

c-MYC mRNA TRANSLATION MODULATORS AND USES THEREOF**IN THE TREATMENT OF CANCER****FIELD OF THE INVENTION**

5 [001] The present invention relates to novel c-MYC mRNA translation modulators, composition and methods of preparation thereof, and uses thereof in the treatment of cancer.

BACKGROUND OF THE INVENTION

10 [002] Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for 1 of every 4 deaths. The 5-year relative survival rate for all cancer patients diagnosed in 1996-2003 is 66%, up from 50% in 1975-1977 (*Cancer Facts & Figures* American Cancer Society: Atlanta, GA (2008)). The rate of new cancer cases decreased by an average 0.6% per year among men between 2000 and 2009 and stayed the same for women. From 2000 through 2009, death rates from all cancers combined decreased on average 1.8% per year among men and 1.4% per year among women. This improvement in survival reflects progress in diagnosing at an earlier stage and improvements in treatment. Discovering highly effective anticancer agents with low toxicity is a primary goal of cancer research.

20 [003] The Myc family includes three major members, the proto-oncogene c-Myc (cellular Myelocytomatosis, short Myc), as well as L-myc and N-myc. These three Myc homologs are involved in the early stages of carcinogenesis and metastatic spread in most human cancers. In most types of tumors Myc gene is not mutated or duplicated, but its mRNA and/or protein levels are increased, indicating that in cancer Myc overexpression is induced at the level of transcription, mRNA steady state levels and translation. Indeed, myc gene expression normally depends on growth factor signaling and both myc mRNA and Myc protein have very short half-lives (of 30 and 20 min respectively) [Dang, C. V. (2012). MYC on the path to cancer. *Cell* 149, 22–35]. In tumor cells however, the cellular levels of Myc become independent from such signaling and regulation, and the resulting exacerbated Myc function drives intracellular and extracellular transcription programs that allow tumors to grow and thrive. However, Myc does not necessarily need to be overexpressed in order for a cancer to be highly dependent upon its activity. A study from Soucek et al. (*Nature* (2008) 455(7213):679-83) shows that 30 tumors that express c-Myc at endogenous levels exhibit tumor regression upon Myc inhibition via a genetically engineered system. Therefore, treatment with a Myc inhibitor is not necessarily limited to cancers that overexpress Myc. Compounds according to this invention may also be used to regulate the translation of Myc mRNA, wherein the direct target for the compounds is a protein or RNA which regulate Myc mRNA translation, and as such any tumor which is Myc dependent will benefit from the 35 therapeutic utility of these compounds.

[004] Due to its extensive pathogenic significance, MYC is an important anticancer target. Deregulated Myc gene is found in a wide range of human hematological malignancies and solid tumors, especially in breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma, glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-derived lymphomas, esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer and lung adenocarcinoma. Recent studies also indicate that deregulation of c-MYC is related to the occurrence of BRAF V600E thyroid cancers, choroid plexus carcinoma, and colitis-associated cancer. In addition, amplification of the MYC gene was found in a significant number of epithelial ovarian cancer cases. In TCGA datasets, the amplification of Myc occurs in several cancer types, including breast, colorectal, pancreatic, gastric, and uterine cancers.

[005] Although Myc gene is a very important oncogene and considered as a driver in carcinogenesis and MYC protein is a key transcription factor broadly targeting various genes, rational designing a direct Myc inhibitor is still challenging. This is mainly because MYC protein lacks structural regions amenable to therapeutic inhibition by small molecules and is considered an undruggable target [BioDrugs (2019) 33:539–553].

[006] Designing and developing MYC modulators is challenging, primarily because the MYC protein has a disordered structure which lacks a pocket or groove that can act as a binding site for modulators. Interfering with the MYC transcription, blocking the protein–protein interaction (PPI) of MYC and its cofactors, and influencing on signaling pathways related to MYC were used in the past as potential modulatory targets, but failed to be developed as drug candidates. Myc PPI inhibitors failed to show sufficient efficacy in cell-based assays and animal models due to the requirement of high target occupancy to drive efficacy. Modulators of signaling pathways upstream to myc, for example mTOR modulators, failed due lack of target specificity.

[007] Nevertheless, a therapeutic approach to target c-Myc has remained elusive. The absence of a clear ligand-binding domain establishes a formidable obstacle toward direct inhibition, which is a challenging feature shared among many compelling transcriptional targets in cancer. Thus, alternative modalities that target Myc are required, as outlined herein, namely compounds which regulate Myc mRNA translation.

SUMMARY OF THE INVENTION

[008] This invention provides a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula I and/or I(a)–I(n) and by the structures listed in Table 1, as defined herein below. In various embodiments, the compound is a c-MYC mRNA translation modulator. In various embodiments, the compound is a c-MYC mRNA transcription regulator. In various embodiments, the compound is a c-

MYC inhibitor. In various embodiments, the compound is any combination of a c-MYC mRNA translation modulator, c-MYC mRNA transcription regulator and c-MYC inhibitor.

[009] This invention further provides a pharmaceutical composition comprising a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I** and/or **I(a)-I(n)** and by the structures listed in Table 1, as defined herein below, and a pharmaceutically acceptable carrier.

[0010] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject, comprising administering a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and by the structures listed in Table 1, as defined herein below, to a subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit cancer in said subject.

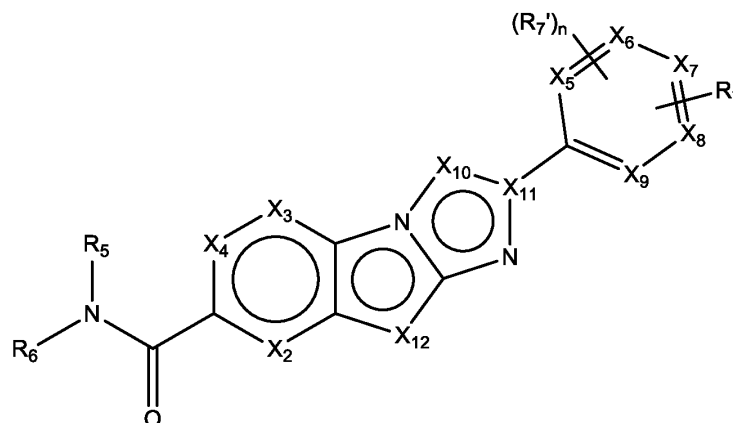
[0011] This invention further provides a method for suppressing, reducing or inhibiting tumor growth in a subject, comprising administering a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and by the structures listed in Table 1, as defined herein below, to a subject, under conditions effective to suppress, reduce or inhibit tumor growth in said subject. In some embodiment, the tumor is cancerous. In some embodiment, the subject suffers from cancer.

[0012] This invention further provides a method of modulating c-MYC mRNA translation in a cell, comprising contacting a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and by the structures listed in Table 1, as defined herein below, with a cell, thereby modulating c-MYC mRNA translation in said cell.

[0013] This invention further provides a method of regulating c-MYC mRNA transcription in a cell, comprising contacting a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and by the structures listed in Table 1, as defined herein below, with a cell, thereby regulating c-MYC mRNA transcription in said cell.

DETAILED DESCRIPTION OF THE INVENTION

[0014] In various embodiments, this invention is directed to a compound represented by the structure of formula (**I**):



(I)

wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl),
 5 C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃),
 C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃, C(OCHF₂),
 C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-
 10 CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N
 or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-
 cyclopropyl);

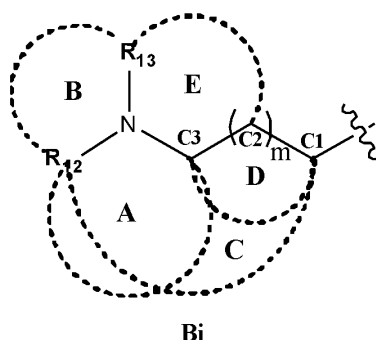
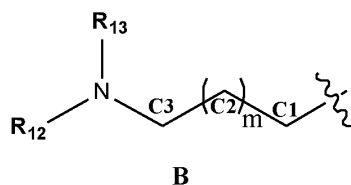
15 R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃,
 (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-
 R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-
 difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol,
 20 CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or
 spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-
 pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-
 piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-
 methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-
 25 methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN,
 -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-
 N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-
 piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂,
 (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃,

-OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R₆ and R₅ are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R₆ is represented by the structure of formula B or Bi:



wherein

m is 0 or 1; and

R₁₂ is R₂₀ or C₁-C₅ C(O)-alkyl, and R₁₃ is R₃₀; or

R₁₂ and R₁₃ are both H;

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

R_{12} and $C3$ are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

5 R_{12} and $C1$ are joined to form ring **C** and R_{13} is R_{30} ; or

$C1$ and $C3$ are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and $C2$ are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B** and $C1$ and $C3$ are joined to form ring **D**;

wherein

10 Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine,
15 methylpiperidine;

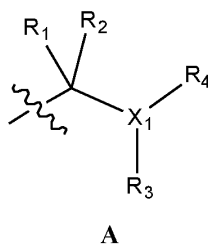
Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine,
20 thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

25 Ring **D** is a substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclobutane, cyclohexane);

R_7 is H, F, Cl, Br, I, OH, $O-R_{20}$, SH, R_8 -OH, R_8 -SH, SR_{10} , $-R_8-O-R_{10}$, $-R_8-S-R_{10}$, R_8 -(C_3 - C_8 cycloalkyl), CF_3 , CD_3 , OCD_3 , CN, NO_2 , $-CH_2CN$, $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, R_8 - $N(R_{10})(R_{11})$, R_9 - R_8 - $N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-R_{10}$, C_1 - C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$ (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)NH(CH_3)$, $C(O)NH(CH_2CH_2OCH_3)$, $C(O)NH(CH_2CH_2OH)$), SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1 - C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C_1 - C_5 linear or branched, substituted or unsubstituted alkenyl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl (e.g., CHF_2), C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein
30 at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1 - C_5 linear or branched thioalkyl, C_1 - C_5 linear or branched thioalkoxy, C_1 - C_5 linear or branched haloalkoxy, C_1 - C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g.,

morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R_8 -(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted benzyl;

or R_7 is represented by the structure of formula A:



wherein

X_1 is N or O;

R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF_3 , substituted or unsubstituted C_1 - C_5 alkyl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl, substituted or unsubstituted C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy;

R_1 and R_2 are joined to form =O or a C_3 - C_8 carbocyclic or heterocyclic ring (e.g., cyclopropyl);

R_3 and R_4 are each independently H, Me, substituted or unsubstituted C_1 - C_5 alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), $-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), $R_8-N(R_{10})(R_{11})$ (e.g., $(CH_2)_2-NH(CH_3)$), substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R_{20} ;

R_3 and R_4 are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

or R_2 and R_4 are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole), wherein if the ring is aromatic, then R_1 and/or R_3 are absent;

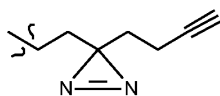
wherein if X_1 is O then R_4 is absent;

R_7 is H, F, Cl, Br, I, OH, $O-R_{20}$, SH, R_8-OH , R_8-SH , $-R_8-O-R_{10}$, $R_8-(C_3-C_8$ cycloalkyl), R_8 -(3-8 membered heterocyclic ring), CF_3 , CD_3 , OCD_3 , CN, NO_2 , $-CH_2CN$, $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $R_8-N(R_{10})(R_{11})$, $R_9-R_8-N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-R_{10}$, C_1 - C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$, SO_2R , $SO_2N(R_{10})(R_{11})$,

CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

- 10 or R₇ and R₇' are joined to form a 5 or 6 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., piperidine, pyrrolidine, tetrahydrofuran, tetrahydropyran);

R₂₀ is represented by the following structure:



- 15 R₃₀ is H, R₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

- R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

each R₈ is independently [CH₂]_p

wherein p is between 1 and 10 (e.g., 1, 2);

- 35 R₉ is [CH]_q, [C]_q

wherein q is between 2 and 10;

R_{10} and R_{11} are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), R_{20} , C(O)R, or S(O)₂R;

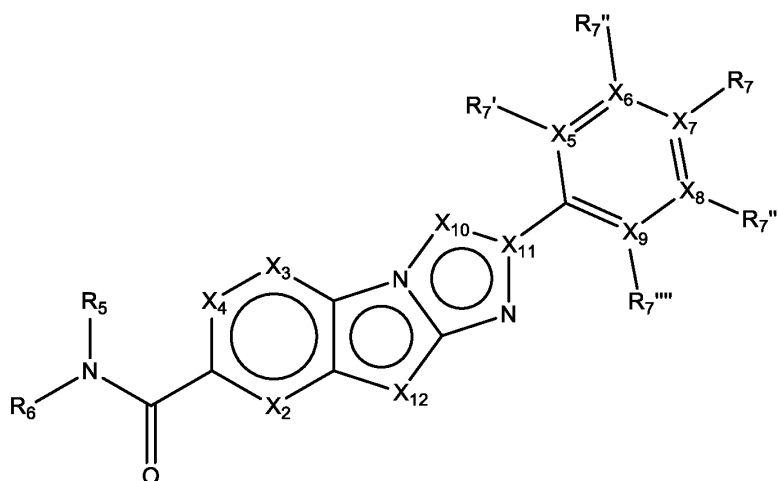
or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0015] In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R). In some embodiments, X_{11} is N. In some embodiments, X_{12} is not S. In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S. In some embodiments, R is not H.

[0016] In various embodiments, this invention is directed to a compound represented by the structure of formula I(a):



I(a)

wherein

X_2 , X_3 , and X_4 are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-*i*Pr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_7 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' , R_7 , R_7''' , and R_7'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

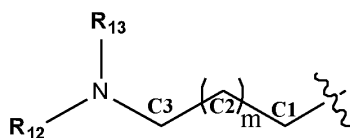
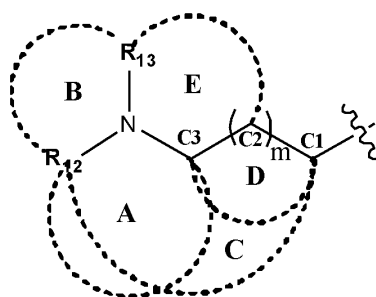
R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂, (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-

tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R_8 -aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R_6 and R_5 are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

5 or R_6 is represented by the structure of formula **B** or **Bi**:

**B****Bi**

wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H;

15 R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

R_{12} and C_3 are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

R_{12} and C_1 are joined to form ring **C** and R_{13} is R_{30} ; or

20 C_1 and C_3 are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and C_2 are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B** and C_1 and C_3 are joined to form ring **D**;

wherein

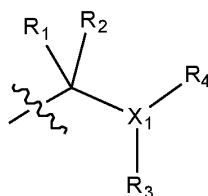
Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single
 25 spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇ is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), C(O)NH(CH₂CH₂OH)), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g., morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted benzyl;

or **R**₇ is represented by the structure of formula A:



A

wherein

X₁ is N or O;

R₁ and **R₂** are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

R₁ and **R₂** are joined to form =O or a C₃-C₈ carbocyclic or heterocyclic ring (e.g., cyclopropyl);

R₃ and **R₄** are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

R₃ and **R₄** are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

or **R₂** and **R₄** are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole), wherein if the ring is aromatic, then **R₁** and/or **R₃** are absent;

wherein if X₁ is O then R₄ is absent;

R₇', **R₇''**, **R₇'''** and **R₇''''** are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

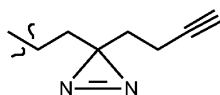
or **R₇'** and **R₇''** are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R₇''** and **R₇** are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7 and R_7''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R_{20} is represented by the following structure:



R_{30} is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, $CH_2-CH_2-O-CH_2-CH_2-O-CH_3$, $CH_2-O-CH_2-CH_2-O-CH_3$), C_1-C_5 linear or branched alkoxy, C_1-C_5 linear or branched haloalkyl (e.g., CHF_2 , CF_3 , CF_2CH_3 , CH_2CF_3 , $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)-CH(CH_3)_2$), R_8 -aryl (e.g., CH_2-Ph), $-R_8-O-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-(CH_2)_2-O-CH_3$), $-R_8-O-R_{10}$, $-R_8-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, $COOH$, $CO(R_{10})$ (e.g., $C(O)CH_3$), $NH(R_{10})$, $NH-CH_2$ -cyclopropyl, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr , CH_2 -cyclopropyl, CH_2-OH , CH_2-CH_2-OH , $CH_2-CH_2-O-CH_2-CH_2-O-CH_3$, $CH_2-O-CH_2-CH_2-O-CH_3$), C_3-C_8 substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C_1-C_5 linear or branched alkoxy, (e.g., methoxy, ethoxy, $O-(CH_2CH_3)$, $OCHF_2$, $O-(CH_2)_2-O-CH_3$, isopropoxy, $O-(CH_2)$ -cyclopropyl, $O-CH_2$ -methylcyclobutyl, $O-CH_2$ -3-methyloxetane, $O-CH(CH_3)-CH_2-O-CH_3$), C_1-C_5 linear or branched haloalkyl (e.g., CHF_2 , CF_3 , CF_2CH_3 , CH_2CF_3 , $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)-CH(CH_3)_2$), R_8 -aryl (e.g., CH_2-Ph), $-R_8-O-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-(CH_2)_2-O-CH_3$), $-R_8-O-R_{10}$, $O-R_8-R_{10}$ (e.g., $O-(CH_2)_2-O-CH_3$, $O-(CH_2CH_3)$, $O-(CH_2)$ -cyclopropyl), $-R_8-R_{10}$ (e.g., (CH_2) -cyclopropyl, $(CH_2)_2-O-CH_3$, $(CH_2)-OH$, $(CH_2)_2-OH$, $(CH_2)-COOH$), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

each R_8 is independently $[CH_2]_p$

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is $[CH]_q$, $[C]_q$

wherein q is between 2 and 10;

R_{10} and R_{11} are each independently H, OH, $COOH$, C_1-C_5 substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH_2 -cyclopropyl, $CH_2-CH_2-O-CH_3$), C_3-C_8 substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C_1-C_5 substituted or unsubstituted linear or branched haloalkyl (e.g., CH_2CF_3), C_1-C_5 linear or branched alkoxy (e.g., $O-CH_3$), R_{20} , $C(O)R$, or $S(O)_2R$;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

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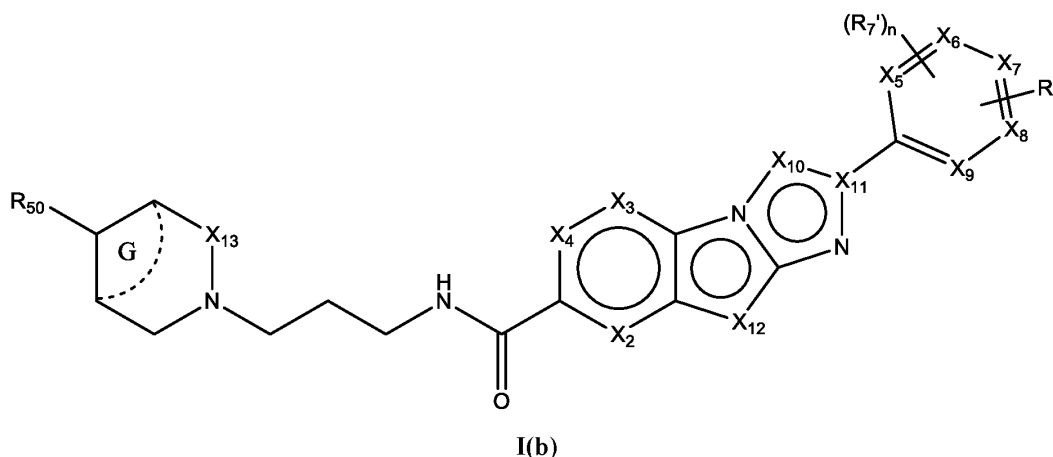
[0017] In some embodiments, at least one of R_7 , R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7 , R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are different than each other. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H and are different than each other.

10

[0018] In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R). In some embodiments, X_{11} is N. In some embodiments, X_{12} is not S. In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S. In some embodiments, R is not H.

15

[0019] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(b)**:



20 wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-*i*Pr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

25

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

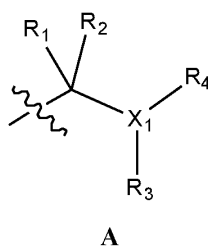
X_{12} is S, SO_2 , O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

X_{13} is CH₂, CH(R) (e.g., CH-CH₃), C(R)₂, or C=O;

5 Ring G is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);

R_7 is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁),
 10 COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), C(O)NH(CH₂CH₂OH)), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl
 15 (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g.,
 20 morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted
 25 benzyl;

or R_7 is represented by the structure of formula A:



wherein

30 X_1 is N or O;

R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

R₁ and **R₂** are joined to form =O or a C₃-C₈ carbocyclic or heterocyclic ring (e.g., cyclopropyl);

R₃ and **R₄** are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

R₃ and **R₄** are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

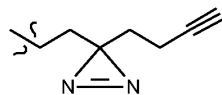
or **R₂** and **R₄** are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole), wherein if the ring is aromatic, then **R₁** and/or **R₃** are absent;

wherein if X₁ is O then R₄ is absent;

R₇ is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or **R₇** and **R₇** are joined to form a 5 or 6 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., piperidine, pyrrolidine, tetrahydrofuran, tetrahydropyran);

R₂₀ is represented by the following structure:



R₃₀ is H, **R₂₀**, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃,

CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R₅₀ is H, R₂₀, F, Cl, Br, I, OH, SH, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃), C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g., O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each R₈ is independently [CH₂]_p

wherein p is between 1 and 10 (e.g., 1, 2);

R₉ is [CH]_q, [C]_q

wherein q is between 2 and 10;

R₁₀ and R₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), R₂₀, C(O)R, or S(O)₂R;

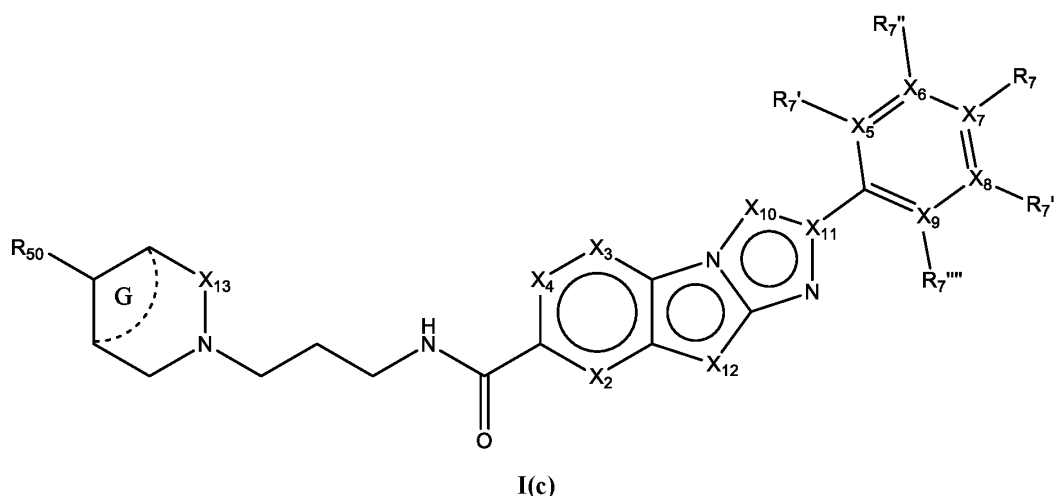
or R₁₀ and R₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, N-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0020] In some embodiments, at least one of X₂, X₃, and X₄ is C(R). In some embodiments, X₁₁ is N. In some embodiments, X₁₂ is not S. In some embodiments, at least one of X₂, X₃, and X₄ is C(R); X₁₁ is N; or X₁₂ is not S. In some embodiments, R is not H.

[0021] In various embodiments, this invention is directed to a compound represented by the structure of formula I(c):



wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_7 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' , R_7''' , and R_7'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

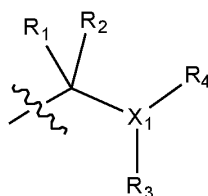
X_{13} is CH₂, CH(R) (e.g., CH-CH₃), C(R)₂, or C=O;

Ring G is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);

R_7 is H, F, Cl, Br, I, OH, O-R₁₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), C(O)NH(CH₂CH₂OH)), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C₁-C₅ linear

or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g., morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted benzyl;

or R₇ is represented by the structure of formula A:



A

wherein

X₁ is N or O;

R₁ and R₂ are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

R₁ and R₂ are joined to form =O or a C₃-C₈ carbocyclic or heterocyclic ring (e.g., cyclopropyl);

R₃ and R₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

R₃ and R₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

or R₂ and R₄ are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofurane, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole), wherein if the ring is aromatic, then R₁ and/or R₃ are absent;

wherein if X_1 is O then R_4 is absent;

R_7' , R_7'' , R_7''' and R_7'''' are each independently H, F, Cl, Br, I, OH, O- R_{20} , SH, R_8 -OH, R_8 -SH, $-R_8$ -O- R_{10} , R_8 -(C₃-C₈ cycloalkyl), R_8 -(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R_8 -N(R₁₀)(R₁₁), R_9 - R_8 -N(R₁₀)(R₁₁), B(OH)₂,
 5 -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R_8 -C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic
 10 alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine),
 15 substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

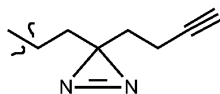
or R_7' and R_7'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7'' and R_7 are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or
 20 heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7 and R_7''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R_{20} is represented by the following structure:



R_{30} is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R_8 -aryl (e.g., CH₂-Ph), $-R_8$ -O- R_8 -O- R_{10} (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), $-R_8$ -O- R_{10} , $-R_8$ - R_{10} (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R_{50} is H, R_{20} , F, Cl, Br, I, OH, SH, $N(R)_{20}$, $NH(R_{10})$, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1 - C_5 linear or branched, substituted or unsubstituted alkyl C_1 - C_5 linear or branched alkoxy, C_1 - C_5 linear or branched haloalkyl, $-R_8-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

5 R is H, F, Cl, Br, I, OH, SH, $COOH$, $CO(R_{10})$ (e.g., $C(O)CH_3$), $NH(R_{10})$, $NH-CH_2$ -cyclopropyl, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1 - C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, *i*Pr, CH_2 -cyclopropyl, CH_2-OH , CH_2-CH_2-OH , $CH_2-CH_2-O-CH_2-CH_2-O-CH_3$, $CH_2-O-CH_2-CH_2-O-CH_3$), C_3 - C_8 substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C_1 - C_5 linear or branched alkoxy, (e.g., methoxy, ethoxy, $O-(CH_2CH_3)$, $OCHF_2$, $O-(CH_2)_2-O-CH_3$, isopropoxy, 10 $O-(CH_2)$ -cyclopropyl, $O-CH_2$ -methylcyclobutyl, $O-CH_2$ -3-methyloxetane, $O-CH(CH_3)-CH_2-O-CH_3$) C_1 - C_5 linear or branched haloalkyl (e.g., CHF_2 , CF_3 , CF_2CH_3 , CH_2CF_3 , $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)-CH(CH_3)_2$), R_8 -aryl (e.g., CH_2-Ph), $-R_8-O-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-(CH_2)_2-O-CH_3$), $-R_8-O-R_{10}$, $O-R_8-R_{10}$ (e.g., $O-(CH_2)_2-O-CH_3$, $O-(CH_2CH_3)$, $O-(CH_2)$ -cyclopropyl), $-R_8-R_{10}$ (e.g., (CH_2) -cyclopropyl, $(CH_2)_2-O-CH_3$, $(CH_2)-OH$, $(CH_2)_2-OH$, $(CH_2)-COOH$), substituted or unsubstituted 15 aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

each R_8 is independently $[CH_2]_p$

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is $[CH]_q$, $[C]_q$

wherein q is between 2 and 10;

20 R_{10} and R_{11} are each independently H, OH, $COOH$, C_1 - C_5 substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH_2 -cyclopropyl, $CH_2-CH_2-O-CH_3$), C_3 - C_8 substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C_1 - C_5 substituted or unsubstituted linear or branched haloalkyl (e.g., CH_2CF_3), C_1 - C_5 linear or branched alkoxy (e.g., $O-CH_3$), R_{20} , $C(O)R$, or $S(O)_2R$;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic 25 ring (e.g., piperazine, piperidine),

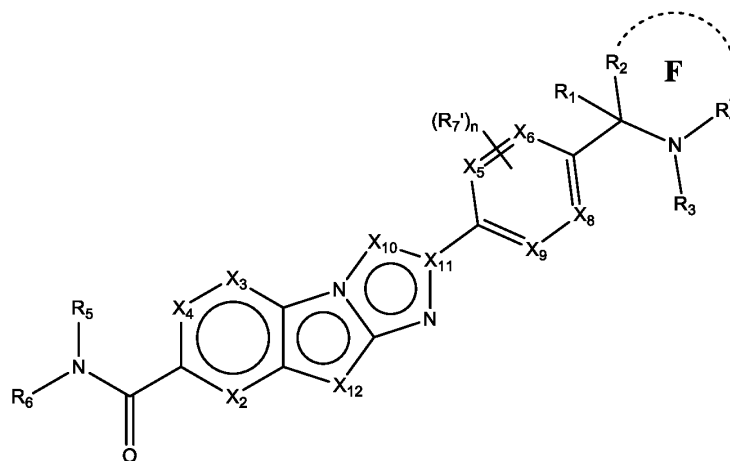
n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

30 [0022] In some embodiments, at least one of R_7 , R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7 , R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are different than 35 each other. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H and are different than each other.

[0023] In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R). In some embodiments, X_{11} is N. In some embodiments, X_{12} is not S. In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S. In some embodiments, R is not H.

- 5 [0024] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(d)**:



I(d)

wherein

- 10 X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

- 15 X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

- 20 X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

Ring F is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

- 25 R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

or **R**₁ and **R**₂ are joined to form a C=O, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

or **R**₂ and **R**₄ are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then **R**₁ and/or **R**₃ are absent;

R₃ and **R**₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

or **R**₃ and **R**₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

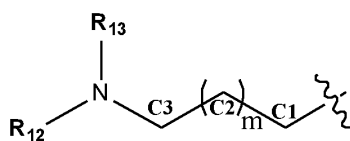
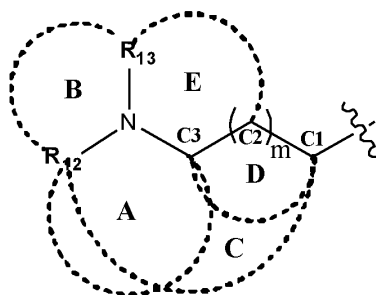
R₅ is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R₆ is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂, (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl,

methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R_8 -(substituted or unsubstituted C_3 - C_8 cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R_8 -aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R_6 and R_5 are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide);

or R_6 is represented by the structure of formula **B** or **Bi**:

**B****Bi**

wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H;

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

R_{12} and C_3 are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

R_{12} and C_1 are joined to form ring **C** and R_{13} is R_{30} ; or

C_1 and C_3 are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and C_2 are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B** and C_1 and C_3 are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine,

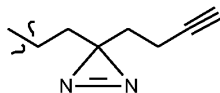
ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

5 Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

15 **R**₇' is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

R₂₀ is represented by the following structure:



30 **R** is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃)

C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R₃₀ is H, **R**₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R**₈ is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

R₉ is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

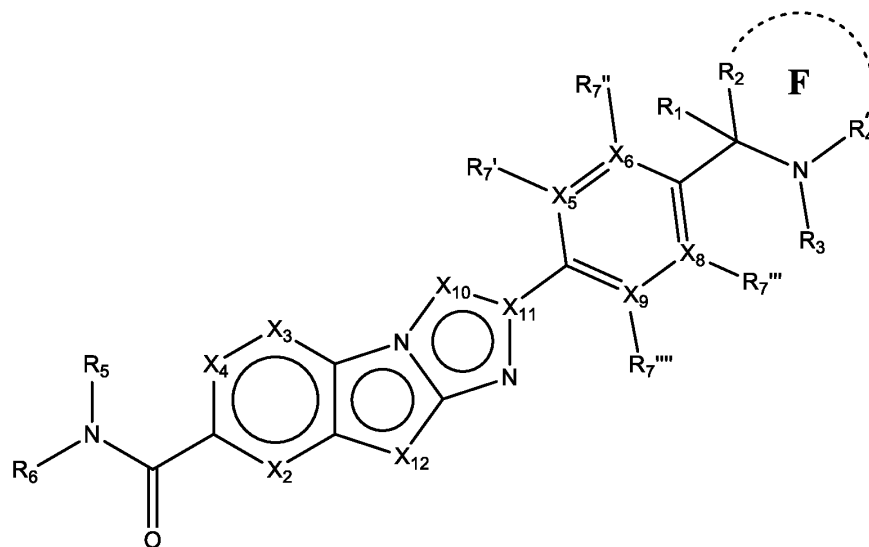
R₁₀ and **R**₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)R, or S(O)₂R; or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0025] In some embodiments, at least one of **X**₂, **X**₃, and **X**₄ is C(R). In some embodiments, **X**₁₁ is N. In some embodiments, **X**₁₂ is not S. In some embodiments, at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, **R** is not H. In some embodiments, if **R**₁ and **R**₂ are joined to form a C=O, then at least one of **X**₂, **X**₃, **X**₄, and **X**₁₀ is not CH;

[0026] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(e)**:



wherein

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or **R**₂ and **R**₄ are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then **R**₁ and/or **R**₃ are absent;

R₃ and **R**₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -**R**₈-O-**R**₁₀ (e.g., (CH₂)₂-O-CH₃), **R**₈-N(**R**₁₀)(**R**₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or **R**₂₀;

or **R**₃ and **R**₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

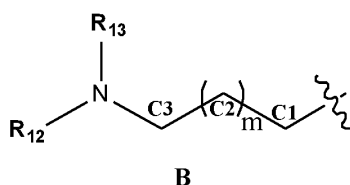
R₅ is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R₆ is H, F, Cl, Br, I, OH, SH, **R**₈-OH, **R**₈-SH, -**R**₈-O-**R**₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), **R**₈-S-**R**₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), **R**₈-NHC(O)-**R**₁₀, -O-**R**₈-**R**₁₀, **R**₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), **R**₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -**R**₈CN, NH₂, NHR, N(**R**)₂, NH(**R**₁₀), N(**R**₁₀)(**R**₁₁), **R**₈-N(**R**₁₀)(**R**₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂, (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), **R**₉-**R**₈-N(**R**₁₀)(**R**₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-**R**₁₀, NHCO-N(**R**₁₀)(**R**₁₁), COOH, -C(O)Ph, C(O)O-**R**₁₀, **R**₈-C(O)-**R**₁₀, C(O)H, C(O)-**R**₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(**R**₁₀)(**R**₁₁), SO₂R, SO₂N(**R**₁₀)(**R**₁₁), CH(CF₃)(NH-**R**₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), **R**₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered

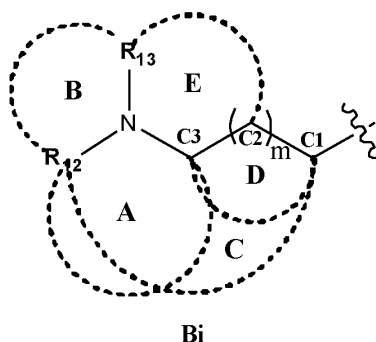
heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R_8 -aryl (e.g., benzyl), substituted or unsubstituted benzyl;

- 5 or R_6 and R_5 are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R_6 is represented by the structure of formula **B** or **Bi**:



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wherein

m is 0 or 1; and

- 15 R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or
 R_{12} and R_{13} are both H;
 R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);
 R_{12} and C_3 are joined to form ring **A** and R_{13} is R_{30} ; or
20 R_{12} and R_{13} are joined to form ring **B**; or
 R_{12} and C_1 are joined to form ring **C** and R_{13} is R_{30} ; or
 C_1 and C_3 are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or
 R_{13} and C_2 are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or
 R_{12} and R_{13} are joined to form ring **B** and C_1 and C_3 are joined to form ring **D**;
25 wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-

azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

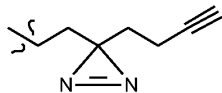
Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇', **R**₇'', **R**₇''' and **R**₇'''' are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or **R**₇' and **R**₇' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R**₇''' and **R**₇'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R₂₀ is represented by the following structure:



R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl,

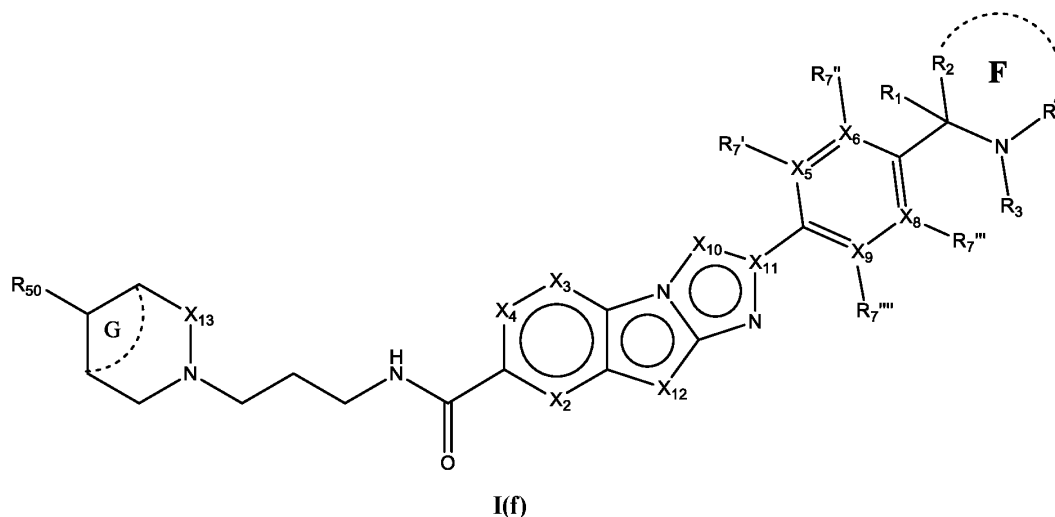
- ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃, C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃)
- 5 C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);
- 10 **R**₃₀ is H, **R**₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);
- 15 each **R**₈ is independently [CH₂]_p
 wherein **p** is between 1 and 10 (e.g., 1, 2);
R₉ is [CH]_q, [C]_q
 20 wherein **q** is between 2 and 10;
R₁₀ and **R**₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)R, or S(O)₂R;
 25 or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),
n is an integer between 0 and 4 (e.g., 1, 2);
 or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or
 30 any combination thereof.

[0027] In some embodiments, at least one of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' is not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are different than each other. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H and are different than each other.

[0028] In some embodiments, at least one of **X**₂, **X**₃, and **X**₄ is C(R). In some embodiments, **X**₁₁ is N. In some embodiments, **X**₁₂ is not S. In some embodiments, at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is

N; or X_{12} is not S. In some embodiments, R is not H. In some embodiments, if R_1 and R_2 are joined to form a C=O, then at least one of X_2 , X_3 , X_4 , and X_{10} is not CH;

[0029] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(f)**:



wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' ,

R_7''' , and R_7'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

X_{13} is CH₂, CH(R) (e.g., CH-CH₃), C(R)₂, or C=O;

Ring **G** is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);

Ring **F** is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofurane, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF_3 , substituted or unsubstituted C_1 - C_5 alkyl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl, substituted or unsubstituted C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy;

or R_1 and R_2 are joined to form a $C=O$, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

or R_2 and R_4 are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then R_1 and/or R_3 are absent;

R_3 and R_4 are each independently H, Me, substituted or unsubstituted C_1 - C_5 alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), $-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), $R_8-N(R_{10})(R_{11})$ (e.g., $(CH_2)_2-NH(CH_3)$), substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R_{20} ;

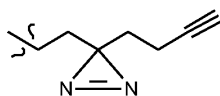
or R_3 and R_4 are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

R_7' , R_7'' , R_7''' and R_7'''' are each independently H, F, Cl, Br, I, OH, $O-R_{20}$, SH, R_8-OH , R_8-SH , $-R_8-O-R_{10}$, $R_8-(C_3-C_8 \text{ cycloalkyl})$, $R_8-(3-8 \text{ membered heterocyclic ring})$, CF_3 , CD_3 , OCD_3 , CN, NO_2 , $-CH_2CN$, $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $R_8-N(R_{10})(R_{11})$, $R_9-R_8-N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-R_{10}$, C_1 - C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$, SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1 - C_5 linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C_1 - C_5 linear or branched, substituted or unsubstituted alkenyl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl (e.g., CHF_2), C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1 - C_5 linear or branched thioalkoxy, C_1 - C_5 linear or branched haloalkoxy, C_1 - C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or R_7' and R_7'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R_{20} is represented by the following structure:



R₃₀ is H, **R₂₀**, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R₈**-aryl (e.g., CH₂-Ph), -**R₈**-O-**R₈**-O-**R₁₀** (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R₈**-O-**R₁₀**, -**R₈**-**R₁₀** (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R₅₀ is H, **R₂₀**, F, Cl, Br, I, OH, SH, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl, -**R₈**-**R₁₀** (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R₈**-aryl (e.g., CH₂-Ph), -**R₈**-O-**R₈**-O-**R₁₀** (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R₈**-O-**R₁₀**, O-**R₈**-**R₁₀** (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -**R₈**-**R₁₀** (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

each **R₈** is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

R₉ is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R₁₁** are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R₂₀**, C(O)R, or S(O)₂R;

or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

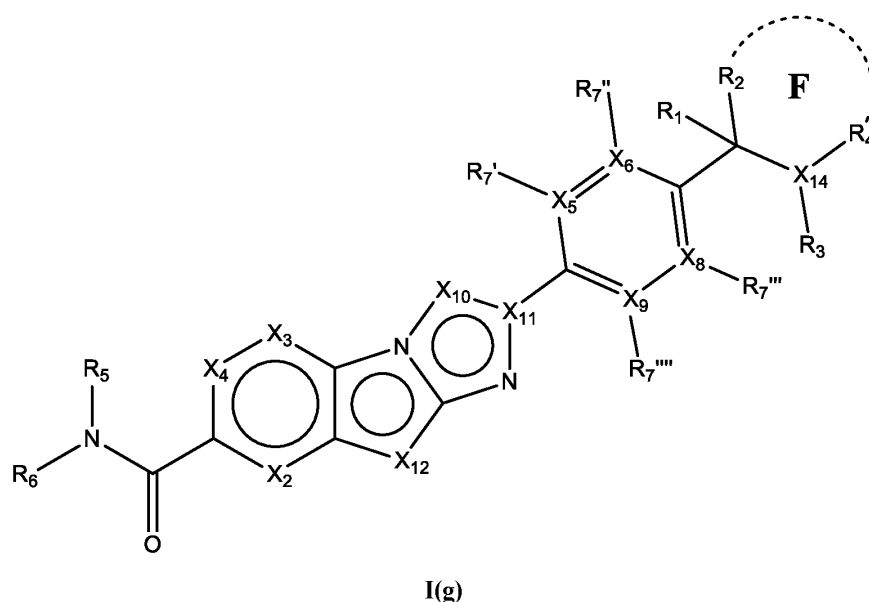
n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0030] In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are different than each other. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H and are different than each other. In some embodiments, if R_1 and R_2 are joined to form a C=O, then at least one of X_2 , X_3 , X_4 , and X_{10} is not CH;

[0031] In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R). In some embodiments, X_{11} is N. In some embodiments, X_{12} is not S. In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S. In some embodiments, R is not H.

[0032] In various embodiments, this invention is directed to a compound represented by the structure of formula I(g):



wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methyleclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' , R_7''' , and R_7'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO_2 , O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

X_{14} is S, O, N or CH, wherein if X_{14} is CH then Ring F is not absent and if X_{14} is S or O then R_3 is absent;

Ring F is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

or R_1 and R_2 are joined to form a C=O, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

or R_2 and R_4 are joined to form Ring F as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if Ring F is aromatic, then R_1 and/or R_3 are absent;

R_3 and R_4 are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

or R_3 and R_4 are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

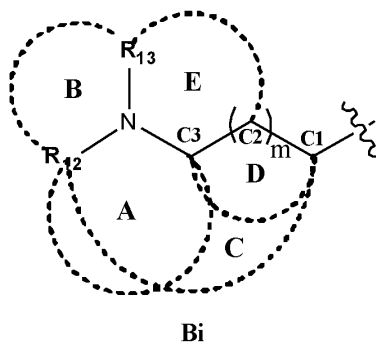
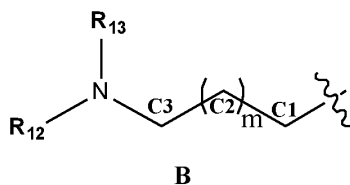
wherein if X_{14} is S or O then R_3 is absent;

R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂,

- (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), substituted or unsubstituted benzyl;
- or R₆ and R₅ are joined to for a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide);

or R₆ is represented by the structure of formula B or Bi:



wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H;

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

5 R_{12} and $C3$ are joined to form ring A and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring B; or

R_{12} and $C1$ are joined to form ring C and R_{13} is R_{30} ; or

$C1$ and $C3$ are joined to form ring D and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and $C2$ are joined to form ring E, m is 1, and R_{12} is R_{30} ; or

10 R_{12} and R_{13} are joined to form ring B and $C1$ and $C3$ are joined to form ring D;

wherein

Ring A, C and E are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., A: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); C: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; E: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

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Ring B is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (B: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

25

Ring D is a substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclobutane, cyclohexane);

R_7' , R_7'' , R_7''' and R_7'''' are each independently H, F, Cl, Br, I, OH, O- R_{20} , SH, R_8 -OH, R_8 -SH, $-R_8$ -O- R_{10} , R_8 -(C_3 - C_8 cycloalkyl), R_8 -(3-8 membered heterocyclic ring), CF_3 , CD_3 , OCD_3 , CN, NO_2 , $-CH_2CN$, $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $R_8-N(R_{10})(R_{11})$, $R_9-R_8-N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-R_{10}$, C_1 - C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$, SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1 - C_5 linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C_1 - C_5 linear or branched, substituted or unsubstituted alkenyl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl (e.g., CHF_2), C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1 - C_5 linear or branched thioalkoxy, C_1 - C_5 linear or branched haloalkoxy, C_1 - C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl,

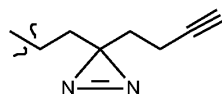
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cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or R_7' and R_7'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, 5 unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

10 R_{20} is represented by the following structure:



R is H, F, Cl, Br, I, OH, SH, COOH, CO(R_{10}) (e.g., C(O)CH₃), NH(R_{10}), NH-CH₂-cyclopropyl, N(R_{10})(R_{11}), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R_{30} is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R_{10}), N(R_{10})(R_{11}), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

30 each R_8 is independently [CH₂]_p

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is [CH]_q, [C]_q

wherein q is between 2 and 10;

R_{10} and R_{11} are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear 35 or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or

unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), R₂₀, C(O)R, or S(O)₂R;

or R₁₀ and R₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

5 n is an integer between 0 and 4 (e.g., 1, 2);

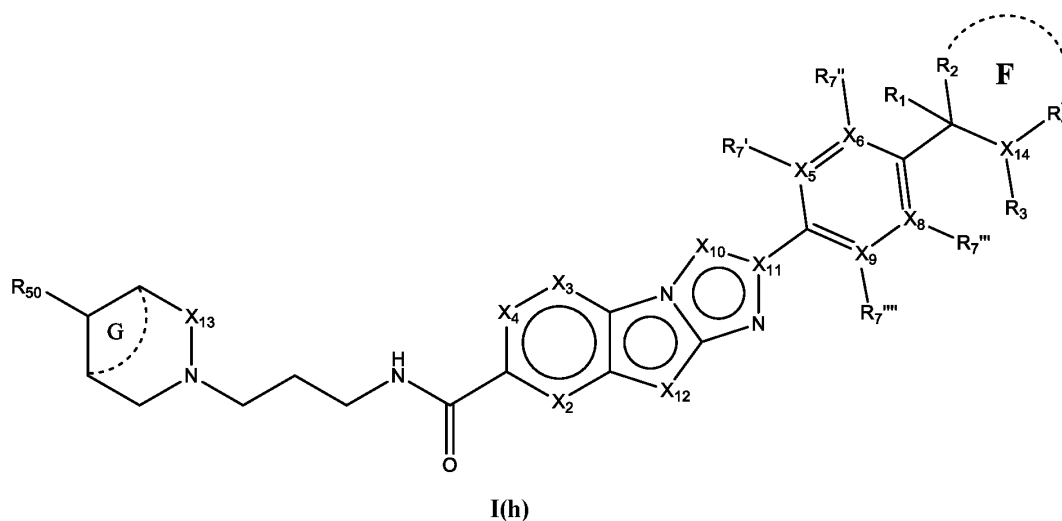
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, N-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

10 [0033] In some embodiments, at least one of R₇', R₇'', R₇''' and R₇'''' is not H. In some embodiments, at least two of R₇', R₇'', R₇''' and R₇'''' are not H. In some embodiments, at least two of R₇', R₇'', R₇''' and R₇'''' are different then each other. In some embodiments, at least two of R₇', R₇'', R₇''' and R₇'''' are not H and are different then each other.

[0034] In some embodiments, at least one of X₂, X₃, and X₄ is C(R). In some embodiments, X₁₁ is N.

