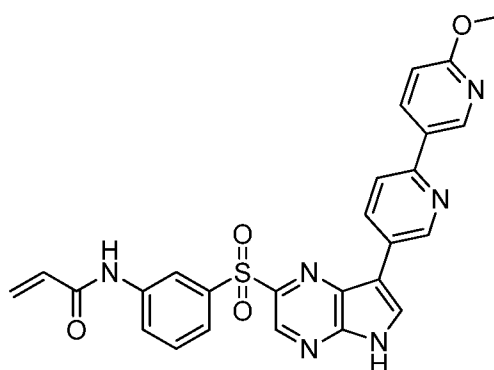
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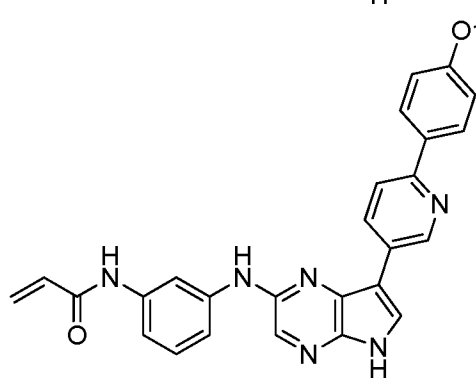
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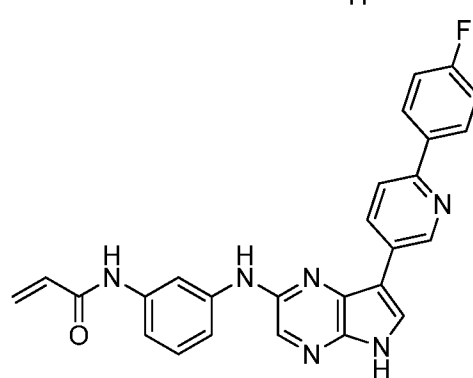
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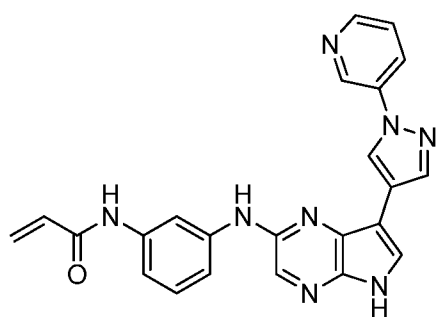
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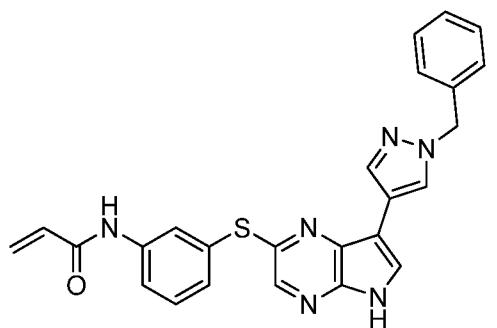
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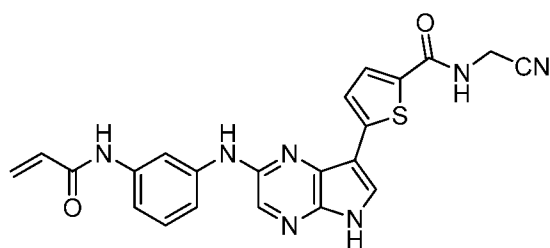
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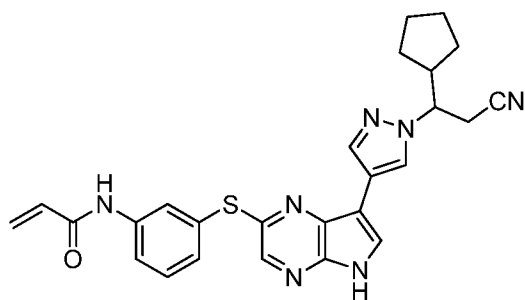
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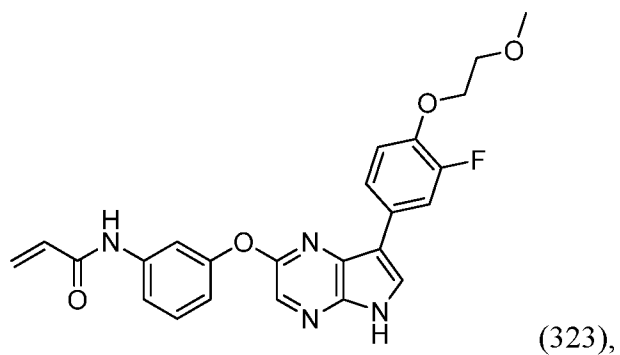
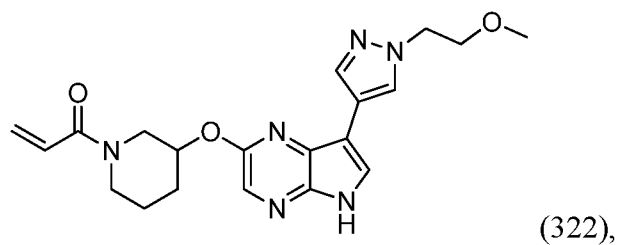
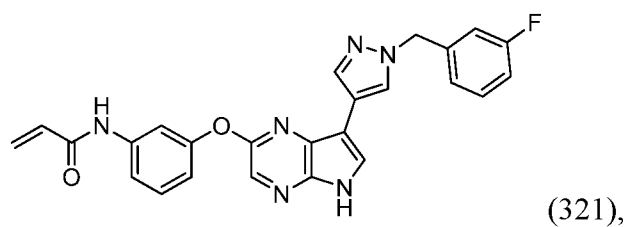
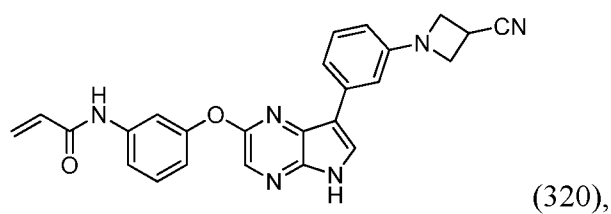
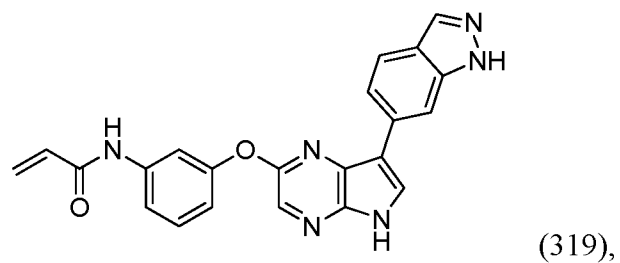
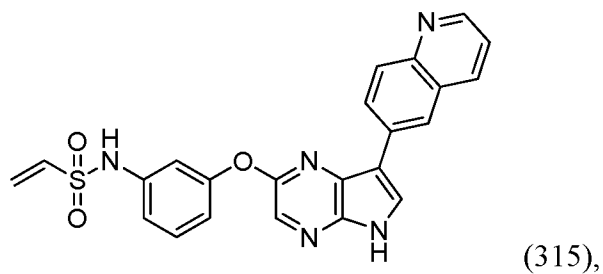