15 In some embodiments, X₁₂ is not S. In some embodiments, at least one of X₂, X₃, and X₄ is C(R); X₁₁ is N; or X₁₂ is not S. In some embodiments, R is not H. In some embodiments, if R₁ and R₂ are joined to form a C=O, then at least one of X₂, X₃, X₄, and X₁₀ is not CH;

[0035] In various embodiments, this invention is directed to a compound represented by the structure of formula I(h):



X₂, X₃, and X₄, are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X₅, X₆, X₇, X₈ and X₉ are each independently nitrogen or carbon atoms;

wherein if either one of **X**₅, **X**₆, **X**₈ and **X**₉ is nitrogen, then the respective **R**₇['], **R**₇^{''}, **R**₇^{'''}, and **R**₇^{''''} substitution is absent;

X₁₀ is N, CH, C(R), or C=O; wherein if **X**₁₀ is C=O then **X**₁₁ is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

5 **X**₁₁ is N or C; wherein if **X**₁₁ is N then **X**₁₀ is C=O;

X₁₂ is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

X₁₃ is CH₂, CH(R) (e.g., CH-CH₃), C(R)₂, or C=O;

10 **X**₁₄ is S, O, N or CH, wherein if **X**₁₄ is CH then Ring **F** is not absent and if **X**₁₄ is S or O then **R**₃ is absent;

Ring **G** is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);

15 **Ring F** is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

R₁ and **R**₂ are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

or **R**₁ and **R**₂ are joined to form a C=O, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

or **R**₂ and **R**₄ are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then **R**₁ and/or **R**₃ are absent;

R₃ and **R**₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or **R**₂₀;

30 or **R**₃ and **R**₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, , pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

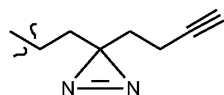
R₇['], **R**₇^{''}, **R**₇^{'''} and **R**₇^{''''} are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅

linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or R₇' and R₇'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇''' and R₇'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R₂₀ is represented by the following structure:



R₃₀ is H, R₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R₅₀ is H, R₂₀, F, Cl, Br, I, OH, SH, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g.,

(CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R₈** is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

5 **R₉** is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R₁₁** are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R₂₀**, C(O)**R**, or S(O)₂**R**;

10 or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

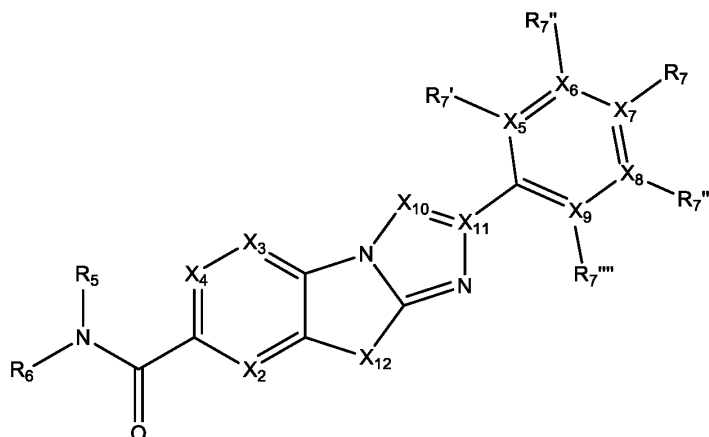
n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse
15 amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0036] In some embodiments, at least one of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** is not H. In some embodiments, at least two of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** are not H. In some embodiments, at least two of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** are different then each other. In some embodiments, at least two of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** are not H and are different then each other.

[0037] In some embodiments, at least one of **X₂**, **X₃**, and **X₄** is C(R). In some embodiments, **X₁₁** is N. In some embodiments, **X₁₂** is not S. In some embodiments, at least one of **X₂**, **X₃**, and **X₄** is C(R); **X₁₁** is N; or **X₁₂** is not S. In some embodiments, **R** is not H.

25 [0038] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(i)**:



I(i)

wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X_5 , X_6 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' ,

R_7''' , and R_7'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

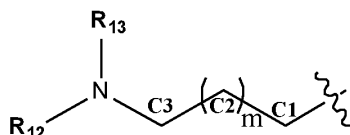
R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrrole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrrole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-

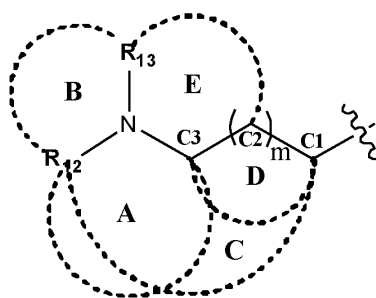
piperidine, $(\text{CH}_2)_4\text{-NH}(\text{CH}_3)$, $(\text{CH}_2)_3\text{-NH-CH}_3$, $(\text{CH}_2)_3\text{-NH-CH}_2\text{CH}_3$, $(\text{CH}_2)_3\text{-N}(\text{CH}_2\text{CH}_3)_2$, $(\text{CH}_2)_3\text{-NH}_2$, $(\text{CH}_2)_3\text{-N}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{CF}_3)$, $\text{R}_9\text{-R}_8\text{-N}(\text{R}_{10})(\text{R}_{11})$ (e.g., $(\text{CH}_2)_2\text{-C}(\text{O})\text{-piperidine}$), $\text{B}(\text{OH})_2$, $-\text{OC}(\text{O})\text{CF}_3$, $-\text{OCH}_2\text{Ph}$, $\text{NHC}(\text{O})\text{-R}_{10}$, $\text{NHCO-N}(\text{R}_{10})(\text{R}_{11})$, COOH , $-\text{C}(\text{O})\text{Ph}$, $\text{C}(\text{O})\text{O-R}_{10}$, $\text{R}_8\text{-C}(\text{O})\text{-R}_{10}$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{-R}_{10}$ (e.g., $\text{C}(\text{O})\text{CH}_3$), $\text{C}_1\text{-C}_5$ linear or branched $\text{C}(\text{O})\text{-haloalkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}$, $\text{C}(\text{O})\text{N}(\text{R}_{10})(\text{R}_{11})$, SO_2R , $\text{SO}_2\text{N}(\text{R}_{10})(\text{R}_{11})$, $\text{CH}(\text{CF}_3)(\text{NH-R}_{10})$, $\text{C}_1\text{-C}_5$ linear or branched, substituted or unsubstituted alkyl (e.g., $\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{NH}_2$, $\text{CH}(\text{CH}_3)\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $\text{CH}_2\text{-CH}(\text{OH})\text{Ph}$, $(\text{CH}_2)_3\text{N}(\text{H})\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)(\text{CH}_2)_2\text{OH}$, $\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2\text{CH}_3)$, $(\text{CH}_2)_3\text{-OCH}_3$, $(\text{CH}_2)_2\text{-OCH}_3$, $(\text{CH}_2)_2\text{-OCH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2\text{CH}(\text{CH}_3)_2)$, $\text{CH}_2\text{CH}(\text{CH}_3)(\text{OCH}_3)$, $\text{CH}_2\text{CH}(\text{N}(\text{CH}_3)_2)(\text{CH}_2\text{CH}_3)$, benzyl, methyl, ethyl, $\text{CH}_2\text{-OCH}_2\text{-CH}_2\text{-O-CH}_3$, $\text{CH}(\text{CH}_3)\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $\text{C}_1\text{-C}_5$ linear or branched, substituted or unsubstituted alkenyl, $\text{C}_1\text{-C}_5$ linear or branched, or $\text{C}_3\text{-C}_8$ cyclic haloalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_5$ linear or branched, or $\text{C}_3\text{-C}_8$ cyclic alkoxy (e.g. methoxy, $\text{O}-(\text{CH}_2)_2\text{-O-CH}_3$), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, $\text{C}_1\text{-C}_5$ linear or branched thioalkoxy, $\text{C}_1\text{-C}_5$ linear or branched haloalkoxy, $\text{C}_1\text{-C}_5$ linear or branched alkoxyalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), $\text{R}_8\text{-(substituted or unsubstituted } \text{C}_3\text{-C}_8 \text{ cycloalkyl)}$, substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted $\text{R}_8\text{-aryl}$ (e.g., benzyl), substituted or unsubstituted benzyl;

or R_6 and R_5 are joined to for a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R_6 is represented by the structure of formula **B** or **Bi**:



B



Bi

wherein

m is 0 or 1; and

R₁₂ is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are both H;

R₁₂ and **R**₁₃ are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl);

R₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B**; or

R₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

C1 and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇, **R**_{7'}, **R**_{7''}, **R**_{7'''} and **R**_{7''''} are each independently H, F, Cl, Br, I, OH, O-**R**₂₀, SH, **R**₈-OH, **R**₈-SH, -**R**₈-O-**R**₁₀, **R**₈-(C₃-C₈ cycloalkyl), **R**₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -**R**₈CN, NH₂, NHR, N(**R**)₂, NH(**R**₁₀), N(**R**₁₀)(**R**₁₁), **R**₈-N(**R**₁₀)(**R**₁₁), **R**₉-**R**₈-N(**R**₁₀)(**R**₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-**R**₁₀, NHCO-N(**R**₁₀)(**R**₁₁), COOH, -C(O)Ph, C(O)O-**R**₁₀, **R**₈-C(O)-**R**₁₀, C(O)H, C(O)-**R**₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(**R**₁₀)(**R**₁₁), SO₂R, SO₂N(**R**₁₀)(**R**₁₁), CH(CF₃)(NH-**R**₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched

haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

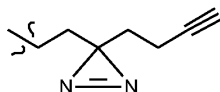
5 or **R**₇' and **R**₇'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R**₇'' and **R**₇ are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, 10 pyrrolidine);

or **R**₇ and **R**₇''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R**₇''' and **R**₇'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, 15 pyrrolidine);

R₂₀ is represented by the following structure:



R is H, F, Cl, Br, I, OH, SH, COOH, CO(**R**₁₀) (e.g., C(O)CH₃), NH(**R**₁₀), NH-CH₂-cyclopropyl, 20 N(**R**₁₀)(**R**₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) 25 C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R**₈-aryl (e.g., CH₂-Ph), -**R**₈-O-**R**₈-O-**R**₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R**₈-O-**R**₁₀, O-**R**₈-**R**₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -**R**₈-**R**₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

30 **R**₃₀ is H, **R**₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(**R**)₂, NH(**R**₁₀), N(**R**₁₀)(**R**₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R**₈-aryl (e.g., CH₂-Ph), -**R**₈-O-**R**₈-O-**R**₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R**₈-O-**R**₁₀, -**R**₈-**R**₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., 35 pyridine (2, 3, and 4-pyridine));

R_{50} is H, R_{20} , F, Cl, Br, I, OH, SH, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1 - C_5 linear or branched, substituted or unsubstituted alkyl C_1 - C_5 linear or branched alkoxy, C_1 - C_5 linear or branched haloalkyl, $-R_8-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

5 R is H, F, Cl, Br, I, OH, SH, $COOH$, $CO(R_{10})$ (e.g., $C(O)CH_3$), $NH(R_{10})$, $NH-CH_2$ -cyclopropyl, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1 - C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH_2 -cyclopropyl, CH_2-OH , CH_2-CH_2-OH , $CH_2-CH_2-O-CH_2-CH_2-O-CH_3$, $CH_2-O-CH_2-CH_2-O-CH_3$), C_3 - C_8 substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C_1 - C_5 linear or branched alkoxy, (e.g., methoxy, ethoxy, $O-(CH_2CH_3)$, $OCHF_2$, $O-(CH_2)_2-O-CH_3$, isopropoxy, 10 $O-(CH_2)$ -cyclopropyl, $O-CH_2$ -methylcyclobutyl, $O-CH_2$ -3-methyloxetane, $O-CH(CH_3)-CH_2-O-CH_3$) C_1 - C_5 linear or branched haloalkyl (e.g., CHF_2 , CF_3 , CF_2CH_3 , CH_2CF_3 , $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)-CH(CH_3)_2$), R_8 -aryl (e.g., CH_2-Ph), $-R_8-O-R_8-O-R_{10}$ (e.g., $(CH_2)_2-O-(CH_2)_2-O-CH_3$), $-R_8-O-R_{10}$, $O-R_8-R_{10}$ (e.g., $O-(CH_2)_2-O-CH_3$, $O-(CH_2CH_3)$, $O-(CH_2)$ -cyclopropyl), $-R_8-R_{10}$ (e.g., (CH_2) -cyclopropyl, $(CH_2)_2-O-CH_3$, $(CH_2)-OH$, $(CH_2)_2-OH$, $(CH_2)-COOH$), substituted or unsubstituted 15 aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

each R_8 is independently $[CH_2]_p$

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is $[CH]_q$, $[C]_q$

wherein q is between 2 and 10;

20 R_{10} and R_{11} are each independently H, OH, $COOH$, C_1 - C_5 substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH_2 -cyclopropyl, $CH_2-CH_2-O-CH_3$), C_3 - C_8 substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C_1 - C_5 substituted or unsubstituted linear or branched haloalkyl (e.g., CH_2CF_3), C_1 - C_5 linear or branched alkoxy (e.g., $O-CH_3$), R_{20} , $C(O)R$, or $S(O)_2R$;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic 25 ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

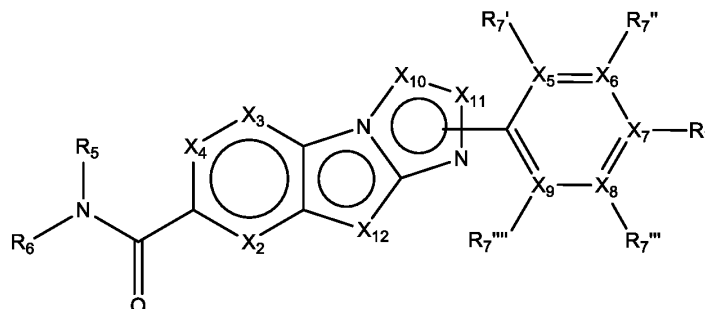
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, N -oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

30

[0039] In some embodiments, at least one of R_7 , R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7 , R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are different then 35 each other. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H and are different then each other.

[0040] In some embodiments, at least one of X_2 , X_3 , and X_4 is $C(R)$. In some embodiments, R is not H.

[0041] In various embodiments, this invention is directed to a compound represented by the structure of formula I(j):



I(j)

5 wherein

X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

10 X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_7 , X_8 and X_9 is nitrogen, then the respective R_7' ,

R_7'' , R_7 , R_7''' , and R_7'''' substitution is absent;

X_{10} is nitrogen, carbon, CH or C(R) (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

15 X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

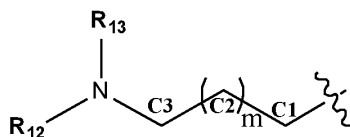
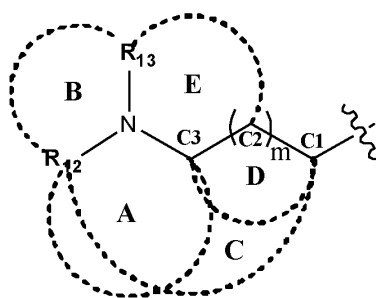
20 R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or

25 spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN,

30 -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂,

- (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), substituted or unsubstituted benzyl;
- or R₆ and R₅ are joined to form a substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R₆ is represented by the structure of formula **B** or **Bi**:

**B****Bi**

wherein

m is 0 or 1; and

R₁₂ is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are both H;

R₁₂ and **R**₁₃ are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl);

R₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B**; or

R₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

C1 and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇, **R**_{7'}, **R**_{7''}, **R**_{7'''} and **R**_{7''''} are each independently H, F, Cl, Br, I, OH, O-**R**₂₀, SH, **R**₈-OH, **R**₈-SH, -**R**₈-O-**R**₁₀, **R**₈-(C₃-C₈ cycloalkyl), **R**₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -**R**₈CN, NH₂, NHR, N(**R**)₂, NH(**R**₁₀), N(**R**₁₀)(**R**₁₁), **R**₈-N(**R**₁₀)(**R**₁₁), **R**₉-**R**₈-N(**R**₁₀)(**R**₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-**R**₁₀, NHCO-N(**R**₁₀)(**R**₁₁), COOH, -C(O)Ph, C(O)O-**R**₁₀, **R**₈-C(O)-**R**₁₀, C(O)H, C(O)-**R**₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(**R**₁₀)(**R**₁₁), SO₂R, SO₂N(**R**₁₀)(**R**₁₁), CH(CF₃)(NH-**R**₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched

haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

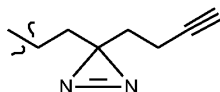
5 or **R**₇' and **R**₇'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R**₇'' and **R**₇ are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, 10 pyrrolidine);

or **R**₇ and **R**₇''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R**₇''' and **R**₇'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, 15 pyrrolidine);

R₂₀ is represented by the following structure:



R is H, F, Cl, Br, I, OH, SH, COOH, CO(**R**₁₀) (e.g., C(O)CH₃), NH(**R**₁₀), NH-CH₂-cyclopropyl, 20 N(**R**₁₀)(**R**₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) 25 C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R**₈-aryl (e.g., CH₂-Ph), -**R**₈-O-**R**₈-O-**R**₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R**₈-O-**R**₁₀, O-**R**₈-**R**₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -**R**₈-**R**₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

30 **R**₃₀ is H, **R**₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(**R**)₂, NH(**R**₁₀), N(**R**₁₀)(**R**₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R**₈-aryl (e.g., CH₂-Ph), -**R**₈-O-**R**₈-O-**R**₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -**R**₈-O-**R**₁₀, -**R**₈-**R**₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., 35 pyridine (2, 3, and 4-pyridine));

each R_8 is independently $[CH_2]_p$

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is $[CH]_q$, $[C]_q$

wherein q is between 2 and 10;

5 R_{10} and R_{11} are each independently H, OH, COOH, C_1 - C_5 substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH_2 -cyclopropyl, CH_2 - CH_2 -O- CH_3), C_3 - C_8 substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C_1 - C_5 substituted or unsubstituted linear or branched haloalkyl (e.g., CH_2CF_3), C_1 - C_5 linear or branched alkoxy (e.g., O- CH_3), R_{20} , C(O)R, or S(O) $_2$ R;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

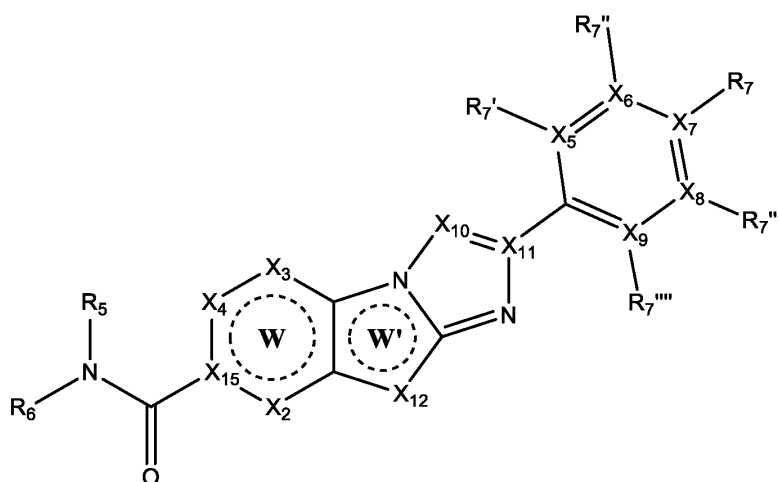
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

15 [0042] In some embodiments, at least one of R_7 , R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7 , R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are different than each other. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' are not H and are different than each other.

20 [0043] In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R). In some embodiments, X_{11} is N. In some embodiments, X_{12} is not S. In some embodiments, at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S. In some embodiments, R is not H.

25

[0044] In various embodiments, this invention is directed to a compound represented by the structure of formula I(k):



I(k)

wherein

Ring W may be either aromatic or non-aromatic ring,

wherein if **ring W** is aromatic then

5 X_2 , X_3 , and X_4 , are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

10 X_{15} is C;

wherein if **ring W** is non-aromatic then

X_2 , X_3 , and X_4 , are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S, S=O or SO₂ (e.g., CH₂);

X_{15} is CH, C(R) or N (e.g., CH, N);

15 X_5 , X_6 , X_7 , X_8 and X_9 are each independently nitrogen or carbon atoms;

wherein if either one of X_5 , X_6 , X_7 , X_8 and X_9 is nitrogen, then the respective **R**₇', **R**₇'', **R**₇'', and **R**₇'''' substitution is absent;

X_{10} is N, CH, C(R), or C=O; wherein if X_{10} is C=O then X_{11} is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

20 X_{11} is N or C; wherein if X_{11} is N then X_{10} is C=O;

Ring W' may be either aromatic or non-aromatic ring,

wherein if **ring W'** is aromatic then

25 X_{12} is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

wherein if **ring W'** is non-aromatic then

X_{12} is CH=CH, CH=CH(R), C(R)=CH, OCH₂, CH₂O, SCH₂, CH₂S, CH=N, C(R)=N, N=CH, N=C(R);

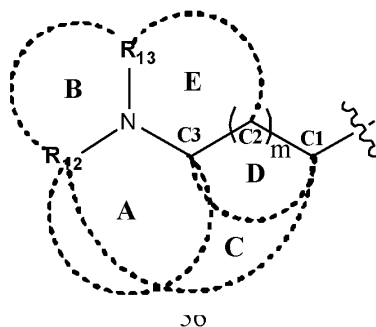
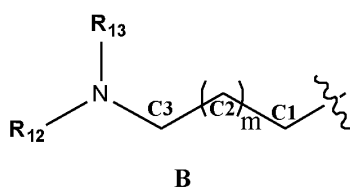
R₅ is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

30 **R**₆ is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-

methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂, (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂, C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R₆ and R₅ are joined to for a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R₆ is represented by the structure of formula B or Bi:



Bi

wherein

m is 0 or 1; and

R₁₂ is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are both H;

R₁₂ and **R**₁₃ are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl);

R₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B**; or

R₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

C1 and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

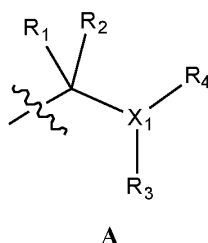
Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇ is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), C(O)NH(CH₂CH₂OH)), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl

(e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g., morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted benzyl;

or R₇ is represented by the structure of formula A:



wherein

X₁ is N or O;

R₁ and R₂ are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

R₁ and R₂ are joined to form =O or a C₃-C₈ carbocyclic or heterocyclic ring (e.g., cyclopropyl);

R₃ and R₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

R₃ and R₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

or R₂ and R₄ are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole), wherein if the ring is aromatic, then R₁ and/or R₃ are absent;

wherein if X₁ is O then R₄ is absent;

R_7' , R_7'' , R_7''' and R_7'''' are each independently H, F, Cl, Br, I, OH, O- R_{20} , SH, R_8 -OH, R_8 -SH, $-R_8$ -O- R_{10} , R_8 -(C₃-C₈ cycloalkyl), R_8 -(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, - R_8 CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R_8 -N(R₁₀)(R₁₁), R_9 - R_8 -N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)- R_{10} , NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O- R_{10} , R_8 -C(O)- R_{10} ,
 5 C(O)H, C(O)- R_{10} , C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH- R_{10}), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced
 10 with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

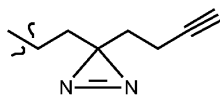
15 or R_7' and R_7'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7'' and R_7 are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran,
 20 pyrrolidine);

or R_7 and R_7''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

25 or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R_{20} is represented by the following structure:



R_{30} is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅
 30 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R_8 -aryl (e.g., CH₂-Ph), - R_8 -O- R_8 -O- R_{10} (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), - R_8 -O- R_{10} , - R_8 - R_{10} (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g.,
 35 pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃), C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g., O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R**₈ is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

R₉ is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R**₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)R, or S(O)₂R;

or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

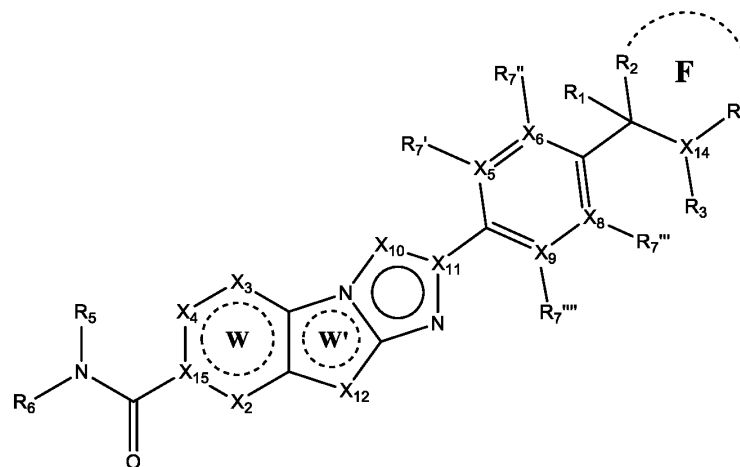
n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0045] In some embodiments, at least one of **R**₇, **R**₇', **R**₇'', **R**₇''' and **R**₇'''' is not H. In some embodiments, at least two of **R**₇, **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H. In some embodiments, at least one of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' is not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are different than each other. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H and are different than each other.

[0046] In some embodiments, **Ring W** is aromatic and at least one of **X**₂, **X**₃, and **X**₄ is C(R). In some embodiments, **Ring W** is aromatic and **X**₁₁ is N. In some embodiments, **Ring W** is aromatic and **X**₁₂ is not S. In some embodiments, if **Ring W** is aromatic then at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, **R** is not H. In some embodiments, if both **Ring W** and **Ring W'** are aromatic, then at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is N; or **X**₁₂ is not S.

[0047] In various embodiments, this invention is directed to a compound represented by the structure of formula I(I):



I(I)

5 wherein

Ring W may be either aromatic or non-aromatic ring,

wherein if **ring W** is aromatic then

X₂, X₃, and X₄, are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl),
 10 C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X₁₅ is C;

wherein if **ring W** is non-aromatic then

X₂, X₃, and X₄, are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S,
 15 S=O or SO₂ (e.g., CH₂);

X₁₅ is CH, C(R) or N (e.g., CH, N);

X₅, X₆, X₇, X₈ and X₉ are each independently nitrogen or carbon atoms;

wherein if either one of **X₅, X₆, X₇, X₈ and X₉** is nitrogen, then the respective **R₇'**, **R₇''**,

20 **R₇'**, **R₇'''**, and **R₇''''** substitution is absent;

X₁₀ is N, CH, C(R), or C=O; wherein if **X₁₀** is C=O then **X₁₁** is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X₁₁ is N or C; wherein if **X₁₁** is N then **X₁₀** is C=O;

Ring W' may be either aromatic or non-aromatic ring,

25 wherein if **ring W'** is aromatic then

X₁₂ is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);

wherein if **ring W'** is non-aromatic then

X_{12} is CH=CH, CH=CH(R), C(R)=CH, OCH₂, SCH₂, CH=N, C(R)=N, N=CH, N=C(R);

X_{14} is S, O, N or CH, wherein if X_{14} is CH then Ring F is not absent and if X_{14} is S or O then

5 R_3 is absent;

Ring F is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

10 R_1 and R_2 are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

or R_1 and R_2 are joined to form a C=O, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

15 or R_2 and R_4 are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then R_1 and/or R_3 are absent;

R_3 and R_4 are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

or R_3 and R_4 are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, , pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

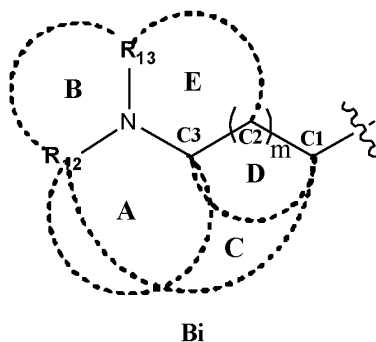
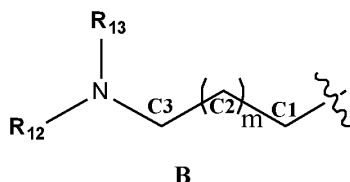
wherein if X_{14} is S or O then R_3 is absent;

25 R_5 is H or C₁-C₅ linear or branched alkyl (e.g. methyl);

R_6 is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-4-cyano-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂,

- (CH₂)₃-N(CH₂CH₃)(CH₂CF₃)), R₉-R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-C(O)-piperidine), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), substituted or unsubstituted benzyl;
- or R₆ and R₅ are joined to for a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide);

or R₆ is represented by the structure of formula B or Bi:



wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H;

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

5 R_{12} and $C3$ are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

R_{12} and $C1$ are joined to form ring **C** and R_{13} is R_{30} ; or

$C1$ and $C3$ are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and $C2$ are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

10 R_{12} and R_{13} are joined to form ring **B** and $C1$ and $C3$ are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

15

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

25

Ring **D** is a substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclobutane, cyclohexane);

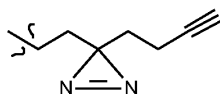
R_7' , R_7'' , R_7''' and R_7'''' are each independently H, F, Cl, Br, I, OH, O- R_{20} , SH, R_8 -OH, R_8 -SH, $-R_8$ -O- R_{10} , R_8 -(C_3 - C_8 cycloalkyl), R_8 -(3-8 membered heterocyclic ring), CF_3 , CD_3 , OCD_3 , CN, NO_2 ,
 30 $-CH_2CN$, $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $R_8-N(R_{10})(R_{11})$, $R_9-R_8-N(R_{10})(R_{11})$, $B(OH)_2$,
 $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$,
 $C(O)H$, $C(O)-R_{10}$, C_1 - C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$,
 SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1 - C_5 linear or branched, substituted or unsubstituted alkyl
 (e.g., isopropyl, methyl, ethyl), C_1 - C_5 linear or branched, substituted or unsubstituted alkenyl, C_1 - C_5
 35 linear or branched, or C_3 - C_8 cyclic haloalkyl (e.g., CHF_2), C_1 - C_5 linear or branched, or C_3 - C_8 cyclic
 alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced
 with an oxygen atom, C_1 - C_5 linear or branched thioalkoxy, C_1 - C_5 linear or branched haloalkoxy, C_1 - C_5
 linear or branched alkoxyalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclopropyl,

cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or R_7' and R_7'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, 5 unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R_7''' and R_7'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

10 R_{20} is represented by the following structure:



R is H, F, Cl, Br, I, OH, SH, COOH, CO(R_{10}) (e.g., C(O)CH₃), NH(R_{10}), NH-CH₂-cyclopropyl, N(R_{10})(R_{11}), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R_{30} is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R_{10}), N(R_{10})(R_{11}), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

30 each R_8 is independently [CH₂]_p

wherein p is between 1 and 10 (e.g., 1, 2);

R_9 is [CH]_q, [C]_q

wherein q is between 2 and 10;

R_{10} and R_{11} are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear 35 or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or

unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)**R**, or S(O)₂**R**;

or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

5 **n** is an integer between 0 and 4 (e.g., 1, 2);

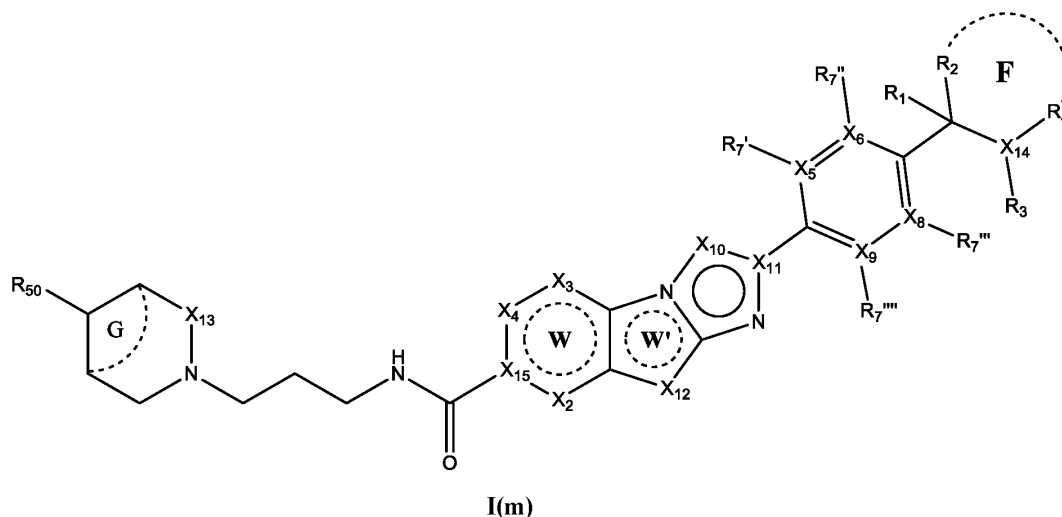
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

10 [0048] In some embodiments, at least one of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' is not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are different then eachother. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H and are different then eachother.

[0049] In some embodiments, **Ring W** is aromatic and at least one of **X**₂, **X**₃, and **X**₄ is C(**R**). In some
15 embodiments, **Ring W** is aromatic and **X**₁₁ is N. In some embodiments, **Ring W** is aromatic and **X**₁₂ is not S. In some embodiments, if **Ring W** is aromatic then at least one of **X**₂, **X**₃, and **X**₄ is C(**R**); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, if both **Ring W** and **Ring W'** are aromatic, then at least one of **X**₂, **X**₃, and **X**₄ is C(**R**); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, **R** is not H.

[0050] In some embodiments, if **R**₁ and **R**₂ are joined to form a C=O, then at least one of **X**₂, **X**₃, **X**₄,
20 and **X**₁₀ is not CH;

[0051] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(m)**:



25

wherein

Ring W may be either aromatic or non-aromatic ring,

wherein if **ring W** is aromatic then

- X₂, X₃, and X₄**, are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃, C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));
- X₁₅** is C;
- wherein if **ring W** is non-aromatic then
- X₂, X₃, and X₄**, are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S, S=O or SO₂ (e.g., CH₂);
- X₁₅** is CH, C(R) or N (e.g., CH, N);
- X₅, X₆, X₇, X₈ and X₉** are each independently nitrogen or carbon atoms;
- wherein if either one of **X₅, X₆, X₈ and X₉** is nitrogen, then the respective **R₇'**, **R₇''**, **R₇'''**, and **R₇''''** substitution is absent;
- X₁₀** is N, CH, C(R), or C=O; wherein if **X₁₀** is C=O then **X₁₁** is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));
- X₁₁** is N or C; wherein if **X₁₁** is N then **X₁₀** is C=O;
- Ring W'** may be either aromatic or non-aromatic ring,
- wherein if **ring W'** is aromatic then
- X₁₂** is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);
- wherein if **ring W'** is non-aromatic then
- X₁₂** is CH=CH, CH=CH(R), C(R)=CH, OCH₂, SCH₂, CH=N, C(R)=N, N=CH, N=C(R);
- X₁₃** is CH₂, CH(R) (e.g., CH-CH₃), C(R)₂, or C=O;
- X₁₄** is S, O, N or CH, wherein if **X₁₄** is CH then **Ring F** is not absent and if **X₁₄** is S or O then **R₃** is absent;
- Ring G** is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);
- Ring F** is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);
- R₁** and **R₂** are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;
- or **R₁** and **R₂** are joined to form a C=O, or a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl);

or **R₂** and **R₄** are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole), wherein if **Ring F** is aromatic, then **R₁** and/or **R₃** are absent;

R₃ and **R₄** are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

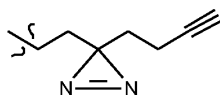
or **R₃** and **R₄** are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole);

R₇', **R₇''**, **R₇'''** and **R₇'''''** are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

or **R₇'** and **R₇''** are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or **R₇'''** and **R₇'''''** are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R₂₀ is represented by the following structure:



R₃₀ is H, **R₂₀**, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-

CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R₅₀ is H, **R**₂₀, F, Cl, Br, I, OH, SH, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃) C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g. (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g. O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R**₈ is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

R₉ is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R**₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)R, or S(O)₂R;

or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

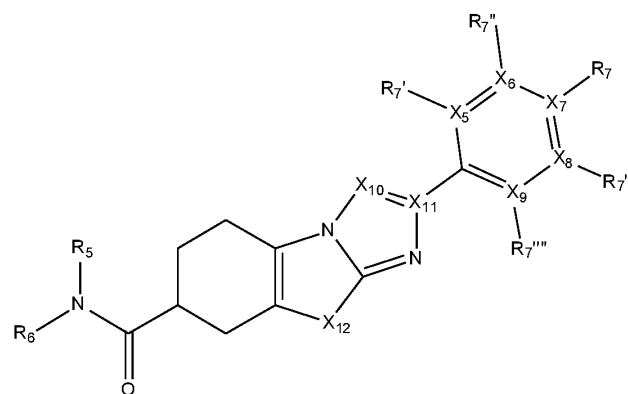
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0052] In some embodiments, at least one of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' is not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are different then eachother. In some embodiments, at least two of **R**₇', **R**₇'', **R**₇''' and **R**₇'''' are not H and are different then eachother.

[0053] In some embodiments, **Ring W** is aromatic and at least one of **X**₂, **X**₃, and **X**₄ is C(R). In some embodiments, **Ring W** is aromatic and **X**₁₁ is N. In some embodiments, **Ring W** is aromatic and **X**₁₂ is

not S. In some embodiments, if **Ring W** is aromatic then at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, if both **Ring W** and **Ring W'** are aromatic, then at least one of **X**₂, **X**₃, and **X**₄ is C(R); **X**₁₁ is N; or **X**₁₂ is not S. In some embodiments, **R** is not H.

- 5 [0054] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(n)**:



I(n)

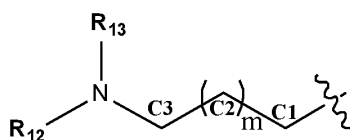
wherein

- 10 **X**₅, **X**₆, **X**₇, **X**₈ and **X**₉ are each independently nitrogen or carbon atoms;
 wherein if either one of **X**₅, **X**₆, **X**₈ and **X**₉ is nitrogen, then the respective **R**_{7'}, **R**_{7''}, **R**_{7'''}, and **R**_{7''''} substitution is absent;
X₁₀ is N, CH, C(R), or C=O; wherein if **X**₁₀ is C=O then **X**₁₁ is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));
 15 **X**₁₁ is N or C; wherein if **X**₁₁ is N then **X**₁₀ is C=O;
X₁₂ is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N (e.g., N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl);
R₅ is H or C₁-C₅ linear or branched alkyl (e.g. methyl);
 20 **R**₆ is H, F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), R₈-(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or
 25 spiro 3-10 membered heterocyclic ring) (e.g., (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrrazole, CH₂-2-oxo-methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN,
 30 -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH₂, (CH₂)₃-

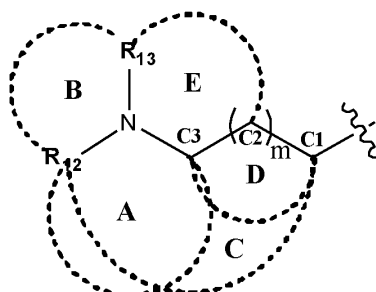
$N(CH_2CH_3)_2$, $(CH_2)_3-N(CH(CH_3)_2)_2$, $(CH_2)_3$ -piperidine, $(CH_2)_3$ -4-fluoro-piperidine, $(CH_2)_3$ -4-cyano-piperidine, $(CH_2)_4-NH(CH_3)$, $(CH_2)_3-NH-CH_3$, $(CH_2)_3-NH-CH_2CH_3$, $(CH_2)_3-N(CH_2CH_3)_2$, $(CH_2)_3-NH_2$, $(CH_2)_3-N(CH_2CH_3)(CH_2CF_3)$, $R_9-R_8-N(R_{10})(R_{11})$ (e.g., $(CH_2)_2-C(O)$ -piperidine), $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-R_{10}$ (e.g., $C(O)CH_3$), C_1-C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$, SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., $CH(CH_3)CH_2OCH_3$, $CH(CH_3)CH_2NH_2$, $CH(CH_3)C(O)N(CH_3)_2$, $CH_2-CH(OH)Ph$, $(CH_2)_3N(H)CH_2CH_3$, $CH(CH_3)(CH_2)_2OH$, $CH(CH_2OH)(CH_2CH_3)$, $(CH_2)_3-OCH_3$, $(CH_2)_2-OCH_3$, $(CH_2)_2-OCH(CH_3)_2$, $CH(CH_2OH)(CH_2CH(CH_3)_2)$, $CH_2CH(CH_3)(OCH_3)$, $CH_2CH(N(CH_3)_2)(CH_2CH_3)$, benzyl, methyl, ethyl, $CH_2-OCH_2-CH_2-O-CH_3$, $CH(CH_3)C(O)N(CH_3)_2$, C_1-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear or branched, or C_3-C_8 cyclic haloalkyl, substituted or unsubstituted C_1-C_5 linear or branched, or C_3-C_8 cyclic alkoxy (e.g. methoxy, $O-(CH_2)_2-O-CH_3$), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R_8 -(substituted or unsubstituted C_3-C_8 cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R_8 -aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R_6 and R_5 are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R_6 is represented by the structure of formula **B** or **Bi**:



B



Bi

wherein

m is 0 or 1; and

R₁₂ is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are both H;

5 **R**₁₂ and **R**₁₃ are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl);

R₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B**; or

R₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

10 **C1** and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**;

wherein

15 Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine);

20 Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, 25 hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

30 **R**₇, **R**_{7'}, **R**_{7''}, **R**_{7'''} and **R**_{7''''} are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, 35 C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy

is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, tetrahydrofuran, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

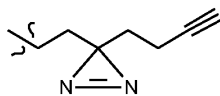
or R₇' and R₇'' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇'' and R₇ are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇ and R₇''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇''' and R₇'''' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R₂₀ is represented by the following structure:



R₃₀ is H, R₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀) (e.g., C(O)CH₃), NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃), C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g., O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g.,

(CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH, substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R₈** is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

5 **R₉** is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R₁₁** are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched
 10 haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R₂₀**, C(O)R, or S(O)₂R;
 or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),
n is an integer between 0 and 4 (e.g., 1, 2);
 or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse
 15 amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0055] In some embodiments, at least one of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** is not H. In some embodiments, at least two of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** are not H. In some embodiments, at least two of **R₇'**, **R₇''**,
 20 **R₇'''** and **R₇''''** are different than each other. In some embodiments, at least two of **R₇'**, **R₇''**, **R₇'''** and **R₇''''** are not H and are different than each other.

[0056] In some embodiments, at least one of **X₂**, **X₃**, and **X₄** is C(R). In some embodiments, **X₁₁** is N. In some embodiments, **X₁₂** is not S. In some embodiments, at least one of **X₂**, **X₃**, and **X₄** is C(R); **X₁₁** is N; or **X₁₂** is not S. In some embodiments, **R** is not H.

25 [0057] In some embodiments, **X₂** of formula **I** and/or **I(a)-I(j)** is N. In other embodiments, **X₂** is a CH. In other embodiments, **X₂** is a C(R). In other embodiments, **X₂** is C(CH₃). In other embodiments, **X₂** is C(CH₂CH₃). In other embodiments, **X₂** is C-*i*Pr. In other embodiments, **X₂** is C-CH₂-cyclopropyl. In other embodiments, **X₂** is C(O-CH₂-cyclopropyl). In other embodiments, **X₂** is C(O-CH₂-methylcyclobutyl). In other embodiments, **X₂** is C(O-CH₂-3-methyloxetane). In other embodiments, **X₂** is C(OCH₃). In other embodiments, **X₂** is C(OCH₂CH₃). In other embodiments, **X₂** is C(O-(CH₂)₂-O-CH₃). In other embodiments, **X₂** is C(NH-CH₂-cyclopropyl). In other embodiments, **X₂** is C(isopropoxy). In other embodiments, **X₂** is C(O-CH(CH₃)-CH₂-O-CH₃). In other embodiments, **X₂** is C(OCHF₂). In other
 30 embodiments, **X₂** is C(Cl). In other embodiments, **X₂** is C(C(O)CH₃). In other embodiments, **X₂** is C(OH).
 35

[0058] In some embodiments, **Ring W** of formula **I(k)-I(m)** is aromatic or non-aromatic. In some embodiments, if **Ring W** is aromatic, then **X₂** is a CH. In other embodiments, if **Ring W** is aromatic, then **X₂** is a C(R). In other embodiments, if **Ring W** is aromatic, then **X₂** is C(CH₃). In other

embodiments, if **Ring W** is aromatic, then X_2 is $C(CH_2CH_3)$. In other embodiments, if **Ring W** is aromatic, then X_2 is $C-iPr$. In other embodiments, if **Ring W** is aromatic, then X_2 is $C-CH_2$ -cyclopropyl. In other embodiments, if **Ring W** is aromatic, then X_2 is $C(O-CH_2$ -cyclopropyl). In other embodiments, if **Ring W** is aromatic, then X_2 is $C(O-CH_2$ -methylcyclobutyl). In other embodiments, if **Ring W** is aromatic, then X_2 is $C(O-CH_2$ -3-methyloxetane). In other embodiments, if **Ring W** is aromatic, then X_2 is $C(OCH_3)$. In other embodiments, if **Ring W** is aromatic, then X_2 is $C(OCH_2CH_3)$. In other embodiments, if **Ring W** is aromatic, then X_2 is $C(O-(CH_2)_2-O-CH_3)$. In other embodiments, if **Ring W** is aromatic X_2 is $C(NH-CH_2$ -cyclopropyl). In other embodiments, if **Ring W** is aromatic X_2 is $C(isopropoxy)$. In other embodiments, if **Ring W** is aromatic X_2 is $C(O-CH(CH_3)-CH_2-O-CH_3)$. In other
10 embodiments, if **Ring W** is aromatic X_2 is $C(OCHF_2)$. In other embodiments, if **Ring W** is aromatic X_2 is $C(Cl)$. In other embodiments, if **Ring W** is aromatic X_2 is $C(C(O)CH_3)$. In other embodiments, if **Ring W** is aromatic X_2 is $C(OH)$. In some embodiments, if **Ring W** is non-aromatic then X_2 is CH_2 . In some embodiments, if **Ring W** is non-aromatic then X_2 is $CH(R)$. In some embodiments, if **Ring W** is non-aromatic then X_2 is $C(R)_2$. In some embodiments, if **Ring W** is non-aromatic then X_2 is NH . In some
15 embodiments, if **Ring W** is non-aromatic then X_2 is $N(R)$. In some embodiments, if **Ring W** is non-aromatic then X_2 is O . In some embodiments, if **Ring W** is non-aromatic then X_2 is S . In some embodiments, if **Ring W** is non-aromatic then X_2 is $S=O$. In some embodiments, if **Ring W** is non-aromatic then X_2 is SO_2 .

[0059] In some embodiments, X_3 of formula **I** and/or **I(a)-I(j)** is N . In other embodiments, X_3 is a CH .
20 In other embodiments, X_3 is a CH . In other embodiments, X_3 is a $C(R)$. In other embodiments, X_3 is $C(CH_3)$. In other embodiments, X_3 is $C(CH_2CH_3)$. In other embodiments, X_3 is $C-iPr$. In other embodiments, X_3 is $C-CH_2$ -cyclopropyl. In other embodiments, X_3 is $C(O-CH_2$ -cyclopropyl). In other embodiments, X_3 is $C(O-CH_2$ -methylcyclobutyl). In other embodiments, X_3 is $C(O-CH_2$ -3-methyloxetane). In other embodiments, X_3 is $C(OCH_3)$. In other embodiments, X_3 is $C(OCH_2CH_3)$. In other
25 embodiments, X_3 is $C(O-(CH_2)_2-O-CH_3)$. In other embodiments, X_3 is $C(NH-CH_2$ -cyclopropyl). In other embodiments, X_3 is $C(isopropoxy)$. In other embodiments, X_3 is $C(O-CH(CH_3)-CH_2-O-CH_3)$. In other embodiments, X_3 is $C(OCHF_2)$. In other embodiments, X_3 is $C(Cl)$. In other embodiments, X_2 is $C(C(O)CH_3)$. In other embodiments, X_3 is $C(OH)$.

[0060] In some embodiments, **Ring W** of formula **I(k)-I(m)** is aromatic or non-aromatic. In some
30 embodiments, if **Ring W** is aromatic, then X_3 is a CH . In other embodiments, if **Ring W** is aromatic, then X_3 is a $C(R)$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C(CH_3)$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C(CH_2CH_3)$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C-iPr$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C-CH_2$ -cyclopropyl. In other embodiments, if **Ring W** is aromatic, then X_3 is $C(O-CH_2$ -cyclopropyl). In other embodiments,
35 if **Ring W** is aromatic, then X_3 is $C(O-CH_2$ -methylcyclobutyl). In other embodiments, if **Ring W** is aromatic, then X_3 is $C(O-CH_2$ -3-methyloxetane). In other embodiments, if **Ring W** is aromatic, then X_3 is $C(OCH_3)$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C(OCH_2CH_3)$. In other embodiments, if **Ring W** is aromatic, then X_3 is $C(O-(CH_2)_2-O-CH_3)$. In other embodiments, if **Ring W**

is aromatic X_3 is C(NH-CH₂-cyclopropyl). In other embodiments, if **Ring W** is aromatic X_3 is C(isopropoxy). In other embodiments, if **Ring W** is aromatic X_3 is C(O-CH(CH₃)-CH₂-O-CH₃). In other embodiments, if **Ring W** is aromatic X_3 is C(OCHF₂). In other embodiments, if **Ring W** is aromatic X_3 is C(Cl). In other embodiments, if **Ring W** is aromatic X_3 is C(C(O)CH₃). In other embodiments, if **Ring W** is aromatic X_3 is C(OH). In some embodiments, if **Ring W** is non-aromatic then X_3 is CH₂. In some embodiments, if **Ring W** is non-aromatic then X_3 is CH(R). In some embodiments, if **Ring W** is non-aromatic then X_3 is C(R)₂. In some embodiments, if **Ring W** is non-aromatic then X_3 is NH. In some embodiments, if **Ring W** is non-aromatic then X_3 is N(R). In some embodiments, if **Ring W** is non-aromatic then X_3 is O. In some embodiments, if **Ring W** is non-aromatic then X_3 is S. In some embodiments, if **Ring W** is non-aromatic then X_3 is S=O. In some embodiments, if **Ring W** is non-aromatic then X_3 is SO₂.