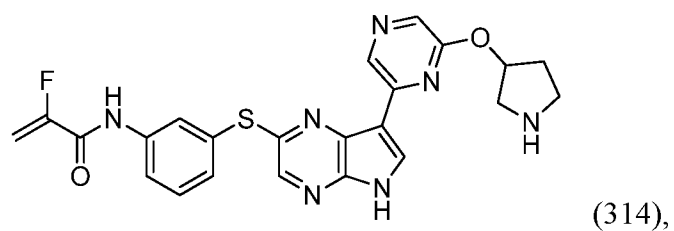
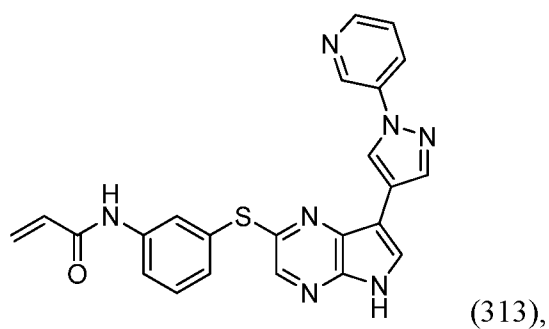
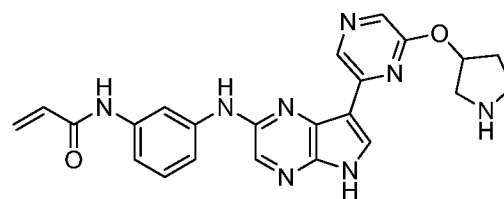
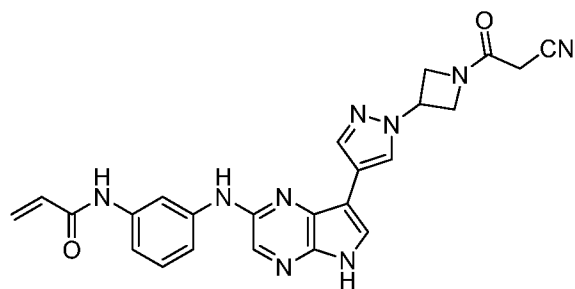
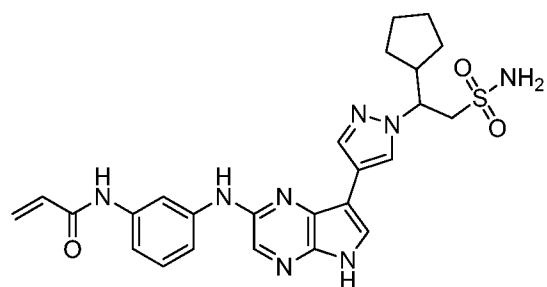
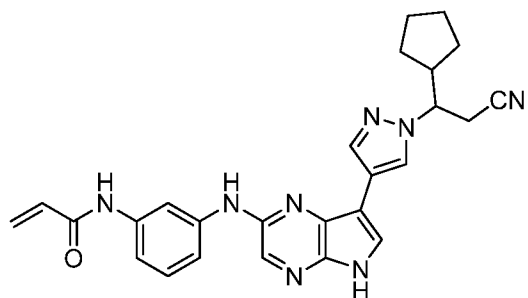
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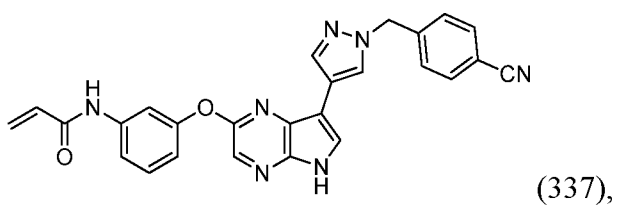
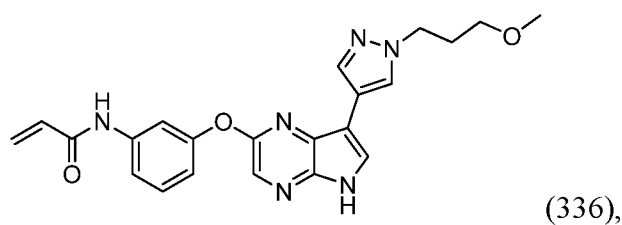
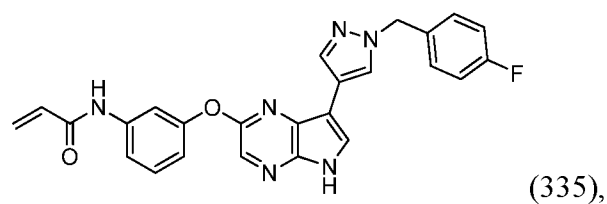
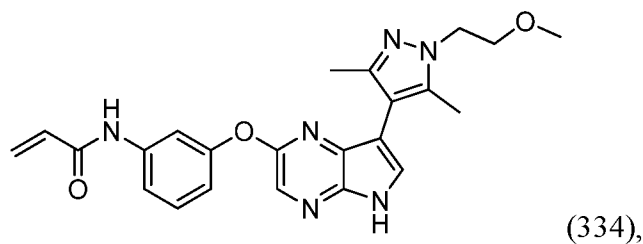
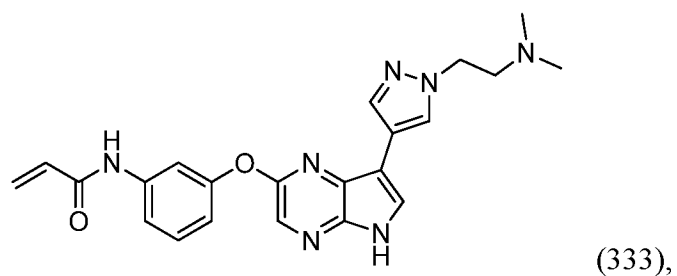
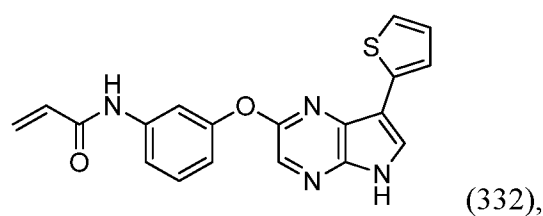
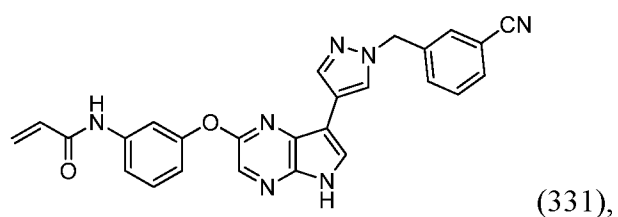
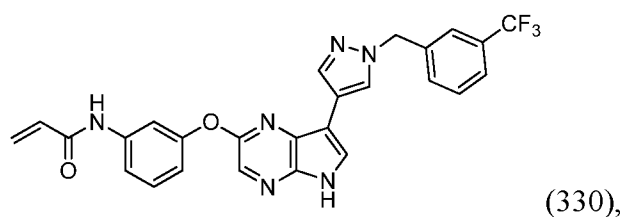
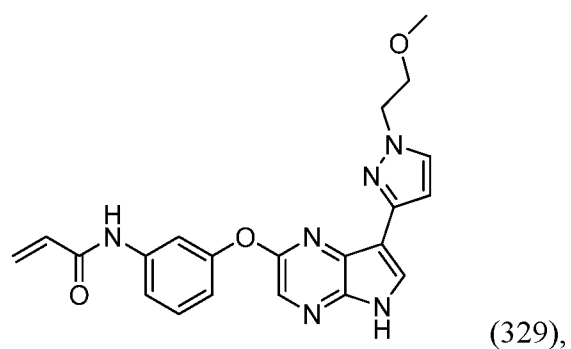
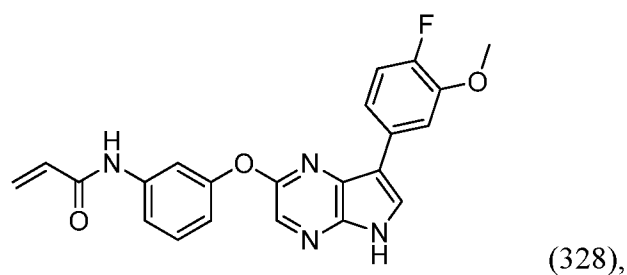
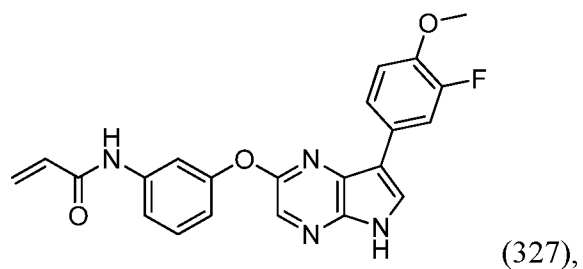
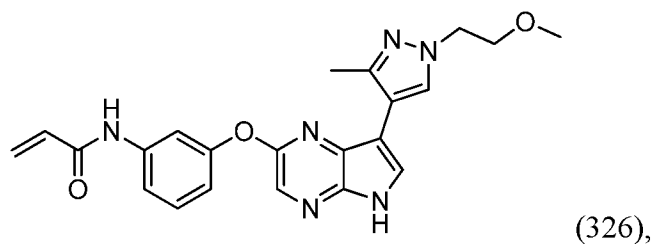
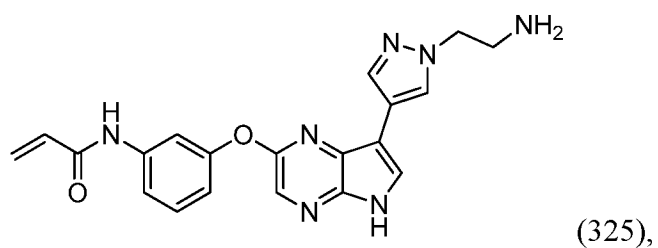
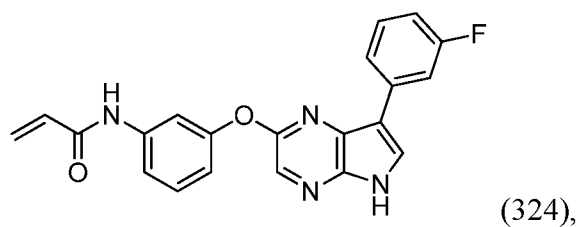


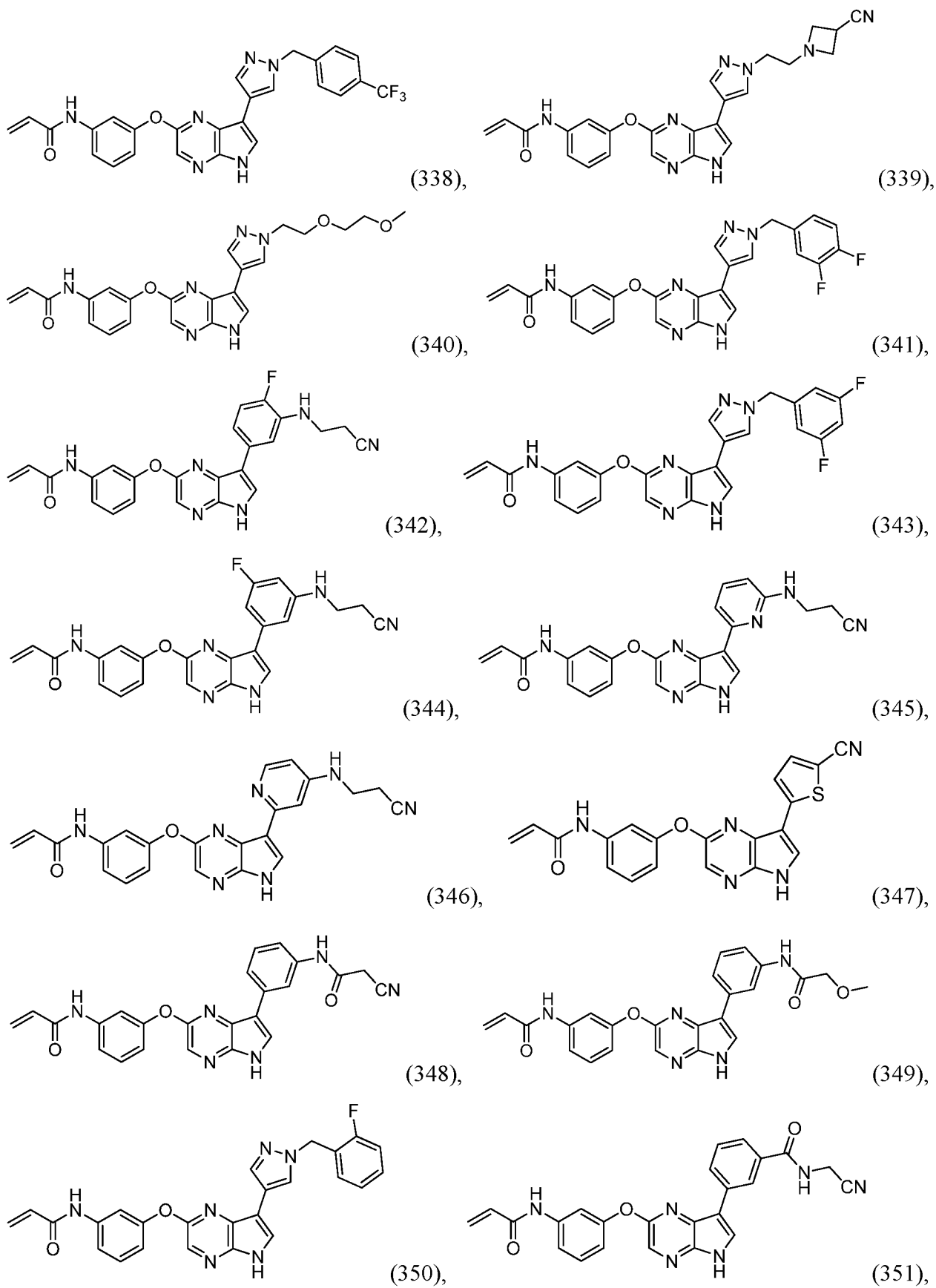
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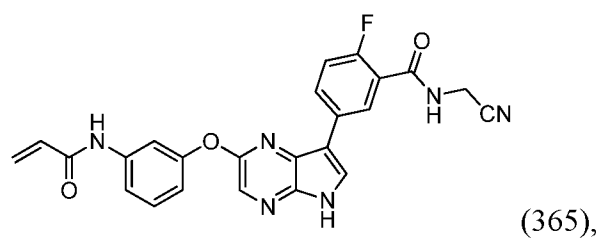
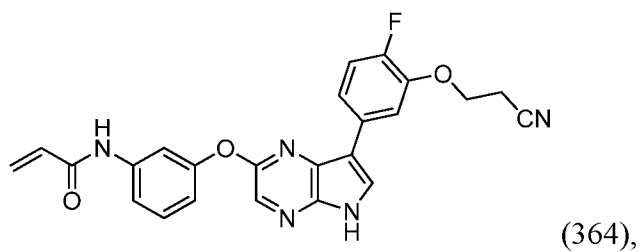
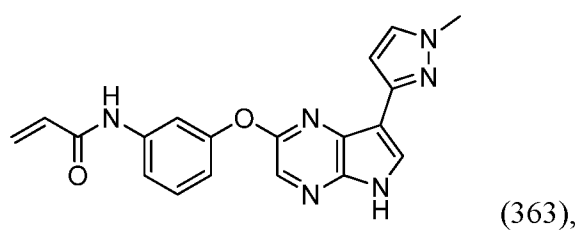
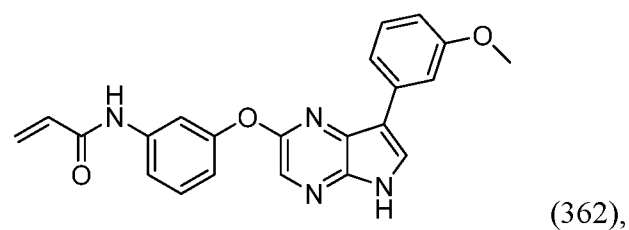
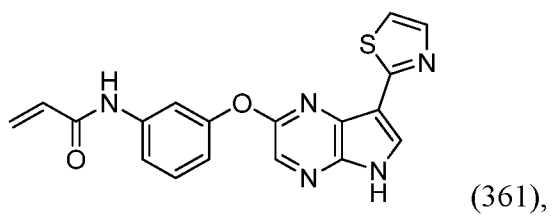
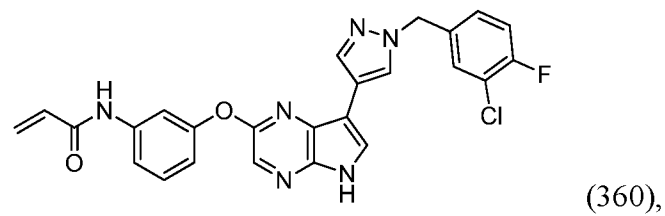