[0061] In some embodiments, X_4 of formula **I** and/or **I(a)-I(j)** is N. In other embodiments, X_4 is a CH. In other embodiments, X_4 is a C(R). In other embodiments, X_4 is C(CH₃). In other embodiments, X_4 is C(CH₂CH₃). In other embodiments, X_4 is C-iPr. In other embodiments, X_4 is C-CH₂-cyclopropyl. In other embodiments, X_4 is C(O-CH₂-cyclopropyl). In other embodiments, X_4 is C(O-CH₂-methylcyclobutyl). In other embodiments, X_4 is C(O-CH₂-3-methyloxetane). In other embodiments, X_4 is C(OCH₃). In other embodiments, X_4 is C(OCH₂CH₃). In other embodiments, X_4 is C(O-(CH₂)₂-O-CH₃). In other embodiments, X_4 is C(NH-CH₂-cyclopropyl). In other embodiments, X_4 is C(isopropoxy). In other embodiments, X_4 is C(O-CH(CH₃)-CH₂-O-CH₃). In other embodiments, X_4 is C(OCHF₂). In other embodiments, X_4 is C(Cl). In other embodiments, X_4 is C(C(O)CH₃). In other embodiments, X_4 is C(OH).

[0062] In some embodiments, **Ring W** of formula **I(k)-I(m)** is aromatic or non-aromatic. In some embodiments, if **Ring W** is aromatic, then X_4 is a CH. In other embodiments, if **Ring W** is aromatic, then X_4 is a C(R). In other embodiments, if **Ring W** is aromatic, then X_4 is C(CH₃). In other embodiments, if **Ring W** is aromatic, then X_4 is C(CH₂CH₃). In other embodiments, if **Ring W** is aromatic, then X_4 is C-iPr. In other embodiments, if **Ring W** is aromatic, then X_4 is C-CH₂-cyclopropyl. In other embodiments, if **Ring W** is aromatic, then X_4 is C(O-CH₂-cyclopropyl). In other embodiments, if **Ring W** is aromatic, then X_4 is C(O-CH₂-methylcyclobutyl). In other embodiments, if **Ring W** is aromatic, then X_4 is C(O-CH₂-3-methyloxetane). In other embodiments, if **Ring W** is aromatic, then X_4 is C(OCH₃). In other embodiments, if **Ring W** is aromatic, then X_4 is C(OCH₂CH₃). In other embodiments, if **Ring W** is aromatic, then X_4 is C(O-(CH₂)₂-O-CH₃). In other embodiments, if **Ring W** is aromatic X_4 is C(NH-CH₂-cyclopropyl). In other embodiments, if **Ring W** is aromatic X_4 is C(isopropoxy). In other embodiments, if **Ring W** is aromatic X_4 is C(O-CH(CH₃)-CH₂-O-CH₃). In other embodiments, if **Ring W** is aromatic X_4 is C(OCHF₂). In other embodiments, if **Ring W** is aromatic X_4 is C(Cl). In other embodiments, if **Ring W** is aromatic X_4 is C(C(O)CH₃). In other embodiments, if **Ring W** is aromatic X_4 is C(OH). In some embodiments, if **Ring W** is non-aromatic then X_4 is CH₂. In some embodiments, if **Ring W** is non-aromatic then X_4 is CH(R). In some embodiments, if **Ring W** is non-aromatic then X_4 is C(R)₂. In some embodiments, if **Ring W** is non-aromatic then X_4 is NH. In some

embodiments, if **Ring W** is non-aromatic then **X₄** is N(R). In some embodiments, if **Ring W** is non-aromatic then **X₄** is O. In some embodiments, if **Ring W** is non-aromatic then **X₄** is S. In some embodiments, if **Ring W** is non-aromatic then **X₄** is S=O. In some embodiments, if **Ring W** is non-aromatic then **X₄** is SO₂.

5 [0063] In some embodiments, **X₅** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other embodiments, **X₅** is a carbon atom. In some embodiments, if **X₅** is nitrogen, then the respective **R₇'** is absent.

[0064] In some embodiments, **X₆** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other embodiments, **X₆** is a carbon atom. In some embodiments, if **X₆** is nitrogen, then the respective **R₇''** is
10 absent.

[0065] In some embodiments, **X₇** of formula **I** and/or **I(a)-I(k)** and/or **I(n)** is a nitrogen atom. In other embodiments, **X₇** is a carbon atom. In some embodiments, if **X₇** is nitrogen, then the respective **R₇** is absent.

[0066] In some embodiments, **X₈** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other
15 embodiments, **X₈** is a carbon atom. In some embodiments, if **X₈** is nitrogen, then the respective **R₇'''** is absent.

[0067] In some embodiments, **X₉** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other embodiments, **X₉** is a carbon atom. In some embodiments, if **X₉** is nitrogen, then the respective **R₇''''** is absent.

20 [0068] In some embodiments, **X₁₀** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other embodiments, **X₁₀** is carbon. In other embodiments, **X₁₀** is N. In other embodiments, **X₁₀** is CH. In other embodiments, **X₁₀** is C(R), wherein R is as defined below. In other embodiments, **X₁₀** is C(R), wherein R is an alkyl. In other embodiments, **X₁₀** is C(R), wherein R is a methyl, a substituted methyl, CH₂-OH, an ethyl, a substituted ethyl, CH₂-CH₂-OH, NH(R₁₀), NH-CH₂-cyclopropyl, COOH, cycloalkyl such as cyclopropyl, alkoxy such as isopropoxy; each represents a separate embodiment according to this
25 invention. In other embodiments, **X₁₀** is C(R), wherein R is a substituted alkyl. In other embodiments, **X₁₀** is C(R), wherein R is CH₂-OH. In other embodiments, **X₁₀** is C(R), wherein R is CH₂-CH₂-OH. In other embodiments, **X₁₀** is C(R), wherein R is a cycloalkyl. In other embodiments, **X₁₀** is C(R), wherein R is a cyclopropyl. In other embodiments, **X₁₀** is C(R), wherein R is not methyl. In other embodiments,
30 **X₁₀** is C(R), wherein R is an alkoxy. In other embodiments, **X₁₀** is C(R), wherein R is an isopropoxy. In other embodiments, **X₁₀** is C(CH₂-OH). In other embodiments, **X₁₀** is C(CH₂-CH₂-OH). In other embodiments, **X₁₀** is C(R), wherein R is N(H)R₁₀; and **R₁₀** is a substituted alkyl. In other embodiments, **X₁₀** is C(NH-CH₂-cyclopropyl). In other embodiments, **X₁₀** is C(COOH). In other embodiments, **X₁₀** is C(CH₃). In other embodiments, **X₁₀** is C(cyclopropyl). In other embodiments, **X₁₀** is C(isopropoxy). In
35 other embodiments, **X₁₀** is C=O. In other embodiments, if **X₁₀** is C=O then **X₁₁** is N.

[0069] In some embodiments, **X₁₁** of formula **I** and/or **I(a)-I(n)** is a nitrogen atom. In other embodiments, **X₁₁** is carbon atom. In other embodiments, **X₁₁** is N. In other embodiments, **X₁₁** is C. In

other embodiments, if X_{11} is N then X_{10} is C=O. In other embodiments, if X_{10} is C=O then X_{11} is N. In some embodiments, X_{11} of formula **I(j)** is CH. In some embodiments, X_{11} of formula **I(j)** is C(R).

[0070] In some embodiments, X_{12} of formula **I** and/or **I(a)-I(j)** is S. In other embodiments, X_{12} is not S. In other embodiments, X_{12} is SO₂. In other embodiments, X_{12} is O. In other embodiments, X_{12} is NH.

5 In other embodiments, X_{12} is N(R). In other embodiments, X_{12} is N-CH₂-COOH. In other embodiments, X_{12} is N-CH₂-CH₂-OH. In other embodiments, X_{12} is N-CH₃. In other embodiments, X_{12} is N-OH. In other embodiments, X_{12} is CH=CH. In other embodiments, X_{12} is CH=CH(R). In other embodiments, X_{12} is C(R)=CH. In other embodiments, X_{12} is N=CH. In other embodiments, X_{12} is N=C(R). In other
10 embodiments, X_{12} is CH=N. In other embodiments, X_{12} is C(R)=N. In other embodiments, X_{12} is N-CH₂CH₃. In other embodiments, X_{12} is N-iPr. In other embodiments, X_{12} is N-cyclopropyl. In other
embodiments, X_{12} is N-CH₂-cyclopropyl.

[0071] In some embodiments, **Ring W'** of formula **I(k)-I(m)** is aromatic or non-aromatic. In some
embodiments, if **Ring W'** is aromatic, then X_{12} is S. In other embodiments, if **Ring W'** is aromatic, then
 X_{12} is not S. In other embodiments, if **Ring W'** is aromatic, then X_{12} is SO₂. In other embodiments, if
15 **Ring W'** is aromatic, then X_{12} is O. In other embodiments, if **Ring W'** is aromatic, then X_{12} is NH. In
other embodiments, if **Ring W'** is aromatic, then X_{12} is N(R). In other embodiments, if **Ring W'** is
aromatic, then X_{12} is N-CH₂-COOH. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N-CH₂-
CH₂-OH. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N-CH₃. In other embodiments, if
Ring W' is aromatic, then X_{12} is N-OH. In other embodiments, if **Ring W'** is aromatic, then X_{12} is
20 CH=CH. In other embodiments, if **Ring W'** is aromatic, then X_{12} is CH=CH(R). In other embodiments,
if **Ring W'** is aromatic, then X_{12} is C(R)=CH. In other embodiments, if **Ring W'** is aromatic, then X_{12}
is N=CH. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N=C(R). In other embodiments, if
Ring W' is aromatic, then X_{12} is CH=N. In other embodiments, if **Ring W'** is aromatic, then X_{12} is
C(R)=N. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N-CH₂CH₃. In other embodiments,
25 if **Ring W'** is aromatic, then X_{12} is N-iPr. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N-
cyclopropyl. In other embodiments, if **Ring W'** is aromatic, then X_{12} is N-CH₂-cyclopropyl. In other
embodiments, if **Ring W'** is non-aromatic, then X_{12} is CH=CH. In other embodiments, if **Ring W'** is
non-aromatic, then X_{12} is CH=CH(R). In other embodiments, if **Ring W'** is non-aromatic, then X_{12} is
C(R)=CH. In other embodiments, if **Ring W'** is non-aromatic, then X_{12} is OCH₂. In other embodiments,
30 if **Ring W'** is non-aromatic, then X_{12} is CH₂O. In other embodiments, if **Ring W'** is non-aromatic, then
 X_{12} is SCH₂. In other embodiments, if **Ring W'** is non-aromatic, then X_{12} is CH₂S. In other embodiments,
if **Ring W'** is non-aromatic, then X_{12} is CH=N. In other embodiments, if **Ring W'** is non-aromatic, then
 X_{12} is C(R)=N. In other embodiments, if **Ring W'** is non-aromatic, then X_{12} is N=CH. In other
embodiments, if **Ring W'** is non-aromatic, then X_{12} is N=C(R).

35 [0072] In some embodiments, X_{13} of formula **I(b)**, **I(c)**, **I(f)**, **I(h)** and/or **I(m)** is CH₂. In other
embodiments, X_{13} is CH(R). In other embodiments, X_{13} is CH-CH₃. In other embodiments, X_{13} is C(R)₂.
In other embodiments, X_{13} is C=O.

[0073] In some embodiments, X_{14} of formula **I(g)**, **I(h)**, **I(l)** and/or **I(m)** is S. In other embodiments, X_{14} is O. In other embodiments, X_{14} is N. In other embodiments, X_{14} is CH. In other embodiments, if X_{14} is CH then Ring **F** is not absent. In other embodiments, if X_{14} is S then R_3 is absent. In other embodiments, if X_{14} is O then R_3 is absent.

5 [0074] In some embodiments, at least one of X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 and X_9 of formula **I**, **I(a)**-**I(c)**, and/or **I(i)**-**I(k)** is a nitrogen atom. In some embodiments, at least one of X_2 , X_3 , X_4 , X_5 , X_6 , X_8 and X_9 of formula **I**, and/or **I(a)**-**I(m)** is a nitrogen atom. In some embodiments, at least one of X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 and X_9 of formula **I(d)** is a nitrogen atom. In some embodiments, at least one of X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 and X_{10} of formula **I(d)** is a nitrogen atom. In some embodiments, if either one of X_5 ,
10 X_6 , X_7 , X_8 and X_9 is nitrogen, then the respective R_7' , R_7'' , R_7 , R_7''' , and R_7'''' substitution is absent.

[0075] In some embodiments, if Ring **W** is aromatic, then X_{15} of formula **I(k)**-**I(m)** is C. In some embodiments, if Ring **W** is non-aromatic, then X_{15} is CH, C(R) or N; each represents a separate embodiment according to this invention. In some embodiments, if Ring **W** is non-aromatic, then X_{15} is CH. In some embodiments, if Ring **W** is non-aromatic, then X_{15} is C(R). In some embodiments, if Ring
15 **W** is non-aromatic, then X_{15} is N.

[0076] In some embodiments, R_5 of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)** and/or **I(i)**-**I(n)** is H. In other embodiments, R_5 is C₁-C₅ linear or branched alkyl. In other embodiments, R_5 is methyl. In other embodiments, R_5 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, iso-butyl, pentyl, neopentyl; each represents a separate embodiment according to this invention.

20 [0077] In some embodiments, R_5 and R_6 of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, and/or **I(i)**-**I(n)** are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring. In some embodiments, R_5 and R_6 are joined to form a substituted 5-8 membered heterocyclic ring. In some embodiments, R_5 and R_6 are joined to form an unsubstituted 5-8 membered heterocyclic ring. In some embodiments, the heterocyclic ring is azepane, piperazine or 2-(piperazin-1-yl)acetamide; each represents a separate
25 embodiment according to this invention. In some embodiments, the heterocyclic ring is substituted with at least one substitution selected from: F, Cl, Br, I, CF₃, R_{20} , C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, OH, alkoxy, R_8 -OH (e.g., CH₂-OH), OMe, amide, C(O)N(R)₂, C(O)N(R₁₀)(R₁₁), R_8 -C(O)N(R₁₀)(R₁₁), C(O)-pyrrolidine, C(O)-piperidine, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), N(CH₃)₂, NH₂, CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclobutanol, substituted
30 or unsubstituted 3-8 membered heterocyclic ring, which may be saturated, unsaturated, aromatic, single fused or spiral, pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole, halophenyl, (benzyloxy)phenyl, CN, and NO₂; each is a separate embodiment according to this invention.

[0078] In some embodiments, R_6 of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is H. In other embodiments, R_6 is H, F, Cl, Br, I, OH, SH, R_8 -OH, R_8 -SH, $-R_8$ -O- R_{10} , CH₂-O-CH₃, (CH₂)₂-O-CH₃, (CH₂)₃-O-CH₃, (CH₂)₂-O-CH(CH₃)₂, R_8 -S- R_{10} , (CH₂)₃-S-(CH₂)₂CH₃, R_8 -NHC(O)- R_{10} , -O- R_8 - R_{10} , R_8 -(substituted or unsubstituted C₃-C₈ cycloalkyl), CH₂-cyclopropyl, CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylecyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol, R_8 -(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or
35

spiro 3-10 membered heterocyclic ring), (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-pyran, (CH₂)₂-pyrrazole, (CH₂)₂-imidazole, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-oxetane, CH₂-piperidine, CH₂-triazole, CH₂-1-oxa-8-azaspiro[4.5]decane, (CH₂)₃-diazabicyclo[2.2.1]heptane, CH₂-methyl-THF, CH₂-ethyl-piperidine, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-2-oxo-

5 methylpyrrolidine, CH₂-methyl-azetidine, CH₂-azaspiroheptane, CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), (CH₂)₂-NH₂, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-N(CH(CH₃)₂)₂, (CH₂)₃-piperidine, (CH₂)₃-4-fluoro-piperidine, (CH₂)₃-piperidine-2-one, (CH₂)₃-4-cyano-piperidine, (CH₂)₃-4-trifluoromethyl-piperidine, (CH₂)₄-NH(CH₃), (CH₂)₃-NH-CH₃, (CH₂)₃-NH-CH₂CH₃, (CH₂)₃-N(CH₂CH₃)₂, (CH₂)₃-NH₂, (CH₂)₃-N(CH₂CH₃)(CH₂CF₃), R₈-C(O)N(R₁₀)(R₁₁),

10 (CH₂)₂-C(O)-piperidine, R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH,

15 CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃, CH(CH₃)C(O)N(CH₃)₂, C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy methoxy, optionally wherein at least one methylene

20 group (CH₂) in the alkoxy is replaced with an oxygen atom, O-(CH₂)₂-O-CH₃, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, cyclopropyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl), substituted or unsubstituted 3-8 membered

25 heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R₈-aryl (e.g., benzyl), or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, R₆ may be further substituted with at

30 least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy, OMe, amide, C(O)N(R)₂, C(O)-alkyl, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), N(CH₃)₂, NH₂, CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclobutanol, substituted or unsubstituted 3-8 membered heterocyclic ring pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole, halophenyl, (benzyloxy)phenyl, CN, and NO₂; each

35 represents a separate embodiment according to this invention. In some embodiments, R₆ is H. In some embodiments, R₆ is -R₈-O-R₁₀. In some embodiments, R₆ is CH₂-O-CH₃. In some embodiments, R₆ is R₈-S-R₁₀. In some embodiments, R₆ is (CH₂)₃-S-(CH₂)₂CH₃. In some embodiments, R₆ is R₈-NHC(O)-R₁₀. In some embodiments, R₆ is (CH₂)₃-NHC(O)-R₁₀. In some embodiments, R₆ is (CH₂)₃-NHC(O)-R₁₀.

In some embodiments, R_6 is R_8 -(substituted or unsubstituted C_3 - C_8 cycloalkyl). Examples of R_8 -(substituted or unsubstituted C_3 - C_8 cycloalkyl) include but not limited to: CH_2 -cyclobutanol, CH_2 -difluorocyclopropyl, CH_2 -methylcyclopropyl, CH_2 -dimethylamino-cyclohexyl, $(CH_2)_2$ -cyclopentanol, and CH_2 -cyclohexanol; each represents a separate embodiment according to this invention. In some

5 embodiments, R_6 is R_8 -(substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted saturated, single 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted unsaturated, single 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted aromatic, single 3-8 membered heterocyclic ring). In some embodiments,

10 R_6 is R_8 -(substituted or unsubstituted saturated, fused 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted unsaturated, fused 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted aromatic, fused 3-8 membered heterocyclic ring). In some embodiments, R_6 is R_8 -(substituted or unsubstituted spiro 3-8 membered heterocyclic ring). Examples of R_8 -(substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or

15 spiro 3-8 membered heterocyclic ring) include but not limited to: $(CH_2)_3$ -piperidine, $(CH_2)_3$ -4-fluoro-piperidine, $(CH_2)_3$ -pyran, $(CH_2)_2$ -pyrazole, $(CH_2)_2$ -imidazole, CH_2 -tetrahydrofuran, CH_2 -dioxane, CH_2 -oxetane, CH_2 -piperidine, CH_2 -triazole, CH_2 -1-oxa-8-azaspiro[4.5]decane, $(CH_2)_3$ -diazabicyclo[2.2.1]heptane, CH_2 -methyl-THF, CH_2 -ethyl-piperidine, CH_2 -oxa-azaspirodecane, $(CH_2)_3$ -dimethylpyrazole, CH_2 -2-oxo-methylpyrrolidine, CH_2 -methyl-azetidine, and CH_2 -azaspiroheptane. In

20 some embodiments, R_6 is NH_2 . In some embodiments, R_6 is NHR . In some embodiments, R_6 is $N(R)_2$. In some embodiments, R_6 is $NH(R_{10})$. In some embodiments, R_6 is $N(R_{10})(R_{11})$. In some embodiments, R_6 is $R_8-N(R_{10})(R_{11})$. In some embodiments, $R_8-N(R_{10})(R_{11})$ includes but not limited to: $(CH_2)_3-N(CH_2CH_3)_2$, $(CH_2)_3-N(CH(CH_3)_2)_2$, $(CH_2)_3$ -piperidine, $(CH_2)_4-NH(CH_3)$, $(CH_2)_3-NH-CH_3$, $(CH_2)_3-NH-CH_2CH_3$, $(CH_2)_3-N(CH_2CH_3)_2$, $(CH_2)_2-NH_2$, $(CH_2)_3-NH_2$, and $(CH_2)_3-N(CH_2CH_3)(CH_2CF_3)$. In

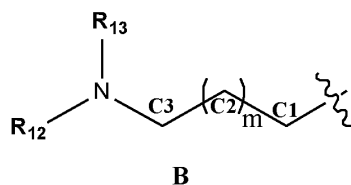
25 some embodiments, R_6 is $R_8-C(O)N(R_{10})(R_{11})$ such as $(CH_2)_2-C(O)$ -piperidine. In some embodiments, R_6 is C_1 - C_5 linear or branched, substituted or unsubstituted alkyl. Examples of C_1 - C_5 linear or branched, substituted or unsubstituted alkyl include but not limited to: $CH(CH_3)CH_2OCH_3$, $CH(CH_3)CH_2NH_2$, $CH(CH_3)C(O)N(CH_3)_2$, $CH_2-CH(OH)Ph$, $(CH_2)_3N(H)CH_2CH_3$, $CH(CH_3)(CH_2)_2OH$, $CH(CH_2OH)(CH_2CH_3)$, $(CH_2)_3-OCH_3$, $(CH_2)_2-OCH_3$, $(CH_2)_2-OCH(CH_3)_2$, $CH(CH_2OH)(CH_2CH(CH_3)_2)$, $CH_2CH(CH_3)(OCH_3)$, $CH_2CH(N(CH_3)_2)(CH_2CH_3)$, $CH(CH_3)C(O)N(CH_3)_2$, benzyl, methyl, ethyl, and $CH_2-OCH_2-CH_2-O-CH_3$. In some embodiments, R_6 is methyl. In some embodiments, R_6 is substituted or unsubstituted C_3 - C_8 cycloalkyl. In some

30 embodiments, substituted or unsubstituted C_3 - C_8 cycloalkyl include: cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, cyclopropyl, aminomethyl-cyclobutyl, methoxycyclobutyl and 2,3-dihydro-1H-indeno. In some embodiments, R_6 is R_8 -(substituted or unsubstituted C_3 - C_8 cycloalkyl). In some embodiments, R_6 is substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring. In some embodiments, the substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered

heterocyclic ring is piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone, quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane; each represents a separate embodiment according to this invention. In some embodiments, R_6 is piperidine. In some embodiments, R_6 is 1-methyl-piperidine. In some
 5 embodiments, R_6 is tetrahydropyran. In some embodiments, R_6 is substituted or unsubstituted R_8 -aryl, such as benzyl. In some embodiments, R_6 may be further substituted by at least one substitution selected from: F, Cl, Br, I, CF_3 , R_{20} , C_1 - C_5 linear or branched alkyl, C_1 - C_5 linear or branched haloalkyl, OH, alkoxy, R_8 -OH (e.g., CH_2 -OH), OMe, amide, $C(O)N(R)_2$, $C(O)N(R_{10})(R_{11})$, $R_8-C(O)N(R_{10})(R_{11})$, $C(O)$ -pyrrolidine, $C(O)$ -piperidine, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $N(CH_3)_2$, NH_2 , CF_3 , aryl, phenyl, heteroaryl,
 10 substituted or unsubstituted C_3 - C_8 cycloalkyl, cyclobutanol, substituted or unsubstituted 3-8 membered heterocyclic ring, which may be saturated, unsaturated, aromatic, single fused or spiral, pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole, halophenyl, (benzyloxy)phenyl, CN, and NO_2 ; each is a separate embodiment according to this invention.

[0079] In some embodiments, R_6 and R_5 of formula I, I(a), I(d), I(e), I(g), I(i), I(j)-I(l) and/or I(n) are
 15 joined to form a substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 5-8 membered heterocyclic ring. In some embodiments, the substituted or unsubstituted saturated, unsaturated or aromatic, single, fused or spiro 5-8 membered heterocyclic ring is azepane, piperazine, or 2-(piperazin-1-yl)acetamide; each represents a separate embodiment according to this invention. In some embodiments, the ring may be further substituted by at least one substitution selected from: F, Cl,
 20 Br, I, C_1 - C_5 linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., $C(O)N(R)_2$, $C(O)$ -pyrrolidine, $C(O)$ -piperidine, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, (e.g., $N(CH_3)_2$, NH_2), CF_3 , aryl, phenyl, heteroaryl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO_2 ; each represents a separate embodiment
 25 according to this invention.

[0080] In some embodiments, R_6 of formula I, I(a), I(d), I(e), I(g), I(i), I(j)-I(l) and/or I(n) is represented by the structure of formula B:



30 wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H; or

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g.,

35 ethyl, trifluoroethyl); or

R_{12} and $C3$ are joined to form ring **A** and R_{13} is R_{30} ; or
 R_{12} and R_{13} are joined to form ring **B**; or
 R_{12} and $C1$ are joined to form ring **C** and R_{13} is R_{30} ; or
 $C1$ and $C3$ are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or
 R_{13} and $C2$ are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or
 R_{12} and R_{13} are joined to form ring **B** and $C1$ and $C3$ are joined to form ring **D**;
 wherein

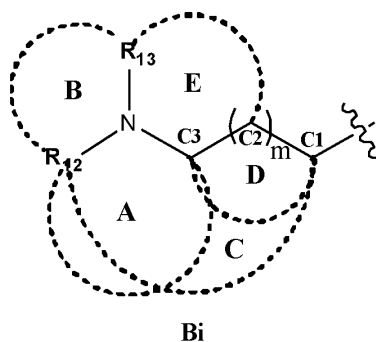
Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic rings;

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring; and

Ring **D** is a substituted or unsubstituted C_3 - C_8 cycloalkyl;

[0081] In some embodiments, formula **B** is represented by formula **Bi**.

[0082] In some embodiments, R_6 of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is represented by the structure of formula **Bi**:



wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H; or

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl); or

R_{12} and $C3$ are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

R_{12} and $C1$ are joined to form ring **C** and R_{13} is R_{30} ; or

$C1$ and $C3$ are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and $C2$ are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B** and $C1$ and $C3$ are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic rings;

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl;

- [0083] In some embodiments, **R**₁₂ of formula **B** and/or **Bi** is H. In some embodiments, **R**₁₂ is **R**₂₀. In other embodiments, **R**₁₂ is **R**₃₀. In some embodiments, **R**₁₂ is C₁-C₅ C(O)-alkyl. In some embodiments, **R**₁₂ is substituted or unsubstituted C₁-C₅ alkyl. In some embodiments, **R**₁₂ is unsubstituted C₁-C₅ alkyl. In some embodiments, the alkyl is ethyl. In some embodiments, **R**₁₂ is substituted C₁-C₅ alkyl. In some embodiments, the alkyl is trifluoroethyl.
- [0084] In some embodiments, **R**₁₃ of formula **B** and/or **Bi** is H. In other embodiments, **R**₁₃ is **R**₃₀. In some embodiments, **R**₁₃ is substituted or unsubstituted C₁-C₅ alkyl. In some embodiments, **R**₁₃ is unsubstituted C₁-C₅ alkyl. In some embodiments, the alkyl is ethyl. In some embodiments, **R**₁₃ is substituted C₁-C₅ alkyl. In some embodiments, the alkyl is trifluoroethyl.
- [0085] In some embodiments, **R**₆ of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is represented by formula **B**. In some embodiments, **R**₁₂ of formula **B** is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀. In some embodiments, **R**₁₂ and **R**₁₃ of formula **B** are both H. In some embodiments, **R**₁₂ and **R**₁₃ of formula **B** are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl). In some embodiments, **R**₁₂ and **R**₁₃ of formula **B** are each independently H or trifluoroethyl. In some embodiments, **R**₁₂ and **C3** of formula **B** are joined to form ring **A** and **R**₁₃ is **R**₃₀. In some embodiments, **R**₁₂ and **R**₁₃ of formula **B** are joined to form ring **B**. In some embodiments, **R**₁₂ and **C1** of formula **B** are joined to form ring **C** and **R**₁₃ is **R**₃₀. In some embodiments, **C1** and **C3** of formula **B** are joined to form ring **D** and **R**₁₂ and **R**₁₃ of formula **B** are each independently **R**₃₀. In some embodiments, **R**₁₃ and **C2** of formula **B** are joined to form ring **E**, *m* is 1, and **R**₁₂ of formula **B** is **R**₃₀. In some embodiments, **R**₁₂ and **R**₁₃ of formula **B** are joined to form ring **B** and **C1** and **C3** of formula **B** are joined to form ring **D**.
- [0086] In some embodiments, **R**₆ of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is represented by formula **Bi**. In some embodiments, **R**₁₂ of formula **Bi** is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ is **R**₃₀. In some embodiments, **R**₁₂ and **R**₁₃ of formula **Bi** are both H. In some embodiments, **R**₁₂ and **R**₁₃ of formula **Bi** are each independently H or substituted or unsubstituted C₁-C₅ alkyl (e.g., ethyl, trifluoroethyl). In some embodiments, **R**₁₂ and **R**₁₃ of formula **Bi** are each independently H or trifluoroethyl. In some embodiments, **R**₁₂ and **C3** of formula **Bi** are joined to form ring **A** and **R**₁₃ is **R**₃₀. In some embodiments, **R**₁₂ and **R**₁₃ of formula **Bi** are joined to form ring **B**. In some embodiments, **R**₁₂ and **C1** of formula **Bi** are joined to form ring **C** and **R**₁₃ is **R**₃₀. In some embodiments, **C1** and **C3** of formula **Bi** are joined to form ring **D** and **R**₁₂ and **R**₁₃ of formula **Bi** are each independently **R**₃₀. In some embodiments, **R**₁₃ and **C2** of formula **Bi** are joined to form ring **E**, *m* is 1, and **R**₁₂ of formula **Bi** is **R**₃₀.
- [0087] In some embodiments, **R**₆ of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is represented by formula **Bi** and/or **B** and

R₁₂ of formula **Bi** and/or **B** is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ of formula **Bi** and/or **B** is **R**₃₀;
or

R₁₂ and **R**₁₃ are both H, or

R₁₂ and **R**₁₃ are each independently H or trifluoroethyl; or

5 **R**₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form a substituted or unsubstituted pyrrolidine ring, piperazine, thiomorpholine 1,1-dioxide 2-oxa-6-azaspiro[3.3]heptane, pyrazole, imidazole, 2,5-diazabicyclo[2.2.1]heptane or a diazabicyclo[2.2.1]heptane; or

R₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

10 **C1** and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**.

[0088] In some embodiments, **R**₆ of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is represented by formula **Bi** and/or **B** and

15 **R**₁₂ of formula **Bi** and/or **B** is **R**₂₀ or C₁-C₅ C(O)-alkyl, and **R**₁₃ of formula **Bi** and/or **B** is **R**₃₀;
or

R₁₂ and **C3** are joined to form ring **A** and **R**₁₃ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form a substituted or unsubstituted pyrrolidine ring, piperazine, thiomorpholine 1,1-dioxide 2-oxa-6-azaspiro[3.3]heptane, pyrazole, imidazole, 2,5-diazabicyclo[2.2.1]heptane or a diazabicyclo[2.2.1]heptane; or

20 **R**₁₂ and **C1** are joined to form ring **C** and **R**₁₃ is **R**₃₀; or

C1 and **C3** are joined to form ring **D** and **R**₁₂ and **R**₁₃ are each independently **R**₃₀; or

R₁₃ and **C2** are joined to form ring **E**, **m** is 1, and **R**₁₂ is **R**₃₀; or

R₁₂ and **R**₁₃ are joined to form ring **B** and **C1** and **C3** are joined to form ring **D**.

25 [0089] In some embodiments, ring **A** of formula **Bi**, is a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring. In some embodiments, ring **A**, is an unsubstituted single 3-8 membered heterocyclic ring. In some embodiments, ring **A**, is an unsubstituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **A**, is an unsubstituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **A**, is a substituted single 3-8 membered heterocyclic ring. In some
30 embodiments, ring **A**, is a substituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **A**, is a substituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **A** is: pyrrolidine, methylpyrrolidine, ethylpyrrolidine, 2-oxopyrrolidine, piperidine, methylpiperidine, methyl-2-oxopyrrolidine, pyran- azetidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, or 2-azaspiro[3.3]heptane; each represents a separate embodiment according to this invention. In some
35 embodiments, ring **A** is: pyrrolidine, methylpyrrolidine, or ethylpyrrolidine; each represents a separate embodiment according to this invention.

[0090] In some embodiments, ring **B** of formula **Bi**, is a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring. In some embodiments, ring **B**, is an unsubstituted single 3-8

membered heterocyclic ring. In some embodiments, ring **B**, is an unsubstituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **B**, is an unsubstituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **B**, is a substituted single 3-8 membered heterocyclic ring. In some embodiments, ring **B**, is a substituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **B**, is a substituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **B** is: pyrrolidine, methylpyrrolidine, ethylpyrrolidine, 2-oxopyrrolidine, hydroxymethyl-pyrrolidine, piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, methylpiperidine, fluoropiperidine, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, difluoropiperidine, piperazine, methyl-piperazine, dimethyl-pyrazole, methyl-2-oxopyrrolidine, pyran-, azetidine, methyl-azetidine, imidazole, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, or 2-azaspiro[3.3]heptane, diazabicyclo[2.2.1]heptane, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, thiomorpholine, or 1,1-dioxide-2-oxa-6-azaspiro[3.3]heptane; each represents a separate embodiment according to this invention. In some embodiments, ring **B** is: piperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, 1,1-dioxide-2-oxa-6-azaspiro[3.3]heptane, hydroxymethyl-pyrrolidine or diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; each represents a separate embodiment according to this invention. In some embodiments, ring **B** is 4-fluoropiperidine.

[0091] In some embodiments, ring **C** of formula **Bi**, is a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is an unsubstituted single 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is an unsubstituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is an unsubstituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is a substituted single 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is a substituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring **C**, is a substituted fused 3-8 membered heterocyclic ring. In some embodiments, ring **C** is: pyrrolidine, methylpyrrolidine, ethylpyrrolidine, 2-oxopyrrolidine, piperidine, methylpiperidine, methyl-2-oxopyrrolidine, pyran- azetidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, or 2-azaspiro[3.3]heptane; each represents a separate embodiment according to this invention. In some embodiments, ring **C** is: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, or 2-azaspiro[3.3]heptane; each represents a separate embodiment according to this invention.

[0092] In some embodiments, ring **D** of formula **Bi**, is a substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, ring **D**, is a substituted C₃-C₈ cycloalkyl. In some embodiments, ring **D**, is an unsubstituted C₃-C₈ cycloalkyl. In some embodiments, ring **D** is cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane; each represents a separate embodiment according to this invention.

[0093] In some embodiments, ring **E** of formula **Bi**, is a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring. In some embodiments, ring **E**, is an unsubstituted single 3-8 membered heterocyclic ring. In some embodiments, ring **E**, is an unsubstituted spiro 3-8 membered

heterocyclic ring. In some embodiments, ring E, is an unsubstituted fused 3-8 membered heterocyclic ring. In some embodiments, ring E, is a substituted single 3-8 membered heterocyclic ring. In some embodiments, ring E, is a substituted spiro 3-8 membered heterocyclic ring. In some embodiments, ring E, is a substituted fused 3-8 membered heterocyclic ring. In some embodiments, ring E is: pyrrolidine, methylpyrrolidine, ethylpyrrolidine, 2-oxopyrrolidine, piperidine, methylpiperidine, methyl-2-oxopyrrolidine, pyran- azetidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, or 2-azaspiro[3.3]heptane; each represents a separate embodiment according to this invention. In some embodiments, ring E is: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, or methylpiperidine; each represents a separate embodiment according to this invention.

- [0094] In some embodiments, **R₆** of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is F, Cl, Br, I, OH, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀ (e.g., CH₂-O-CH₃), R₈-S-R₁₀ (e.g., (CH₂)₃-S-(CH₂)₂CH₃), R₈-NHC(O)-R₁₀, -O-R₈-R₁₀, R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) (e.g., CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol), (CH₂)₃-pyran, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-methyl-THF, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-methyl-azetidine, CH₂-azaspiroheptane, CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀ (e.g., C(O)CH₃), C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂, CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), benzyl, methyl, ethyl, CH₂-OCH₂-CH₂-O-CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-O-CH₃), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., methoxycyclopropyl, methylcyclobutyl, cyclopropyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, 1-methylazepan-2-one, 3-azabicyclo[3.1.0]hexane), substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, **R₆** may be further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂), C(O)-alkyl, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ (e.g., N(CH₃)₂, NH₂), NH(R₁₀), N(R₁₀)(R₁₁), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g.

pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN, and NO₂; each represents a separate embodiment according to this invention.

[0095] In some embodiments, **R₆** of formula **I**, **I(a)**, **I(d)**, **I(e)**, **I(g)**, **I(i)**, **I(j)**-**I(l)** and/or **I(n)** is -R₈-O-R₁₀. In some embodiments, -R₈-O-R₁₀ is CH₂-O-CH₃. In some embodiments, **R₆** is R₈-S-R₁₀. In some
5 embodiments, R₈-S-R₁₀ is (CH₂)₃-S-(CH₂)₂CH₃. In some embodiments, **R₆** is R₈-NHC(O)-R₁₀. In some embodiments, **R₆** is R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl). In some embodiments, the R₈-(substituted or unsubstituted C₃-C₈ cycloalkyl) is CH₂-cyclobutanol, CH₂-difluorocyclopropyl, CH₂-methylcyclopropyl, CH₂-dimethylamino-cyclohexyl, (CH₂)₂-cyclopentanol, CH₂-cyclohexanol). ; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is R₈-
10 (substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or spiro 3-10 membered heterocyclic ring). In some embodiments, **R₆** is (CH₂)₃-piperidine. In some embodiments, **R₆** is (CH₂)₂-NH₂. In some embodiments, **R₆** is (CH₂)₃-NH₂. In some embodiments, **R₆** is (CH₂)₃-4-fluoro-piperidine. In some embodiments, **R₆** is (CH₂)₃-pyran, CH₂-tetrahydrofuran, CH₂-dioxane, CH₂-methyl-THF, CH₂-oxa-azaspirodecane, (CH₂)₃-dimethylpyrazole, CH₂-methyl-azetidine, or CH₂-azaspiroheptane; each
15 represents a separate embodiment according to this invention. In some embodiments, **R₆** is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In some embodiments, **R₆** is C₁-C₅ linear or branched, substituted alkyl. In some embodiments, the substituted alkyl is CH(CH₃)CH₂OCH₃, CH(CH₃)CH₂NH₂, CH(CH₃)C(O)N(CH₃)₂, CH₂-CH(OH)Ph, (CH₂)₃N(H)CH₂CH₃, CH(CH₃)(CH₂)₂OH, CH(CH₂OH)(CH₂CH₃), (CH₂)₃-OCH₃, (CH₂)₂-OCH₃, (CH₂)₂-OCH(CH₃)₂,
20 CH(CH₂OH)(CH₂CH(CH₃)₂), CH₂CH(CH₃)(OCH₃), CH₂CH(N(CH₃)₂)(CH₂CH₃), CH₂-OCH₂-CH₂-O-CH₃ or benzyl; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is C₁-C₅ linear or branched, unsubstituted alkyl. In some embodiments, the unsubstituted alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, or neopentyl; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is
25 substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, **R₆** is substituted C₃-C₈ cycloalkyl. In some embodiments, the substituted cycloalkyl is methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, or methoxycyclobutyl, 2,3-dihydro-1H-indenol; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the unsubstituted cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
30 cycloheptyl or cyclooctyl; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, the substituted heterocyclic ring is piperidine, 1-methyl-piperidine, tetrahydropyran, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, 1-methylazepan-2-one, or 3-azabicyclo[3.1.0]hexane; each represents a separate embodiment according to this invention. In some embodiments, **R₆** is piperidine. .
35 In some embodiments, **R₆** is 1-methyl-piperidine. . In some embodiments, **R₆** is tetrahydropyran.

[0096] In some embodiments, **R₇** of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀),

N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), C(O)NH(CH₃), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, methyl, C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3-8 membered heterocyclic ring, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, R₇ is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂), C(O)-alkyl, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[0097] In some embodiments, R₇ of formula I, I(a)-I(c), I(i), I(j), I(k) and/or I(n) is H. In some embodiments, R₇ is F. In some embodiments, R₇ is Cl. In some embodiments, R₇ is Br. In some embodiments, R₇ is I. In some embodiments, R₇ is OH. In some embodiments, R₇ is O-R₂₀. In some embodiments, R₇ is CF₃. In some embodiments, R₇ is CN. In some embodiments, R₇ is NH₂. In some embodiments, R₇ is NHR. In some embodiments, R₇ is N(R)₂. In some embodiments, R₇ is NH(R₁₀). In some embodiments, R₇ is N(R₁₀)(R₁₁). In some embodiments, R₇ is NHC(O)-R₁₀. In some embodiments, R₇ is COOH. In some embodiments, R₇ is -C(O)Ph. In some embodiments, R₇ is C(O)O-R₁₀. In some embodiments, R₇ is C(O)H. In some embodiments, R₇ is C(O)-R₁₀. In some embodiments, R₇ is C₁-C₅ linear or branched C(O)-haloalkyl. In some embodiments, R₇ is -C(O)NH₂. In some embodiments, R₇ is C(O)NHR. In some embodiments, C(O)NHR is C(O)NH(CH₃). In some embodiments, R₇ is C(O)N(R₁₀)(R₁₁). In some embodiments, C(O)N(R₁₀)(R₁₁) is C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), or C(O)NH(CH₂CH₂OH); each represents a separate embodiment according to this invention. In some embodiments, R₇ is SO₂R. In some embodiments, R₇ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In some embodiments, the alkyl is methylimidazole, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl or hexyl; each represents a separate embodiment according to this invention. In some embodiments, R₇ is C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl. In some embodiments, R₇ is C₁-C₅ linear haloalkyl. In some embodiments, the haloalkyl is CHF₂. In some embodiments, R₇ is C₁-C₅ branched haloalkyl. In some embodiments, R₇ is C₃-C₈ cyclic haloalkyl. In some embodiments, R₇ is C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom. In some embodiments, R₇ is C₁-C₅ linear alkoxy. In some embodiments, the alkoxy is methoxy. In some

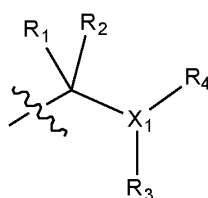
embodiments, the alkoxy is ethoxy. In some embodiments, **R**₇ is C₁-C₅ branched alkoxy. In some embodiments, **R**₇ is C₃-C₈ cyclic alkoxy. In some embodiments, **R**₇ is C₁-C₅ linear or branched thioalkyl. In some embodiments, **R**₇ is C₁-C₅ linear or branched haloalkoxy. In some embodiments, **R**₇ is C₁-C₅ linear haloalkoxy. In some embodiments, **R**₇ is C₁-C₅ branched haloalkoxy. In some embodiments, **R**₇ is C₁-C₅ linear or branched alkoxyalkyl. In some embodiments, **R**₇ is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl, cyclopropanol, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; each represents a separate embodiment according to this invention. In some embodiments, **R**₇ is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, **R**₇ is unsubstituted 3-8 membered heterocyclic ring. In some embodiments, **R**₇ is substituted 3-8 membered heterocyclic ring. In some embodiments, **R**₇ is substituted or unsubstituted 4-7 membered heterocyclic ring. In some embodiments, **R**₇ is unsubstituted 4-7 membered heterocyclic ring. In some embodiments, **R**₇ is substituted 4-7 membered heterocyclic ring. In some embodiments, the heterocyclic ring is morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, or 1-methylpyridine; each represents a separate embodiment according to this invention. In some embodiments, **R**₇ is R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(unsubstituted single 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(unsubstituted fused 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(unsubstituted spiro 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(substituted single 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(substituted fused 3-8 membered heterocyclic ring). In some embodiments, **R**₇ is R₈-(substituted spiro 3-8 membered heterocyclic ring). In some embodiments, the heterocyclic ring may be saturated. In some embodiments, the heterocyclic ring may be unsaturated. In some embodiments, the heterocyclic ring may be aromatic. In some embodiments, **R**₇ is substituted or unsubstituted aryl. In some embodiments, **R**₇ is phenyl. In some embodiments, **R**₇ may be further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[0098] In some embodiments, **R**₇ of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is O-R₂₀. In some embodiments, **R**₇ is substituted or unsubstituted 4-7 membered heterocyclic ring. In some embodiments, **R**₇ is unsubstituted 4-7 membered heterocyclic ring. In some embodiments, **R**₇ is substituted 4-7 membered heterocyclic ring. In some embodiments, the heterocyclic ring is morpholine, (e.g., 2 or 3-morpholine), pyran, oxetane, pyrrolidine, pyrrolidine-3-ol, tetrahydrofuran, imidazole, piperazine, piperidine, piperidine-4-ol, dioxazole, triazole, pyridine, 1-methylpyridine, or 2-oxopyrrolidine; each

represents a separate embodiment according to this invention. In some embodiments, **R**₇ is substituted or unsubstituted aryl. In some embodiments, **R**₇ is phenyl. In some embodiments, **R**₇ may be further substituted with at least one substitution selected from F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[0099] In some embodiments, **R**₇ of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is not H, F, Cl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy, C₁-C₅ linear or branched haloalkoxy or C₁-C₅ linear or branched, substituted or unsubstituted alkyl.

[00100] In some embodiments, **R**₇ of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is represented by the structure of formula **A**:

**A**

wherein

X₁ is N or O;

R₁ and **R**₂ are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy; or **R**₁ and **R**₂ are joined to form =O or a C₃-C₈ carbocyclic or heterocyclic ring (e.g., cyclopropyl); each is a separate embodiment according to this invention;

R₃ and **R**₄ are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethyl, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀; each is a separate embodiment according to this invention;

or **R**₃ and **R**₄ are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole; each is a separate embodiment according to this invention);

or **R**₂ and **R**₄ are joined to form a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl,

oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole; each is a separate embodiment according to this invention), wherein if the ring is aromatic, then **R**₁ and/or **R**₃ are absent;

wherein if **X**₁ is O then **R**₄ is absent;

[00101] In some embodiments, **X**₁ of formula **A** is N. In other embodiments **X**₁ is O.

5 [00102] In some embodiments, **R**₁ of formula **A** is H. In other embodiments **R**₁ is F. In other embodiments **R**₁ is CF₃.

[00103] In some embodiments, **R**₂ of formula **A** is H. In other embodiments **R**₂ is F. In other embodiments **R**₂ is CF₃.

[00104] In some embodiments, **R**₁ and **R**₂ of formula **A** are joined to form =O. In other embodiments, **R**₁ and **R**₂ are joined to form a C₃-C₈ carbocyclic or heterocyclic ring. In other embodiments, **R**₁ and **R**₂ are joined to form a C₃-C₈ carbocyclic ring. In some embodiments, the carbocyclic ring is cyclopropyl. In other embodiments, **R**₁ and **R**₂ are joined to form a 3-8 membered heterocyclic ring.

[00105] In some embodiments, **R**₁ and **R**₂ of formula **A** of formula **I**, **I(a)**-**I(c)**, **I(i)** and/or **I(k)**-**I(n)**, are not joined to form =O.

15 [00106] In some embodiments, **R**₃ of formula **A** is H. In some embodiments, **R**₃ is methyl. In some embodiments, **R**₃ is substituted or unsubstituted C₁-C₅ alkyl. In some embodiments, the alkyl is methoxyethylene, methylaminoethylene, aminoethylene; each represents a separate embodiment according to this invention. In some embodiments, **R**₃ is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, **R**₃ is substituted or unsubstituted 5-7 membered heterocyclic ring. In some embodiments, the heterocyclic ring is pyrrolidine, methylpyrrolidine, or piperidine; each represents a separate embodiment according to this invention. In some embodiments, **R**₃ is R₂₀ as defined hereinbelow.

20 [00107] In some embodiments, **R**₄ of formula **A** is H. In some embodiments, **R**₄ is methyl. In some embodiments, **R**₄ is substituted or unsubstituted C₁-C₅ alkyl. In some embodiments, the alkyl is methoxyethylene, methylaminoethylene, aminoethylene; each represents a separate embodiment according to this invention. In some embodiments, **R**₄ is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, **R**₄ is substituted or unsubstituted 5-7 membered heterocyclic ring. In some embodiments, the heterocyclic ring is pyrrolidine, methylpyrrolidine, or piperidine; each represents a separate embodiment according to this invention. In some embodiments, **R**₄ is R₂₀ as defined hereinbelow.

[00108] In some embodiments, **R**₃ and **R**₄ of formula **A** are joined to form a 3-8 membered heterocyclic ring. In some embodiments, the heterocyclic ring is imidazole, pyrrolidine, 2-oxopyrrolidine, piperidine, morpholine, or piperazine; each represents a separate embodiment according to this invention.

[00109] In some embodiments, if **X**₁ of formula **A** is O then **R**₄ is absent.

35 [00110] In some embodiments, **R**₇ of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is O-R₂₀, substituted or unsubstituted 4-7 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, imidazole, piperazine, piperidine, dioxazole, triazole, 2-oxopyrrolidine), or substituted or unsubstituted aryl. In some embodiments, **R**₇ of formula **I**, **I(a)**-**I(c)**, **I(i)**, **I(j)**, **I(k)** and/or **I(n)** is represented by

formula A, wherein X₁, R₁, R₂, R₃ and R₄ are as defined above except that R₁ and R₂ cannot be joined to form =O.

[00111] In some embodiments, R₇' of formula I, and/or I(a)-I(n) is not H.