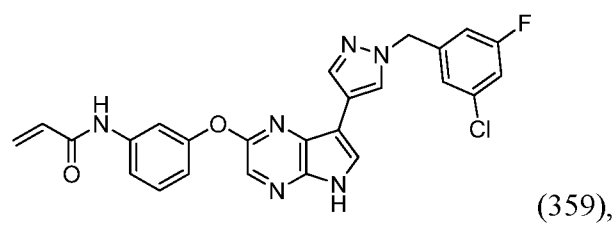
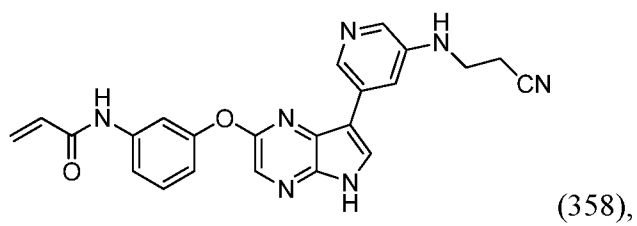
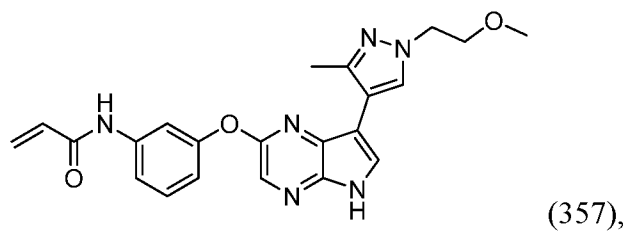
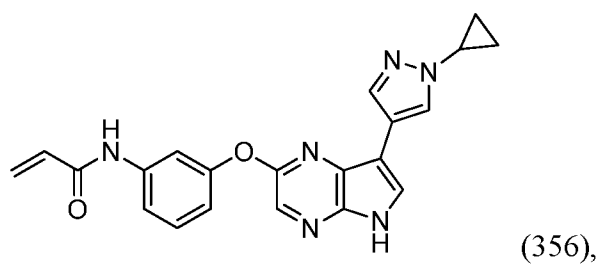
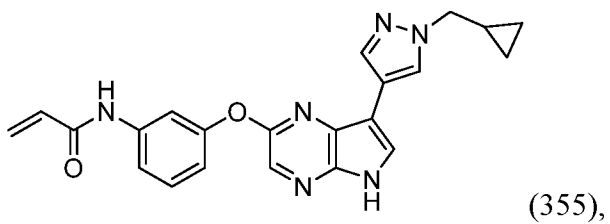
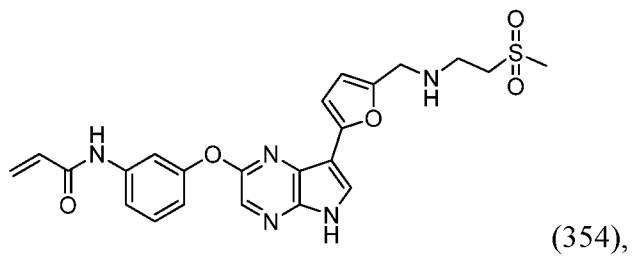
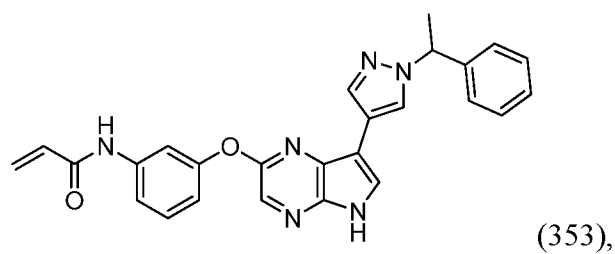
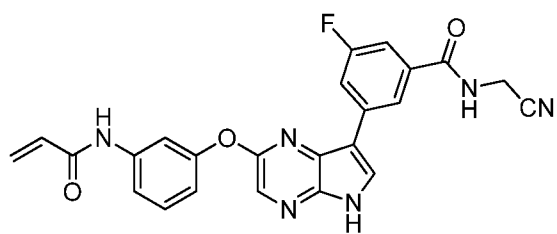