[00112] In some embodiments, R₇' of formula I and/or I(a)-I(n) is H. In some embodiments, R₇' of formula I and/or I(a)-I(n) is F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, isopropyl, methyl, ethyl, C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclopropyl, cyclohexyl, substituted or unsubstituted 3-8 membered heterocyclic ring, substituted or unsubstituted aryl, phenyl, or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, R₇' is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[00113] In some embodiments, R₇' of formula I and/or I(a)-I(n) is H. In some embodiments, R₇' is F. In some embodiments, R₇' is Cl. In some embodiments, R₇' is Br. In some embodiments, R₇' is I. In some embodiments, R₇' is CF₃. In some embodiments, R₇' is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In some embodiments, R₇' is C₁-C₅ linear or branched unsubstituted alkyl. In some embodiments, the alkyl is isopropyl, methyl, ethyl; each represents a separate embodiment according to this invention. In some embodiments, R₇' is C₁-C₅ linear or branched substituted alkyl. In some embodiments, R₇' is isopropyl. In some embodiments, R₇' is methyl. In some embodiments, R₇' is ethyl. In some embodiments, R₇' is C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl. In some embodiments, R₇' is C₁-C₅ linear or branched haloalkyl. In some embodiments, the haloalkyl is CHF₂. In some embodiments, R₇' is C₃-C₈ cyclic haloalkyl. In some embodiments, R₇' is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, the cycloalkyl is cyclohexyl. In some embodiments, R₇' is substituted or unsubstituted aryl. In some embodiments, R₇' is phenyl. In some embodiments, R₇' is C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy. In some embodiments, R₇' is methoxy.

[00114] In some embodiments, **R₇** and **R₇'** of formula **I**, **I(a)**-**I(c)** and/or **I(i)**-**I(n)** are joined to form a 5 or 6 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 5 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form 6 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 5 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form 6 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 6 membered substituted or unsubstituted, aromatic, carbocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 5 or 6 membered substituted or unsubstituted, aromatic, heterocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 5 or 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a piperidine. In some embodiments, **R₇** and **R₇'** are joined to form a tetrahydropyran. In some embodiments, **R₇** and **R₇'** are joined to form a 5 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, **R₇** and **R₇'** are joined to form a pyrrolidine. In some embodiments, **R₇** and **R₇'** are joined to form a tetrahydrofuran.

[00115] In some embodiments, **R₇** and **R₇'** of formula **I**, **I(a)**-**I(c)**, **I(i)**-**I(k)** and/or **I(n)** are different. In some embodiments, **R₇** and **R₇'** of formula **I**, **I(a)**-**I(c)**, **I(i)**-**I(k)** and/or **I(n)** are not H, F, Cl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy, C₁-C₅ linear or branched haloalkoxy or C₁-C₅ linear or branched, substituted or unsubstituted alkyl; each represents a separate embodiment according to this invention.

[00116] In some embodiments, **R₇''** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** is not H.

[00117] In some embodiments, **R₇''** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** is H. In some embodiments, **R₇''** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** is F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclopropyl, cyclohexyl, substituted or unsubstituted 3-8 membered heterocyclic ring, substituted or unsubstituted aryl, phenyl, or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, **R₇''** is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g.,

cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[00118] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is H. In some
 5 embodiments, **R₇'** is F. In some embodiments, **R₇'** is Cl. In some embodiments, **R₇'** is Br. In some
 embodiments, **R₇'** is I. In some embodiments, **R₇'** is CF₃. In some embodiments, **R₇'** is C₁-C₅ linear
 or branched, substituted or unsubstituted alkyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched
 unsubstituted alkyl. In some embodiments, the alkyl is isopropyl, methyl, ethyl; each represents a
 separate embodiment according to this invention. In some embodiments, **R₇'** is C₁-C₅ linear or branched
 10 substituted alkyl. In some embodiments, **R₇'** is isopropyl. In some embodiments, **R₇'** is methyl. In some
 embodiments, **R₇'** is ethyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched, or C₃-C₈ cyclic
 haloalkyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched haloalkyl. In some embodiments, the
 haloalkyl is CHF₂. In some embodiments, **R₇'** is C₃-C₈ cyclic haloalkyl. In some embodiments, **R₇'** is
 substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In
 15 some embodiments, the cycloalkyl is cyclohexyl. In some embodiments, **R₇'** is substituted or
 unsubstituted aryl. In some embodiments, **R₇'** is phenyl. In some embodiments, **R₇'** is C₁-C₅ linear or
 branched, or C₃-C₈ cyclic alkoxy. In some embodiments, **R₇'** is methoxy.

[00119] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is not H.

[00120] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is H. In some
 20 embodiments, **R₇'** of formula **I(i)** is F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈
 cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂,
 NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph,
 NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅
 25 linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁),
 CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, C₁-C₅ linear or
 branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, C₁-
 C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in
 the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or
 branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈
 30 cycloalkyl, cyclopropyl, cyclohexyl, substituted or unsubstituted 3-8 membered heterocyclic ring,
 substituted or unsubstituted aryl, phenyl, or substituted or unsubstituted benzyl; each represents a
 separate embodiment according to this invention. In some embodiments, **R₇'** is cyclopropyl. In some
 embodiments, **R₇'** is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅
 linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-
 35 piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted
 or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered
 heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole),

halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[00121] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is H. In some embodiments, **R₇'** is F. In some embodiments, **R₇'** is Cl. In some embodiments, **R₇'** is Br. In some
 5 embodiments, **R₇'** is I. In some embodiments, **R₇'** is CF₃. In some embodiments, **R₇'** is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched unsubstituted alkyl. In some embodiments, the alkyl is isopropyl, methyl, ethyl; each represents a separate embodiment according to this invention. In some embodiments, **R₇'** is C₁-C₅ linear or branched substituted alkyl. In some embodiments, **R₇'** is isopropyl. In some embodiments, **R₇'** is
 10 methyl. In some embodiments, **R₇'** is ethyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched haloalkyl. In some embodiments, the haloalkyl is CHF₂. In some embodiments, **R₇'** is C₃-C₈ cyclic haloalkyl. In some embodiments, **R₇'** is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, the cycloalkyl is cyclohexyl. In some embodiments,
 15 **R₇'** is substituted or unsubstituted aryl. In some embodiments, **R₇'** is phenyl. In some embodiments, **R₇'** is C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy. In some embodiments, **R₇'** is methoxy.

[00122] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is not H.

[00123] In some embodiments, **R₇'** of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)-I(n)** is H. In some
 20 embodiments, **R₇'** of formula **I(i)** is F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl, C₁-C₅ linear or
 25 branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, cyclopropyl, cyclohexyl, substituted or unsubstituted 3-8 membered heterocyclic ring,
 30 substituted or unsubstituted aryl, phenyl, or substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, **R₇'** is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and
 35 NO₂; each represents a separate embodiment according to this invention.

- [00124] In some embodiments, R_7'''' of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** is H. In some embodiments, R_7'''' is F. In some embodiments, R_7'''' is Cl. In some embodiments, R_7'''' is Br. In some embodiments, R_7'''' is I. In some embodiments, R_7'''' is CF_3 . In some embodiments, R_7'''' is C_1 - C_5 linear or branched, substituted or unsubstituted alkyl. In some embodiments, R_7'''' is C_1 - C_5 linear or branched unsubstituted alkyl. In some embodiments, the alkyl is isopropyl, methyl, ethyl; each represents a separate embodiment according to this invention. In some embodiments, R_7'''' is C_1 - C_5 linear or branched substituted alkyl. In some embodiments, R_7'''' is isopropyl. In some embodiments, R_7'''' is methyl. In some embodiments, R_7'''' is ethyl. In some embodiments, R_7'''' is C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl. In some embodiments, R_7'''' is C_1 - C_5 linear or branched haloalkyl. In some embodiments, the haloalkyl is CHF_2 . In some embodiments, R_7'''' is C_3 - C_8 cyclic haloalkyl. In some embodiments, R_7'''' is substituted or unsubstituted C_3 - C_8 cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, the cycloalkyl is cyclohexyl. In some embodiments, R_7'''' is substituted or unsubstituted aryl. In some embodiments, R_7'''' is phenyl. In some embodiments, R_7'''' is C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy. In some embodiments, R_7'''' is methoxy.
- [00125] In some embodiments, R_7' and R_7'' of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 5 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a cyclopentane. In some embodiments, R_7' and R_7'' are joined to form 6 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a cyclohexane. In some embodiments, R_7' and R_7'' are joined to form a 5 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form 6 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 6 membered substituted or unsubstituted, aromatic, carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 5 or 6 membered substituted or unsubstituted, aromatic, heterocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 5 or 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a piperidine. In some embodiments, R_7' and R_7'' are joined to form a tetrahydropyran. In some embodiments, R_7' and R_7'' are joined to form a 5 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a tetrahydrofuran. In some embodiments, R_7' and R_7'' are joined to form a pyrrolidine.
- [00126] In some embodiments, R_7' and R_7'' of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** are different. In some embodiments, R_7' and R_7'' of formula **I(a)**, **I(c)**, **I(e)**, and/or **I(f)**-**I(n)** are not H, F, Cl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy, C_1 - C_5 linear or branched haloalkoxy or C_1 - C_5 linear or branched, substituted or unsubstituted alkyl; each represents a separate embodiment according to this invention.
- [00127] In some embodiments, R_7'' and R_7 of formula **I(a)**, **I(c)**, **I(i)**, **I(j)**-**I(k)** and/or **I(n)** are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or

heterocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a 5 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a cyclopentane. In some embodiments, R_7'' and R_7 are joined to form 6 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a cyclohexane.

5 In some embodiments, R_7'' and R_7 are joined to form a 5 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7'' and R_7 are joined to form 6 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7' and R_7'' are joined to form a 6 membered substituted or unsubstituted, aromatic, carbocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a 5 or 6 membered substituted or unsubstituted, aromatic, heterocyclic ring. In some

10 embodiments, R_7'' and R_7 are joined to form a 5 or 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7'' and R_7 are joined to form a piperidine. In some embodiments, R_7'' and R_7 are joined to form a tetrahydropyran. In some embodiments, R_7'' and R_7 are joined to form a 5 membered substituted or unsubstituted, heterocyclic ring. In some

15 embodiments, R_7'' and R_7 are joined to form a tetrahydrofuran. In some embodiments, R_7'' and R_7 are joined to form a pyrrolidine.

[00128] In some embodiments, R_7'' and R_7 of formula $I(a)$, $I(c)$, $I(i)$, $I(j)$ - $I(k)$ and/or $I(n)$ are different. In some embodiments, R_7'' and R_7 of $I(a)$, $I(c)$, $I(i)$, $I(j)$ - $I(k)$ and/or $I(n)$ are not H, F, Cl, C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy, C_1 - C_5 linear or branched haloalkoxy or C_1 - C_5 linear or branched,

20 substituted or unsubstituted alkyl; each represents a separate embodiment according to this invention.

[00129] In some embodiments, R_7 and R_7''' of formula $I(a)$, $I(c)$, $I(i)$, $I(j)$ - $I(k)$ and/or $I(n)$ are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 5 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7 and R_7''' are joined to form 6

25 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 5 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7 and R_7''' are joined to form 6 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 6 membered substituted or unsubstituted, aromatic, carbocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 5 or

30 6 membered substituted or unsubstituted, aromatic, heterocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 5 or 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a piperidine. In some embodiments, R_7 and R_7''' are joined to form a tetrahydrofuran. In some embodiments, R_7 and R_7''' are joined to form a

35 tetrahydropyran. In some embodiments, R_7 and R_7''' are joined to form a 5 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7 and R_7''' are joined to form a pyrrolidine. In some embodiments, R_7 and R_7''' are joined to form a cyclopentane. In some embodiments, R_7 and R_7''' are joined to form a cyclohexane.

[00130] In some embodiments, R_7 and R_7''' of formula I(a), I(c), I(i), I(j)-I(k) and/or I(n) are different. In some embodiments, R_7 and R_7''' of formula I(i) are not H, F, Cl, C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy, C₁-C₅ linear or branched haloalkoxy or C₁-C₅ linear or branched, substituted or unsubstituted alkyl; each represents a separate embodiment according to this invention.

5 [00131] In some embodiments, R_7''' and R_7'''' of formula I(a), I(c), I(i), I(j)-I(k) and/or I(n) are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a 5 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form 6 membered unsubstituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a 5 membered substituted saturated or unsaturated carbocyclic ring. In some
10 embodiments, R_7''' and R_7'''' are joined to form 6 membered substituted saturated or unsaturated carbocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a 6 membered substituted or unsubstituted, aromatic, carbocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a 5 or 6 membered substituted or unsubstituted, aromatic, heterocyclic ring. In some embodiments, R_7'''
15 and R_7'''' are joined to form a 5 or 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a 6 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a piperidine. In some embodiments, R_7''' and R_7'''' are joined to form a tetrahydrofuran. In some embodiments, R_7''' and R_7'''' are joined to form a tetrahydropyran. In some embodiments, R_7''' and R_7'''' are joined to form a
20 5 membered substituted or unsubstituted, heterocyclic ring. In some embodiments, R_7''' and R_7'''' are joined to form a pyrrolidine. In some embodiments, R_7''' and R_7'''' are joined to form a cyclopentane. In some embodiments, R_7''' and R_7'''' are joined to form a cyclohexane.

[00132] In some embodiments, R_7''' and R_7'''' of formula I(a), I(c), and/or I(e)-I(n) are different. In some embodiments, R_7''' and R_7'''' of formula I(i) are not H, F, Cl, C₁-C₅ linear or branched, or C₃-C₈
25 cyclic alkoxy, C₁-C₅ linear or branched haloalkoxy or C₁-C₅ linear or branched, substituted or unsubstituted alkyl; each represents a separate embodiment according to this invention.

[00133] In some embodiments, at least one of R_7' , R_7'' , R_7''' and R_7'''' of formula I(a), I(c), and/or I(e)-I(n) is not H. In some embodiments, at least two of R_7' , R_7'' , R_7''' and R_7'''' of formula I(a), I(c), and/or I(e)-I(n) are not H. In some embodiments, at least three of R_7' , R_7'' , R_7''' and R_7'''' of formula
30 I(a), I(c), and/or I(e)-I(n) are not H.

[00134] In some embodiments, at least one of R_7 , R_7' , R_7'' , R_7''' and R_7'''' of formula I(a), I(c), I(i), I(j)-I(k) and/or I(n) is not H. In some embodiments, at least two of R_7 , R_7' , R_7'' , R_7''' and R_7'''' of formula I(a), I(c), I(i), I(j)-I(k) and/or I(n) are not H. In some embodiments, at least three of R_7 , R_7' ,
35 R_7'' , R_7''' and R_7'''' of formula I(a), I(c), I(i), I(j)-I(k) and/or I(n) are not H.

[00135] In some embodiments, R_{30} of formula I and/or I(a)-I(n) is H, R_{20} , F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl, C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl, R₈-aryl, -R₈-O-R₈-O-R₁₀, -R₈-O-R₁₀, -R₈-R₁₀, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each represents

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CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g., O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g., (CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine)); each represents a separate embodiment according to this invention. In some embodiments, R is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention. In some embodiments, R is H. In some embodiments, R is F, Cl, Br, or I. In some embodiments, R is NH(R₁₀). In some embodiments, R is NH-CH₂-cyclopropyl. In some embodiments, R is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is propyl. In some embodiments, R is isopropyl. In some embodiments, R is butyl. In some embodiments, R is substituted alkyl. In some embodiments, R is CH₂-OH. In some embodiments, R is CH₂-CH₂-OH. In some embodiments, R is C₃-C₈ substituted or unsubstituted cycloalkyl. In some embodiments, R is cyclopropyl. In some embodiments, R is C₁-C₅ linear or branched alkoxy. In some embodiments, R is methoxy. In some embodiments, R is ethoxy. In some embodiments, R is propoxy. In some embodiments, R is isopropoxy. In some embodiments, R is O-(CH₂)-cyclopropyl. In some embodiments, R is O-CH₂-methylcyclobutyl. In some embodiments, R is O-CH(CH₃)-CH₂-O-CH₃. In some embodiments, R is O-(CH₂CH₃). In some embodiments, R is OCHF₂. In some embodiments, R is O-(CH₂)₂-O-CH₃. In some embodiments, R is COOH. In some embodiments, R is O-R₈-R₁₀. In some embodiments, R is O-(CH₂)₂-O-CH₃. In some embodiments, R is O-(CH₂CH₃). In some embodiments, R is -R₈-R₁₀. In some embodiments, R is (CH₂)-cyclopropyl. In some embodiments, R is (CH₂)-OH. In some embodiments, R is (CH₂)₂-OH. In some embodiments, R is (CH₂)-COOH. In some embodiments, R is OH. In some embodiments, R is CO(R₁₀).

[00139] In various embodiments, each R₈ of compound of formula I and/or I(a)-I(n) is independently CH₂. In some embodiments, R₈ is CH₂CH₂. In some embodiments, R₈ is CH₂CH₂CH₂. In some embodiments, R₈ is CH₂CH₂CH₂CH₂.

[00140] In some embodiments, p of formula I and/or I(a)-I(n) is 1. In other embodiments, p is 2. In other embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is between 1 and 3. In some embodiments, p is between 1 and 5. In some embodiments, p is between 1 and 10.

[00141] In some embodiments, R₉ of formula I and/or I(a)-I(n) is C≡C. In some embodiments, R₉ is C≡C-C≡C. In some embodiments, R₉ is CH=CH. In some embodiments, R₉ is CH=CH-CH=CH.

[00142] In some embodiments, q of formula I and/or I(a)-I(n) is 2. In some embodiments, q is 4. In some embodiments, q is 6. In some embodiments, q is 8. In some embodiments, q is between 2 and 6.

[00143] In some embodiments, **R**₁₀ of formula **I** and/or **I(a)**-**I(n)** is H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched haloalkyl, CH₂CF₃, C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)R, or S(O)₂R; each represents a separate embodiment according to this invention. In some embodiments, **R**₁₀ is H. In some embodiments, **R**₁₀ is OH. In some embodiments, **R**₁₀ is COOH. In some embodiments, **R**₁₀ is C₁-C₅ substituted or unsubstituted linear or branched alkyl. In some embodiments, **R**₁₀ is C₁-C₅ unsubstituted linear or branched alkyl. In other embodiments, **R**₁₀ is CH₃. In other embodiments, **R**₁₀ is CH₂CH₃. In other embodiments, **R**₁₀ is CH₂CH₂CH₃. In some embodiments, **R**₁₀ is isopropyl. In some embodiments, **R**₁₀ is butyl. In some embodiments, **R**₁₀ is isobutyl. In some embodiments, **R**₁₀ is t-butyl. In some embodiments, **R**₁₀ is pentyl. In some embodiments, **R**₁₀ is isopentyl. In some embodiments, **R**₁₀ is neopentyl. In some embodiments, **R**₁₀ is benzyl. In some embodiments, **R**₁₀ is C₁-C₅ substituted linear or branched alkyl. In other embodiments, **R**₁₀ is CH₂-CH₂-O-CH₃. In some embodiments, **R**₁₀ is C₃-C₈ substituted or unsubstituted cycloalkyl. In some embodiments, **R**₁₀ is cyclopropyl. In other embodiments, **R**₁₀ is CH₂CF₃. In other embodiments, **R**₁₀ is C₁-C₅ substituted or unsubstituted linear or branched haloalkyl. In other embodiments, **R**₁₀ is C₁-C₅ linear or branched alkoxy. In other embodiments, **R**₁₀ is O-CH₃. In other embodiments, **R**₁₀ is **R**₂₀. In other embodiments, **R**₁₀ is C(O)R. In other embodiments, **R**₁₀ is S(O)₂R. In some embodiments, **R**₁₀ is further substituted with at least one substitution selected from: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂ NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

[00144] In some embodiments, **R**₁₁ of formula **I** and/or **I(a)**-**I(n)** is H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₃, CH₂CF₃, C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), C(O)R, or S(O)₂R; each represents a separate embodiment according to this invention. In some embodiments, **R**₁₁ is H. In some embodiments, **R**₁₁ is OH. In some embodiments, **R**₁₁ is COOH. In some embodiments, **R**₁₁ is C₁-C₅ substituted or unsubstituted linear or branched alkyl. In some embodiments, **R**₁₁ is C₁-C₅ unsubstituted linear or branched alkyl. In other embodiments, **R**₁₁ is CH₃. In other embodiments, **R**₁₁ is CH₂CH₃. In other embodiments, **R**₁₁ is CH₂CH₂CH₃. In some embodiments, **R**₁₁ is isopropyl. In some embodiments, **R**₁₁ is butyl. In some embodiments, **R**₁₁ is isobutyl. In some embodiments, **R**₁₁ is t-butyl. In some embodiments, **R**₁₁ is pentyl. In some embodiments, **R**₁₁ is isopentyl. In some embodiments, **R**₁₁ is neopentyl. In some embodiments, **R**₁₁ is benzyl. In some embodiments, **R**₁₁ is C₁-C₅ substituted linear or branched alkyl. In other embodiments, **R**₁₁ is CH₂-CH₂-O-CH₃. In other embodiments, **R**₁₁ is CH₂CF₃. In other embodiments, **R**₁₁ is C₁-C₅ substituted or unsubstituted linear or branched haloalkyl. In other embodiments, **R**₁₁ is C₁-C₅ linear or branched alkoxy. In other embodiments, **R**₁₁ is O-CH₃. In other embodiments, **R**₁₁ is **R**₂₀. In other

embodiments, R_{11} is $C(O)R$. In other embodiments, R_{11} is $S(O)_2R$. In some embodiments, R_{11} is further substituted with at least one substitution selected from: F, Cl, Br, I, C_1 - C_5 linear or branched alkyl, OH, alkoxy (e.g., OMe), amide (e.g., $C(O)N(R)_2$, $C(O)$ -pyrrolidine, $C(O)$ -piperidine, $N(R)_2$ $NH(R_{10})$, $N(R_{10})(R_{11})$, (e.g., $N(CH_3)_2$, NH_2), CF_3 , aryl, phenyl, heteroaryl, substituted or unsubstituted C_3 - C_8 cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO_2 ; each represents a separate embodiment according to this invention.

[00145] In some embodiments, R_{10} and R_{11} of formula **I** and/or **I(a)**-**I(n)** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring. In other embodiments, R_{10} and R_{11} are joined to form a piperazine ring. In other embodiments, R_{10} and R_{11} are joined to form a piperidine ring. In some embodiments, substitutions include: F, Cl, Br, I, C_1 - C_5 linear or branched alkyl, OH, alkoxy, OMe, amide, $C(O)N(R)_2$, $C(O)$ -pyrrolidine, $C(O)$ -piperidine, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $N(CH_3)_2$, NH_2 , CF_3 , aryl, phenyl, heteroaryl, substituted or unsubstituted C_3 - C_8 cycloalkyl, cyclobutanol, substituted or unsubstituted 3-8 membered heterocyclic ring pyran, oxetane, piperidine, pyrazole, methyl-pyrazole, triazole, imidazole, halophenyl, (benzyloxy)phenyl, CN, and NO_2 ; each represents a separate embodiment according to this invention.

[00146] In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is an integer between 0 and 4. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is an integer between 1 and 4. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 0. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 1. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 2. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 3. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 4. In some embodiments, n of formula **I**, **I(b)** and/or **I(d)** is 1 or 2.

[00147] In some embodiments, R_1 of formula **I(d)**-**I(h)**, **I(l)**-**I(m)** and/or **A** is H. In other embodiments R_1 is F. In other embodiments R_1 is CF_3 . In other embodiments R_1 is Cl. In other embodiments R_1 is Br. In other embodiments R_1 is I. In other embodiments R_1 is OH. In other embodiments R_1 is SH. In other embodiments R_1 is substituted or unsubstituted C_1 - C_5 alkyl. In other embodiments R_1 is C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl. In other embodiments R_1 is substituted or unsubstituted C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy.

[00148] In some embodiments, R_2 of formula **I(d)**-**I(h)**, **I(l)**-**I(m)** and/or **A** is H. In other embodiments R_2 is F. In other embodiments R_2 is CF_3 . In other embodiments R_2 is Cl. In other embodiments R_2 is Br. In other embodiments R_2 is I. In other embodiments R_2 is OH. In other embodiments R_2 is SH. In other embodiments R_2 is substituted or unsubstituted C_1 - C_5 alkyl. In other embodiments R_2 is C_1 - C_5 linear or branched, or C_3 - C_8 cyclic haloalkyl. In other embodiments R_2 is substituted or unsubstituted C_1 - C_5 linear or branched, or C_3 - C_8 cyclic alkoxy.

[00149] In some embodiments, R_1 and R_2 of formula **I(d)**-**I(h)**, **I(l)**-**I(m)** and/or **A** are joined to form $C=O$. In other embodiments, R_1 and R_2 are joined to form a 3-8 membered carbocyclic or heterocyclic ring. In other embodiments, R_1 and R_2 are joined to form a 3-8 membered carbocyclic ring. In some embodiments, the carbocyclic ring is cyclopropyl. In other embodiments, R_1 and R_2 are joined to form

a 3-8 membered heterocyclic ring. In some embodiments, the heterocyclic ring is oxetane. In some embodiments, if **R**₁ and **R**₂ are joined to form a C=O, then at least one of **X**₂, **X**₃, **X**₄, and **X**₁₀ is not CH.

[00150] In some embodiments, **R**₃ of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** is H. In some embodiments, **R**₃ is methyl. In some embodiments, **R**₃ is substituted or unsubstituted C₁-C₅ alkyl. In some
5 embodiments, the alkyl is methoxyethylene, methylaminoethylene, aminoethylene; each represents a separate embodiment according to this invention. In some embodiments, **R**₃ is -R₈-O-R₁₀. In some embodiments, **R**₃ is (CH₂)₂-O-CH₃. In some embodiments, **R**₃ is R₈-N(R₁₀)(R₁₁). In some embodiments, **R**₃ is (CH₂)₂-NH(CH₃). In some embodiments, **R**₃ is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, **R**₃ is substituted or
10 unsubstituted 5-7 membered heterocyclic ring. In some embodiments, **R**₃ is pyrrolidine. In some embodiments, **R**₃ is methylpyrrolidine. In some embodiments, **R**₃ is piperidine. In some embodiments, **R**₃ is R₂₀ as defined hereinbelow.

[00151] In some embodiments, **R**₄ of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** is H. In some embodiments, **R**₄ is methyl. In some embodiments, **R**₄ is substituted or unsubstituted C₁-C₅ alkyl. In some
15 embodiments, the alkyl is methoxyethylene, methylaminoethylene, aminoethylene; each represents a separate embodiment according to this invention. In some embodiments, **R**₄ is -R₈-O-R₁₀. In some embodiments, **R**₄ is (CH₂)₂-O-CH₃. In some embodiments, **R**₄ is R₈-N(R₁₀)(R₁₁). In some embodiments, **R**₄ is (CH₂)₂-NH(CH₃). In some embodiments, **R**₄ is substituted or unsubstituted C₃-C₈ cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, **R**₄ is substituted or
20 unsubstituted 5-7 membered heterocyclic ring. In some embodiments, **R**₄ is pyrrolidine. In some embodiments, **R**₄ is methylpyrrolidine. In some embodiments, **R**₄ is piperidine. In some embodiments, **R**₄ is R₂₀ as defined hereinbelow.

[00152] In some embodiments, **R**₂ and **R**₄ of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** are joined to form **Ring F** as defined hereinbelow. In some embodiments, **R**₂ and **R**₄ are joined to form a substituted or
25 unsubstituted, saturated or unsaturated, 4-8 membered heterocyclic or carbocyclic ring. In some embodiments, **R**₂ and **R**₄ are joined to form a substituted or unsubstituted, unsaturated, 4-8 membered heterocyclic ring. In some embodiments, **R**₂ and **R**₄ are joined to form pyrrolidine, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine, pyridine, piperidine, tetrahydrofuran, tetrahydrothiophene, cyclopropyl, oxetane, imidazole, pyrimidine, triazole, oxadiazole, pyrazole; each
30 represents a separate embodiment according to this invention. In some embodiments, **R**₂ and **R**₄ are joined to form pyrrolidine. In some embodiments, **R**₂ and **R**₄ are joined to form 1-methylpyrrolidine. In some embodiments, **R**₂ and **R**₄ are joined to form pyrrolidin-2-one. In some embodiments, **R**₂ and **R**₄ are joined to form pyrrolidin-3-ol. In some embodiments, **R**₂ and **R**₄ are joined to form morpholine. In some embodiments, **R**₂ and **R**₄ are joined to form piperidine. In some embodiments, if **Ring F** is aromatic, then **R**₁ is absent. In some embodiments, if **Ring F** is aromatic, then **R**₃ is absent. In some
35 embodiments, if **Ring F** is aromatic, then **R**₁ and/or **R**₃ are absent.

[00153] In some embodiments, **R**₃ and **R**₄ of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** are joined to form a 3-8 membered heterocyclic ring. In some embodiments, the heterocyclic ring is pyrrolidine, pyrrolidone,

2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole; each represents a separate embodiment according to this invention.

[00154] In some embodiments, **R₁** and **R₂** of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** are joined to form a 3-8 membered carbocyclic or heterocyclic ring. In some embodiments, **R₁** and **R₂** are joined to form a cyclopropyl ring. In some embodiments, **R₁** and **R₂** are joined to form an oxetane ring.

[00155] In some embodiments, **Ring F** of formula **I(d)-I(h)**, **I(l)-I(m)** and/or **A** is absent. In some embodiments, **Ring F** is a substituted or unsubstituted, saturated or unsaturated, 4-8 membered heterocyclic ring. In some embodiments, **Ring F** is a substituted, saturated, 4-8 membered heterocyclic ring. In some embodiments, **Ring F** is a substituted unsaturated, 4-8 membered heterocyclic ring. In some embodiments, **Ring F** is an unsubstituted, saturated, 4-8 membered heterocyclic ring. In some embodiments, **Ring F** is an unsubstituted, unsaturated, 4-8 membered heterocyclic ring. In some embodiments, **Ring F** is pyrrolidine. In some embodiments, **Ring F** is 1-methylpyrrolidine. In some embodiments, **Ring F** is pyrrolidine-2-one. In some embodiments, **Ring F** is pyrrolidin-3-ol. In some embodiments, **Ring F** is morpholine. In some embodiments, **Ring F** is piperidine. In some embodiments, **Ring F** is tetrahydrofurane. In some embodiments, **Ring F** is tetrahydrothiophene. In some embodiments, **Ring F** is cyclopropyl. In some embodiments, **Ring F** is oxetane. In some embodiments, **Ring F** is piperazine. In some embodiments, **Ring F** is morpholine. In some embodiments, **Ring F** is a pyridinyl. In other embodiments, **Ring F** is 2-pyridinyl. In other embodiments, **Ring F** is pyrimidine. In other embodiments, **Ring F** is imidazole. In other embodiments, **Ring F** is pyridazine. In other embodiments, **Ring F** is pyrazine. In other embodiments, **Ring F** is pyrazole. In other embodiments, **Ring F** is thiazole. In other embodiments, **Ring F** is isothiazolyl. In other embodiments, **Ring F** is thiadiazolyl. In other embodiments, **Ring F** is triazolyl. In other embodiments, **Ring F** is thiazolyl. In other embodiments, **Ring F** is oxazolyl. In other embodiments, **Ring F** is isoxazolyl. In other embodiments, **Ring F** is pyrrolyl. In other embodiments, **Ring F** is oxadiazolyl. In other embodiments, **Ring F** is 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4- oxadiazolyl; each is a separate embodiment according to this invention. In other embodiments, **Ring F** is oxazolonyl. In other embodiments, **Ring F** is oxazolidonyl. In other embodiments, **Ring F** is thiazolonyl. In other embodiments, **Ring F** is isothiazolinonyl. In other embodiments, **Ring F** is isoxazolidinonyl. In other embodiments, **Ring F** is imidazolidinonyl. In other embodiments, **Ring F** is pyrazolonyl. In other embodiments, **Ring F** is 2H-pyrrol-2-onyl. In other embodiments, **Ring F** is triazolopyrimidine. In other embodiments, **Ring F** is 3H-[1,2,3]triazolo[4,5-d]pyrimidine, 1H-[1,2,3]triazolo[4,5-d]pyrimidine, [1,2,4]triazolo[4,3-c]pyrimidine, [1,2,4]triazolo[4,3-a]pyrimidine, [1,2,3]triazolo[1,5-a]pyrimidine, [1,2,3]triazolo[1,5-c]pyrimidine, [1,2,4]triazolo[1,5-a]pyrimidine or [1,2,4]triazolo[1,5-c]pyrimidine; each is a separate embodiment according to this invention. In other embodiments, **Ring F** is 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine.

[00156] In some embodiments, **Ring W** of formula **I(k)-I(m)** may be either aromatic or non-aromatic ring. In some embodiments, **Ring W** is aromatic. In some embodiments, if **Ring W** is aromatic, then **X₂**, **X₃**, and **X₄**, are each independently CH, C(R) or N; each represent a separate embodiment according

- to this invention. In some embodiments, if **Ring W** is aromatic, then **X₂**, **X₃**, and **X₄**, are each independently C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), or C(OH);
- 5 each represent a separate embodiment according to this invention. In some embodiments, if **Ring W** is aromatic, then **X₁₅** is C. In some embodiments, if **Ring W** is aromatic, then **X₂**, **X₃**, and **X₄**, are each independently C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), or C(OH);
- 10 each represent a separate embodiment according to this invention and **X₁₅** is C.
- [00157] In some embodiments, **Ring W** is non-aromatic. In some embodiments, **Ring W** is a saturated ring. In some embodiments, **Ring W** is unsaturated, non-aromatic ring. In some embodiments, if **Ring W** is non-aromatic, then **X₂**, **X₃**, and **X₄**, are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S, S=O or SO₂; each represents a separate embodiment according to this invention. In some embodiments,
- 15 if **Ring W** is non-aromatic, then **X₁₅** is CH, C(R) or N; each represents a separate embodiment according to this invention. In some embodiments, if **Ring W** is non-aromatic, then **X₂**, **X₃**, and **X₄**, are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S, S=O or SO₂; each represents a separate embodiment according to this invention, and **X₁₅** is CH, C(R) or N; each represents a separate embodiment according to this invention.
- 20 [00158] In some embodiments, **Ring W** is non-aromatic, and **Ring W'** is aromatic. In some embodiments, **Ring W** is non-aromatic, and **Ring W'** is non-aromatic. In some embodiments, **Ring W** is aromatic, and **Ring W'** is non-aromatic. In some embodiments, **Ring W** is aromatic, and **Ring W'** is aromatic. In some embodiments, if both **Ring W** and **Ring W'** are aromatic, then at least one of **X₂**, **X₃**, and **X₄** is C(R); **X₁₁** is N; or **X₁₂** is not S.
- 25 [00159] In some embodiments, **Ring W'** of formula **I(k)-I(m)** may be either aromatic or non-aromatic ring. In some embodiments, **Ring W'** is aromatic. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is S, SO₂, O, NH, N(R), N-OH, CH=CH, CH=CH(R), C(R)=CH, N=CH, N=C(R), CH=N or C(R)=N; each represents a separate embodiment according to this invention. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-CH₂-COOH, N-CH₂-CH₂-OH, N-CH₃, N-CH₂CH₃, N-iPr, N-cyclopropyl, N-CH₂-cyclopropyl; each represents a separate embodiment according to this invention. In
- 30 some embodiments, if **Ring W'** is aromatic, then **X₁₂** is SO₂. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is O. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is NH. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N(R). In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-CH₃. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-CH₂CH₃. In some
- 35 embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-iPr. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-cyclopropyl. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is N-CH₂-cyclopropyl. In some embodiments, if **Ring W'** is aromatic, then **X₁₂** is CH=CH. In some embodiments,

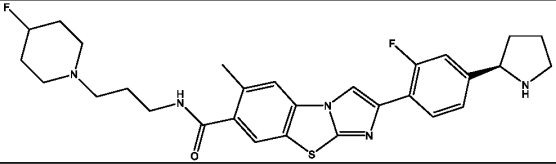
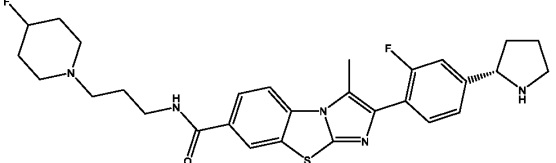
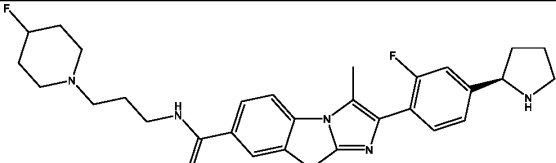
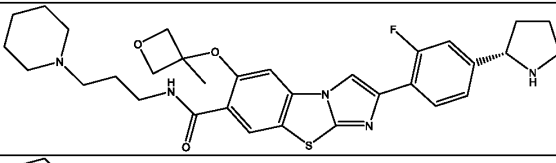
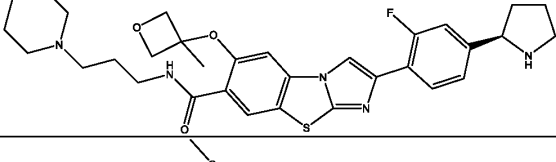
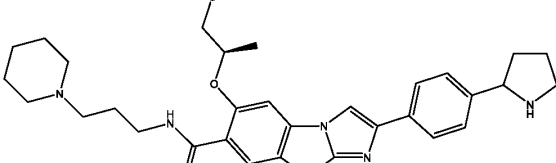
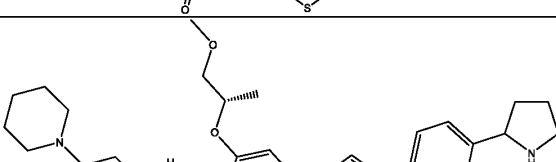
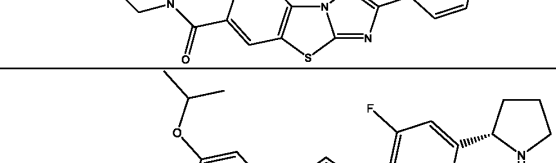
if **Ring W'** is aromatic, then X_{12} is $CH=CH(R)$. In some embodiments, if **Ring W'** is aromatic, then X_{12} is $C(R)=CH$.

[00160] In some embodiments, **Ring W'** is non-aromatic. In some embodiments, **Ring W'** is a saturated ring. In some embodiments, **Ring W'** is unsaturated, non-aromatic ring. In some embodiments, if **Ring W'** is non-aromatic, then X_{12} is $CH=CH$, $CH=CH(R)$, $C(R)=CH$, OCH_2 , CH_2O , SCH_2 , CH_2S , $CH=N$, $C(R)=N$, $N=CH$, $N=C(R)$; each represents a separate embodiment according to this invention. In some embodiments, if **Ring W'** is non-aromatic, then X_{12} is $CH=CH$. In some embodiments, if **Ring W'** is non-aromatic, then X_{12} is OCH_2 . In some embodiments, if **Ring W'** is non-aromatic, then X_{12} is $CH=N$. In some embodiments, if **Ring W'** is non-aromatic, then X_{12} is $N=CH$.

[00161] In various embodiments, this invention is directed to the compounds presented in Table 1, pharmaceutical compositions and/or method of use thereof, each represents a separate embodiment according to this invention:

Table 1:

Comp. No.	Structure	Compound Name
100R		(R)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
100S		(S)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
101R		6-(((R)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
101S		6-(((S)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
102S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

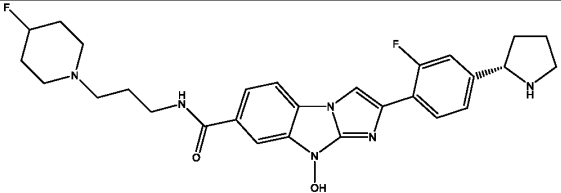
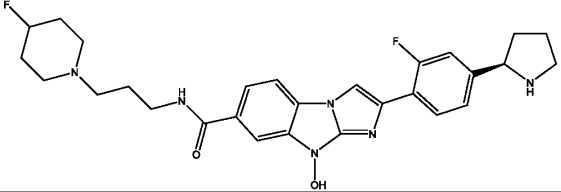
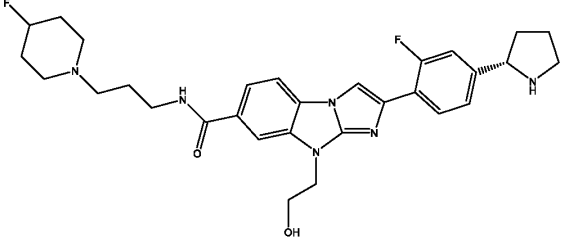
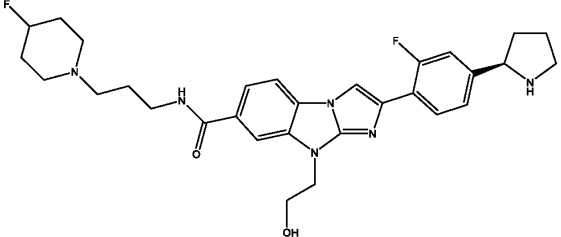
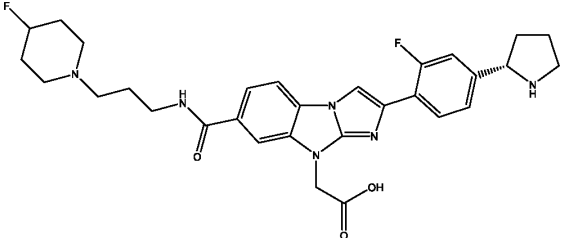
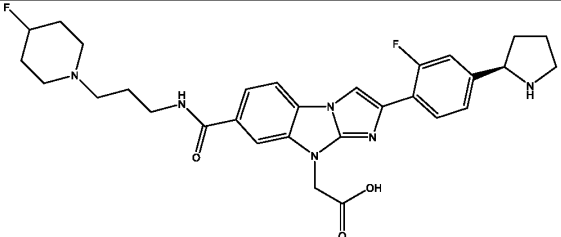
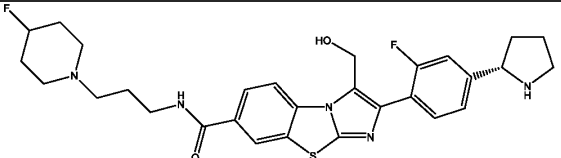
102R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
103S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
103R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
104S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
104R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
105R		6-(((R)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
105S		6-(((S)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
106S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

106R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
107S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
107R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
108S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-8-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
108R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-8-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
109S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-isopropoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
109R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-isopropoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
110S		(S)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-((3-methyloxetan-3-yl)methoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

110R		(R)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-((3-methyloxetan-3-yl)methoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
111S		(S)-6-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
111R		(R)-6-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
112		6-(cyclopropylmethoxy)-2-(2-fluoro-4-(1-hydroxycyclopropyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
113		6-(cyclopropylmethoxy)-2-(2-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
114S		(S)-3-cyclopropyl-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
114R		(R)-3-cyclopropyl-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
115S		(S)-3-cyclopropyl-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
115R		(R)-3-cyclopropyl-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

116S		(S)-3-((cyclopropylmethyl)amino)-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
116R		(R)-3-((cyclopropylmethyl)amino)-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
117S		(S)-3-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
117R		(R)-3-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
118S		(S)-6-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
118R		(R)-6-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
119S		(S)-5-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
119R		(R)-5-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

120S		(S)-8-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
120R		(R)-8-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
121S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
121R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
122S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
122R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
123S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]oxazole-7-carboxamide
123R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]oxazole-7-carboxamide

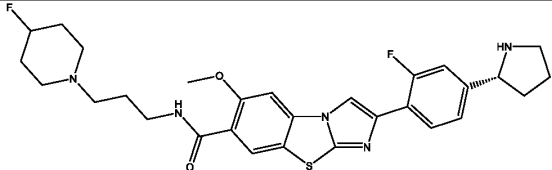
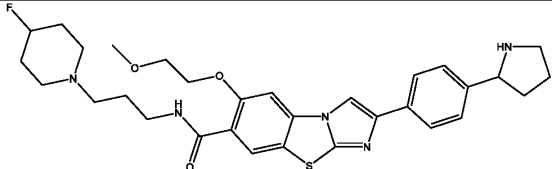
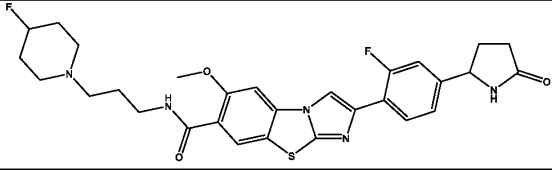
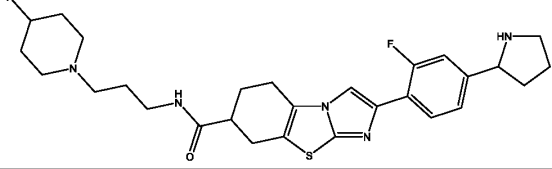
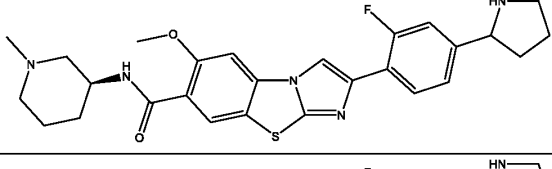
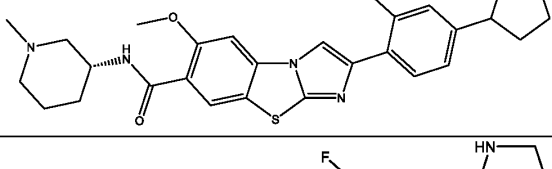
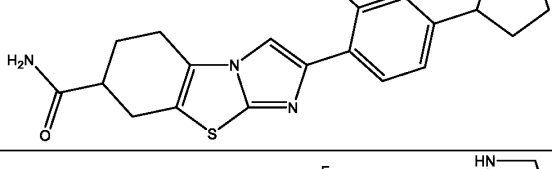
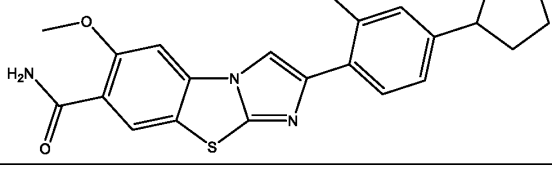
124S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-hydroxy-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
124R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-hydroxy-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
125S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-(2-hydroxyethyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
125R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-(2-hydroxyethyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
126S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)acetic acid
126R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)acetic acid
127S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-(hydroxymethyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

127R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-(hydroxymethyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
128S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-(2-hydroxyethyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
128R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-(2-hydroxyethyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
129S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazole-3-carboxylic acid
129R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazole-3-carboxylic acid
130R		(R)-3-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
130S		(S)-3-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
131S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-oxo-2,3-dihydrobenzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide

131R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-oxo-2,3-dihydrobenzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
132S		(S)-2-(3-fluoro-5-(pyrrolidin-2-yl)-[1,1'-biphenyl]-2-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
132R		(R)-2-(3-fluoro-5-(pyrrolidin-2-yl)-[1,1'-biphenyl]-2-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
133S		(S)-2-(2-cyclohexyl-6-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
133R		(R)-2-(2-cyclohexyl-6-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
134S		(S)-2-(5-cyclopropyl-2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
134R		(R)-2-(5-cyclopropyl-2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
135		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinoxaline-7-carboxamide

136		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinazoline-7-carboxamide
137S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-8-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
137R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-8-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
138		9-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
139		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-isopropyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
140		9-cyclopropyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
141		9-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide

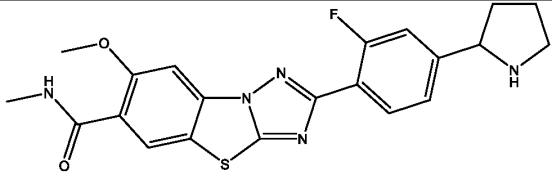
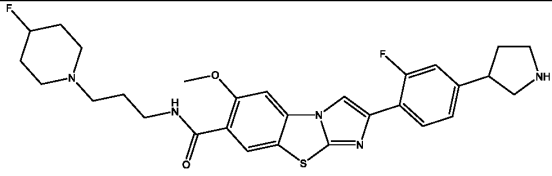
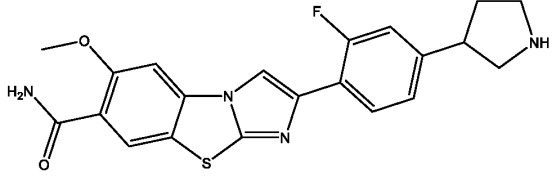
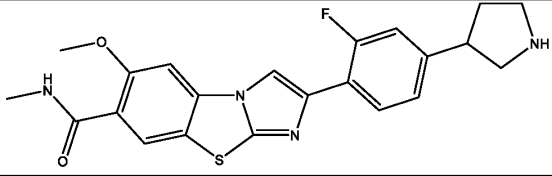
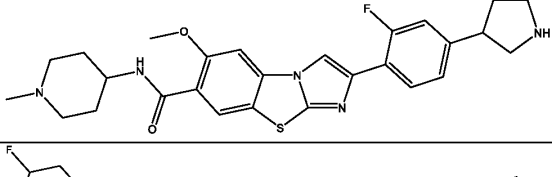
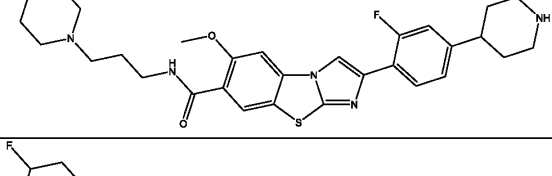
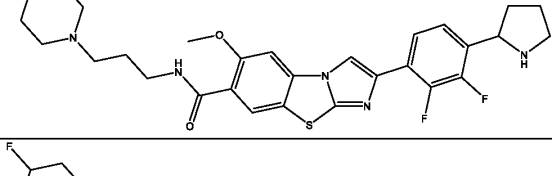
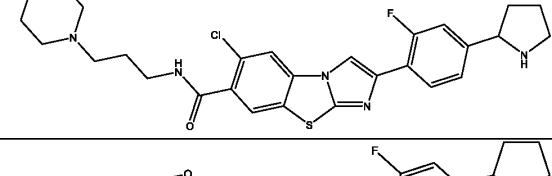
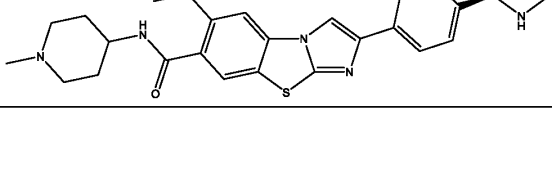
142		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-5,8-dihydroimidazo[2',1':2,3]thiazolo[5,4-c]pyridine-7(6H)-carboxamide
143		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-isopropylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
144		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
145		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6,9-dimethyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
146		6-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
147		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-isopropoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
148		8-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
149S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

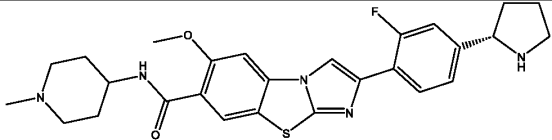
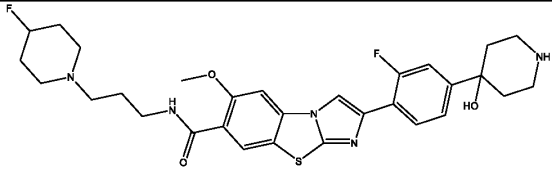
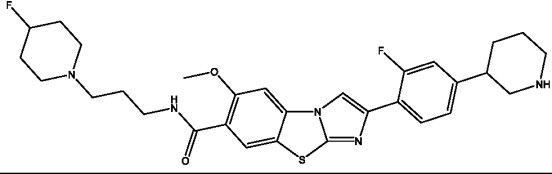
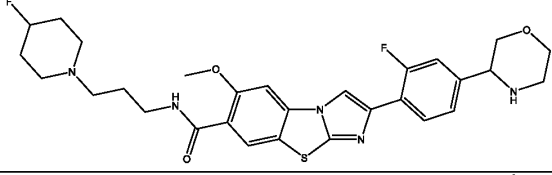
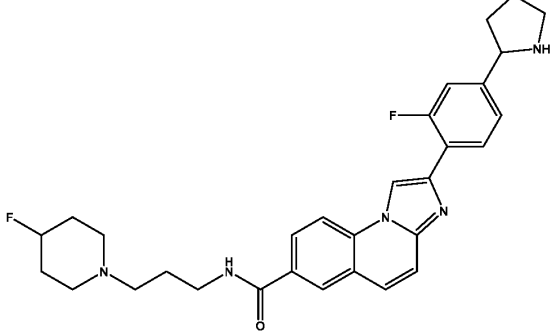
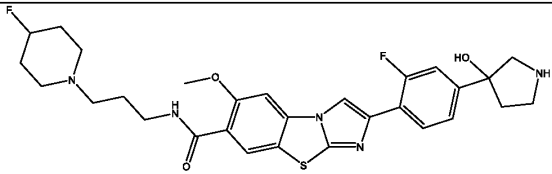
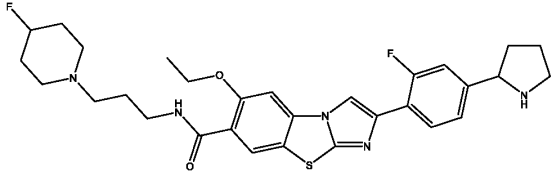
149R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
150		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
151		2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
152		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
153S		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((S)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
153R		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((R)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
154		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
155		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

156		6-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
157		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
158		8-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
159		2-(2-fluoro-4-(methylcarbamoyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
160		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
161		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
162		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
163		6-methoxy-N-(1-methylpiperidin-3-yl)-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

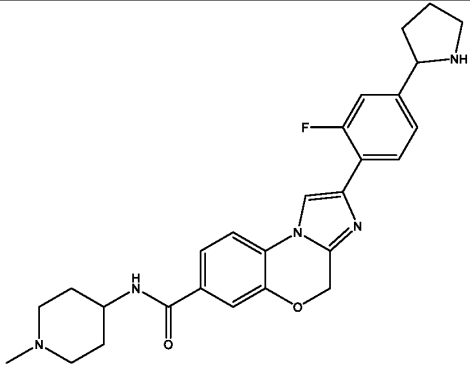
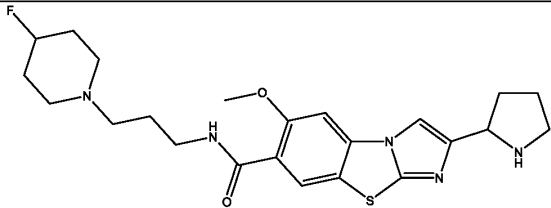
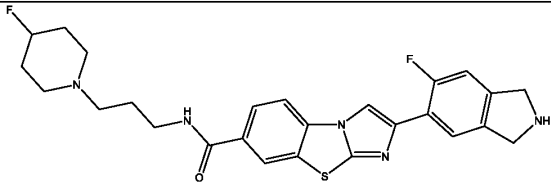
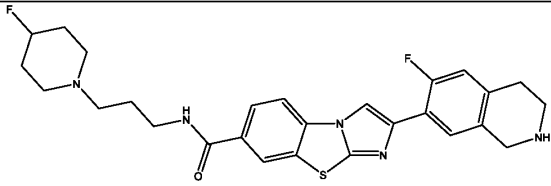
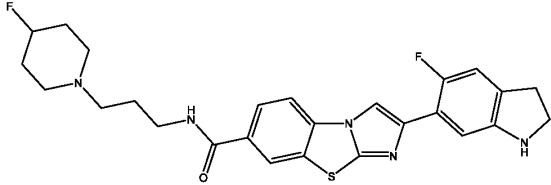
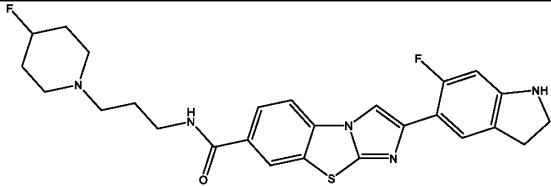
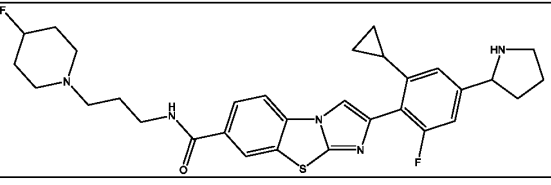
164		6-(difluoromethoxy)-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
165		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(2-methylpyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
166		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
167		2-(2-fluoro-5-methylphenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
168		2-(2-fluoro-4-(methylcarbamoyl)phenyl)-6-methoxy-N-(1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
169		6-methoxy-N-(1-methylpiperidin-3-yl)-2-(pyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
170		6-methoxy-N-(piperidin-4-yl)-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
171		N-(2-aminoethyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

172		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]oxazole-7-carboxamide
173		N-(3-aminopropyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
174		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N,N-dimethylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
175		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
176		N-(2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-7-yl)acetamide
177		N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxy-2-(m-tolyl)benzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
178		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxybenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
179		2-(2-fluoro-4-(methylcarbamoyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxybenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
180		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-hydroxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

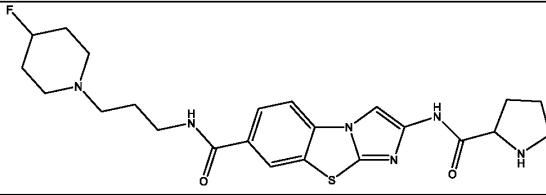
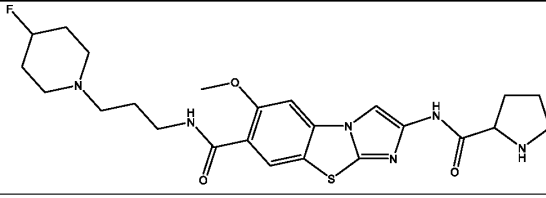
181		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-methoxy-N-methylbenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
182		2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
183		2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
184		2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
185		2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
186		2-(2-fluoro-4-(piperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
187		2-(2,3-difluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
188		6-chloro-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
189		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

190		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
191		2-(2-fluoro-4-(4-hydroxypiperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
192		2-(2-fluoro-4-(piperidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
195		2-(2-fluoro-4-(morpholin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
196		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinoline-7-carboxamide
197		2-(2-fluoro-4-(3-hydroxypyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
198		6-ethoxy-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

199		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-4H-benzo[b]imidazo[1,2-d][1,4]oxazine-7-carboxamide
200S		2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
200R		2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
201S		2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
201R		2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
202S		2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
202R		2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
203S		2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
203R		2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

204		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(1-methylpiperidin-4-yl)-4H-benzo[b]imidazo[1,2-d][1,4]oxazine-7-carboxamide
205		N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyrrolidin-2-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
300		2-(6-fluoroindolin-5-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
301		2-(6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
302		2-(5-fluoroindolin-6-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
303		2-(6-fluoroindolin-5-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
304		2-(2-cyclopropyl-6-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

305		2-(3-chloro-5-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
306		2-(2-fluoro-5-methoxy-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
400S		(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-6-carboxamide
400R		(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-6-carboxamide
401		7-bromo-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxybenzo[d]imidazo[2,1-b]thiazole
402		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid
403		2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid
404		2-bromo-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
408		N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(pyrrolidin-2-ylethynyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

409		<i>N</i> -(3-(4-fluoropiperidin-1-yl)propyl)-2-(pyrrolidine-2-carboxamido)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
410		<i>N</i> -(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyrrolidine-2-carboxamido)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

[00162] It is well understood that in structures presented in this invention wherein the carbon atom has less than 4 bonds, H atoms are present to complete the valence of the carbon. It is well understood that in structures presented in this invention wherein the nitrogen atom has less than 3 bonds, H atoms are present to complete the valence of the nitrogen.

[00163] In some embodiments, this invention is directed to the compounds listed hereinabove, pharmaceutical compositions and/or method of use thereof, wherein the compound is pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, pharmaceutical product or any combination thereof. In some embodiments, the compounds are c-MYC mRNA translation modulators. In some embodiments, the compounds are c-MYC mRNA translation inhibitors. In some embodiments, the compounds are c-MYC inhibitors. In various embodiments, the compounds are c-MYC mRNA transcription regulators. In various embodiments, the compounds are any combination of c-MYC mRNA translation modulators, c-MYC mRNA transcription regulators and c-MYC inhibitors.

[00164] As used herein, the term “alkyl” can be any straight- or branched-chain alkyl group containing up to about 30 carbons unless otherwise specified. In various embodiments, an alkyl includes C₁-C₅ carbons. In some embodiments, an alkyl includes C₁-C₆ carbons. In some embodiments, an alkyl includes C₁-C₈ carbons. In some embodiments, an alkyl includes C₁-C₁₀ carbons. In some embodiments, an alkyl is a C₁-C₁₂ carbons. In some embodiments, an alkyl is a C₁-C₂₀ carbons. In some embodiments, branched alkyl is an alkyl substituted by alkyl side chains of 1 to 5 carbons. In various embodiments, the alkyl group may be unsubstituted. In some embodiments, the alkyl group may be substituted by a halogen, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof.

[00165] The alkyl group can be a sole substituent, or it can be a component of a larger substituent, such as in an alkoxy, alkoxyalkyl, haloalkyl, arylalkyl, alkylamino, dialkylamino, alkylamido, alkylurea, etc.

Preferred alkyl groups are methyl, ethyl, and propyl, and thus halomethyl, dihalomethyl, trihalomethyl, haloethyl, dihaloethyl, trihaloethyl, halopropyl, dihalopropyl, trihalopropyl, methoxy, ethoxy, propoxy, arylmethyl, aryloethyl, arylpropyl, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylamido, acetamido, propylamido, halomethylamido, haloethylamido, halopropylamido, methyl-urea, ethyl-urea, propyl-urea, 2, 3, or 4-CH₂-C₆H₄-Cl, C(OH)(CH₃)(Ph), etc.

[00166] As used herein, the term "aryl" refers to any aromatic ring that is directly bonded to another group and can be either substituted or unsubstituted. The aryl group can be a sole substituent, or the aryl group can be a component of a larger substituent, such as in an arylalkyl, arylamino, arylamido, etc. In some embodiments, the term aryl according to this invention, includes also heteroaryl. Exemplary aryl groups include, without limitation, phenyl, tolyl, xylyl, furanyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thiazolyl, oxazolyl, isooxazolyl, pyrazolyl, imidazolyl, thiophene-yl, pyrrolyl, indolyl, phenylmethyl, phenylethyl, phenylamino, phenylamido, 3-methyl-4H-1,2,4-triazolyl, oxadiazolyl, 5-methyl-1,2,4-oxadiazolyl, isothiazolyl, thiadiazolyl, triazolyl, etc. Substitutions include but are not limited to: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, CN, NO₂, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, hydroxyl, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, COOH, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof.

[00167] As used herein, the term "alkoxy" refers to an ether group substituted by an alkyl group as defined above. Alkoxy refers both to linear and to branched alkoxy groups. Nonlimiting examples of alkoxy groups are methoxy, ethoxy, propoxy, *iso*-propoxy, *tert*-butoxy.

[00168] As used herein, the term "aminoalkyl" refers to an amine group substituted by an alkyl group as defined above. Aminoalkyl refers to monoalkylamine, dialkylamine or trialkylamine. Nonlimiting examples of aminoalkyl groups are -N(Me)₂, -NHMe, -NH₃.

[00169] A "haloalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. The term "haloalkyl" include but is not limited to fluoroalkyl, i.e., to an alkyl group bearing at least one fluorine atom. Nonlimiting examples of haloalkyl groups are CF₃, CF₂CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂ and CF(CH₃)-CH(CH₃)₂.

[00170] A "halophenyl" group refers, in some embodiments, to a phenyl substituent which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. In one embodiment, the halophenyl is 4-chlorophenyl.

[00171] An "alkoxyalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by alkoxy group as defined above, e.g. by methoxy, ethoxy, propoxy, *i*-propoxy, *t*-butoxy etc. Nonlimiting examples of alkoxyalkyl groups are -CH₂-O-CH₃, -CH₂-O-CH(CH₃)₂, -CH₂-O-C(CH₃)₃, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-CH(CH₃)₂, -CH₂-CH₂-O-C(CH₃)₃.

[00172] A "cycloalkyl" or "carbocyclic" group refers, in various embodiments, to a ring structure comprising carbon atoms as ring atoms, which may be either saturated or unsaturated, substituted or unsubstituted, single or fused. In some embodiments the cycloalkyl is a 3-10 membered ring. In some

embodiments the cycloalkyl is a 3-12 membered ring. In some embodiments the cycloalkyl is a 6 membered ring. In some embodiments the cycloalkyl is a 5-7 membered ring. In some embodiments the cycloalkyl is a 3-8 membered ring. In some embodiments, the cycloalkyl group may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof. In some embodiments, the cycloalkyl ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the cycloalkyl ring is a saturated ring. In some embodiments, the cycloalkyl ring is an unsaturated ring. Non limiting examples of a cycloalkyl group comprise cyclohexyl, cyclohexenyl, cyclopropyl, cyclopropenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclobutyl, cyclobutenyl, cycloctyl, cycloctadienyl (COD), cyclooctaene (COE) etc.

[00173] A "heterocycle" or "heterocyclic" group refers, in various embodiments, to a ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. A "heteroaromatic ring" refers in various embodiments, to an aromatic ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-10 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-12 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 6 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 5-7 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-8 membered ring. In some embodiments, the heterocycle group or heteroaromatic ring may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof. In some embodiments, the heterocycle ring or heteroaromatic ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the heterocyclic ring is a saturated ring. In some embodiments, the heterocyclic ring is an unsaturated ring. Non limiting examples of a heterocyclic ring or heteroaromatic ring systems comprise pyridine, piperidine, morpholine, piperazine, thiophene, pyrrole, benzodioxole, benzofuran-2(3H)-one, benzo[d][1,3]dioxole, indole, oxazole, isoxazole, imidazole and 1-methylimidazole, furane, triazole, pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), naphthalene, tetrahydrothiophene 1,1-dioxide, thiazole, benzimidazole, piperidine, 1-methylpiperidine, isoquinoline, 1,3-dihydroisobenzofuran, benzofuran, 3-methyl-4H-1,2,4-triazole, oxadiazolyl, 5-methyl-1,2,4-oxadiazole, pyrazole, isothiazole, thiadiazole, tetrahydrofurane, oxazolone, oxazolidone, thiazolone, isothiazolinone, isoxazolidinone, imidazolidinone, pyrazolone, 2H-pyrrol-2-one, furanone, thiophenone, thiane 1,1-dioxide, triazolopyrimidine, 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine or indole.

[00174] In some embodiments, “heterocyclic ring” according to this invention refers to substituted or unsubstituted, 3 to 8 membered, saturated, unsaturated or aromatic, single, fused or spiro rings, which comprise at least one heteroatom selected from: N, O or S. In some embodiments, the heterocyclic ring may be substituted, unsubstituted, saturated, unsaturated, aromatic, single, fused or spiro ring; each represent a separate embodiment according to this invention. The heterocyclic ring(s) may be 3-10; 3-9; 3-8; 3-7; 3-6; 3-5; 4-6; 4-7; 4-8; 4-9; 5-6; 5-7; 5-8; 5-10 or 5-9 membered ring(s); each represents a separate embodiment according to this invention. Examples of heterocyclic rings include, but not limited to: pyran, tetrahydropyran, pyrazole, imidazole, furan, tetrahydrofuran, dioxane, azetidine, pyridine, pyridazine, pyrimidine, piperidine, piperazine, triazole, oxadiazole, tetrahydrofuran (THF), tetrahydrofurane, morpholine, thiomorpholine, 1,1-dioxide, oxa-azaspirodecane, azaspiroheptane, 5-azaspiro[2.4]heptane, 2-azaspiro[3.3]heptane, oxa-azaspiroheptane, 2-oxa-6-azaspiro[3.3]heptane, pyrrol, pyrrolidine, pyrrolidine-2-one, 2-oxo-pyrrolidine, pyrrolidinone, quinuclidine, oxetane, azepane, azepan-2-one, azabicyclohexane, 2-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.1.0]hexane, 1-oxa-8-azaspiro[4.5]decane, diazabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.1]heptane. In some embodiments, the heterocyclic ring may be further substituted with at least one group selected from: F, Cl, Br, I, CF₃, R₂₀ as defined hereinbelow, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl, propyl), alkyleneamine (e.g., CH₂-NH₂), C₁-C₅ linear or branched haloalkyl, OH, alkoxy (e.g., OCH₃), alkylene-OH (e.g., CH₂-OH), amide, alkylene-amide (e.g., CH₂-C(O)NH₂), C(O)-heterocyclic ring, amine (e.g., NH₂), alkylamine (e.g., NH(CH₃)), dialkylamine (e.g., N(CH₃)₂), CF₃, aryl, phenyl, halophenyl, heteroaryl, C₃-C₈ cycloalkyl (e.g., cyclopropyl), saturated, unsaturated, aromatic, single fused or spiral 3-8 membered heterocyclic ring, CN, and NO₂; each is a separate embodiment according to this invention.

[00175] In some embodiments, “single or fused saturated, unsaturated or aromatic heterocyclic ring” or “saturated, unsaturated, aromatic, single, fused or spiro heterocyclic ring” can be any such ring(s), which comprise at least one heteroatom selected from: N, O or S, including but not limited to: pyridinyl, (2-, 3-, and 4-pyridinyl), quinolinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, quinolinyl, isoquinolinyl, 2,3-dihydroindenyl, indenyl, tetrahydronaphthyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepine, benzodioxolyl, benzo[d][1,3]dioxole, tetrahydronaphthyl, indolyl, 1H-indole, isoindolyl, anthracenyl, benzimidazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxaline, 1-(pyridin-1(2H)-yl)ethanone, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzofuran-2(3H)-one, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[c]thiophenyl, benzodioxolyl, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4- oxadiazolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine,

2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-imidazo[4,5-c]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, 1H-pyrrolo[2,3-b]pyridine, pyrido[2,3-b]pyrazine, pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole etc. In some embodiments, the heterocyclic ring according to this invention includes: pyran, tetrahydropyran, pyrrole, imidazole, furan, tetrahydrofuran, dioxane, oxetane, azetidine, pyridine, pyridazine, pyrimidine, piperidine, piperazine, triazole, oxadiazole, tetrahydrofuran (THF), tetrahydrofurane, morpholine, thiomorpholine 1,1-dioxide, oxa-azaspirodecane, azaspiroheptane, 5-azaspiro[2.4]heptane, 2-azaspiro[3.3]heptane, oxa-azaspiroheptane, pyrrol, pyrrolidine, pyrrolidine-2-one, 2-oxo-pyrrolidine, pyrrolidinone, quinuclidine, azepane, azepan-2-one, azabicyclohexane, 2-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.1.0]hexane, 1-oxa-8-azaspiro[4.5]decane, and/or diazabicyclo[2.2.1]heptane; each represent a separate embodiment according to this invention. In some embodiments, the heterocyclic ring may be further substituted with at least one group selected from: F, Cl, Br, I, CF₃, R₂₀ as defined hereinbelow, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl, propyl), alkyleneamine (e.g., CH₂-NH₂), C₁-C₅ linear or branched haloalkyl, OH, alkoxy (e.g., OCH₃), alkylene-OH (e.g., CH₂-OH), amide, alkylene-amide (e.g., CH₂-C(O)NH₂), C(O)-heterocyclic ring, amine (e.g., NH₂), alkylamine (e.g., NH(CH₃)), dialkylamine (e.g., N(CH₃)₂), CF₃, aryl, phenyl, halophenyl, heteroaryl, C₃-C₈ cycloalkyl (e.g., cyclopropyl), saturated, unsaturated, aromatic, single fused or spiral 3-8 membered heterocyclic ring, CN, and NO₂; each is a separate embodiment according to this invention.

[00176] In various embodiments, this invention provides a compound of this invention or its isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, polymorph, or crystal or combinations thereof. In various embodiments, this invention provides an isomer of the compound of this invention. In some embodiments, this invention provides a metabolite of the compound of this invention. In some embodiments, this invention provides a pharmaceutically acceptable salt of the compound of this invention. In some embodiments, this invention provides a pharmaceutical product of the compound of this invention. In some embodiments, this invention provides a tautomer of the compound of this invention. In some embodiments, this invention provides a hydrate of the compound of this invention. In some embodiments, this invention provides an *N*-oxide of the compound of this invention. In some embodiments, this invention provides a reverse amide analog of the compound of this invention. In some embodiments, "reverse amide analog" refers to acyclic amides or amides of acyclic amines. In some embodiments, this invention provides a prodrug of the compound of this invention. In some embodiments, this invention provides an isotopic variant (including but not limited to deuterated analog) of the compound of this invention. In some embodiments, this invention provides a PROTAC (Proteolysis targeting chimera) of the compound of this invention. In some embodiments, this invention provides a polymorph of the compound

of this invention. In some embodiments, this invention provides a crystal of the compound of this invention. In some embodiments, this invention provides composition comprising a compound of this invention, as described herein, or, In some embodiments, a combination of an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, polymorph, or crystal of the compound of this invention.

[00177] In various embodiments, the term “isomer” includes, but is not limited to, stereoisomers including optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like. In some embodiments, the isomer is a stereoisomer. In another embodiment, the isomer is an optical isomer.

[00178] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[00179] In various embodiments, this invention encompasses the use of various stereoisomers of the compounds of the invention. It will be appreciated by those skilled in the art that the compounds of the present invention may contain at least one chiral center. Accordingly, the compounds used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. The compounds according to this invention may further exist as stereoisomers which may be also optically-active isomers (e.g., enantiomers such as (*R*) or (*S*)), as enantiomerically enriched mixtures, racemic mixtures, or as single diastereomers, diastereomeric mixtures, or any other stereoisomers, including but not limited to: (*R*)(*R*), (*R*)(*S*), (*S*)(*S*), (*S*)(*R*), (*R*)(*R*)(*R*), (*R*)(*R*)(*S*), (*R*)(*S*)(*R*), (*S*)(*R*)(*R*), (*R*)(*S*)(*S*), (*S*)(*R*)(*S*), (*S*)(*S*)(*R*) or (*S*)(*S*)(*S*) stereoisomers. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of the various conditions described herein.

[00180] It is well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[00181] The compounds of the present invention can also be present in the form of a racemic mixture, containing substantially equivalent amounts of stereoisomers. In some embodiments, the compounds of the present invention can be prepared or otherwise isolated, using known procedures, to obtain a stereoisomer substantially free of its corresponding stereoisomer (i.e., substantially pure). By substantially pure, it is intended that a stereoisomer is at least about 80% pure, more preferably at least about 95% pure, even more preferably at least about 98% pure, most preferably at least about 99% pure. In various embodiments, the compound according to the invention comprises a substantially pure stereoisomer. In some embodiments, the substantially pure stereoisomer is at least 70%; 75%; 80%; 85%; 90%; 93%; 95%; 97%; 98%; 99%; 99.5% pure; each represents a separate embodiment according to this invention.

[00182] In various embodiments, the compound comprises a single stereoisomer in a purity of >80%; >85%; >90%; >91%; >92%; >93%; >94%; >95%; >96%; >97%; >98%; >99%; >99.5% enantiomeric excess (*ee*); each represents a separate embodiment according to this invention. In various embodiments, the compound comprises a single stereoisomer in a purity >80%; >85%; >90%; >91%; >92%; >93%; >94%; >95%; >96%; >97%; >98%; >99%; >99.5% enantiomeric ratio (*er*); each represents a separate embodiment according to this invention. In various embodiments, the compound comprises a single stereoisomer in a purity higher than 80%; 85%; 90%; 91%; 92%; 93%; 94%; 95%; 96%; 97%; 98%; 99%; 99.5%; each represents a separate embodiment according to this invention.

[00183] In various embodiments, the compound is a substantially pure single enantiomer. In various embodiments, the compound comprises a mixture of enantiomers. In various embodiments, the compound is a racemate.

[00184] In various embodiments, the compound has two chiral centers. In various embodiments, the compound comprises a mixture of stereoisomers. In various embodiments, the compound comprises a mixture of 2, 3, or 4 stereoisomers; each represents a separate embodiment according to this invention.

In various embodiments, the compound is a single stereoisomer. In various embodiments, the compound is a substantially pure single stereoisomer. In various embodiments, the substantially pure stereoisomer has at least 80%, 85%, 90%, 95%, 97%, 98%, 99% purity; each represents a separate embodiment according to this invention. In various embodiments, the compound is the substantially pure **RR** stereoisomer. In various embodiments, the compound is the substantially pure **SS** stereoisomer. In various embodiments, the compound is the substantially pure **RS** stereoisomer. In various embodiments, the compound is the substantially pure **SR** stereoisomer.

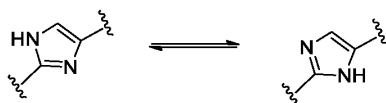
[00185] Compounds of the present invention can also be in the form of a hydrate, which means that the compound further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00186] As used herein, when some chemical functional group (e.g., alkyl or aryl) is said to be “substituted”, it is herein defined that one or more substitutions are possible. In some embodiments, the term “substituted” according to this invention, refers to but is not limited to at least one group selected from: halogen, substituted or unsubstituted C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl, propyl, isopropyl, CH(Me)CH₂-OMe), OH, C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), linear, branched or cyclic alkoxy (e.g., OMe, oxetane), amide (e.g., C(O)N(R)₂, C(O)-pyrrolidine, C(O)-piperidine, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), (e.g., N(CH₃)₂, NH₂), CF₃, aryl, phenyl, heteroaryl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutanol), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g. pyran, oxetane, piperidine, pyrazole, methylpyrrole, triazole, imidazole), halophenyl, (benzyloxy)phenyl, CN and NO₂; each represents a separate embodiment according to this invention.

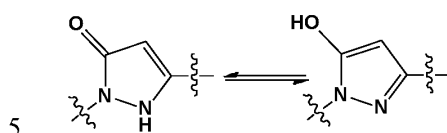
[00187] Compounds of the present invention may exist in the form of one or more of the possible tautomers and depending on the conditions it may be possible to separate some or all of the tautomers into individual and distinct entities. It is to be understood that all of the possible tautomers, including all

additional enol and keto tautomers and/or isomers are hereby covered. For example, the following tautomers, but not limited to these, are included:

Tautomerization of the imidazole ring



Tautomerization of the pyrazolone ring:



[00188] The invention includes “pharmaceutically acceptable salts” of the compounds of this invention, which may be produced, by reaction of a compound of this invention with an acid or base. Certain compounds, particularly those possessing acid or basic groups, can also be in the form of a salt, preferably a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to those salts that retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, *N*-acetylcysteine and the like. Other salts are known to those of skill in the art and can readily be adapted for use in accordance with the present invention.

[00189] Suitable pharmaceutically acceptable salts of amines of the compounds of this invention may be prepared from an inorganic acid or from an organic acid. In various embodiments, examples of inorganic salts of amines are bisulfates, borates, bromides, chlorides, hemisulfates, hydrobromates, hydrochlorates, 2-hydroxyethylsulfonates (hydroxyethanesulfonates), iodates, iodides, isethionates, nitrates, persulfates, phosphate, sulfates, sulfamates, sulfanilates, sulfonic acids (alkylsulfonates, arylsulfonates, halogen substituted alkylsulfonates, halogen substituted arylsulfonates), sulfonates and thiocyanates.

[00190] In various embodiments, examples of organic salts of amines may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are acetates, arginines, aspartates, ascorbates, adipates, anthranilates, alkane carboxylates, substituted alkane carboxylates, alginates, benzenesulfonates, benzoates, bisulfates, butyrates, bicarbonates, bitartrates, citrates, camphorates, camphorsulfonates, cyclohexylsulfamates, cyclopentanepropionates, calcium edetates, camsylates, carbonates, clavulanates, cinnamates, dicarboxylates, digluconates, dodecylsulfonates, dihydrochlorides, decanoates, enanthates, ethanesulfonates, edetates, edisylates, estolates, esylates, fumarates, formates, fluorides, galacturonates, gluconates, glutamates, glycolates, glucorate, glucoheptanoates, glycerophosphates, gluceptates,

glycolylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxylic acids, hexylresorcinates, hydroxybenzoates, hydroxynaphthoates, hydrofluorates, lactates, lactobionates, laurates, malates, maleates, methylenebis(beta-oxynaphthoate), malonates, mandelates, mesylates, methane sulfonates, methylbromides, methylnitrates, methylsulfonates, 5 monopotassium maleates, mucates, monocarboxylates, naphthalenesulfonates, 2-naphthalenesulfonates, nicotines, nitrates, napsylates, *N*-methylglucamines, oxalates, octanoates, oleates, pamoates, phenylacetates, picrates, phenylbenzoates, pivalates, propionates, phthalates, phenylacetate, pectinates, phenylpropionates, palmitates, pantothenates, polygalacturates, pyruvates, quinate, salicylates, succinates, stearates, sulfanilate, subacetates, tartrates, theophyllineacetates, *p*-toluenesulfonates 10 (tosylates), trifluoroacetates, terephthalates, tannates, teoclates, trihaloacetates, triethiodide, tricarboxylates, undecanoates and valerates.

[00191] In various embodiments, examples of inorganic salts of carboxylic acids or hydroxyls may be selected from ammonium, alkali metals to include lithium, sodium, potassium, cesium; alkaline earth metals to include calcium, magnesium, aluminium; zinc, barium, cholines, quaternary ammoniums.

15 [00192] In some embodiments, examples of organic salts of carboxylic acids or hydroxyl may be selected from arginine, organic amines to include aliphatic organic amines, alicyclic organic amines, aromatic organic amines, benzathines, *t*-butylamines, benethamines (*N*-benzylphenethylamine), dicyclohexylamines, dimethylamines, diethanolamines, ethanolamines, ethylenediamines, hydrabamines, imidazoles, lysines, methylamines, meglumines, *N*-methyl-*D*-glucamines, *N,N'*- 20 dibenzylethylenediamines, nicotinamides, organic amines, ornithines, pyridines, picolines, piperazines, procain, tris(hydroxymethyl)methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines and ureas.

[00193] In various embodiments, the salts may be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate 25 acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed in vacuo or by freeze drying or by exchanging the ions of an existing salt for another ion or suitable ion-exchange resin.

Pharmaceutical composition

30 [00194] Another aspect of the present invention relates to a pharmaceutical composition including a pharmaceutically acceptable carrier and a compound according to the aspects of the present invention. The pharmaceutical composition can contain one or more of the above-identified compounds of the present invention. Typically, the pharmaceutical composition of the present invention will include a compound of the present invention or its pharmaceutically acceptable salt, as well as a pharmaceutically acceptable 35 carrier. The term "pharmaceutically acceptable carrier" refers to any suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, or emulsions.

- [00195] Typically, the composition will contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active compound(s), together with the adjuvants, carriers and/or excipients. While individual needs may vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 0.01 to about 100 mg/kg body wt. The preferred dosages comprise about 0.1 to about 100 mg/kg body wt. The most preferred dosages comprise about 1 to about 100 mg/kg body wt. Treatment regimen for the administration of the compounds of the present invention can also be determined readily by those with ordinary skill in art. That is, the frequency of administration and size of the dose can be established by routine optimization, preferably while minimizing any side effects.
- [00196] The solid unit dosage forms can be of the conventional type. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In some embodiments, these compounds are tabulated with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.
- [00197] The tablets, capsules, and the like can also contain a binder such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.
- [00198] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.
- [00199] For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 mg and 800 mg of active compound.
- [00200] The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they can be enclosed in hard- or soft-shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet.
- [00201] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against

the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

5 [00202] The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipient. Such adjuvants, carriers and/or excipients include, but are not limited to, sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable components. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral
10 oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

[00203] These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and
15 mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

20 [00204] For use as aerosols, the compounds of the present invention in solution or suspension may be packaged in a pressurized aerosol container together with suitable propellants, for example, hydrocarbon propellants like propane, butane, or isobutane with conventional adjuvants. The materials of the present invention also may be administered in a non-pressurized form such as in a nebulizer or atomizer.

[00205] In various embodiments, the compounds of this invention are administered in combination with
25 an anti-cancer therapy. Examples of such therapies include but are not limited to: chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, and combinations thereof. In various embodiments, the compound is administered in combination with an anti-cancer agent by administering the compounds as herein described, alone or in combination with other agents.

[00206] When administering the compounds of the present invention, they can be administered
30 systemically or, alternatively, they can be administered directly to a specific site where cancer is present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the cancerous cells. Exemplary modes of administration include, without limitation, administering the compounds or compositions orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary
35 or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes.

Biological Activity

[00207] In various embodiments, the invention provides compounds and compositions, including any embodiment described herein, for use in any of the methods of this invention. In various embodiments, use of a compound of this invention or a composition comprising the same, will have utility in inhibiting, suppressing, enhancing, or stimulating a desired response in a subject, as will be understood by one skilled in the art. In some embodiments, the compositions may further comprise additional active ingredients, whose activity is useful for the particular application for which the compound of this invention is being administered.

[00208] The invention relates to the treatment, inhibition, and reduction of cancer, employing the use of a compound according to this invention or a pharmaceutically acceptable salt thereof. Accordingly, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject, comprising administering a compound according to this invention, to a subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit cancer in said subject. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is any combination of a c-MYC mRNA translation modulator, a c-MYC mRNA transcription regulator and a c-MYC inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the cancer is early cancer. In some embodiments, the cancer is advanced cancer. In some embodiments, the cancer is invasive cancer. In some embodiments, the cancer is metastatic cancer. In some embodiments, the cancer is drug resistant cancer.

[00210] In some embodiments, the cancer is selected from the following list: bladder cancer (urothelial carcinoma), myelodysplasia, breast cancer, cervix cancer, endometrium cancer, esophagus cancer, head and neck cancer (squamous cell carcinoma), kidney cancer (e.g., renal cell carcinoma, clear cell renal cell carcinoma), liver cancer (hepatocellular carcinoma), lung cancer (e.g., metastatic, non-small cell, NSCLC, squamous cell carcinoma, small cell (SCLC)), metastatic cancer (e.g., to brain), nasopharynx cancer, solid tumor cancer, stomach cancer, adrenocortical carcinoma, Glioblastoma multiforme, acute myeloid leukemia, chronic lymphocytic leukemia, lymphoma (e.g., Hodgkin's (classical), diffuse large B-cell, primary central nervous system), malignant melanoma, uveal melanoma, meningioma, multiple myeloma, breast cancer, metastatic breast cancer, anus cancer (e.g. squamous cell), biliary cancer, bladder cancer, muscle invasive urothelial carcinoma, colorectal cancer, metastatic colorectal cancer, fallopian tube cancer, gastroesophageal junction cancer (e.g., adenocarcinoma), larynx cancer (e.g., squamous cell), merkel cell cancer, mouth cancer, ovary cancer (e.g., epithelial), pancreas cancer (e.g., adenocarcinoma, metastatic), penis cancer (e.g., squamous cell carcinoma), peritoneum cancer, prostate cancer (e.g., castration-resistant, metastatic), rectum cancer, skin cancer (e.g., basal cell carcinoma, squamous cell carcinoma), small intestine cancer (e.g., adenocarcinoma), testicle cancer, thymus cancer,

- anaplastic thyroid cancer, cholangiocarcinoma, chordoma, cutaneous T-cell lymphoma, digestive-gastrointestinal cancer, familial pheochromocytoma-paraganglioma, Glioma, HTLV-1-associated adult T-cell leukemia-lymphoma, hematologic-blood cancer, hepatitis C (HCV), papillomaviral respiratory Infection, uterine leiomyosarcoma, acute lymphocytic leukemia, chronic myeloid leukemia, T-cell
- 5 Lymphoma, follicular lymphoma, primary mediastinal large B-cell lymphoma, diffuse large B-cell testicular lymphoma, melanoma, malignant mesothelioma, pleural mesothelioma, mycosis fungoides, neuroendocrine cancer, oral epithelial dysplasia, Sarcoma, severe sepsis, sezary syndrome, smoldering myeloma, soft tissue sarcoma, nasal natural killer (NK) cell T-cell lymphoma, peripheral T-cell lymphoma.
- 10 [00211] In some embodiments, the cancer is selected from a list including but not limited to: breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma, glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-derived lymphomas, esophageal squamous cell carcinoma,
- 15 osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, BRAF V600E thyroid cancer, choroid plexus carcinoma, colitis-associated cancer, epithelial ovarian cancer, colorectal cancer, pancreatic cancer and uterine cancer.
- [00212] In some embodiments, the cancer may be selected from solid tumors and non-solid tumors.
- [00213] In various embodiments, this invention is directed to a method for suppressing, reducing or
- 20 inhibiting tumor growth in a subject, comprising administering a compound of this invention, to a subject under conditions effective to suppress, reduce or inhibit tumor growth in said subject.
- [00214] In some embodiments, the tumor may be a solid tumor or a non-solid tumor.
- [00215] In some embodiments, the solid tumor cancer is selected from a list including but not limited to: breast cancer, ovarian carcinoma, prostate cancer, colon cancer, gastric cancer, glioblastoma,
- 25 medulloblastoma, melanoma, non-small cell lung carcinoma, esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, BRAF V600E thyroid cancer, choroid plexus carcinoma, colitis-associated cancer, epithelial ovarian cancer, colorectal cancer, pancreatic cancer and uterine cancer.
- [00216] In some embodiments, the non-solid tumors include but not limited to: hematological
- 30 malignancies including leukemia, lymphoma or myeloma and inherited cancers such as retinoblastoma and Wilm's tumor.
- [00217] In some embodiments, the non-solid tumor cancer is selected from a list including but not limited to: acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, primary central nervous system lymphoma, glioblastoma,
- 35 medulloblastoma, germinal center-derived lymphomas, myeloma, retinoblastoma and Wilm's tumor.
- [00218] Therefore, and in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound of this invention to a subject suffering from cancer under conditions effective

to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the cancer. In some embodiments, the cancer is early cancer. In some embodiments, the cancer is advanced cancer. In some embodiments, the cancer is invasive cancer. In some embodiments, the cancer is metastatic cancer. In some embodiments, the cancer is drug resistant cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00219] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting breast cancer comprising administering a compound of this invention to a subject suffering from breast cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the breast cancer. In some embodiments, the breast cancer is early breast cancer. In some embodiments, the breast cancer is advanced breast cancer. In some embodiments, the breast cancer is invasive breast cancer. In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is drug resistant breast cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00220] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting ovarian carcinoma comprising administering a compound of this invention to a subject suffering from ovarian carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the ovarian carcinoma. In some embodiments, the ovarian carcinoma is early ovarian carcinoma. In some embodiments, the ovarian carcinoma is advanced ovarian carcinoma. In some embodiments, the ovarian carcinoma is invasive ovarian carcinoma. In some embodiments, the ovarian carcinoma is metastatic ovarian carcinoma. In some embodiments, the ovarian carcinoma is drug resistant ovarian carcinoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00221] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting acute myeloid leukemia comprising administering a compound of this invention to a subject suffering from acute myeloid leukemia under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the acute myeloid leukemia. In some embodiments, the acute myeloid leukemia is early acute myeloid leukemia. In some embodiments, the acute myeloid leukemia is advanced acute myeloid leukemia. In some embodiments, the acute myeloid leukemia is invasive acute myeloid leukemia. In some embodiments, the acute myeloid leukemia is metastatic acute myeloid leukemia. In some embodiments, the acute myeloid leukemia is drug resistant acute myeloid leukemia. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00222] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting chronic myelogenous leukemia comprising administering a compound of this invention to a subject suffering from chronic myelogenous leukemia under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the chronic myelogenous leukemia. In some embodiments, the chronic myelogenous leukemia is early chronic myelogenous leukemia. In some embodiments, the chronic myelogenous leukemia is advanced chronic myelogenous leukemia. In some embodiments, the chronic myelogenous leukemia is invasive chronic myelogenous leukemia. In some embodiments, the chronic myelogenous leukemia is metastatic chronic myelogenous leukemia. In some embodiments, the chronic myelogenous leukemia is drug resistant chronic myelogenous leukemia. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00223] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting Hodgkin's and/or Burkitt's lymphoma comprising administering a compound of this invention to a subject suffering from Hodgkin's and/or Burkitt's lymphoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the Hodgkin's and/or Burkitt's lymphoma. In some embodiments, the Hodgkin's and/or Burkitt's lymphoma is early Hodgkin's and/or Burkitt's lymphoma. In some embodiments, the Hodgkin's and/or Burkitt's lymphoma is advanced Hodgkin's and/or Burkitt's lymphoma. In some embodiments, the Hodgkin's and/or Burkitt's lymphoma is invasive Hodgkin's and/or Burkitt's

lymphoma. In some embodiments, the Hodgkin's and/or Burkitt's lymphoma is metastatic Hodgkin's and/or Burkitt's lymphoma. In some embodiments, the Hodgkin's and/or Burkitt's lymphoma is drug resistant Hodgkin's and/or Burkitt's lymphoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00224] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting diffuse large Bcell lymphoma comprising administering a compound of this invention to a subject suffering from diffuse large Bcell lymphoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the diffuse large Bcell lymphoma. In some embodiments, the diffuse large Bcell lymphoma is early diffuse large Bcell lymphoma. In some embodiments, the diffuse large Bcell lymphoma is advanced diffuse large Bcell lymphoma. In some embodiments, the diffuse large Bcell lymphoma is invasive diffuse large Bcell lymphoma. In some embodiments, the diffuse large Bcell lymphoma is metastatic diffuse large Bcell lymphoma. In some embodiments, the diffuse large Bcell lymphoma is drug resistant diffuse large Bcell lymphoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00225] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting prostate cancer comprising administering a compound of this invention to a subject suffering from prostate cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the prostate cancer. In some embodiments, the prostate cancer is early prostate cancer. In some embodiments, the prostate cancer is advanced prostate cancer. In some embodiments, the prostate cancer is invasive prostate cancer. In some embodiments, the prostate cancer is metastatic prostate cancer. In some embodiments, the prostate cancer is drug resistant prostate cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00226] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting colon cancer comprising administering a

compound of this invention to a subject suffering from colon cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the colon cancer. In some embodiments, the colon cancer is early colon cancer. In some embodiments, the colon cancer is advanced colon cancer. In some embodiments, the colon cancer is invasive colon cancer. In some
5 embodiments, the colon cancer is metastatic colon cancer. In some embodiments, the colon cancer is drug resistant colon cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some
10 embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00227] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting gastric cancer comprising administering a compound of this invention to a subject suffering from gastric cancer under conditions effective to treat,
15 suppress, reduce the severity, reduce the risk of developing, or inhibit the gastric cancer. In some embodiments, the gastric cancer is early gastric cancer. In some embodiments, the gastric cancer is advanced gastric cancer. In some embodiments, the gastric cancer is invasive gastric cancer. In some
20 embodiments, the gastric cancer is metastatic gastric cancer. In some embodiments, the gastric cancer is drug resistant gastric cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some
25 embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00228] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting lymphoma comprising administering a compound of this invention to a subject suffering from lymphoma under conditions effective to treat,
30 suppress, reduce the severity, reduce the risk of developing, or inhibit the lymphoma. In some embodiments, the lymphoma is early lymphoma. In some embodiments, the lymphoma is advanced lymphoma. In some embodiments, the lymphoma is invasive lymphoma. In some embodiments, the
35 lymphoma is metastatic lymphoma. In some embodiments, the lymphoma is drug resistant lymphoma. In some embodiments, the lymphoma is primary central nervous system lymphoma. In some embodiments, the lymphoma is germinal center-derived lymphoma. In some embodiments, the lymphoma is Hodgkin's lymphoma. In some embodiments, the lymphoma is Burkitt's lymphoma. In
some embodiments, the lymphoma is diffuse large B-cell lymphoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the

compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

5 [00229] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting glioblastoma comprising administering a compound of this invention to a subject suffering from glioblastoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the glioblastoma. In some
10 embodiments, the glioblastoma is early glioblastoma. In some embodiments, the glioblastoma is advanced glioblastoma. In some embodiments, the glioblastoma is invasive glioblastoma. In some
15 embodiments, the glioblastoma is metastatic glioblastoma. In some embodiments, the glioblastoma is drug resistant glioblastoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some
20 embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc
25 protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00230] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting medulloblastoma comprising administering a
20 compound of this invention to a subject suffering from medulloblastoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the medulloblastoma. In
25 some embodiments, the medulloblastoma is early medulloblastoma. In some embodiments, the medulloblastoma is advanced medulloblastoma. In some embodiments, the medulloblastoma is invasive
30 medulloblastoma. In some embodiments, the medulloblastoma is metastatic medulloblastoma. In some
35 embodiments, the medulloblastoma is drug resistant medulloblastoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC
mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription
regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the
compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any
one of the compounds listed in Table 1; each compound represents a separate embodiment according to
this invention.