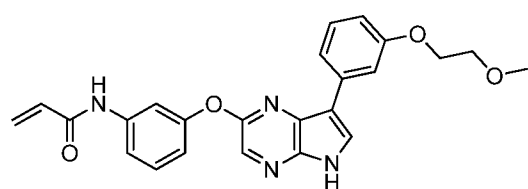
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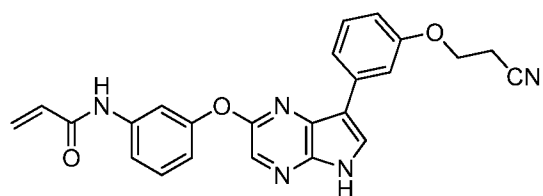




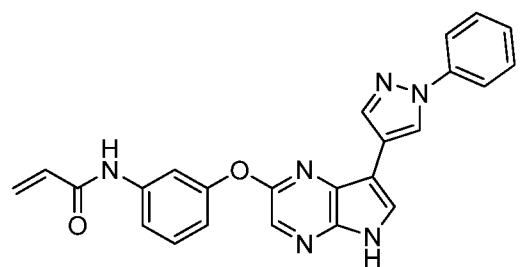




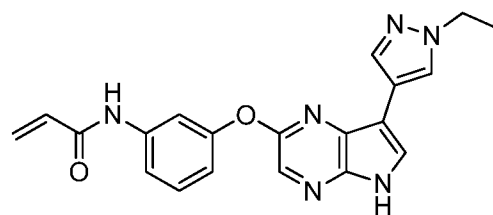
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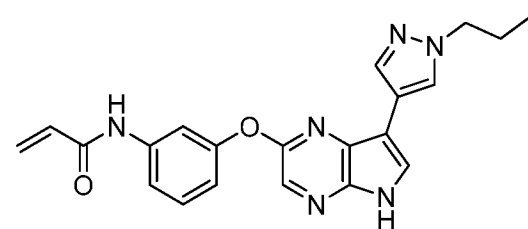
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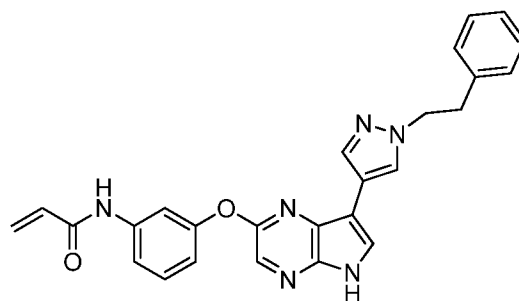
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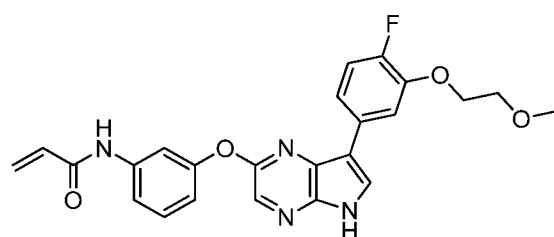
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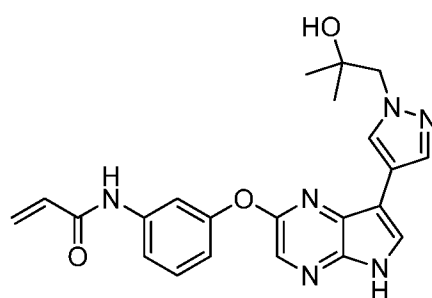
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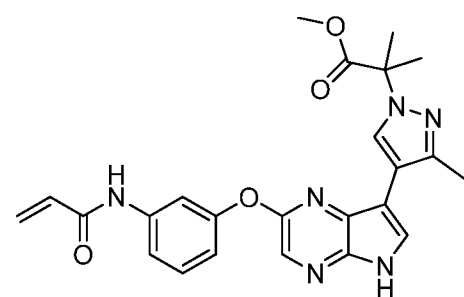
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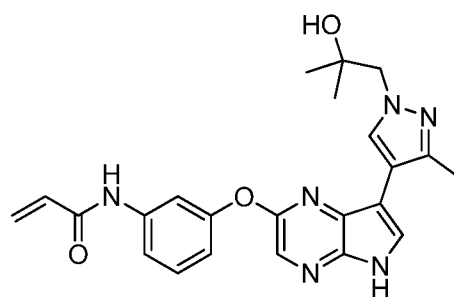
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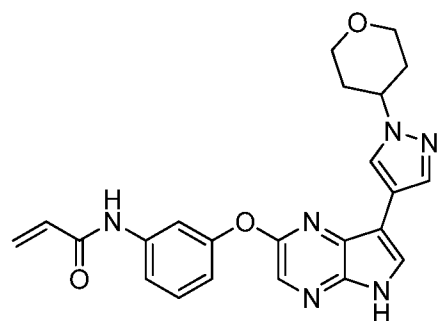
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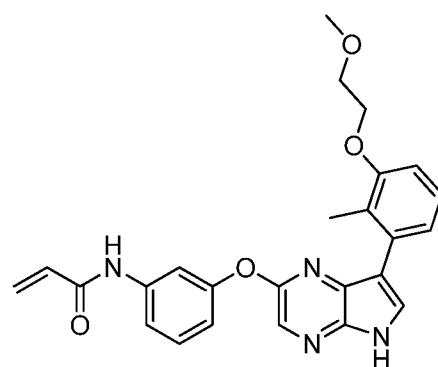
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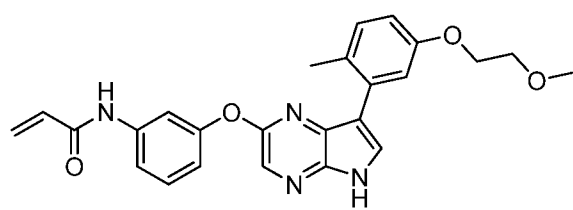
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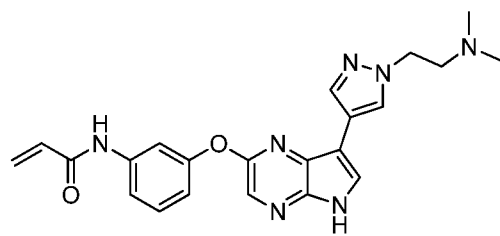
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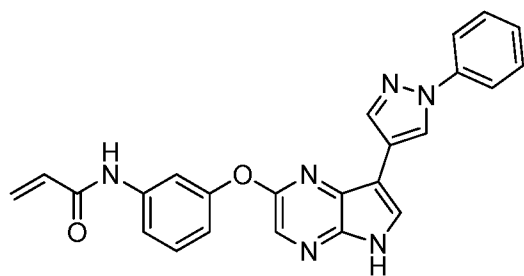
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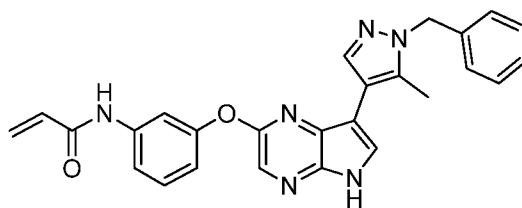
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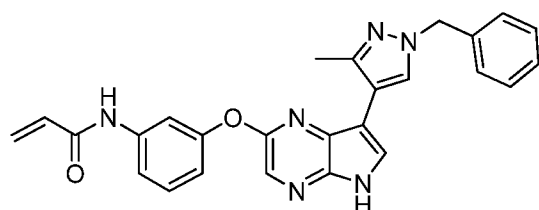
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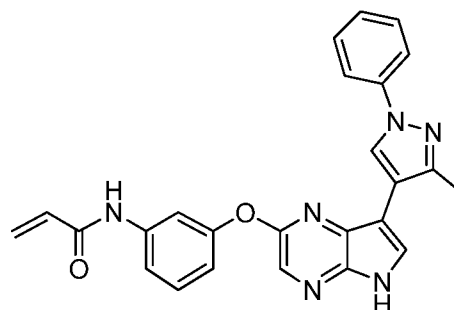
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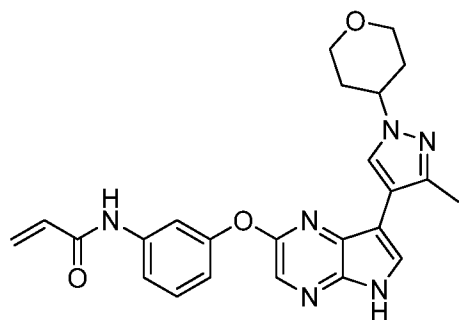
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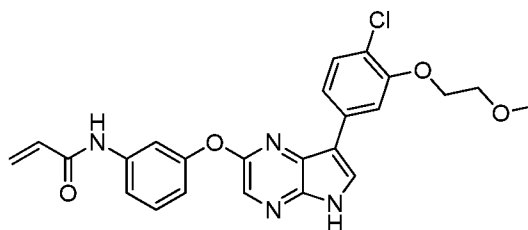
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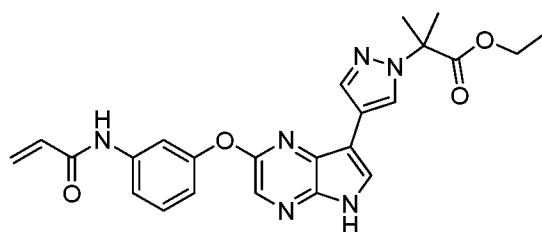
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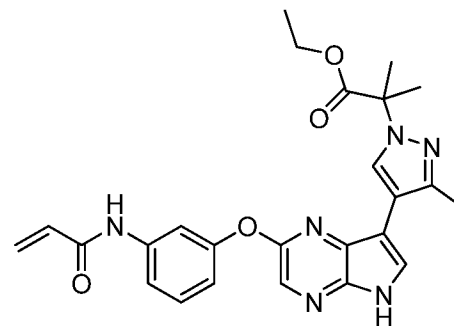
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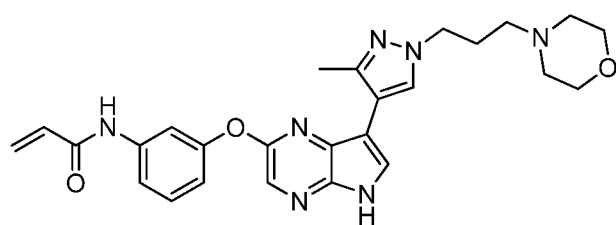
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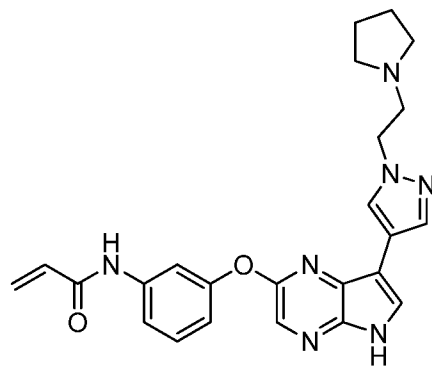
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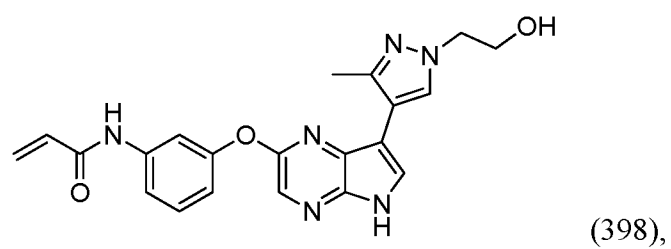
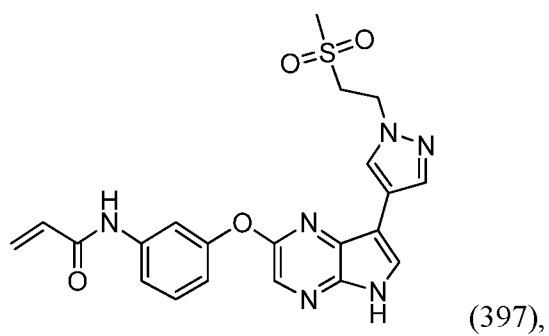
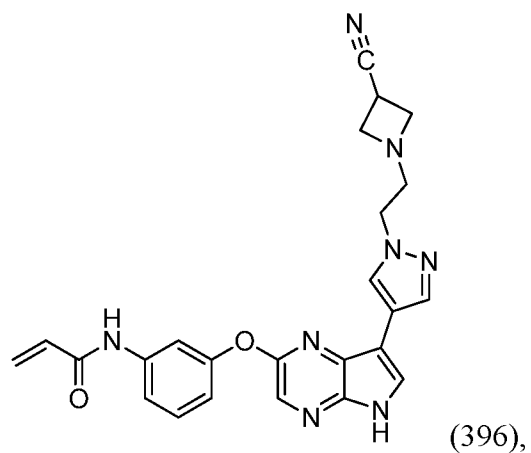
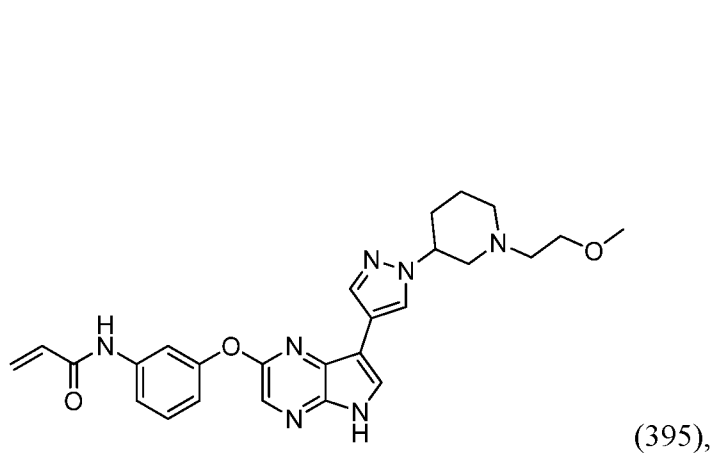
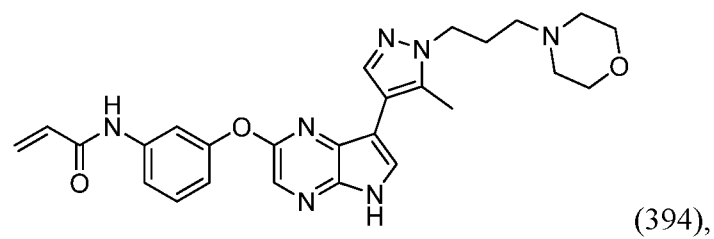
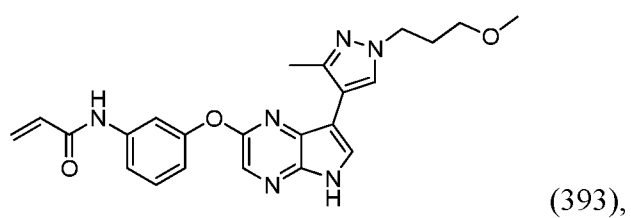
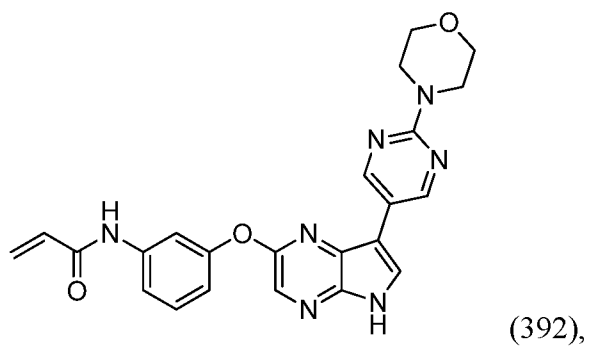
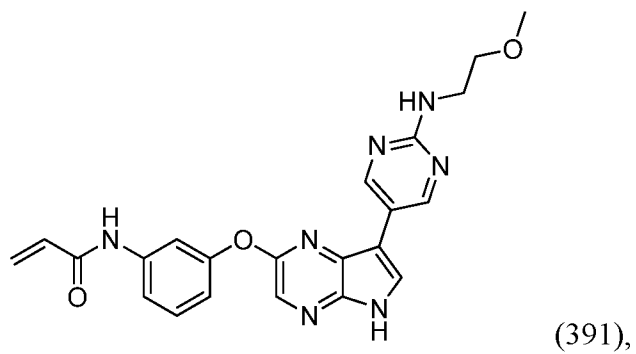
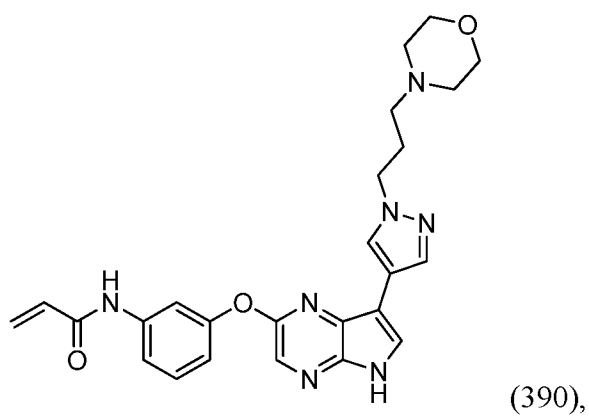
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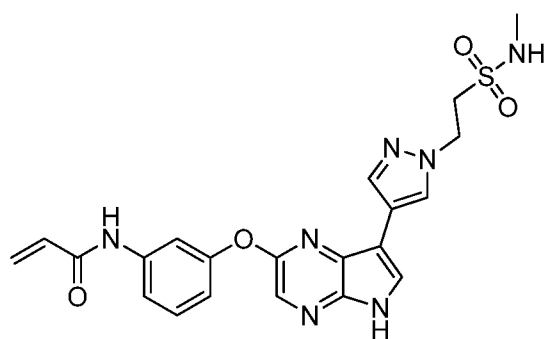