[00231] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting melanoma comprising administering a
35 compound of this invention to a subject suffering from melanoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the melanoma. In some
embodiments, the melanoma is early melanoma. In some embodiments, the melanoma is advanced
melanoma. In some embodiments, the melanoma is invasive melanoma. In some embodiments, the
melanoma is metastatic melanoma. In some embodiments, the melanoma is drug resistant melanoma. In
some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments,

the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00232] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-small cell lung carcinoma comprising administering a compound of this invention to a subject suffering from non-small cell lung carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the non-small cell lung carcinoma. In some embodiments, the non-small cell lung carcinoma is early non-small cell lung carcinoma. In some embodiments, the non-small cell lung carcinoma is advanced non-small cell lung carcinoma. In some embodiments, the non-small cell lung carcinoma is invasive non-small cell lung carcinoma. In some embodiments, the non-small cell lung carcinoma is metastatic non-small cell lung carcinoma. In some embodiments, the non-small cell lung carcinoma is drug resistant non-small cell lung carcinoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00233] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting esophageal squamous cell carcinoma comprising administering a compound of this invention to a subject suffering from esophageal squamous cell carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the esophageal squamous cell carcinoma. In some embodiments, the esophageal squamous cell carcinoma is early esophageal squamous cell carcinoma. In some embodiments, the esophageal squamous cell carcinoma is advanced esophageal squamous cell carcinoma. In some embodiments, the esophageal squamous cell carcinoma is invasive esophageal squamous cell carcinoma. In some embodiments, the esophageal squamous cell carcinoma is metastatic esophageal squamous cell carcinoma. In some embodiments, the esophageal squamous cell carcinoma is drug resistant esophageal squamous cell carcinoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00234] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting osteosarcoma comprising administering a

compound of this invention to a subject suffering from osteosarcoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the osteosarcoma. In some embodiments, the osteosarcoma is early osteosarcoma. In some embodiments, the osteosarcoma is advanced osteosarcoma. In some embodiments, the osteosarcoma is invasive osteosarcoma. In some
5 embodiments, the osteosarcoma is metastatic osteosarcoma. In some embodiments, the osteosarcoma is drug resistant osteosarcoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc
10 protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00235] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting bladder cancer comprising administering a compound of this invention to a subject suffering from bladder cancer under conditions effective to treat,
15 suppress, reduce the severity, reduce the risk of developing, or inhibit the bladder cancer. In some embodiments, the bladder cancer is early bladder cancer. In some embodiments, the bladder cancer is advanced bladder cancer. In some embodiments, the bladder cancer is invasive bladder cancer. In some embodiments, the bladder cancer is metastatic bladder cancer. In some embodiments, the bladder cancer is drug resistant bladder cancer. In some embodiments, the compound is a c-MYC mRNA translation
20 modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00236] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting pancreatic cancer comprising administering a compound of this invention to a subject suffering from pancreatic cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the pancreatic cancer. In
25 some embodiments, the pancreatic cancer is early pancreatic cancer. In some embodiments, the pancreatic cancer is advanced pancreatic cancer. In some embodiments, the pancreatic cancer is invasive pancreatic cancer. In some embodiments, the pancreatic cancer is metastatic pancreatic cancer. In some embodiments, the pancreatic cancer is drug resistant pancreatic cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC
30 mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00237] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting lung adenocarcinoma comprising administering a compound of this invention to a subject suffering from lung adenocarcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the lung adenocarcinoma. In some embodiments, the lung adenocarcinoma is early lung adenocarcinoma. In some embodiments, the lung adenocarcinoma is advanced lung adenocarcinoma. In some embodiments, the lung adenocarcinoma is invasive lung adenocarcinoma. In some embodiments, the lung adenocarcinoma is metastatic lung adenocarcinoma. In some embodiments, the lung adenocarcinoma is drug resistant lung adenocarcinoma. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00238] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting thyroid cancer comprising administering a compound of this invention to a subject suffering from thyroid cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the thyroid cancer. In some embodiments, the thyroid cancer is early thyroid cancer. In some embodiments, the thyroid cancer is advanced thyroid cancer. In some embodiments, the thyroid cancer is invasive thyroid cancer. In some embodiments, the thyroid cancer is metastatic thyroid cancer. In some embodiments, the thyroid cancer is drug resistant thyroid cancer. In some embodiments, the thyroid cancer is BRAF V600E thyroid cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00239] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting choroid plexus carcinoma comprising administering a compound of this invention to a subject suffering from choroid plexus carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the choroid plexus carcinoma. In some embodiments, the choroid plexus carcinoma is early choroid plexus carcinoma. In some embodiments, the choroid plexus carcinoma is advanced choroid plexus carcinoma. In some embodiments, the choroid plexus carcinoma is invasive choroid plexus carcinoma. In some embodiments, the choroid plexus carcinoma is metastatic choroid plexus carcinoma. In some embodiments, the choroid plexus carcinoma is drug resistant choroid plexus carcinoma. In some

embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00240] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting colitis-associated cancer comprising administering a compound of this invention to a subject suffering from colitis-associated cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the colitis-associated cancer. In some embodiments, the colitis-associated cancer is early colitis-associated cancer. In some embodiments, the colitis-associated cancer is advanced colitis-associated cancer. In some embodiments, the colitis-associated cancer is invasive colitis-associated cancer. In some embodiments, the colitis-associated cancer is metastatic colitis-associated cancer. In some embodiments, the colitis-associated cancer is drug resistant colitis-associated cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00241] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting ovarian cancer comprising administering a compound of this invention to a subject suffering from ovarian cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the ovarian cancer. In some embodiments, the ovarian cancer is early ovarian cancer. In some embodiments, the ovarian cancer is advanced ovarian cancer. In some embodiments, the ovarian cancer is invasive ovarian cancer. In some embodiments, the ovarian cancer is metastatic ovarian cancer. In some embodiments, the ovarian cancer is drug resistant ovarian cancer. In some embodiments, the ovarian cancer is epithelial ovarian cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00242] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting colorectal cancer comprising administering a compound of this invention to a subject suffering from colorectal cancer under conditions effective to

treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the colorectal cancer. In some embodiments, the colorectal cancer is early colorectal cancer. In some embodiments, the colorectal cancer is advanced colorectal cancer. In some embodiments, the colorectal cancer is invasive colorectal cancer. In some embodiments, the colorectal cancer is metastatic colorectal cancer. In some
5 embodiments, the colorectal cancer is drug resistant colorectal cancer. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any
10 one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00243] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting uterine cancer comprising administering a compound of this invention to a subject suffering from uterine cancer under conditions effective to treat,
15 suppress, reduce the severity, reduce the risk of developing, or inhibit the uterine cancer. In some embodiments, the uterine cancer is early uterine cancer. In some embodiments, the uterine cancer is advanced uterine cancer. In some embodiments, the uterine cancer is invasive uterine cancer. In some embodiments, the uterine cancer is metastatic uterine cancer. In some embodiments, the uterine cancer is drug resistant uterine cancer. In some embodiments, the compound is a c-MYC mRNA translation
20 modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00244] In various embodiments, this invention provides methods for increasing the survival of a subject suffering from metastatic cancer comprising the step of administering to said subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination thereof. In some embodiments,
30 the compound is a c-MYC mRNA translation modulator. In some embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some embodiments, the cancer is breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia,
35 Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma, glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-derived lymphomas, esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, thyroid cancer, choroid plexus

carcinoma, colitis-associated cancer, colorectal cancer, or uterine cancer; each represents a separate embodiment according to this invention.

[00245] In various embodiments, this invention provides methods for treating, suppressing, reducing the severity, reducing the risk, or inhibiting advanced cancer comprising the step of administering to said
5 subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination thereof. In some embodiments, the compound is a c-MYC mRNA translation modulator. In some
10 embodiments, the compound is a c-MYC mRNA translation inhibitor. In some embodiments, the compound is a c-MYC mRNA transcription regulator. In some embodiments, the compound is selective to c-MYC. In some embodiments, the compound reduces the amount of c-Myc protein in a cell. In some
15 embodiments, the cancer is breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma, glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-derived lymphomas,
20 esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, thyroid cancer, choroid plexus carcinoma, colitis-associated cancer, colorectal cancer, or uterine cancer; each represents a separate embodiment according to this invention.

[00246] The compounds of the present invention are useful in the treatment, reducing the severity,
20 reducing the risk of developing, or inhibition of early cancer, metastatic cancer, advanced cancer, drug resistant cancer, and various forms of cancer. In a preferred embodiment the cancer is breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma, glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-
25 derived lymphomas, esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, thyroid cancer, choroid plexus carcinoma, colitis-associated cancer, colorectal cancer, or uterine cancer; each represents a separate embodiment according to this invention. Based upon their believed mode of action, it is believed that other forms of cancer will likewise be treatable or preventable upon administration of the compounds or compositions of the present invention to a patient.
30 Preferred compounds of the present invention are selectively disruptive to cancer cells, causing ablation of cancer cells but preferably not normal cells. Significantly, harm to normal cells is minimized because the cancer cells are susceptible to disruption at much lower concentrations of the compounds of the present invention.

[00247] In various embodiments, other types of cancers that may be treatable with the c-MYC mRNA
35 translation modulators according to this invention include: adrenocortical carcinoma, anal cancer, bladder cancer, brain tumor, brain stem tumor, breast cancer, glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal, pineal tumors, hypothalamic glioma, carcinoid tumor, carcinoma, cervical cancer, colon cancer, central nervous system (CNS) cancer,

endometrial cancer, esophageal cancer, extrahepatic bile duct cancer, Ewing's family of tumors (Pnet), extracranial germ cell tumor, eye cancer, intraocular melanoma, gallbladder cancer, gastric cancer, germ cell tumor, extragonadal, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma, laryngeal cancer, leukemia, acute lymphoblastic, leukemia, oral cavity cancer, liver

5 cancer, lung cancer, non-small cell lung cancer, small cell, lymphoma, AIDS-related lymphoma, central nervous system (primary), lymphoma, cutaneous T-cell, lymphoma, Hodgkin's disease, non-Hodgkin's disease, malignant mesothelioma, melanoma, Merkel cell carcinoma, metastatic squamous carcinoma, multiple myeloma, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian

10 epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, exocrine, pancreatic cancer, islet cell carcinoma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pheochromocytoma cancer, pituitary cancer, plasma cell neoplasm, prostate cancer, rhabdomyosarcoma, rectal cancer, renal cancer, renal cell cancer, salivary gland cancer, Sezary syndrome, skin cancer, cutaneous T-cell lymphoma, Kaposi's sarcoma, melanoma, small intestine cancer, soft tissue

15 sarcoma, testicular cancer, thymoma, malignant, thyroid cancer, urethral cancer, uterine cancer, sarcoma, unusual cancer of childhood, vaginal cancer, vulvar cancer, Wilms' tumor, hepatocellular cancer, hematological cancer or any combination thereof. In some embodiments the cancer is invasive. In some embodiments the cancer is metastatic cancer. In some embodiments the cancer is advanced cancer. In some embodiments the cancer is drug resistant cancer.

20 [00248] In various embodiments "metastatic cancer" refers to a cancer that spread (metastasized) from its original site to another area of the body. Virtually all cancers have the potential to spread. Whether metastases develop depends on the complex interaction of many tumor cell factors, including the type of cancer, the degree of maturity (differentiation) of the tumor cells, the location and how long the cancer has been present, as well as other incompletely understood factors. Metastases spread in three ways - by local

25 extension from the tumor to the surrounding tissues, through the bloodstream to distant sites or through the lymphatic system to neighboring or distant lymph nodes. Each kind of cancer may have a typical route of spread. The tumor is called by the primary site (ex. breast cancer that has spread to the brain is called metastatic breast cancer to the brain).

[00249] In various embodiments "drug-resistant cancer" refers to cancer cells that acquire resistance to

30 chemotherapy. Cancer cells can acquire resistance to chemotherapy by a range of mechanisms, including the mutation or overexpression of the drug target, inactivation of the drug, or elimination of the drug from the cell. Tumors that recur after an initial response to chemotherapy may be resistant to multiple drugs (they are multidrug resistant). In the conventional view of drug resistance, one or several cells in the tumor population acquire genetic changes that confer drug resistance. Accordingly, the reasons for

35 drug resistance, *inter alia*, are: a) some of the cells that are not killed by the chemotherapy mutate (change) and become resistant to the drug. Once they multiply, there may be more resistant cells than cells that are sensitive to the chemotherapy; b) Gene amplification. A cancer cell may produce hundreds of copies of a particular gene. This gene triggers an overproduction of protein that renders the anticancer

drug ineffective; c) cancer cells may pump the drug out of the cell as fast as it is going in using a molecule called p-glycoprotein; d) cancer cells may stop taking in the drugs because the protein that transports the drug across the cell wall stops working; e) the cancer cells may learn how to repair the DNA breaks caused by some anti-cancer drugs; f) cancer cells may develop a mechanism that inactivates the drug. One major contributor to multidrug resistance is overexpression of P-glycoprotein (P-gp). This protein is a clinically important transporter protein belonging to the ATP-binding cassette family of cell membrane transporters. It can pump substrates including anticancer drugs out of tumor cells through an ATP-dependent mechanism; g) Cells and tumors with activating RAS mutations are relatively resistant to most anti-cancer agents. Thus, the resistance to anticancer agents used in chemotherapy is the main cause of treatment failure in malignant disorders, provoking tumors to become resistant. Drug resistance is the major cause of cancer chemotherapy failure.

[00250] In various embodiments "resistant cancer" refers to drug-resistant cancer as described herein above. In some embodiments "resistant cancer" refers to cancer cells that acquire resistance to any treatment such as chemotherapy, radiotherapy or biological therapy.

[00251] In various embodiments, this invention is directed to treating, suppressing, reducing the severity, reducing the risk of developing, or inhibiting cancer in a subject, wherein the subject has been previously treated with chemotherapy, radiotherapy or biological therapy.

[00252] In various embodiments "Chemotherapy" refers to chemical treatment for cancer such as drugs that kill cancer cells directly. Such drugs are referred as "anti-cancer" drugs or "antineoplastics." Today's therapy uses more than 100 drugs to treat cancer. Chemotherapy is used to control tumor growth when cure is not possible; to shrink tumors before surgery or radiation therapy; to relieve symptoms (such as pain); and to destroy microscopic cancer cells that may be present after the known tumor is removed by surgery (called adjuvant therapy). Adjuvant therapy is given to prevent a possible cancer reoccurrence.

[00253] In various embodiments, "Radiotherapy" (also referred herein as "Radiation therapy") refers to high energy x-rays and similar rays (such as electrons) to treat disease. Many people with cancer will have radiotherapy as part of their treatment. This can be given either as external radiotherapy from outside the body using x-rays or from within the body as internal radiotherapy. Radiotherapy works by destroying the cancer cells in the treated area. Although normal cells can also be damaged by the radiotherapy, they can usually repair themselves. Radiotherapy treatment can cure some cancers and can also reduce the chance of a cancer coming back after surgery. It may be used to reduce cancer symptoms.

[00254] In various embodiments "Biological therapy" refers to substances that occur naturally in the body to destroy cancer cells. There are several types of treatment including: monoclonal antibodies, cancer growth inhibitors, vaccines and gene therapy. Biological therapy is also known as immunotherapy.

[00255] When the compounds or pharmaceutical compositions of the present invention are administered to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit a cancerous condition, the pharmaceutical composition can also contain, or can be administered in conjunction with, other therapeutic agents or treatment regimen presently known or hereafter developed for the treatment of

various types of cancer. Examples of other therapeutic agents or treatment regimen include, without limitation, radiation therapy, immunotherapy, chemotherapy, surgical intervention, and combinations thereof.

[00256] In various embodiments, the compound according to this invention, is administered in combination with an anti-cancer therapy. Examples of such therapies include but are not limited to: chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, and combinations thereof.

[00257] In various embodiments, the compound is administered in combination with an anti-cancer agent by administering the compounds as herein described, alone or in combination with other agents.

[00258] In various embodiments, the composition for cancer treatment of the present invention can be used together with existing chemotherapy drugs or be made as a mixture with them. Such a chemotherapy drug includes, for example, alkylating agents, nitrosourea agents, antimetabolites, antitumor antibiotics, alkaloids derived from plant, topoisomerase inhibitors, hormone therapy medicines, hormone antagonists, aromatase inhibitors, P-glycoprotein inhibitors, platinum complex derivatives, other immunotherapeutic drugs, and other anticancer agents. Further, they can be used together with hypoleukocytosis (neutrophil) medicines that are cancer treatment adjuvant, thrombopenia medicines, antiemetic drugs, and cancer pain medicines for patient's QOL recovery or be made as a mixture with them.

[00259] In various embodiments, this invention provides a method of modulating c-MYC mRNA translation in a cell, comprising contacting a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and/or by the structures listed in Table 1, as defined herein above, with a cell, thereby modulating c-MYC mRNA translation in said cell. In some embodiments, the method is carried out by regulating c-MYC mRNA splicing. In some embodiments, the method is carried out by inclusion or exclusion of untranslated region or alternative usage of exons. In some embodiments, the method is carried out by regulation of c-MYC mRNA modifications. In some embodiments, the method is carried out by regulation of the interaction of RNA binding protein with c-MYC mRNA thereby changing mRNA localization. In some embodiments, the method is carried out by regulating c-MYC mRNA localization in the cytoplasm. In some embodiments, the method is carried out by regulating ribosomes or ribosome accessory factor to c-MYC mRNA. In some embodiments, the method is carried out by reducing the amount of c-MYC protein in the cell.

[00260] This invention further provides a method of regulating c-MYC mRNA transcription in a cell, comprising contacting a compound represented by the structure of formula **I** and/or **I(a)-I(n)** and/or by the structures listed in Table 1, as defined herein above, with a cell, thereby regulating c-MYC mRNA transcription in said cell. In some embodiments, the method is carried out by regulating c-MYC mRNA splicing. In some embodiments, the method is carried out by inclusion or exclusion of untranslated region or alternative usage of exons. In some embodiments, the method is carried out by regulation of c-MYC mRNA modifications. In some embodiments, the method is carried out by regulation of the interaction of RNA binding protein with c-MYC mRNA thereby changing mRNA localization. In some

embodiments, the method is carried out by regulating c-MYC mRNA localization in the cytoplasm. In some embodiments, the method is carried out by regulating ribosomes or ribosome accessory factor to c-MYC mRNA. In some embodiments, the method is carried out by reducing the amount of c-MYC protein in the cell.

5 [00261] In various embodiments, this invention is directed to a method of destroying a cancerous cell comprising providing a compound of this invention and contacting the cancerous cell with the compound under conditions effective to destroy the contacted cancerous cell. According to various embodiments of destroying the cancerous cells, the cells to be destroyed can be located either *in vivo* or *ex vivo* (i.e., in culture).

10 [00262] A still further aspect of the present invention relates to a method of treating or preventing a cancerous condition that includes providing a compound of the present invention and then administering an effective amount of the compound to a patient in a manner effective to treat or prevent a cancerous condition.

[00263] According to one embodiment, the patient to be treated is characterized by the presence of a precancerous condition, and the administering of the compound is effective to prevent development of the precancerous condition into the cancerous condition. This can occur by destroying the precancerous cell prior to or concurrent with its further development into a cancerous state.

[00264] According to other embodiments, the patient to be treated is characterized by the presence of a cancerous condition, and the administering of the compound is effective either to cause regression of the cancerous condition or to inhibit growth of the cancerous condition, i.e., stopping its growth altogether or reducing its rate of growth. This preferably occurs by destroying cancer cells, regardless of their location in the patient body. That is, whether the cancer cells are located at a primary tumor site or whether the cancer cells have metastasized and created secondary tumors within the patient body.

[00265] As used herein, subject or patient refers to any mammalian patient, including without limitation, humans and other primates, dogs, cats, horses, cows, sheep, pigs, rats, mice, and other rodents. In various embodiments, the subject is male. In some embodiments, the subject is female. In some embodiments, while the methods as described herein may be useful for treating either males or females.

[00266] When administering the compounds of the present invention, they can be administered systemically or, alternatively, they can be administered directly to a specific site where cancer cells or precancerous cells are present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the cancer cells or precancerous cells. Exemplary modes of administration include, without limitation, administering the compounds or compositions orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes.

[00267] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

5

EXAMPLES

EXAMPLE 1

General Synthetic Details for Compounds of the Invention (Schemes 1-9)

General Methods

- 10 [00268] All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Reagent grade solvents were used in all cases, unless otherwise specified. Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). ¹H-NMR and ¹⁹F-NMR spectra were recorded on a Bruker Bruker Avance 400MHz or Avance III 400MHz spectrometer. The chemical shifts are expressed in ppm using the residual solvent as internal standard.
- 15 Splitting patterns are designated as *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *t* (triplet), *dt* (doublet of triplets), *q* (quartet), *m* (multiplet) and *br s* (broad singlet).

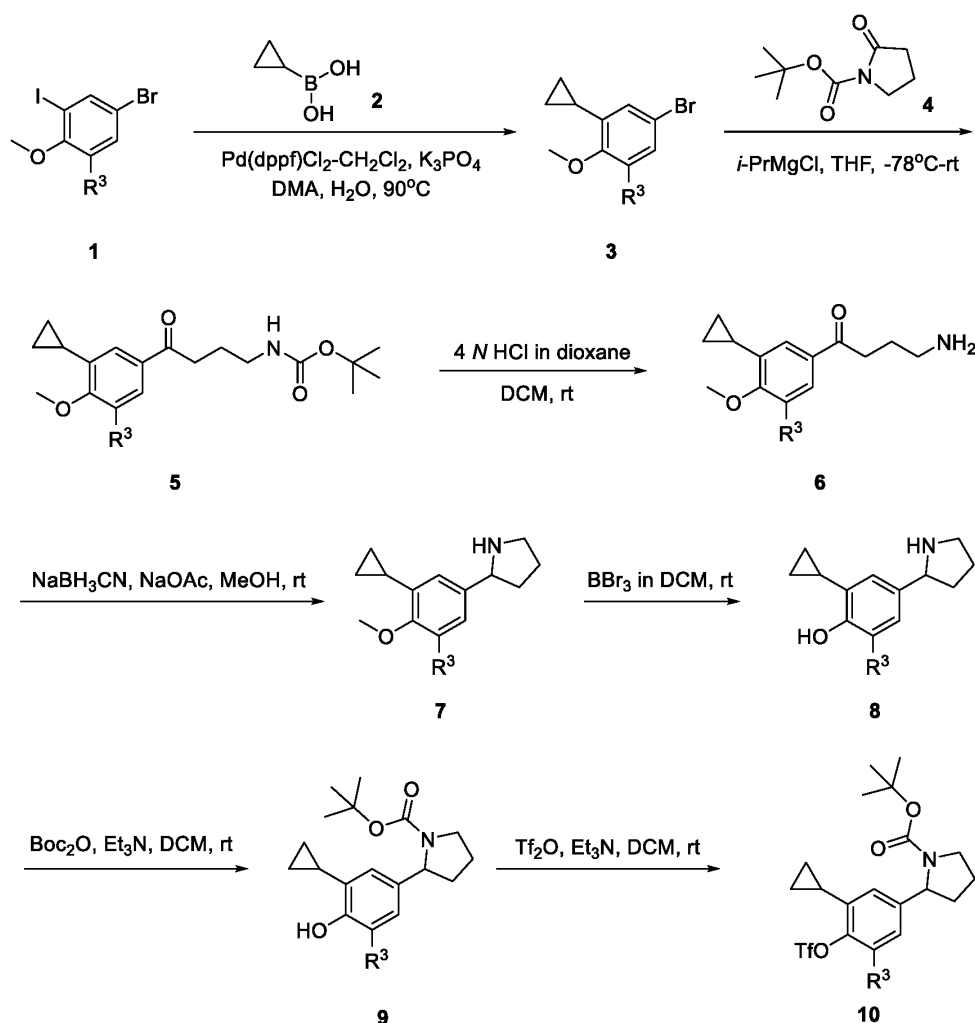
Abbreviations

- | | |
|----------------|---|
| AcOH | Acetic acid |
| 20 amphos | <i>Bis</i> (di- <i>tert</i> -butyl(4-dimethylaminophenyl)phosphine |
| Boc | <i>tert</i> -Butyloxycarbonyl |
| BuLi | <i>n</i> -butyllithium |
| <i>t</i> -BuLi | <i>tert</i> -butyllithium |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| 25 dppb | 1,4- <i>Bis</i> (diphenylphosphino)butane |
| dppf | 1,1'- <i>Bis</i> (diphenylphosphino)ferrocene |
| DCM | Dichloromethane |
| DCE | 1,2-Dichloroethane |
| DIBAL-H | Diisobutylaluminum hydride |
| 30 DIPEA | <i>N,N</i> -Diisopropylethylamine |
| DMF | <i>N,N</i> -Dimethylformamide |
| DMA | <i>N,N</i> -Dimethylacetamide |
| DMAP | 4-Dimethylaminopyridine |
| DME | 1,2-Dimethoxyethane |
| 35 DMSO | Dimethylsulfoxide |
| DPPA | Diphenyl phosphoryl azide |
| DTBF | 1,1'- <i>Bis</i> (di- <i>tert</i> -butylphosphino)ferrocene |
| EDC.HCl | <i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride |

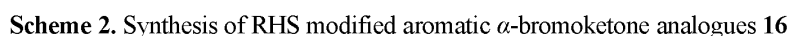
	HATU	[O-(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium-hexafluorophosphate]
	HPLC	High performance liquid chromatography
	MsCl	Methanesulfonyl chloride
	NBS	<i>N</i> -Bromosuccinimide
5	POBr ₃	Phosphorus(V) oxybromide
	Py-HBr ₃	Pyridinium tribromide
	SEM	2-(Trimethylsilyl)ethoxymethyl
	T3P	Propylphosphonic anhydride
	TBAF	Tetrabutylammonium fluoride
10	TCFH	<i>N,N,N',N'</i> -tetramethylchloroformamidinium hexafluorophosphate
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TMS-OTf	Trimethylsilyl trifluoromethanesulfonate

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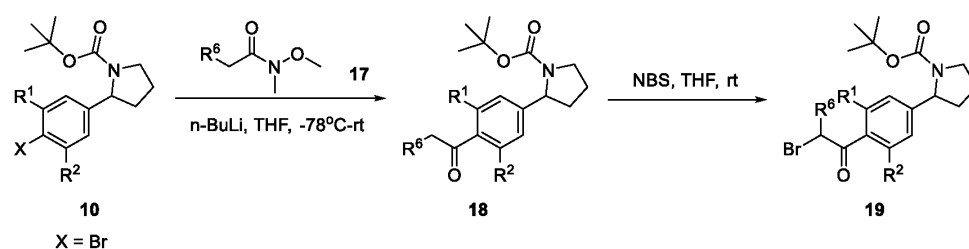
General synthesis of compounds of the invention

**Scheme 1.** Synthesis of RHS modified phenyl trifluoromethanesulfonate analogues 10

[00269] The first step of the synthesis involved a Suzuki coupling reaction between poly-substituted iodobenzenes 1 and cyclopropylboronic acid 2 to afford intermediates 3. Halogen magnesium exchange of intermediates 3 by isopropylmagnesium bromide at low temperature formed new aryl magnesium reagents, which were treated with *tert*-butyl 2-oxopyrrolidine-1-carboxylate 4 to generate aryl alkyl ketones 5. Subsequently the *N*-Boc group was removed under acidic conditions to give amine intermediates 6 as the corresponding hydrochloride salts or free bases. Intermediates 6 were subjected to an intramolecular reductive amination reaction to generate intermediates 7. The methoxy protecting groups of aryl methyl ether intermediates 7 were removed using boron tribromide to give amino poly-substituted phenols 8. Intermediates 8 were subjected to amino group protection with *Boc* groups to generate intermediates 9. In the final step the hydroxyl groups of intermediates 9 were converted to the corresponding trifluoromethanesulfonates by treatment with trifluoromethanesulfonic anhydride under basic conditions to give elaborated intermediates 10.

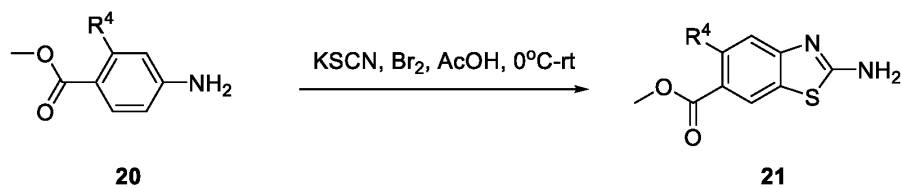


[00270] The first 3 steps were conducted using similar methodology the corresponding steps described in **Scheme 1** to generate intermediates **10**. Subsequently a 1-ethoxyvinyl group was introduced *via* Stille coupling of intermediates **10** with tributyl(1-ethoxyvinyl)stannane **14** affording intermediates **15**. Intermediates **15** were treated with NBS in THF and water to give the corresponding aromatic α -bromoketones **16**.



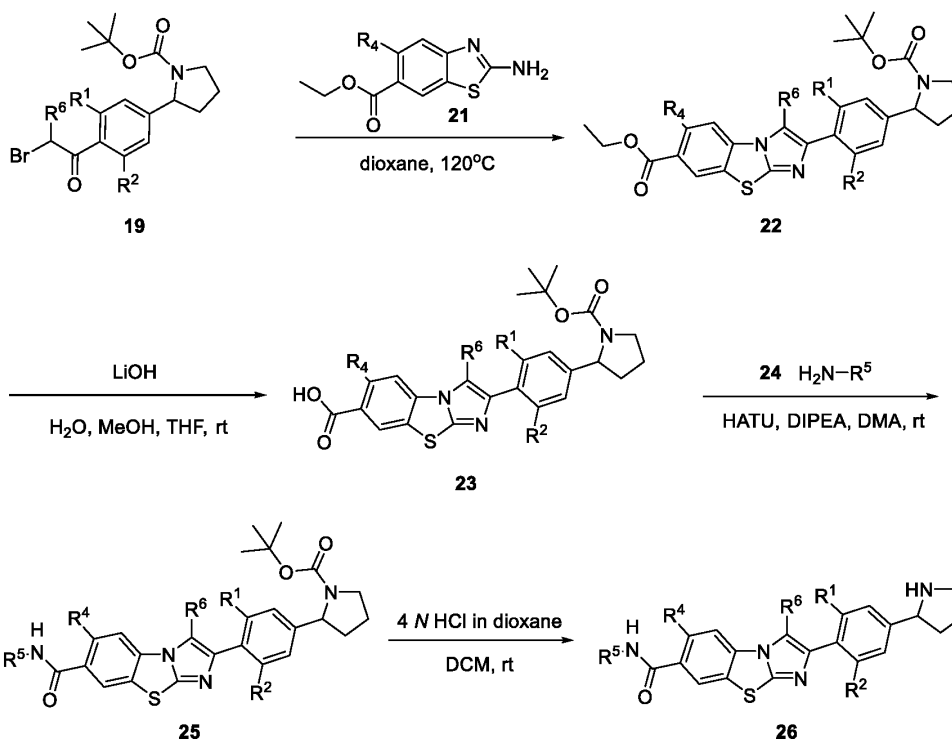
Scheme 3. Synthesis of RHS modified aromatic α -bromoketone analogues 19.

[00271] The corresponding step involved lithium halogen exchange of intermediates **10** with *n*-butyllithium, followed by quenching with substituted Weinreb amides **17** forming α -substituted aromatic ketone intermediates **18**. Subsequent bromination at α -position of ketone intermediates **18** with brominating reagents such as NBS generated α -bromoketone intermediates **19**.



Scheme 4. Synthesis of 5-substituted methyl 2-aminobenzo[d]thiazole-6-carboxylate **21**

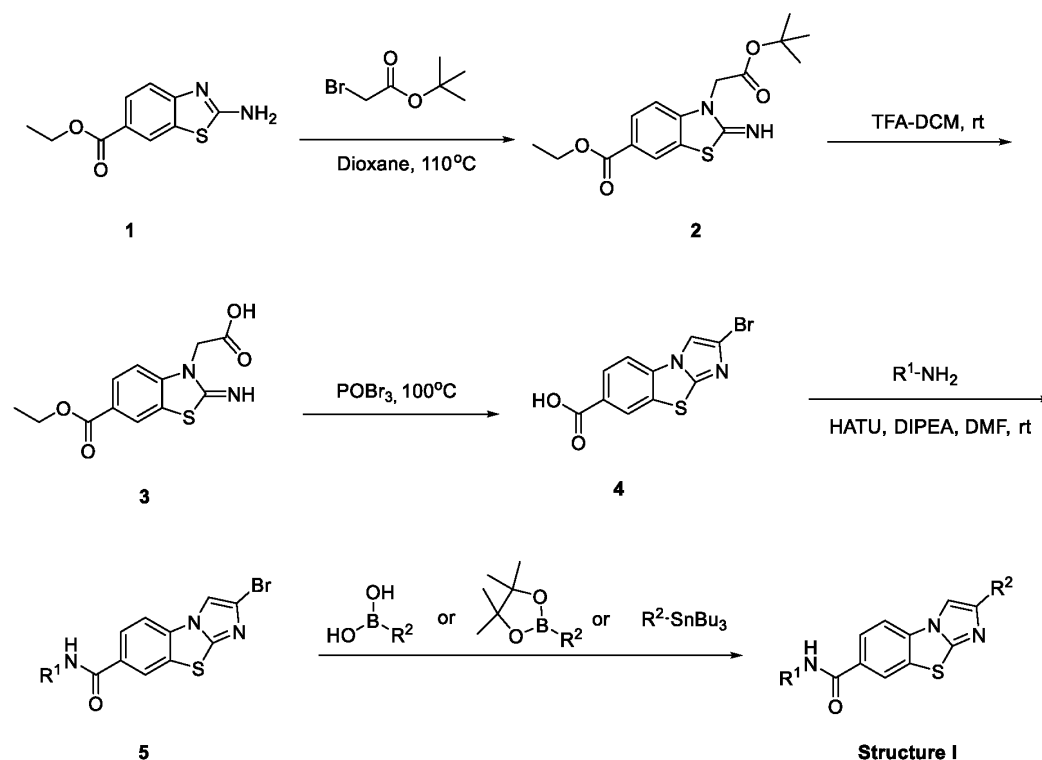
[00272] Intermediates **20** were treated with potassium thiocyanate and bromine in acetic acid to generate corresponding 2-aminobenzo[d]thiazoles **21**.



Scheme 5. Synthesis of functionalized Analogues **26**.

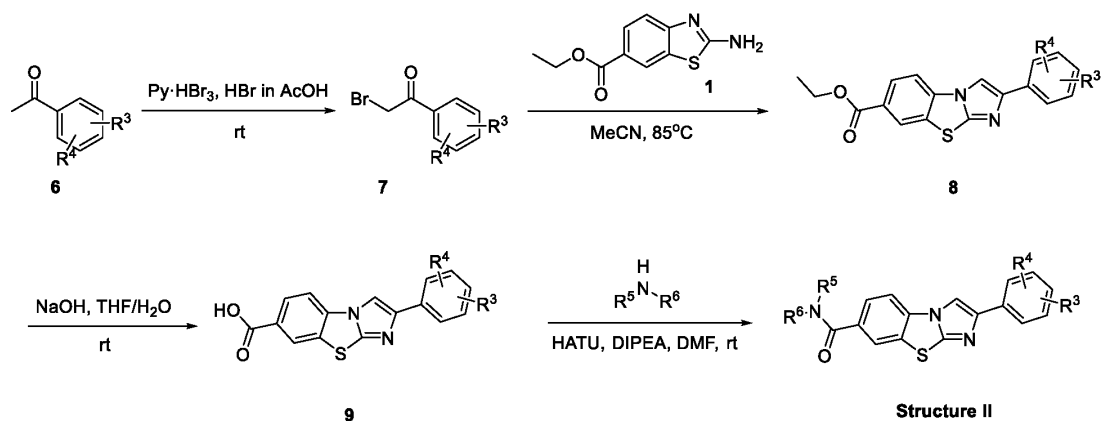
[00273] The initial step involved a cyclization reaction between modified α -bromoketone analogues **19** and corresponding 2-aminobenzo[d]thiazole **21** affording substituted tricyclic benzo[d]imidazo[2,1-*b*]thiazole intermediates **22**. The carboxylic esters **22** were hydrolyzed under basic conditions such as aqueous lithium hydroxide to afford carboxylic acids **23**. Subsequent condensation reaction of intermediates **23** with corresponding amines afforded *N*-Boc protected amides **25**. Intermediates **25** were deprotected under acidic conditions such as hydrogen chloride in dioxane solution to generate final compounds **26**.

Synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, Structure I



Scheme 6. First generation synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, Structure I.

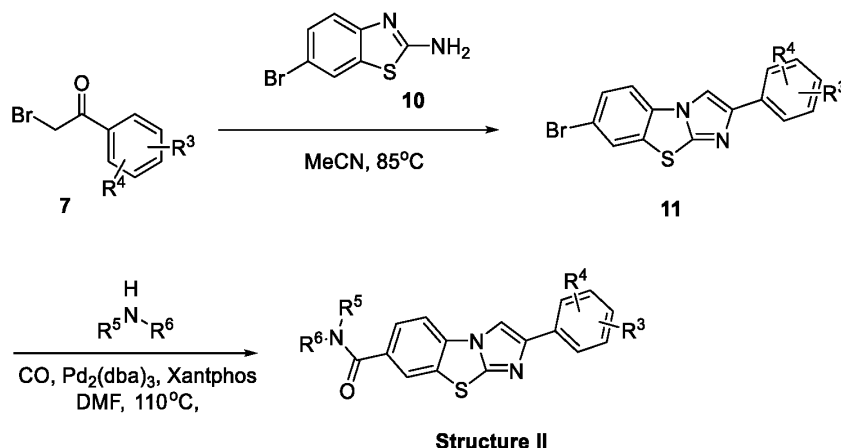
- 5 [00274] The first step of the synthesis involves alkylation of ethyl 2-aminobenzothiazole-6-carboxylate **1** (Scheme 6) with *tert*-butyl bromoacetate at elevated temperature affording alkylated intermediate **2** (Scheme 6). The *tert*-butyl group was removed using a mixture of TFA-DCM to generate the carboxylic acid intermediate **3**. Treatment of the carboxylic acid intermediate **3** (Scheme 6) with phosphorus(V) oxybromide at elevated temperature results in intramolecular cyclization to form the benzo[d]imidazo[2,1-b]thiazole intermediate **4** (Scheme 6). The acid moiety of the left-hand side (LHS) of intermediate **4** (Scheme 6) was elaborated to the amides, by HATU mediated coupling with a variety of amines affording the amide intermediates **5** (Scheme 6). The final step of the synthetic sequence involves palladium catalyzed cross-coupling to introduce an aryl / heteroaryl component at the bromo substituent of the heterocyclic intermediate **5** (Scheme 6). Cross-coupling partners to introduce R² include various boronic acid / esters (Suzuki-Miyaura coupling) or various organostannane reagents (Stille coupling) to furnish the final compounds with various right-hand sides (RHS), **Structure I** (Scheme 6).
- 10
- 15

Synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, *Structure II***Scheme 7.** Second generation synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, **Structure II**.

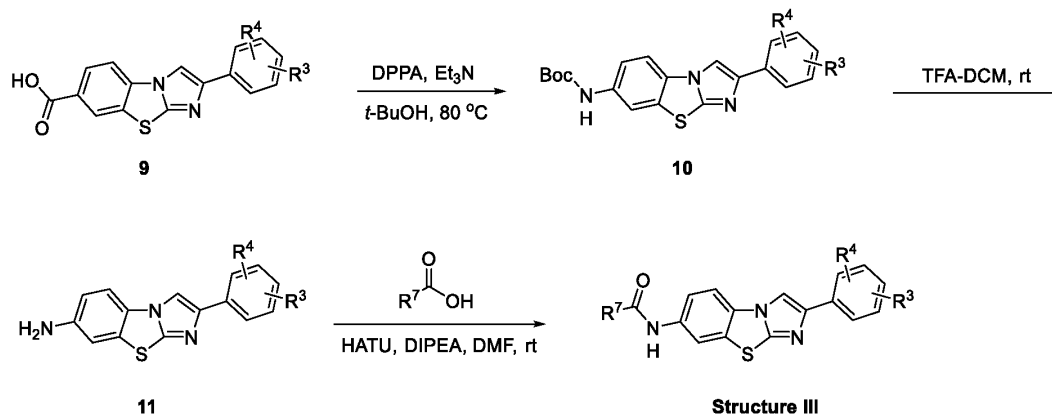
5

[00275] The first step of the synthesis involves bromination of the α -carbonyl position of various substituted aryl methyl ketones **6** (Scheme 7), using pyridinium tribromide in the presence of HBr in acetic acid affording substituted phenacyl bromide intermediates **7** (Scheme 7). These intermediates **7** (Scheme 7) facilitate ready diversification of the right-hand side (RHS) of the final compounds, **Structure II**. Intermediate **7** (Scheme 7) undergoes a alkylation reaction followed by intramolecular cyclization with ethyl 2-aminobenzothiazole-6-carboxylate **1** (Scheme 7) at elevated temperature to form ester benzo[d]imidazo[2,1-b]thiazole intermediate **8** (Scheme 7). Hydrolysis of ester intermediate **8** (Scheme 7) with sodium hydroxide in water/THF mixture affords acid intermediate **9** (Scheme 7). The final step involves an amide coupling of various primary\secondary amines with acid intermediate **9** (Scheme 7), using HATU as a coupling reagent delivering the final compounds with various left-hand side (LHS) amides, **Structure II** (Scheme 7).

15

Alternative synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, *Structure II***Scheme 8.** Alternative synthesis of benzo[d]imidazo[2,1-b]thiazole compounds, **Structure II**.

[00276] The first step involves a “one-pot” alkylation and intramolecular cyclization reaction between substituted phenacyl bromide intermediates **7** (as in **Scheme 7**) and 2-amino-6-bromobenzothiazole **10** (Scheme 8) at elevated temperature affording 7-bromo-2-aryl-1benzo[d]imidazo[2,1-b]thiazole intermediates **11** (Scheme 8). The bromo heterocyclic intermediate **11** (Scheme 8) is employed as the key starting material for the final palladium-catalyzed aminocarbonylation reaction at elevated temperature. Various primary/secondary amines are used in this final palladium-catalyzed aminocarbonylation reaction to provide a variety of left-hand side (LHS) amides, **Structure II** (Scheme 8).

Synthesis of reverse amide benzo[d]imidazo[2,1-b]thiazole compounds, *Structure III***Scheme 9.** Synthesis of reverse amide benzo[d]imidazo[2,1-b]thiazole compounds, **Structure III**.

[00277] The first step of the synthesis proceeds *via* a Curtius Rearrangement, using diphenyl phosphoryl azide (DPPA) and *tert*-butanol in the presence of triethylamine at elevated temperature affording *N*-Boc amine intermediate **10** (Scheme 9). *N*-Boc deprotection of intermediate **10** (Scheme 9) using a mixture of TFA in DCM enabled ready access to the 7-amino-2-aryl-1benzo[d]imidazo[2,1-

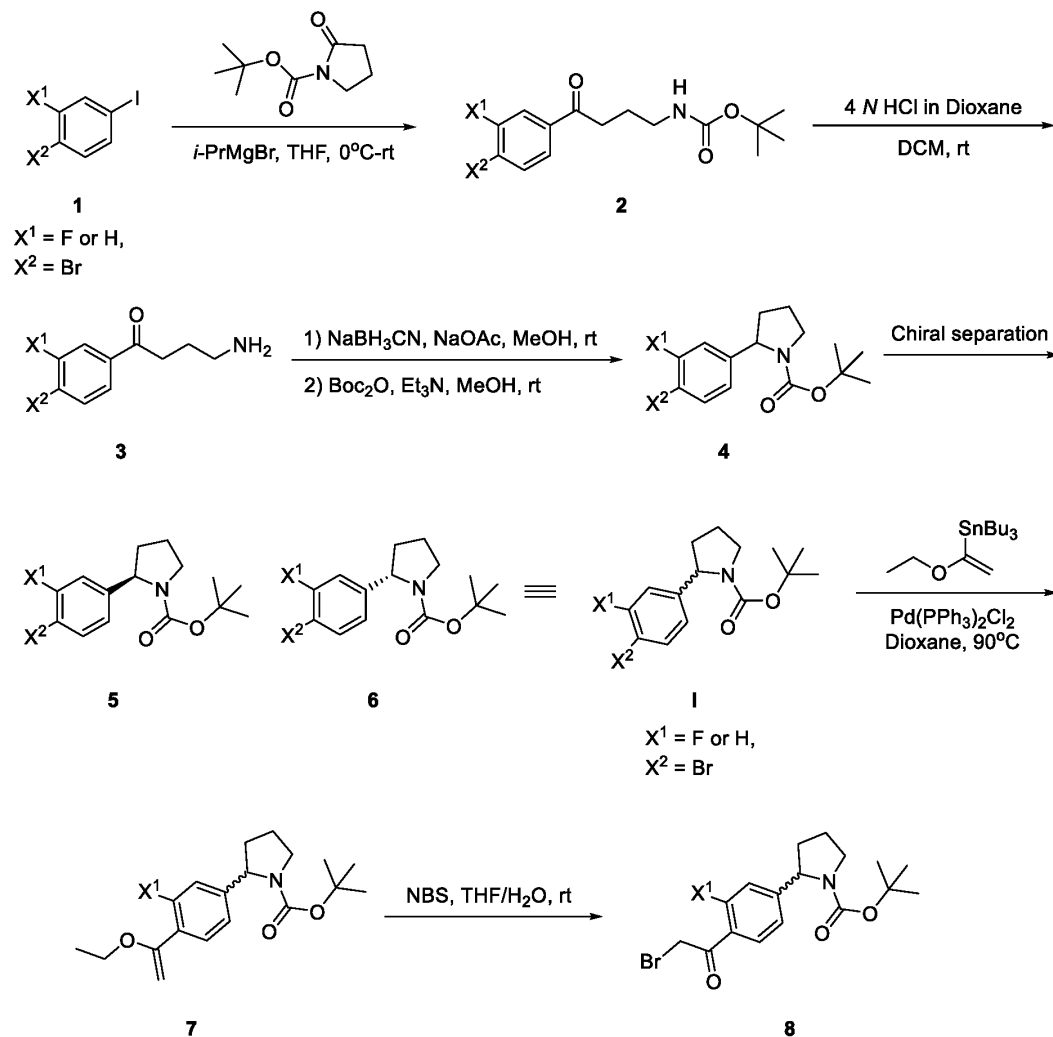
b]thiazole intermediate **11** (Scheme 9). The final step involves amide coupling of the amine intermediate **11** (Scheme 9) with a variety of carboxylic acids, using HATU as a coupling reagent to furnish the desired left-hand side (LHS) reverse amides, **Structure III** (Scheme 9).

5

EXAMPLE 2

General Synthetic Details for Additional Compounds of the Invention (Schemes 10-56)

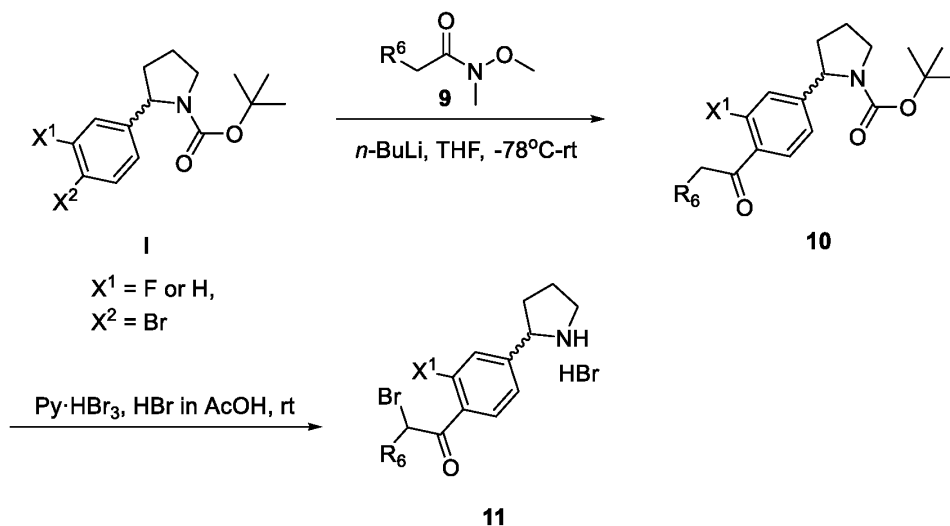
General synthesis of compounds of the invention



Scheme 10. General synthesis of modified aromatic α -bromoketone analogues **8**.

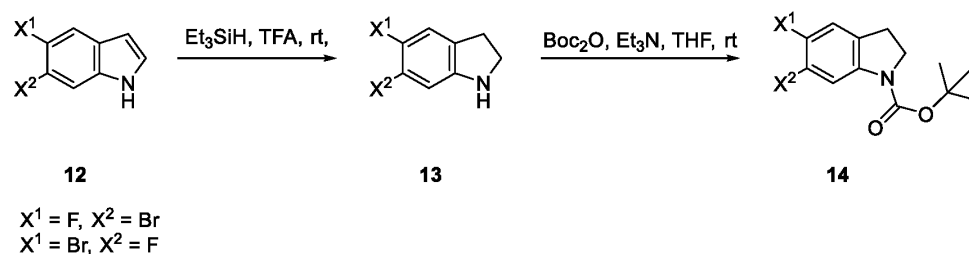
- 10 [00278] Compounds **1** were reacted with isopropylmagnesium bromide at low temperatures to generate the corresponding phenylmagnesium bromide, which were then treated with *tert*-butyl 2-oxopyrrolidine-1-carboxylate to generate ketones **2**. The *N*-Boc protecting group of **2** was removed under acidic conditions to generate terminal amines **3** as the hydrochloride salts. Then an intramolecular reductive amination reaction was carried out and the resulting endo-amines were protected as the Boc carbamates *in-situ* to

generate intermediates **4**. Separation by chiral resolution gave two enantiomers **5** and **6**. Intermediates **4**, **5** and **6** could be expressed as common compounds **I**. Compounds **I** were reacted with tributyl(1-ethoxyvinyl)stannane in the presence of catalytic palladium at elevated temperature to generate vinyl ethyl ethers **7**. These were treated with *N*-bromosuccinimide in aqueous conditions to generate aromatic α -bromoketone analogues **8**.



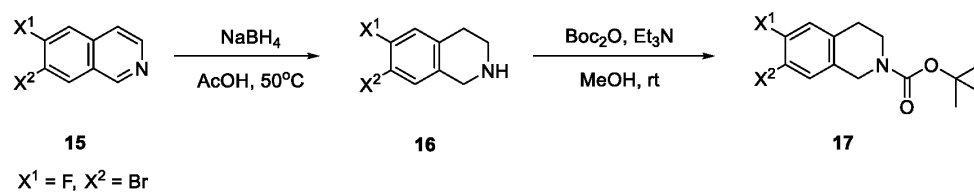
Scheme 11. An alternative synthesis of modified aromatic α -bromoketone analogues **11**.

[00279] Lithium-halogen exchange was carried out on Compounds **I** using *n*-butyl lithium at low temperature. Subsequent trapping with various Weinreb amides **9** generated ketones **10**. These were brominated by pyridinium tribromide to generate additional aromatic α -bromoketone analogues **11**.



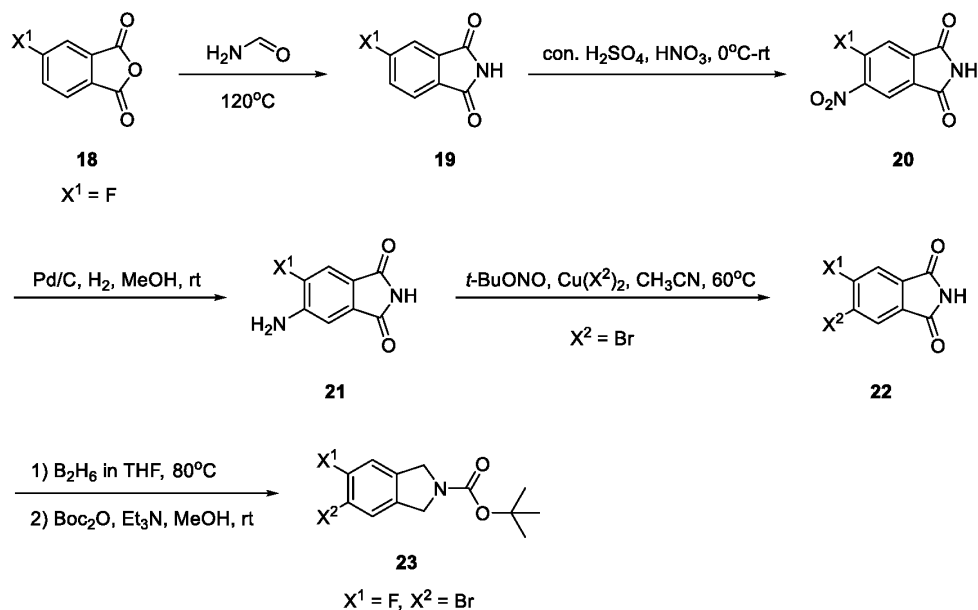
Scheme 12. General synthesis of *N*-Boc protected multi-substituted indoline **14**.