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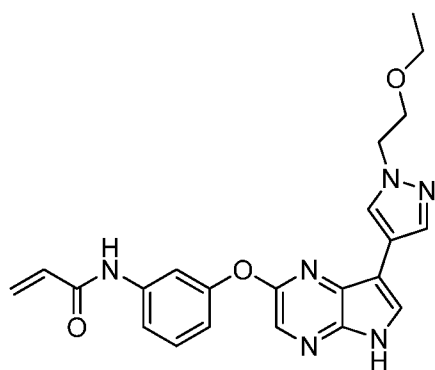


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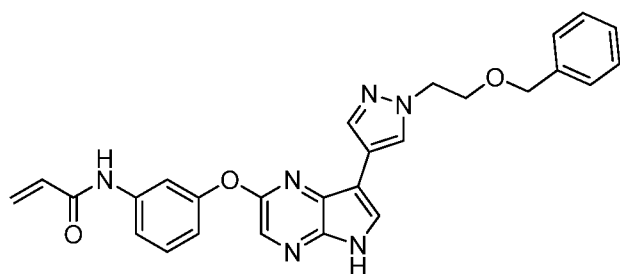




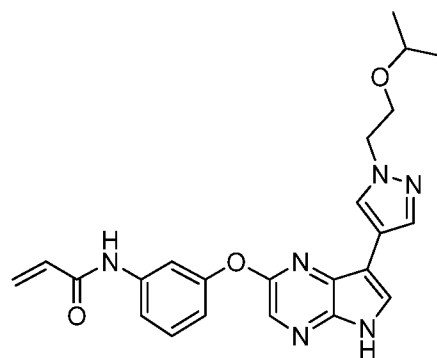
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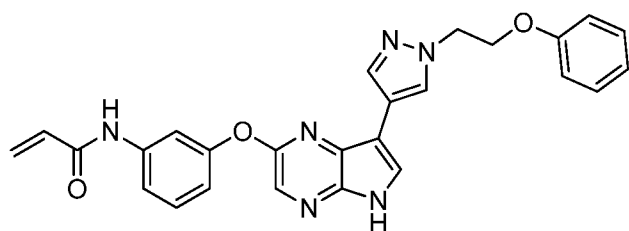
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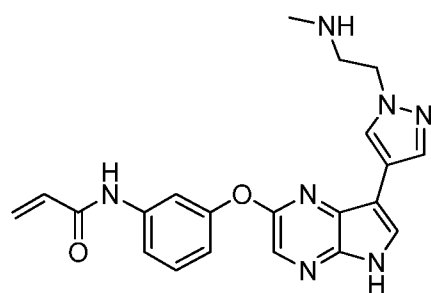
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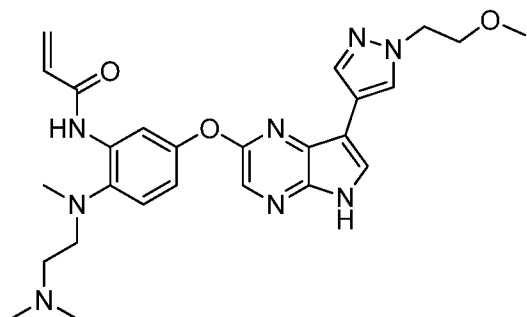
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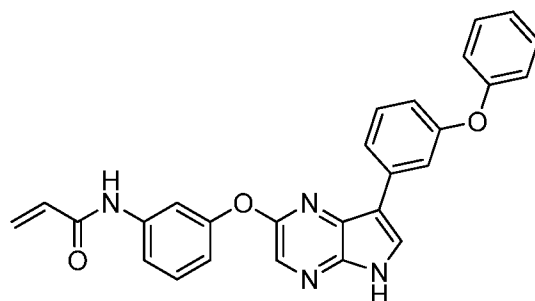
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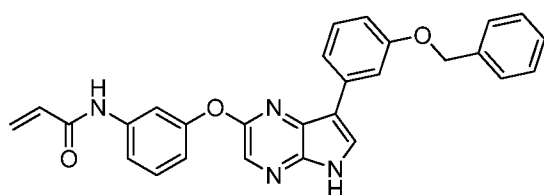
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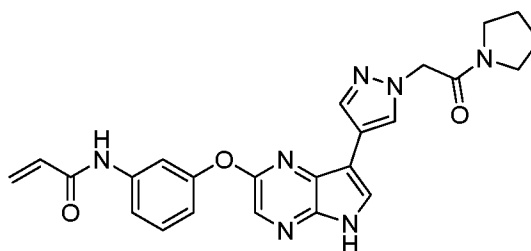
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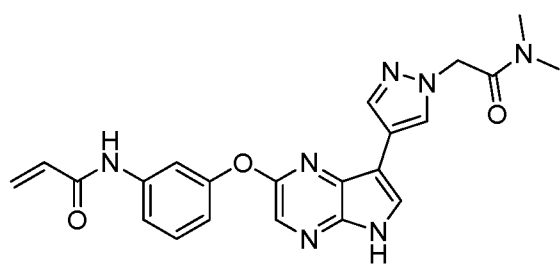
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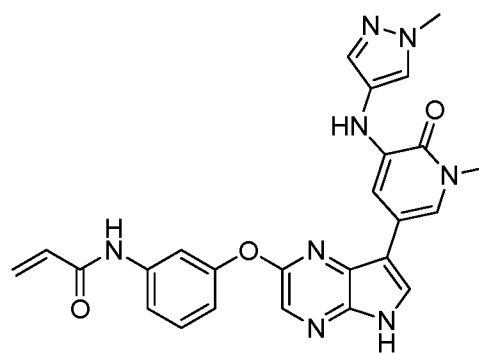
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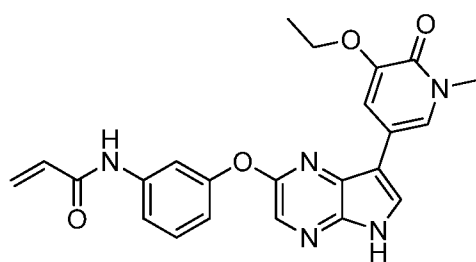
(408),