[00280] Substituted indoles **12** were reduced using triethylsilane under acidic conditions to afford indolines **13**. The resulting anilines were protected by Boc group to generate intermediates **14**.



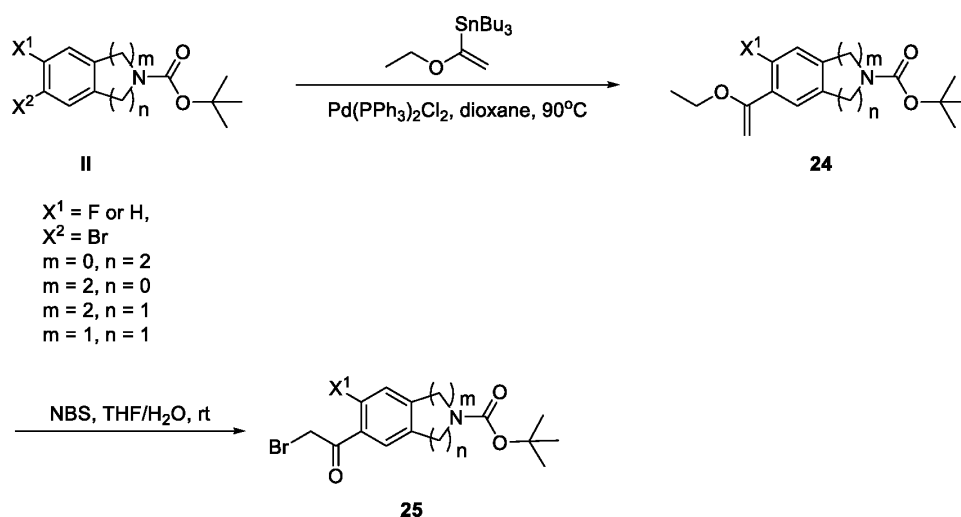
Scheme 13. General synthesis of *N*-Boc protected multi-substituted tetrahydroisoquinoline **17**.

[00281] Substituted isoquinoline **15** was reduced to 1,2,3,4-tetrahydroisoquinoline **16**. The resulting amine **16** was protected as the Boc carbamate to generate intermediate **17**.



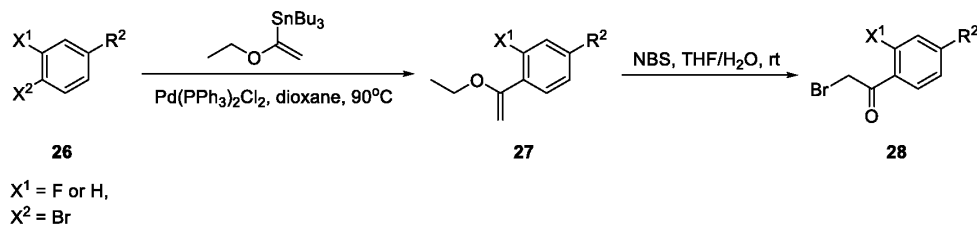
Scheme 14. General synthesis of *N*-Boc protected multi-substituted isoindoline **23**.

[00282] A reaction of 5-halidoisobenzofuran-1,3-dione **18** with formamide at elevated temperature afforded 5-halidoisoindoline-1,3-dione intermediate **19**. Then a nitration reaction was carried out to generate intermediate **20**. The nitro group of **20** was reduced by hydrogenation generating intermediate **21**. The aniline was converted to halide with *t*-butyl nitrite and copper(II) halide to provide intermediate **22**. Subsequent reduction reaction using diborane in tetrahydrofuran at elevated temperature followed by protection of the resulting endocyclic amine with a Boc group *in-situ* afforded intermediate **23** to complete the synthesis.



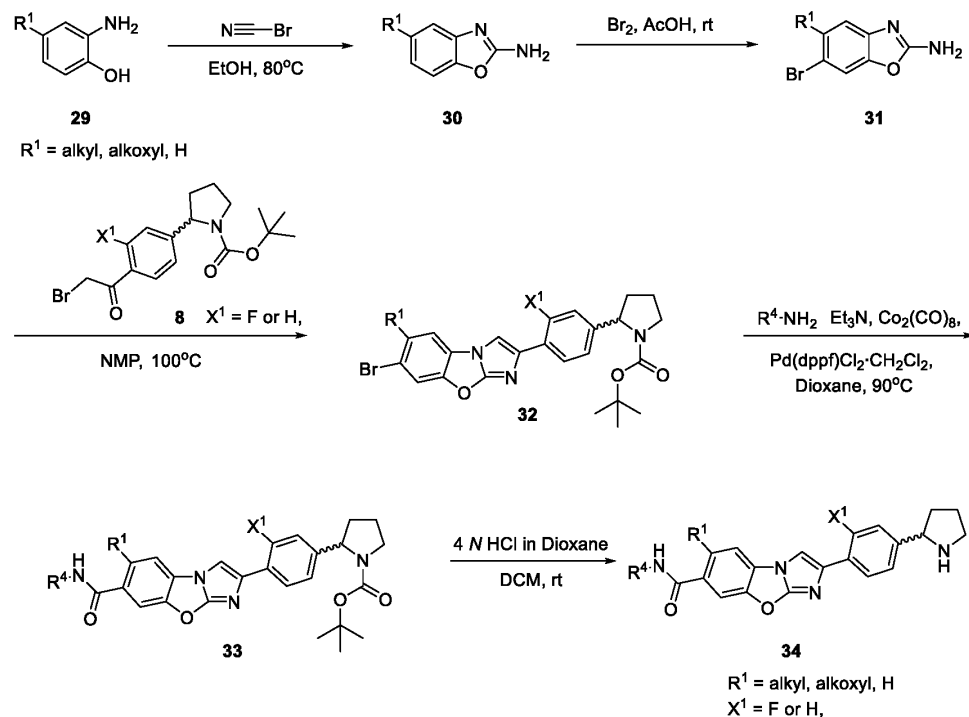
Scheme 15. General synthesis of multi-substituted α -bromoketone analogues **25**.

[00283] Intermediates **14**, **17** and **23** could be expressed as common compounds **II**, which were used as starting materials following the same synthetic sequence as in **Scheme 10**, to generate the third α -bromoketone analogues **25**.



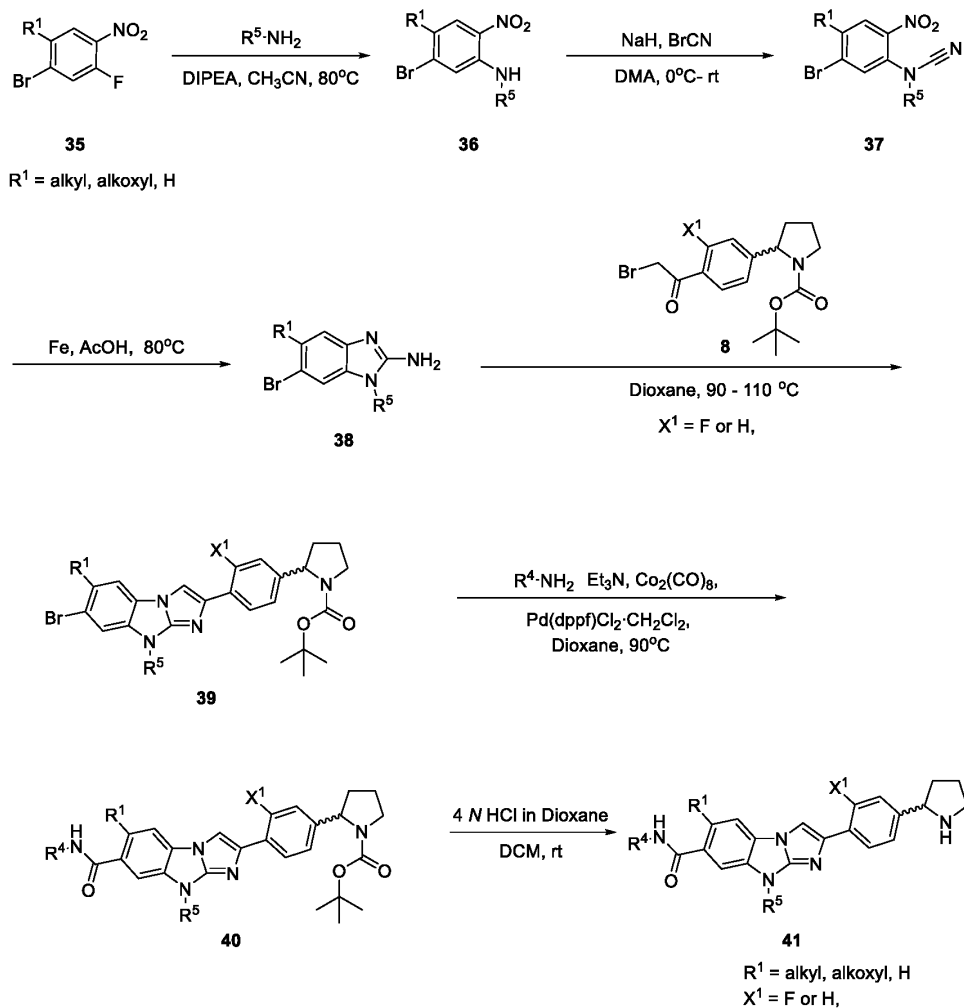
Scheme 16. General synthesis of multi-substituted α -bromoketone analogues **28**.

[00284] The fourth α -bromoketone analogues **28** were synthesized following the same synthetic sequence as in **Scheme 10** using starting materials **26**.



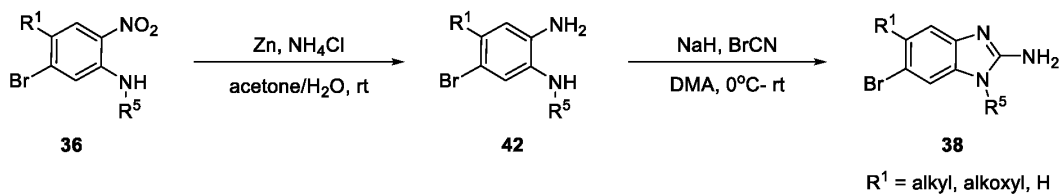
Scheme 17. General synthesis of benzo[d]imidazo[2,1-b]oxazole analogues **34**.

[00285] 2-aminophenol compounds **29**, were cyclized by reaction with cyanic bromide. A subsequent bromination reaction was performed to generate intermediates **31**. This was followed by another cyclization with α -bromoketone analogues **8** at elevated temperature to generate intermediates **32**. The bromide of intermediates **32** was converted to various amides via aminocarbonylation reaction to generate intermediates **33**. The *N*-Boc protecting group was removed using 4 *N* hydrochloride in 1,4-dioxane to produce the final benzo[d]imidazo[2,1-b]oxazole analogues **34** as a free base or a hydrochloride salt.



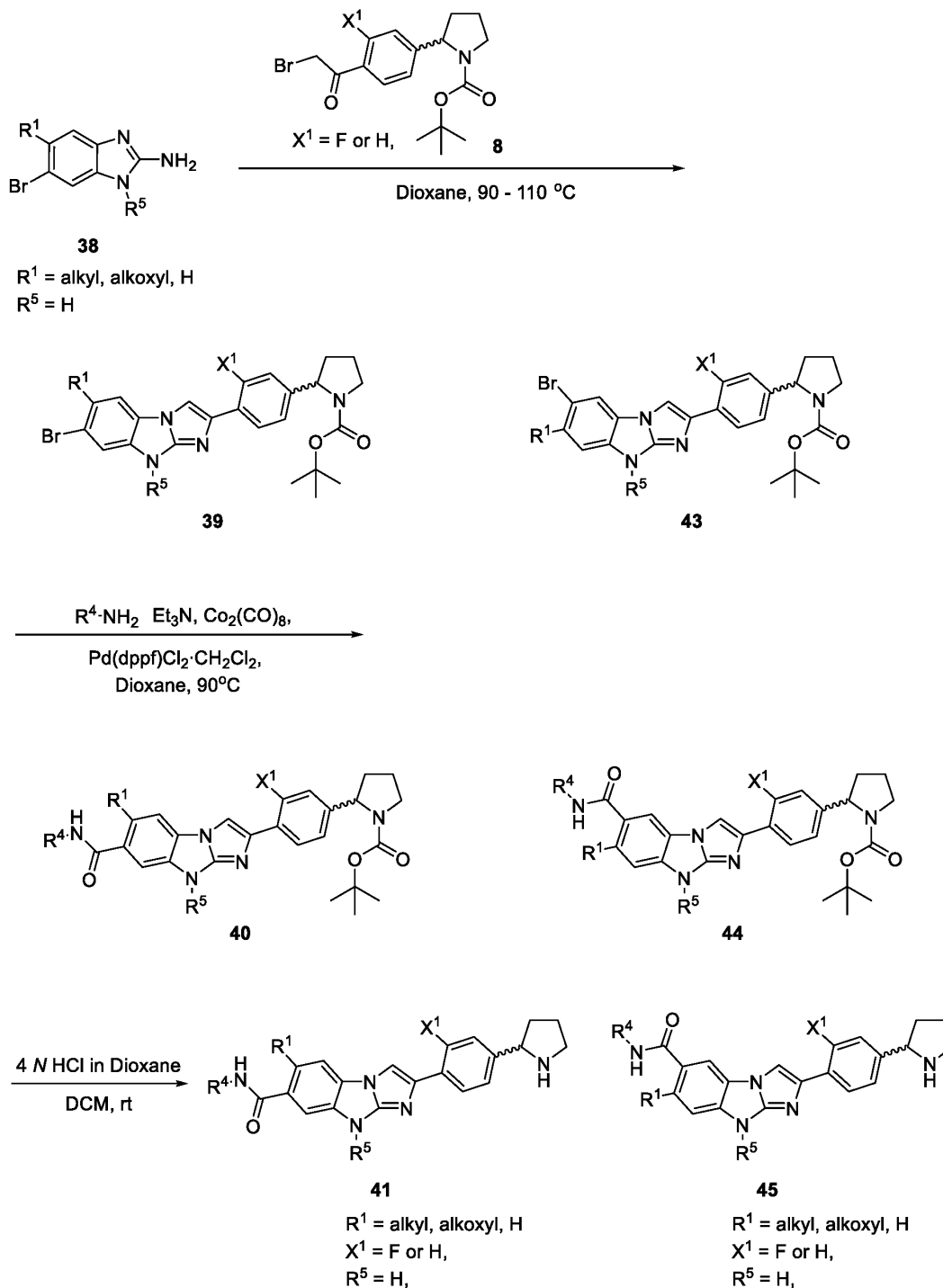
Scheme 18. General synthesis of 9-substituted-9H-benzo[d]imidazo[1,2-a]imidazole analogues **41**.

[00286] The fluoride of 2-fluoronitrobenzene compounds **35** was substituted by various amines to generate secondary anilines **36**. These were reacted with cyanic bromide using strong base to generate phenylcyanamides **37**. Intermediates **37** go through a reductive cyclization reaction to generate 2-aminobenzo[d]imidazoles **38**. Final compounds **41** were synthesized as the free base or as the hydrochloride salt from intermediates **38** following the same synthetic sequence as in **Scheme 17**



Scheme 19. An alternative synthesis of 2-aminobenzo[d]imidazoles intermediates **38**.

[00287] The nitro group of intermediates **36** were reduced by zinc powder to generate benzene-1,2-diamine intermediates **42**. These were reacted with cyanic bromide under strong base to generate 2-aminobenzo[d]imidazoles intermediates **38**.

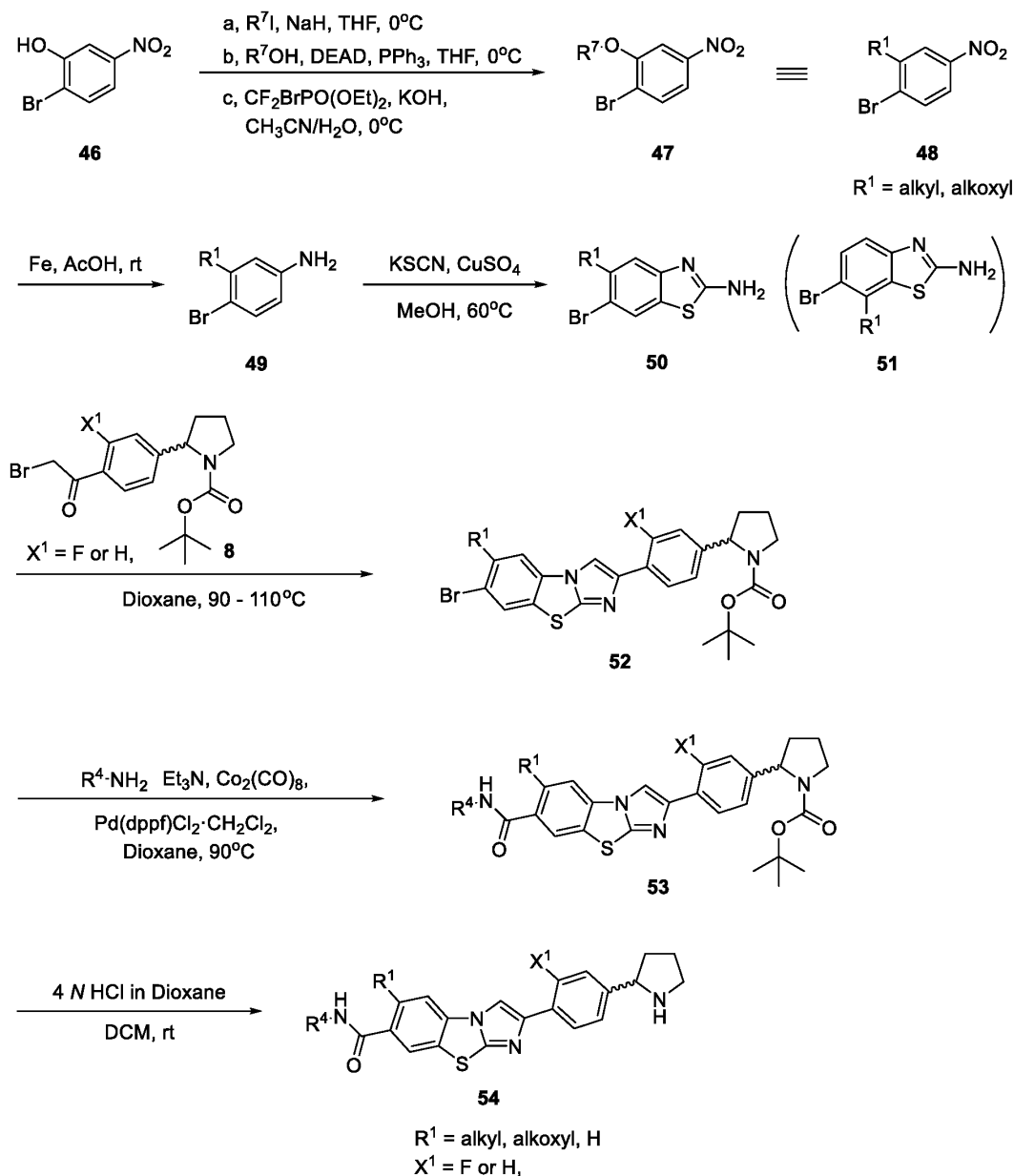


Scheme 20. General synthesis of 9H-benzo[d]imidazo[1,2-a]imidazole analogues **41** and **45**.

[00288] Regioisomers **39** and **43** were formed when intermediates **38** $R^5=\text{H}$. The mixture of bromide intermediates **39** and **43** were converted to the corresponding amides **40** and **44** following the description in **Scheme 18** step 5. The amide diastereomers **40** and **44** were separated by Chiral resolution. The *N*-Boc

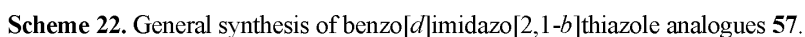
5

group of each isomer was removed under acidic conditions to generate final 9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole analogues **41** and **45** respectively as the free base or salt.



Scheme 21. General synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole analogues **54**.

- 5 [00289] An etherification of phenol compounds **46** through substitution or Mitsunobu reaction gave phenyl alkyl ether intermediates **47**, which could be expressed as compounds **48**. The nitro group of **48** was reduced by iron powder to generate aniline intermediates **49**. Then a cyclization reaction was carried out on **49** with potassium thiocyanate catalyzed by copper sulfate to generate 2-amine benzothiazole regioisomers **50** and **51** with various ratios according to the steric hindrance of R^1 group. Compounds **50** were converted to the final benzo[*d*]imidazo[2,1-*b*]thiazole analogues **54** as free base or salt in the same manner as in
- 10 **Scheme 17**. Chiral resolution was performed on amides **53** to generate final enantiomers if required.

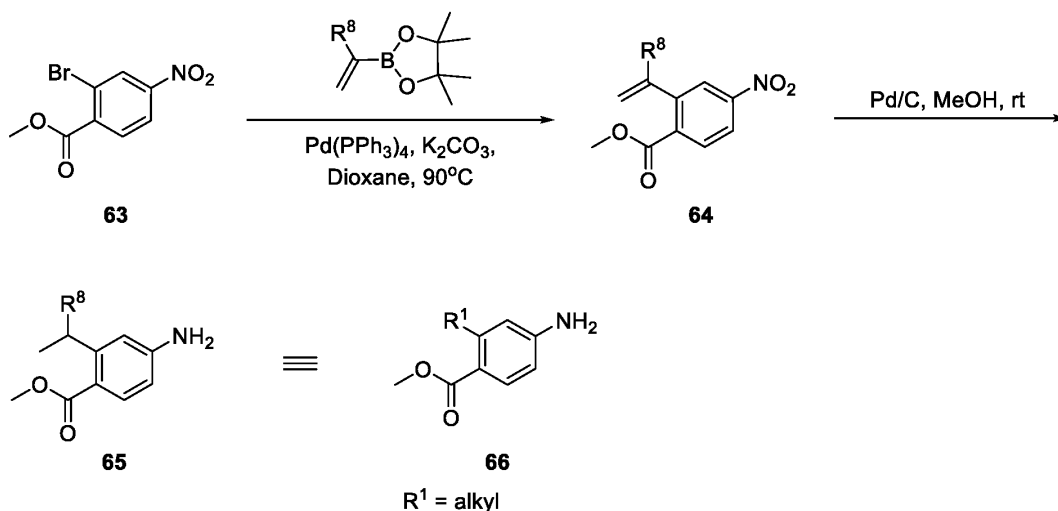


$$\begin{array}{c}
 \text{58} \xrightarrow[\text{THF, } 0^{\circ}\text{C} - \text{rt}]{\text{R}^8\text{-MgBr}} \text{59} \xrightarrow[\text{DCM, rt}]{\text{Et}_3\text{SiH, TFA}} \text{60} \\
 \text{60} \xrightarrow[\text{rt}]{\text{NBS, CH}_3\text{CN}} \text{61} \xrightarrow[\text{rt}]{\text{TFA, DCM}} \text{62} \equiv \text{49} \\
 \text{R}^1 = \text{alkyl}
 \end{array}$$

Scheme 23. General synthesis of aniline compounds **49**.

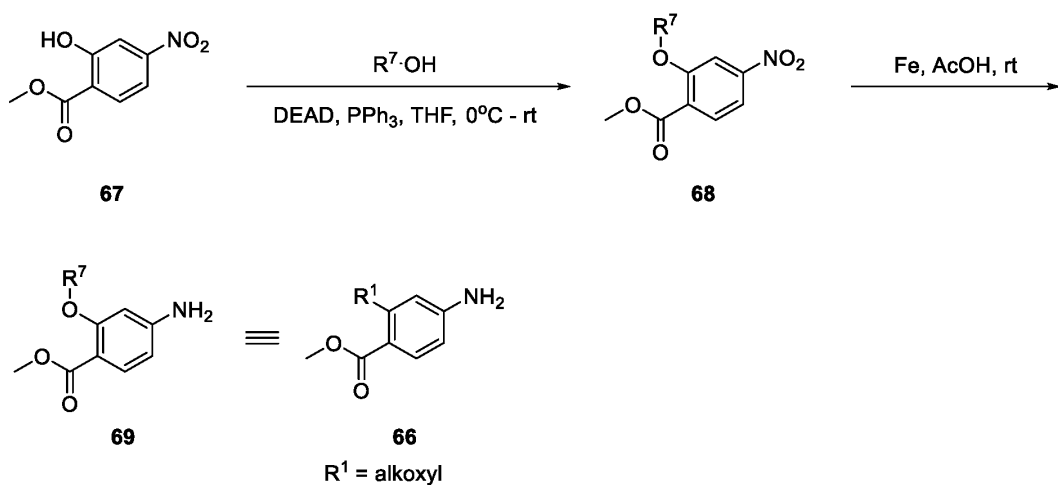
[00291] Addition of Grignard reagents to benzaldehyde **58** gave benzyl alcohol compounds **59**. Reduction using triethylsilane/trifluoroacetic acid resulted intermediates **60**. These were brominated with

N-bromosuccinimide to generate intermediates **61**. The *N*-Boc protecting group was removed under acidic conditions to generate common compounds **49**.



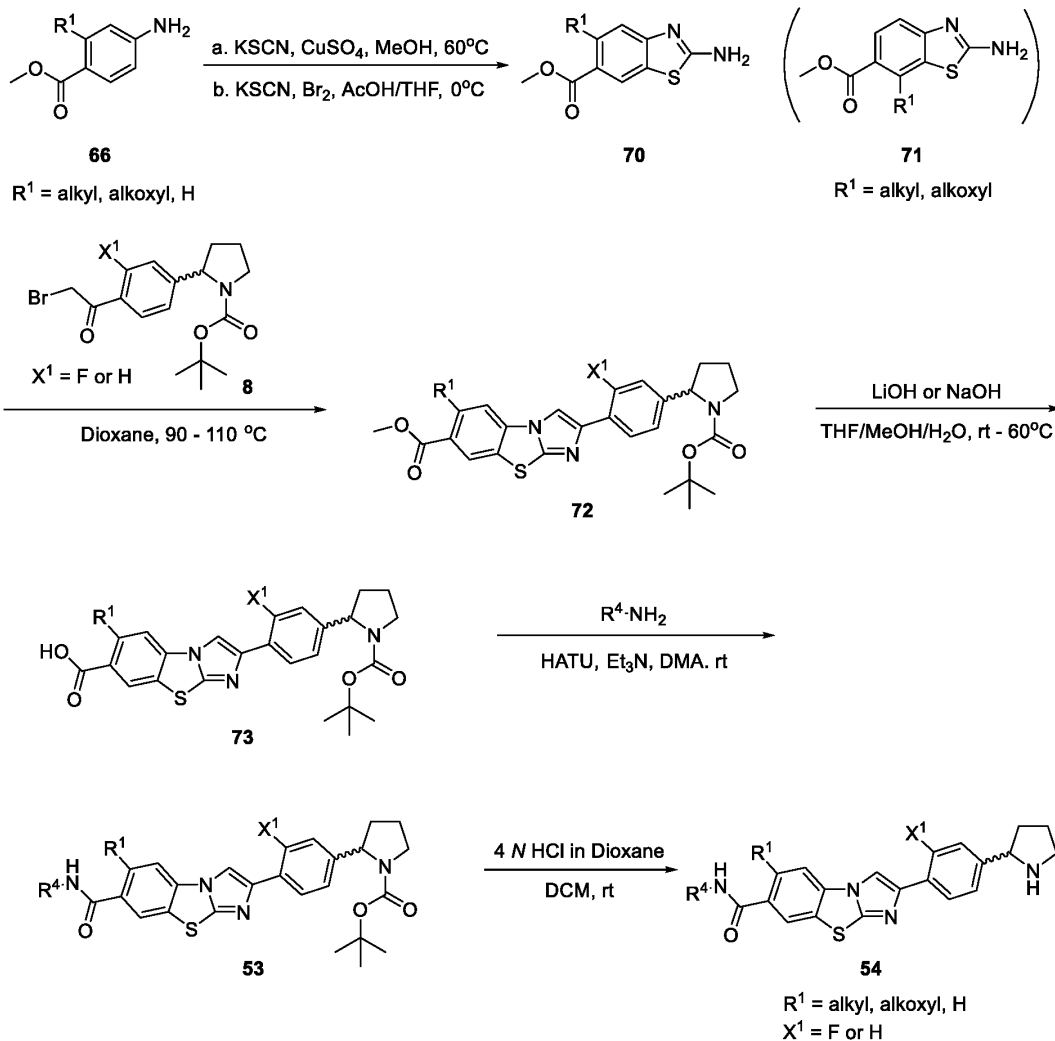
Scheme 24. General synthesis of aniline compounds **66**.

- 5 [00292] Substituted olefins were introduced to compound **63** via Suzuki cross-coupling reaction to generate intermediates **64**. Reduction of both the olefin and nitro group by hydrogenation gave the common aniline compounds **66**.



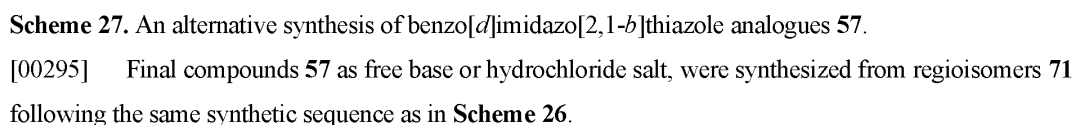
Scheme 25. An alternative synthesis of aniline compounds **66**.

- 10 [00293] Etherification of compound **67** via Mitsunobu reaction generated ether compounds **68**. Nitro group was reduced by iron powder to generate common aniline compounds **66**.

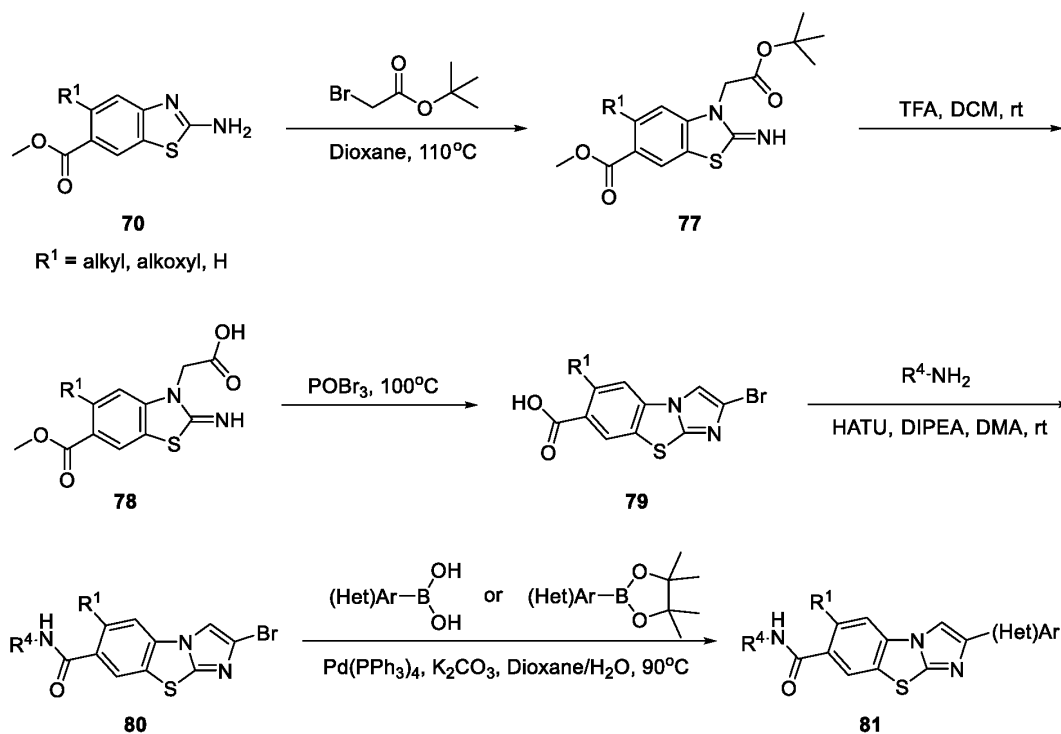


Scheme 26. An alternative synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **54**.

[00294] Ester compounds **72** were synthesized from aniline compounds **66** following the descriptions in **Scheme 21**. The ester was hydrolyzed to form carboxylic acids **73**. Amide coupling reaction on **73** with various amines gave amides **53**. The *N*-Boc protecting group was removed by 4 *N* hydrochloride in 1,4-dioxane to generate benzo[d]imidazo[2,1-*b*]thiazole analogues **54** as a free base or as the hydrochloride salt.

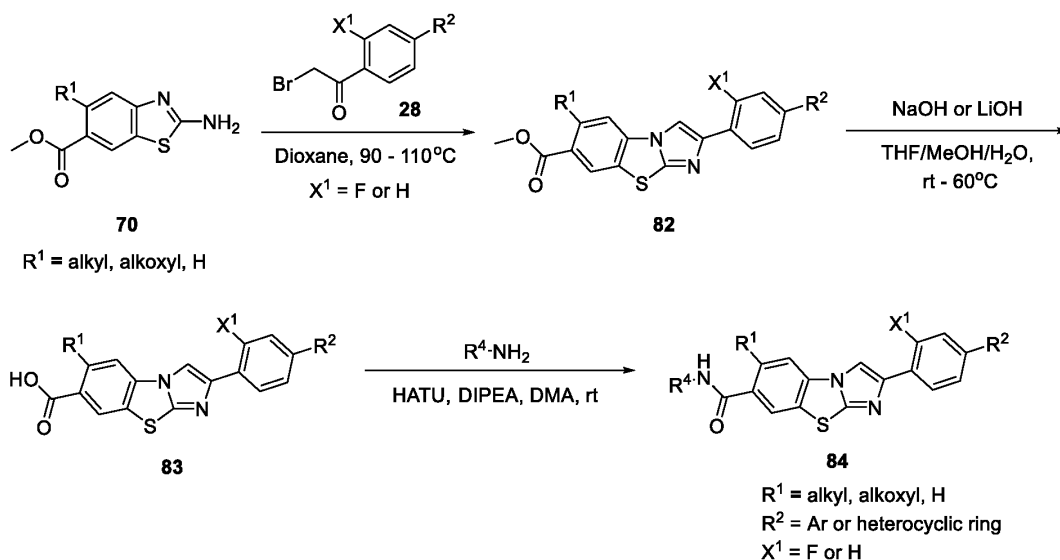


[00296] The *N*-Boc protecting group of **73** was directly removed to generate compounds **76** as a free base or salt.



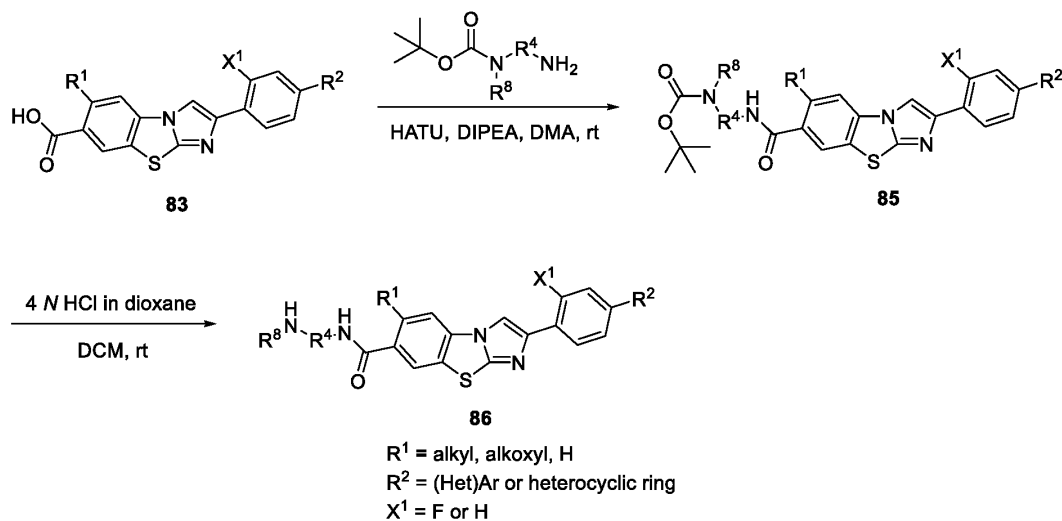
Scheme 29. General synthesis of benzo[d]imidazo[2,1-*b*]thiazole analogues **81**.

[00297] Compounds **70** were reacted with *tert*-butyl 2 bromoacetate at elevated temperature to generate intermediates **77**. The *tert*-butyl ester of **77** was hydrolyzed by trifluoroacetic acid to generate carboxylic acid compounds **78**, which were treated with phosphoryl tribromide to generate bromo acid compounds **79**. Amide coupling reaction of **79** with various amines generated bromo amide common intermediates **80**. A Suzuki cross-coupling reaction of **80** with aromatic boronic acids or borates produced the final benzo[d]imidazo[2,1-*b*]thiazole analogues **81** as a free base or as the hydrochloride salt.



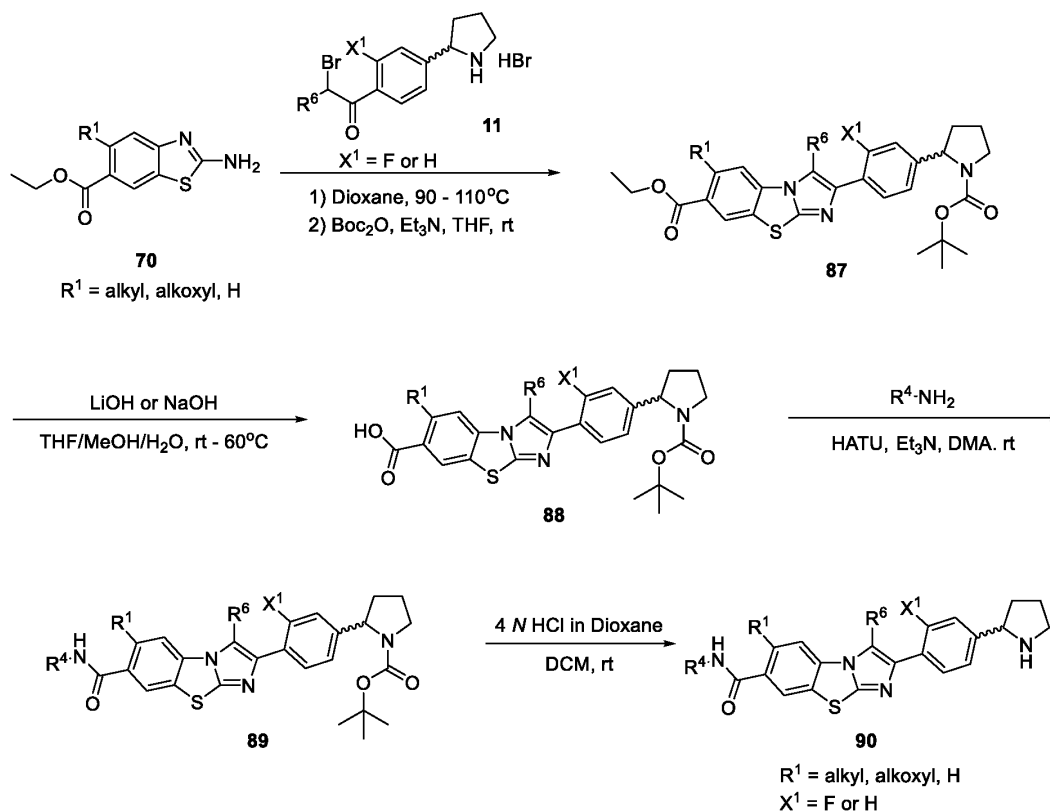
Scheme 30. General synthesis of benzo[d]imidazo[2,1-*b*]thiazole analogues **84**.

[00298] Final compounds **84** were synthesized from compounds **70** following the same synthetic sequence as in Scheme 26.



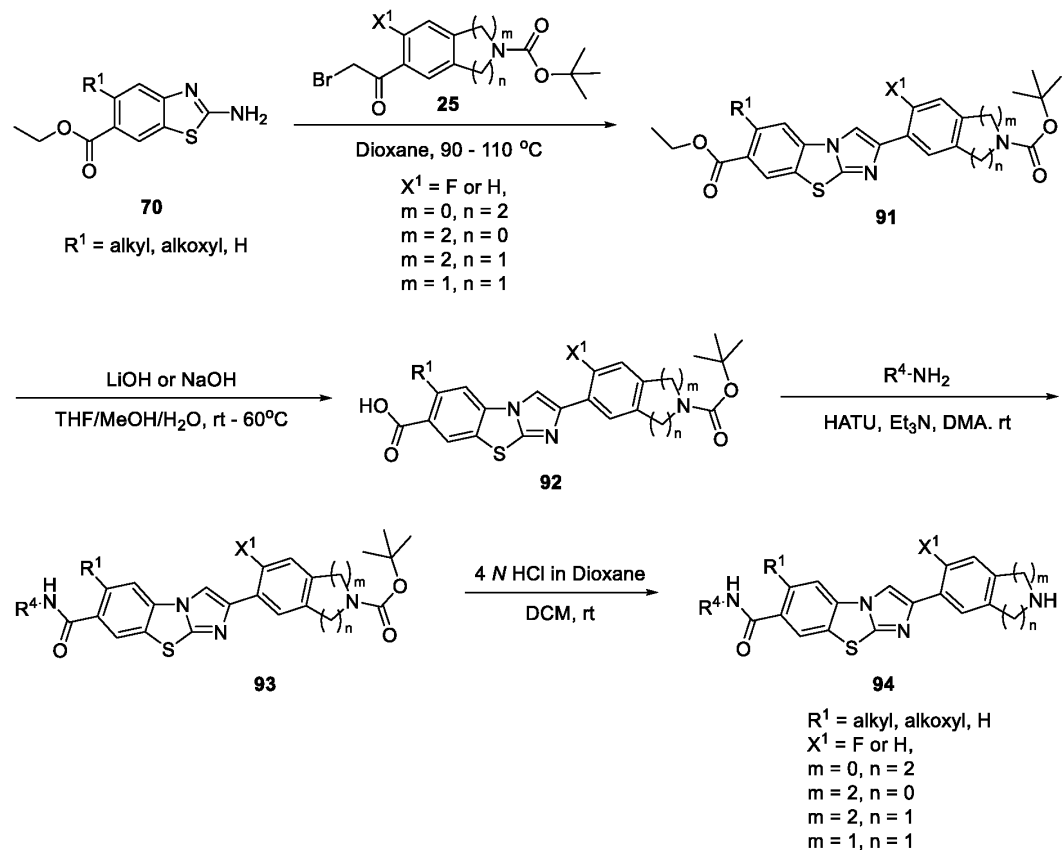
Scheme 31. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **86**.

- 5 [00299] An amide coupling reaction was performed on acids **83** with various amines to generate amides **85**. The *N*-Boc protecting group of **85** was removed to generate benzo[d]imidazo[2,1-b]thiazole analogues **86** as the free base or as a hydrochloride salt.



Scheme 32. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **90**.

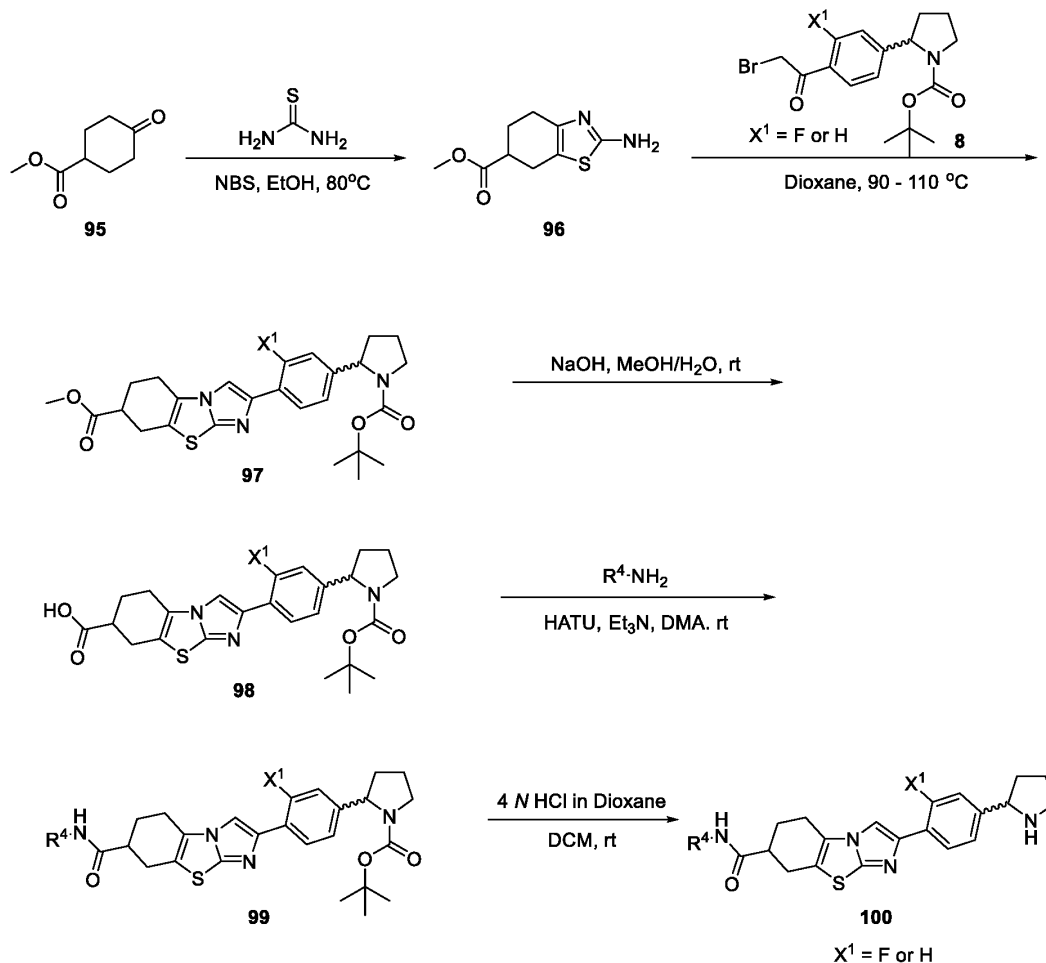
[00300] The first step of the synthesis involves a cyclization followed by protecting the endo-amine as the Boc carbamate *in-situ* to generate esters **87**. The final compounds **90** were isolated as the free base or as the hydrochloride salt following the same synthetic sequence as in **Scheme 26**. Chiral resolution was performed on amide compounds **89** if required.



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Scheme 33. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **94**.

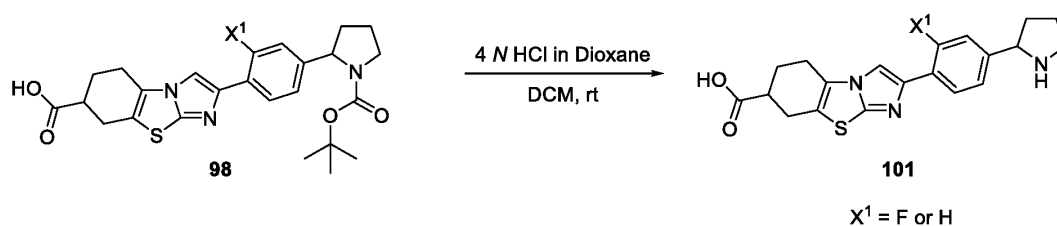
[00301] The final compounds **94** were synthesized from compounds **70** following the same synthetic sequence as in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt.



Scheme 34. General synthesis of imidazo[2,1-*b*]thiazole analogues **100**.

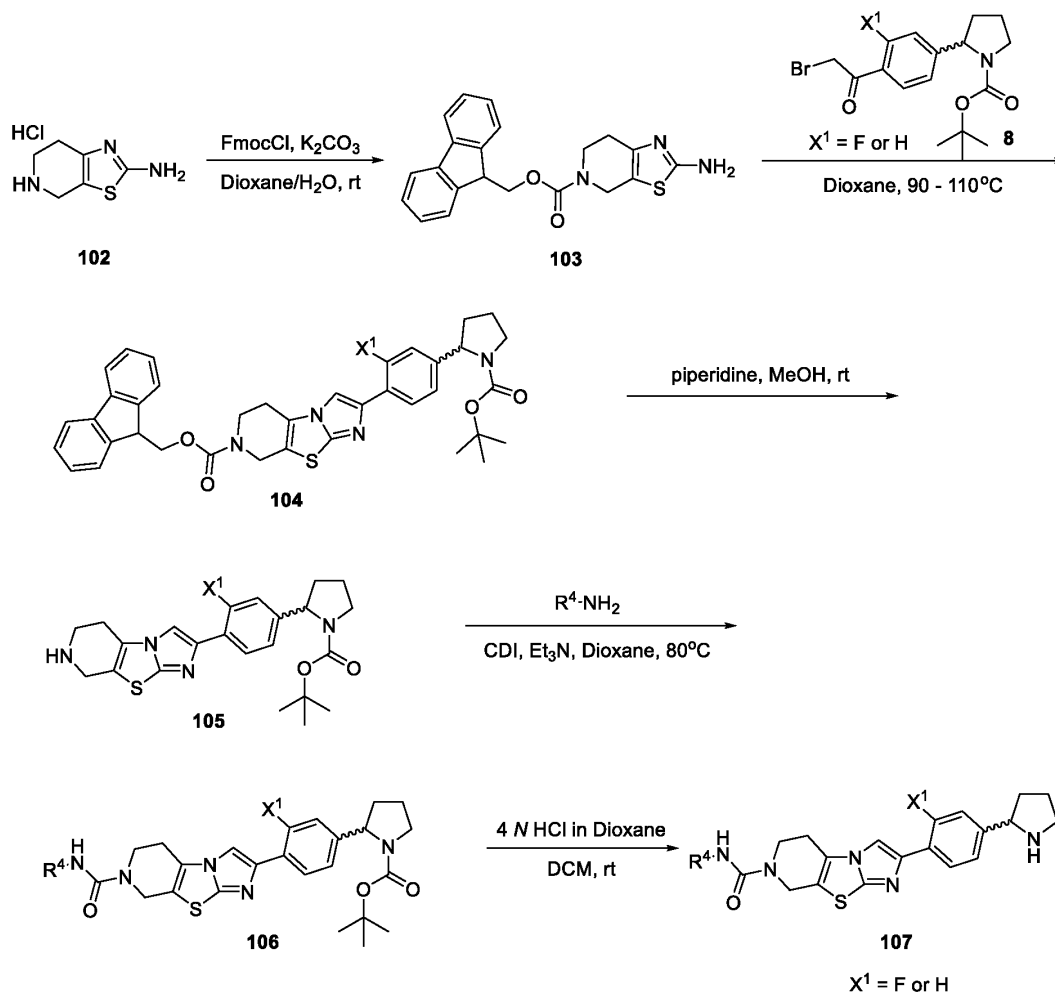
[00302] A cyclisation reaction with ketone **95** and thiourea gave 2-aminothiazole **96**. The final compounds **100** were isolated as the free base or as the hydrochloride salt, following the same synthetic sequence applied in **Scheme 26**.