(409),



(410) or



(411).

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20.
22. The pharmaceutical composition of claim 21 further comprising at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants or vehicles.
23. The pharmaceutical composition of claim 21 or 22 further comprising an additional therapeutic agent selected from a chemotherapeutic agent or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, or an agent for treating autoimmune disease.
24. Use of the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23 in the manufacture a medicament for preventing, managing, treating or lessening an autoimmune disease or a proliferative disease in a patient.
25. The use of claim 24, wherein the autoimmune disease is lupus, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, psoriasis, type I diabetes, complications of organ transplantation, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorder, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia or lymphoma; and wherein the proliferative disease is metastatic carcinoma, colon cancer, gastric adenocarcinoma, bladder carcinoma, breast carcinoma, renal carcinoma, liver cancer, lung cancer, thyroid cancer, head and neck cancer, prostatic cancer, pancreatic cancer, CNS (central nervous system) cancer, spongioblastoma, myeloproliferative disease, or atherosclerosis or pulmonary fibrosis.

26. Use of the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23 in the manufacture of a medicament for inhibiting or regulating the activity of protein kinase in a biological sample.
27. The use of claim 26, wherein the protein kinase comprises BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M.
28. A method for preventing, managing, treating or lessening an autoimmune disease or a proliferative disease in a patient comprising administering to the patient in need of such treatment a therapeutically effective amount of the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23.
29. The method of claim 28, wherein the autoimmune disease is lupus, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, psoriasis, type I diabetes, complications of organ transplantation, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorder, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia or lymphoma; and wherein the proliferative disease is metastatic carcinoma, colon cancer, gastric adenocarcinoma, bladder carcinoma, breast carcinoma, renal carcinoma, liver cancer, lung cancer, thyroid cancer, head and neck cancer, prostatic cancer, pancreatic cancer, CNS (central nervous system) cancer, spongioblastoma, myeloproliferative disease, or atherosclerosis or pulmonary fibrosis.
30. A method for inhibiting or regulating the activity of protein kinase in a biological sample comprising contacting the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23 to the biological sample.
31. The method of claim 30, wherein the protein kinase comprises BLK, JAK1, JAK2, JAK3, BMX, TEC, ITK, TXK, HER2, HER4, BTK, EGFR or EGFR T790M.
32. The compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23 for use in preventing, managing, treating or lessening an autoimmune disease or a proliferative disease in a patient.
33. The compound or pharmaceutical composition of claim 32, wherein the autoimmune disease is lupus, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, psoriasis, type I diabetes, complications of organ transplantation, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorder, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia or lymphoma; and wherein the proliferative disease is metastatic carcinoma,

colon cancer, gastric adenocarcinoma, bladder carcinoma, breast carcinoma, renal carcinoma, liver cancer, lung cancer, thyroid cancer, head and neck cancer, prostatic cancer, pancreatic cancer, CNS (central nervous system) cancer, spongioblastoma, myeloproliferative disease, or atherosclerosis or pulmonary fibrosis.

34. The compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 23 for use inhibiting or regulating the activity of protein kinase in a biological sample.

35. The compound or pharmaceutical composition of claim 34, wherein the protein kinase comprises BLK, JAK1, JAK2, JAK3, BTK, BMX, TEC, ITK, TXK, HER2, HER4, EGFR or EGFR T790M.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/083033

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i; C07D 519/00(2006.01)i; A61K 31/485(2006.01)i; A61K 31/437(2006.01)i; A61P 37/02(2006.01)i; A61P 17/06(2006.01)i; A61P 19/00(2006.01)i

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)

C07D 471,C05D 519,A61K 31,A61P

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)

CNKI,CNABS,VEN,CAPLUS,REGISTRY(STN),+pyrazol+,+imidazol+,+pyrimidin+,+lene,+vinyl+,cancer?,tumo?r?,
+immuno+,autoimmune,inflam+,structure of compounds in claim 1**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9723480 A1 (DU PONT MERCK PHARMAET AL.) 03 July 1997 (1997-07-03) see the whole document	1-27
A	Hao, Baoyu et al. "Synthesis of 4-Chloro-7H-pyrrolo[2, 3-d]pyrimidine and 2, 4-Dichloro-7H-pyrrolo[2, 3-d]pyrimidine" <i>Chinese Journal of Organic Chemistry</i> , Vol. Vol.30, No. No.6, 31 December 2010 (2010-12-31), pages 918-922	1-27



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

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

08 September 2015

Date of mailing of the international search report

21 September 2015

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/083033

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **28-35**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 28-35 seek to protect the methods of treatment of a mammal. Therefore, claims 28-35 relate to the methods for treatment of the human or animal body by therapy, and do not comply with the requirement of PCT Rule 39.1.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2015/083033

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	9723480	A1	03 July 1997	EP	0939757	A1	08 September 1999
				CA	2240439	A1	03 July 1997
				AU	1345697	A	17 July 1997
				HR	P960611	A2	30 April 1998
				JP	2000501105	A	02 February 2000
				ZA	9610873	A	23 June 1998
				US	5760028	A	02 June 1998