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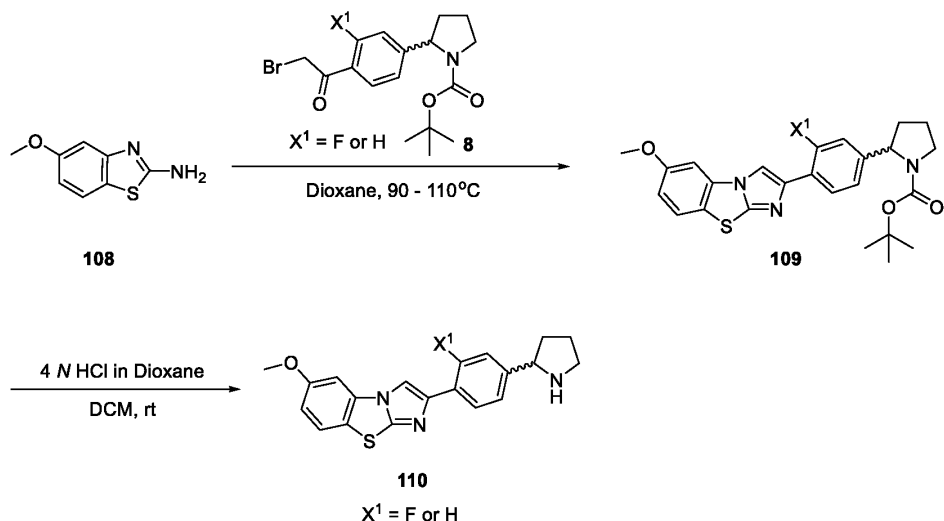
Scheme 35. General synthesis of imidazo[2,1-*b*]thiazole analogues **101**.

[00303] The *N*-Boc of compounds **98** was removed to generate compounds **101** as the free base or as a hydrochloride salt.



Scheme 36. General synthesis of imidazo[2,1-*b*]thiazole analogues **107**.

[00304] The cyclic amine of compound **102** was protected as the Fmoc carbamate to generate compound **103**. It was reacted with intermediates **8** to generate intermediates **104**. The Fmoc group was removed with piperidine to generate unprotected amine **105**. Urea **106** was formed from amine **105** and various amines. The *N*-Boc protecting group was removed to generate final compounds **107** as a free base or as the hydrochloride salt.



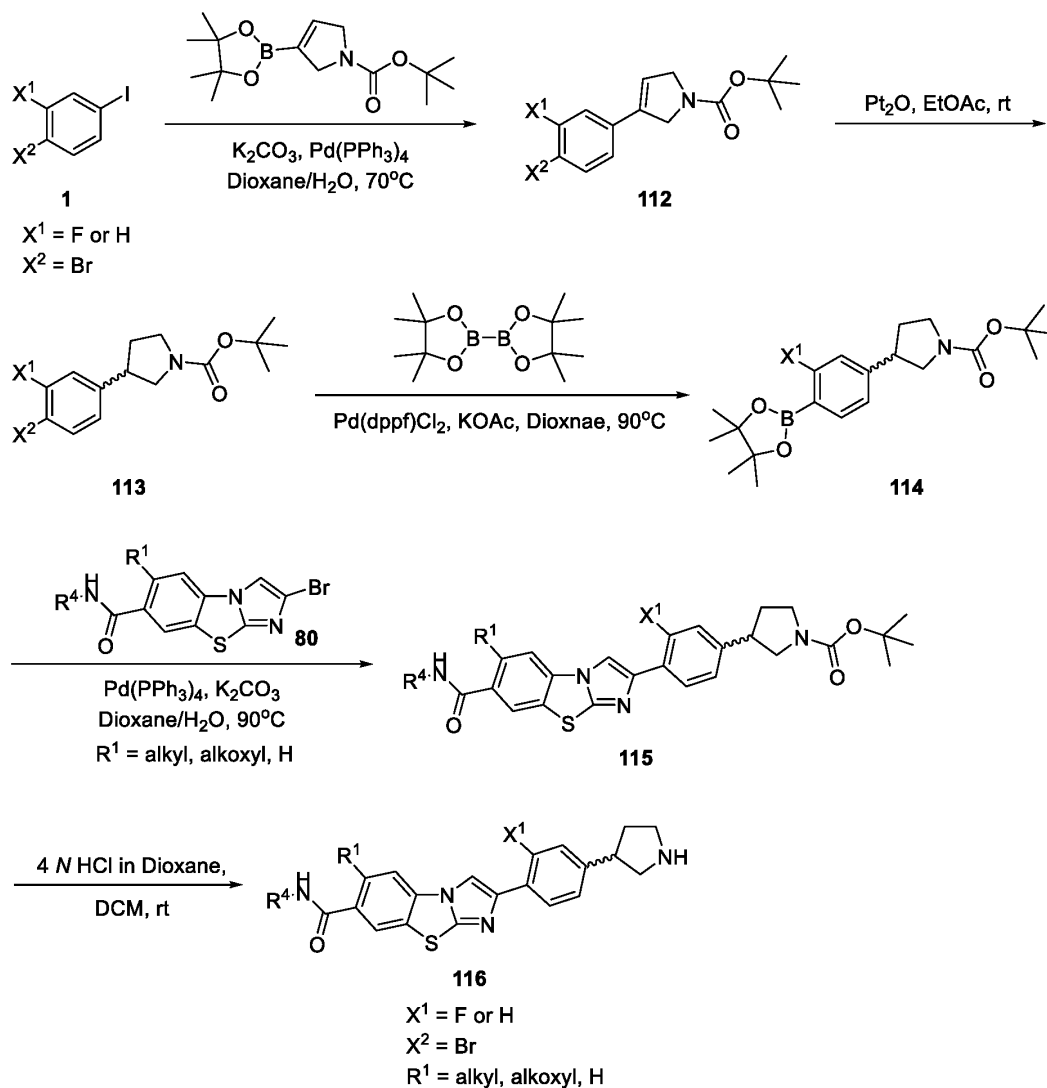
Scheme 37. General synthesis of benzo[d]imidazo[2,1-*b*]thiazole analogues **110**.

[00305] Compounds **110** were synthesized from commercial available 5-methoxybenzo[d]thiazol-2-amine, **108**, following the same synthetic sequence as in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt.



Scheme 38. General synthesis of benzo[d]imidazo[2,1-*b*]thiazole analogues **111**.

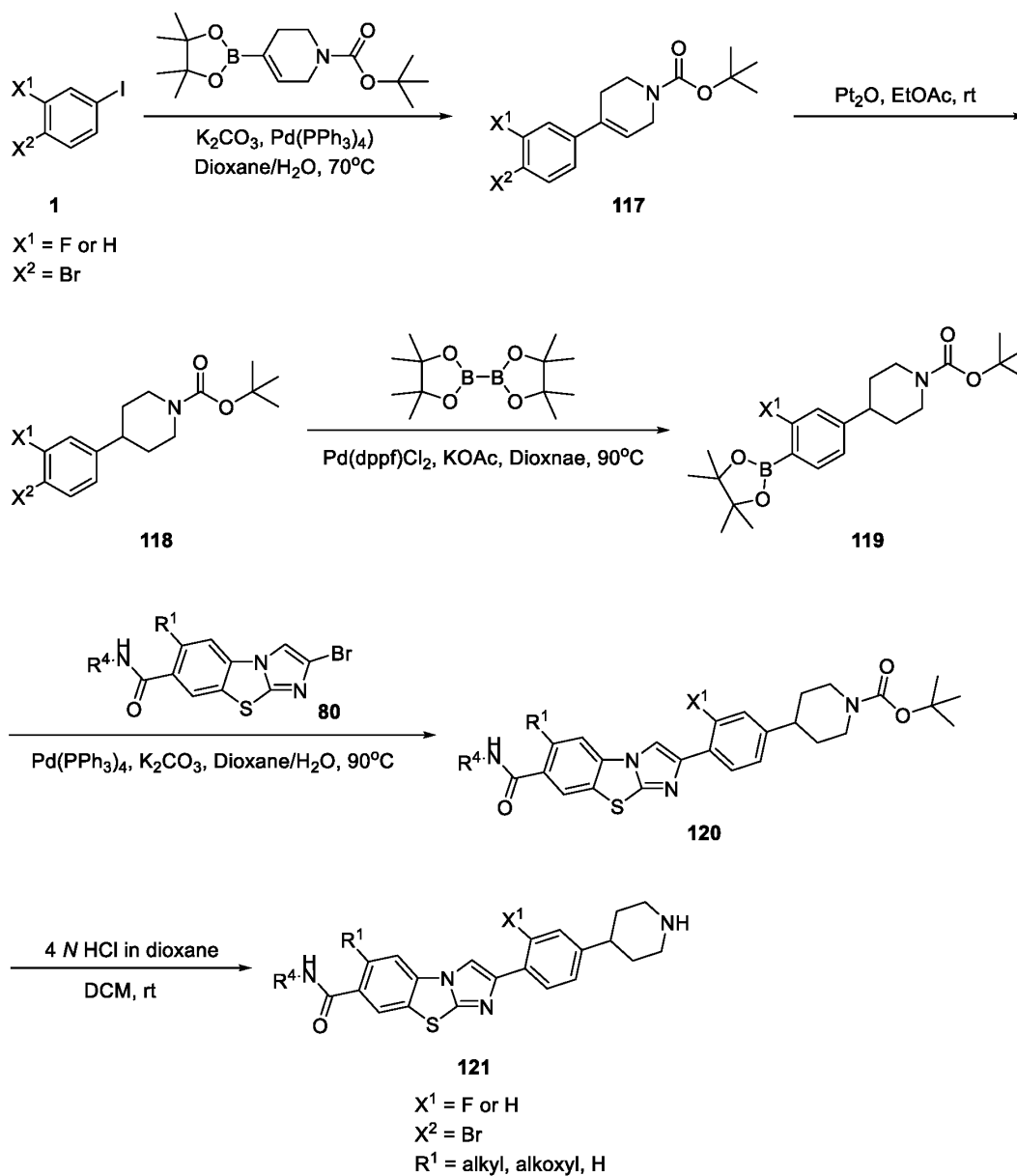
[00306] Methyl group of compounds **109** was removed by tribromoborane to generate compounds **111** as the free base or as the hydrochloride salt.



Scheme 39. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **116**.

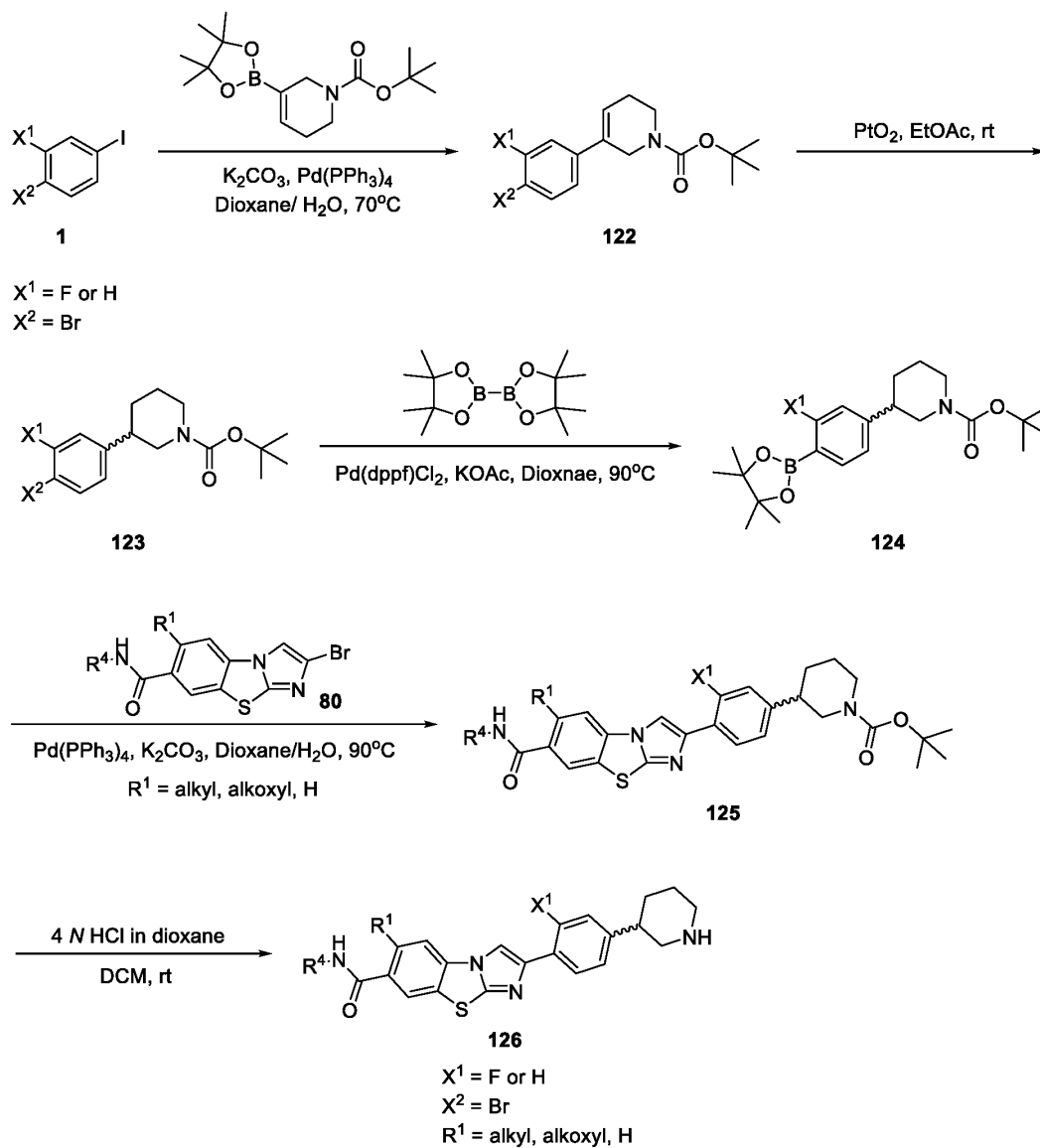
[00307] A Suzuki cross-coupling reaction of **1** with *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate produced the olefin intermediates **112**.

- 5 Reduction of the olefin by hydrogenation gave intermediates **113**. The Miyaura borylation reaction on intermediates **113** generated boronic ester intermediates **114**, which were subject to a second Suzuki cross-coupling reaction with intermediates **80** to produce intermediates **115**. The *N*-Boc protecting group was removed produced final compounds **116** as the free base or as the hydrochloride salt. Chiral resolution was performed on amides **115** to generate final enantiomers if required.



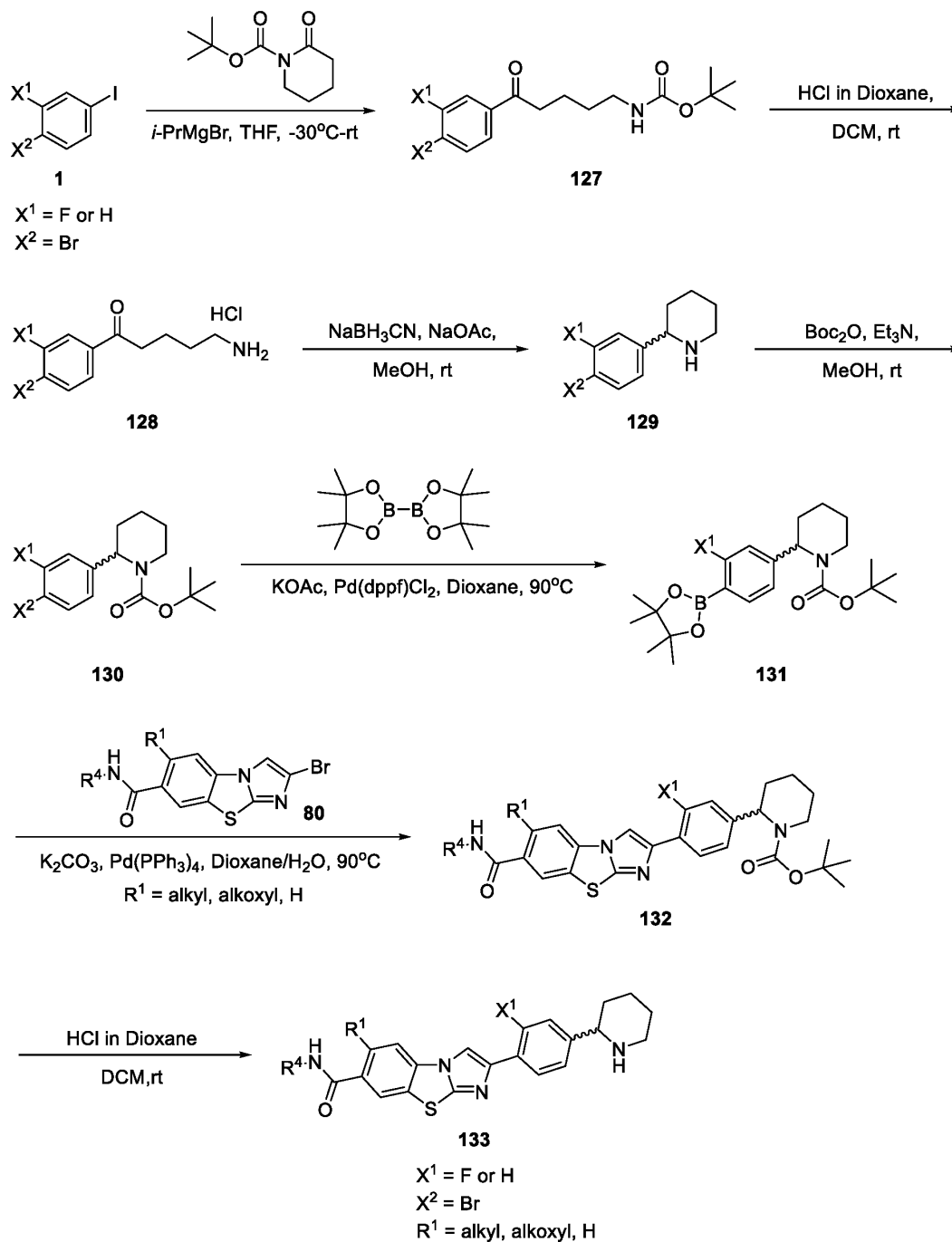
Scheme 40. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **121**.

[00308] The final compounds **121** were synthesized from compounds **1** following the same synthetic sequence as in **Scheme 39**. The compounds were isolated as the free base or as the hydrochloride salt.



Scheme 41. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **126**.

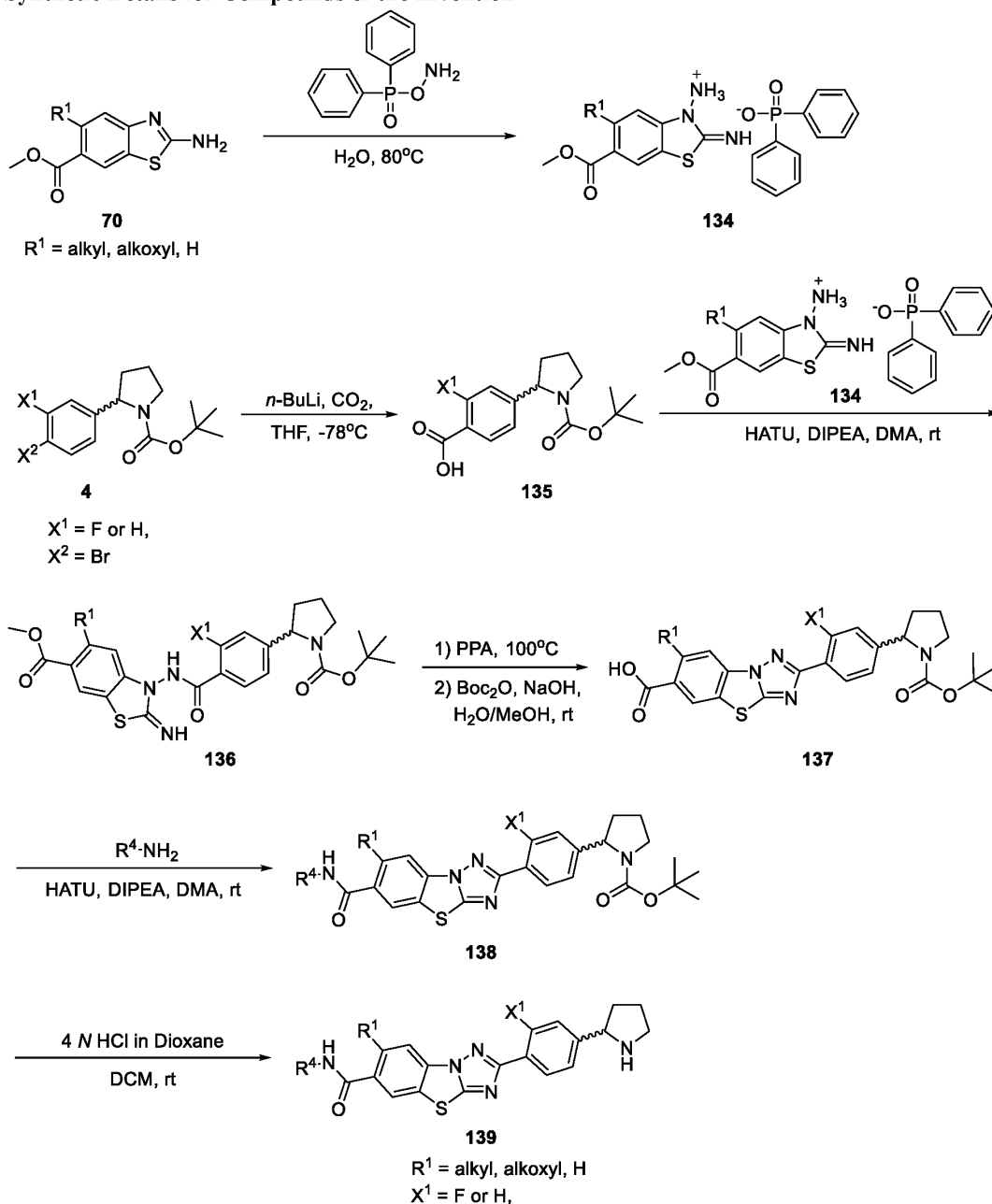
[00309] The final compounds **126** were synthesized from compounds **1** following the same synthetic sequence as in **Scheme 39**. The compounds were isolated as the free base or as the hydrochloride salt. Chiral resolution was performed on amides **125** to generate final enantiomers if required.



Scheme 42. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **133**.

[00310] Intermediates **130** were synthesized from compounds **1** following the same synthetic sequence as in **Scheme 10**. The final compounds **133** were synthesized from compounds **130** following the same synthetic sequence as in **Scheme 39**. The compounds were isolated as the free base or as the hydrochloride salt. Chiral resolution was performed on amides **132** to generate final enantiomers if required.

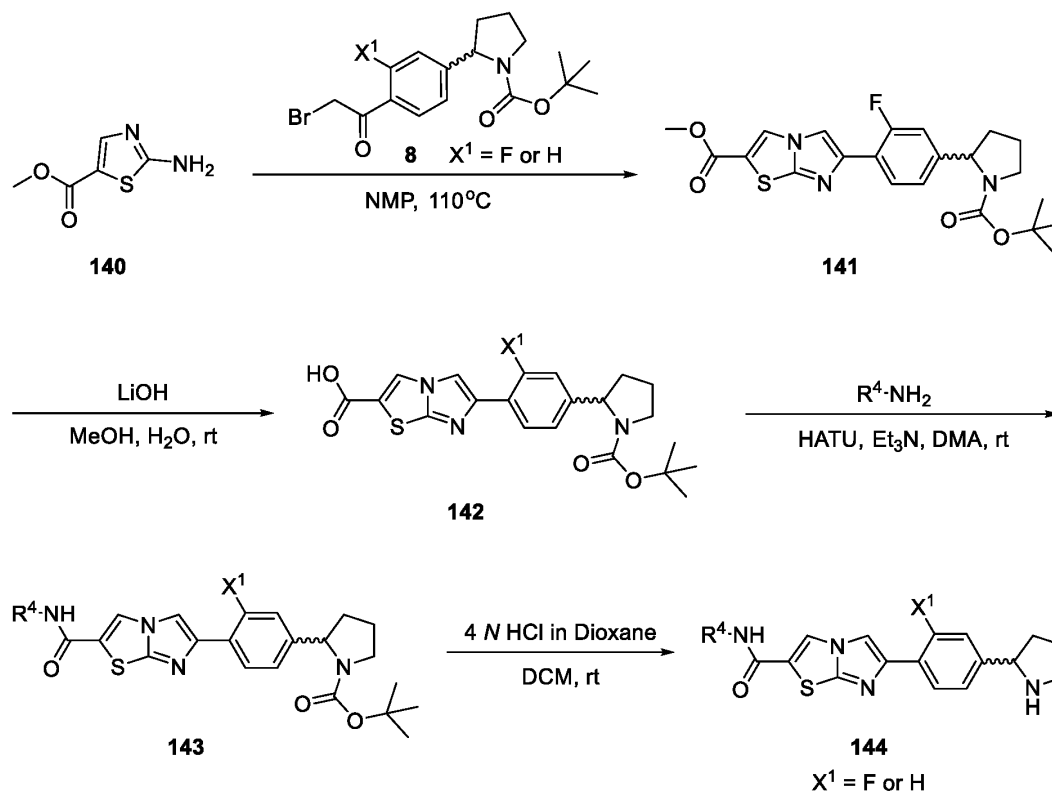
Synthetic Details for Compounds of the Invention



Scheme 43. General synthesis of benzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole analogues **139**.

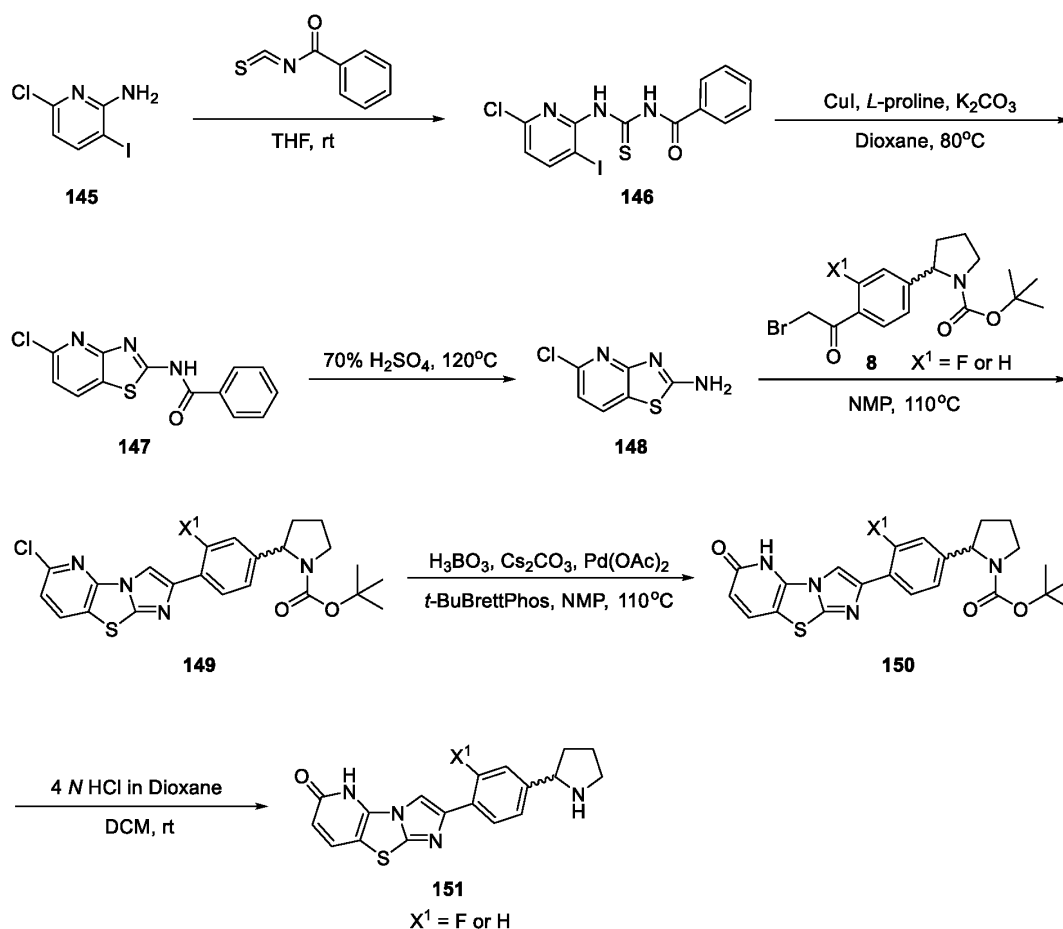
[00311] Common intermediates ammonium salts **134** were synthesized from 2-aminobenzothiazoles **70** and (aminooxy)diphenylphosphine oxide. Intermediates **4** were subjected to lithium-halogen exchange with *n*-butyl lithium at low temperature followed by treatment with dry ice to yield carboxylic acid intermediates **135**. A condensation reaction between **135** and **134** generated amide intermediates **136**. Intramolecular cyclization reaction was performed in polyphosphoric acid and then the *N*-Boc protecting group was reintroduced *in-situ* to generate carboxylic acids **137**. The final compounds **139** were synthesized from

intermediates **137** following the same synthetic sequence as in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt.



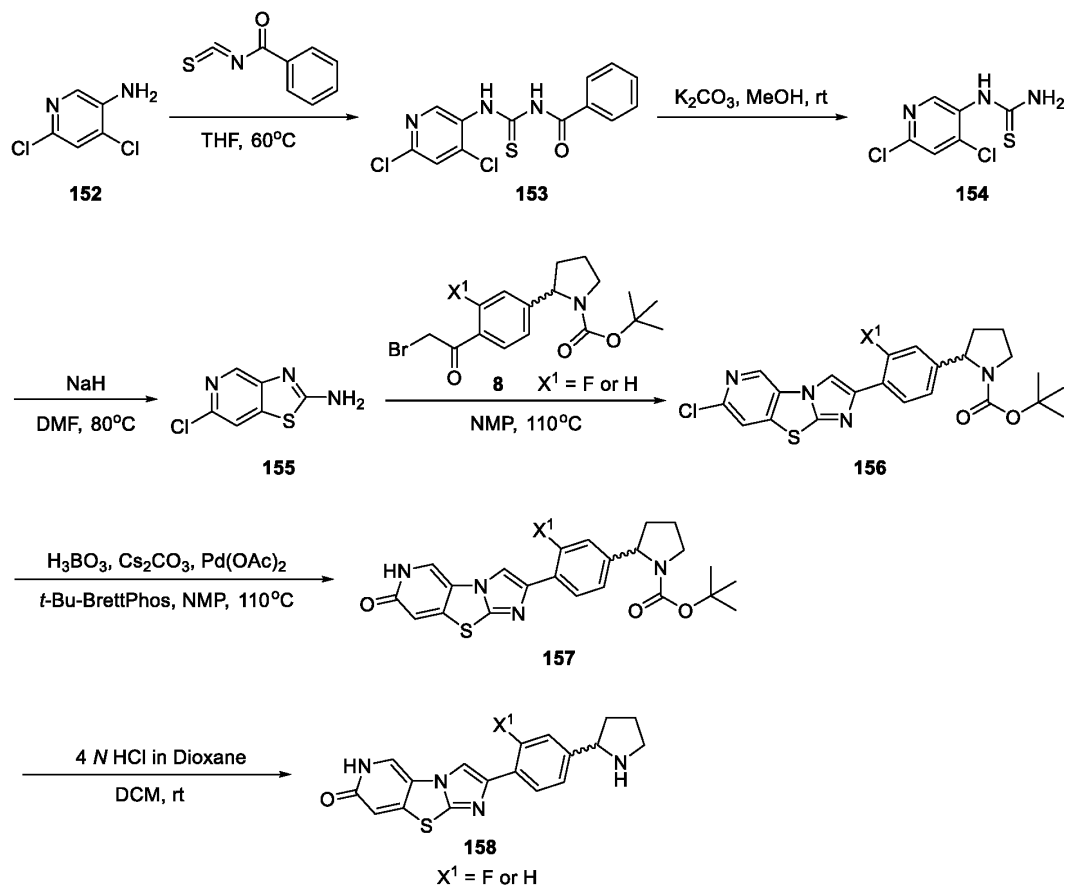
Scheme 44. General synthesis of imidazo[2,1-*b*]thiazole analogues **144**.

- 5 [00312] The final compounds **144** were synthesized from compounds **140** following the same synthetic sequence as in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt.



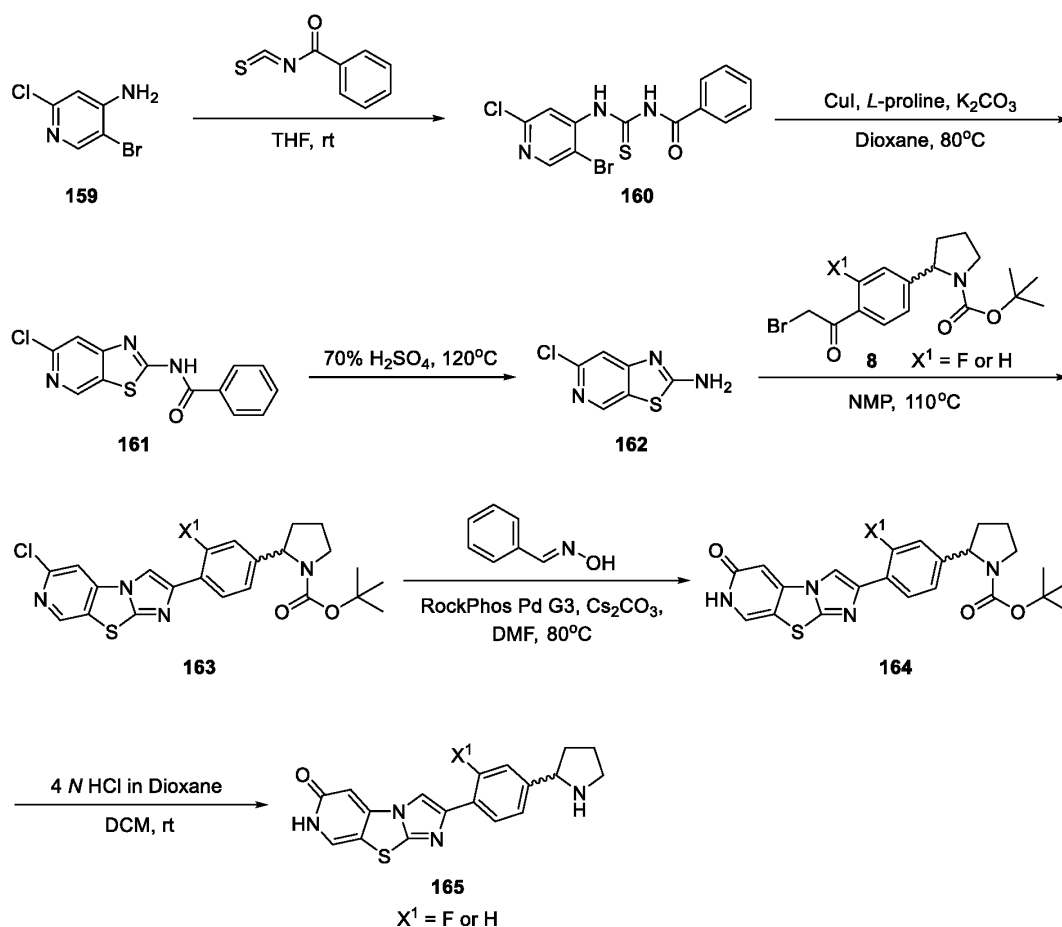
Scheme 45. General synthesis of analogues **151**.

[00313] Compound **145** was reacted with benzoyl isothiocyanate to generate thiourea intermediates **146**. An intramolecular cyclization reaction catalyzed by copper iodide produced intermediates **147**. Hydrolysis under acidic conditions generated thiazole intermediates **148**. Cyclization with compound **8** at elevated temperature generated intermediates **149**. The *o*-chloride of the pyridine ring was hydrolyzed by boric acid/palladium catalyst system to generate pyridone compounds **150**. The *N*-Boc protecting group was removed to produce final compounds **151** as the free base or as the hydrochloride salt. Chiral resolution was performed on *N*-Boc protected compounds **150** to generate final enantiomers if required.



Scheme 46. General synthesis of analogues **158**.

[00314] Intermediate **153** was synthesized from compound **152** and benzoyl isothiocyanate. The benzoyl group was removed by potassium carbonate/methanol treatment to generate thiourea **154**. Treatment with strong base at elevated temperature produced cyclized intermediate **155**. The final compounds **158** were synthesized from compound **155** following the same synthetic sequence as in **Scheme 45**. The compounds were isolated as the free base or as the hydrochloride salt. Chiral resolution was performed on *N*-Boc protected compounds **157** to generate final enantiomers if required.

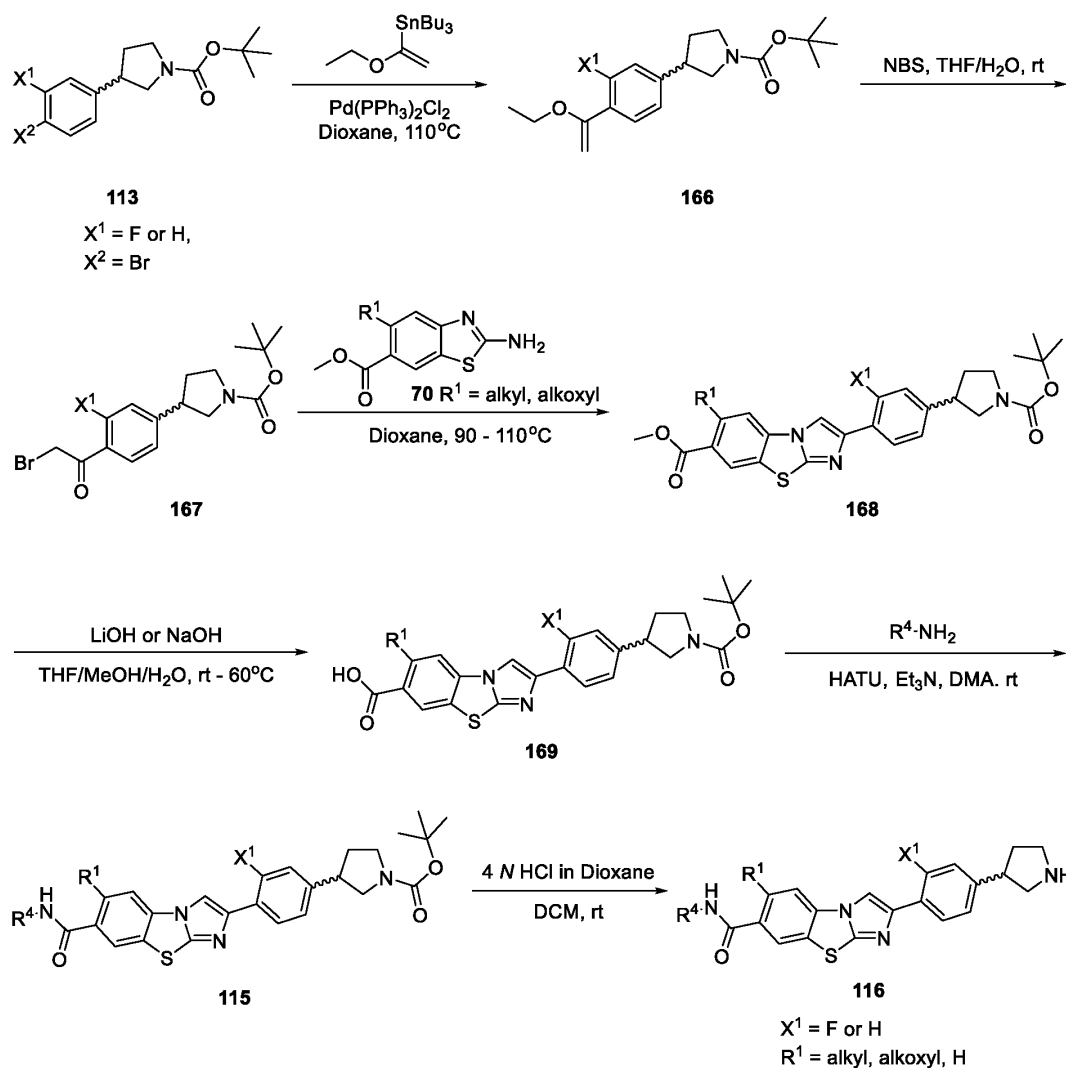


Scheme 47. General synthesis of analogues **165**.

[00315] Compounds **163** were synthesized from compound **159** following the same synthetic sequence as in **Scheme 45**. Pyridone compounds **164** were synthesized from *o*-chloride pyridines **163** using an alternative benzaldehyde oxime/palladium catalyst system. The *N*-Boc protecting group was removed to produce final compounds **165** as the free base or as the hydrochloride salt. Chiral resolution was performed on *N*-Boc protected compounds **164** to generate final enantiomers if required.

Synthetic Details for Additional Compounds of the Invention

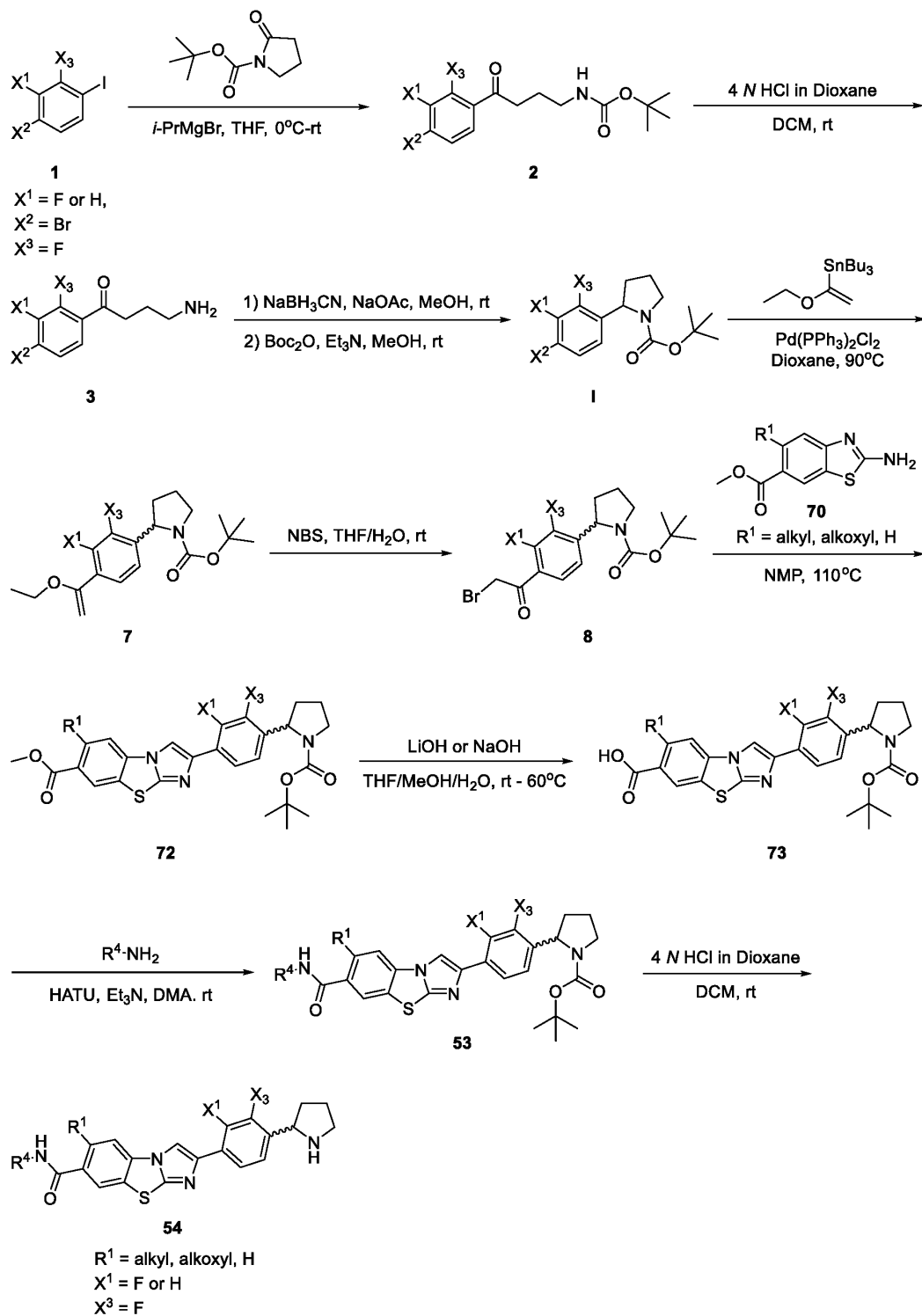
- 10 [00316] Compounds **72** (**Scheme 26**) were synthesized from aniline compounds **66** (**Scheme 26**) following the descriptions outlined in **Scheme 21**. The ester was hydrolyzed to form carboxylic acids **73**. Amide coupling reactions on **73** with various amines gave amides **53**. The *N*-Boc protecting group was removed by 4 *N* hydrochloride in 1,4-dioxane to generate benzo[*d*]imidazo[2,1-*b*]thiazole analogues **54** as a free base or as the hydrochloride salt (**Scheme 26**).



Scheme 48. An alternative synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **116**.

[00317] α -bromoketone analogues **167** were synthesized from building blocks **113** following the same synthetic sequence described in **Scheme 10**. The final compounds **116** were synthesized from α -bromoketone analogues **167** following the same synthetic sequence outlined in **Scheme 26**. The compounds

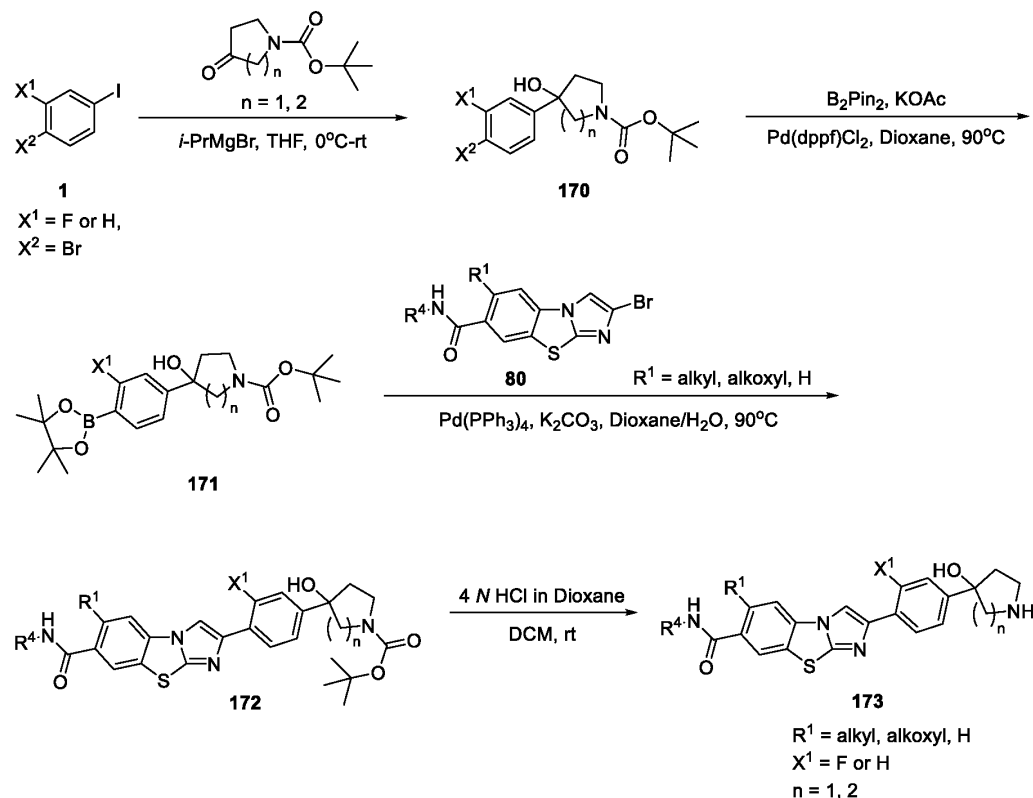
5 were isolated as the free base or as the hydrochloride salt.



Scheme 49. Another alternative synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole analogues **54**.

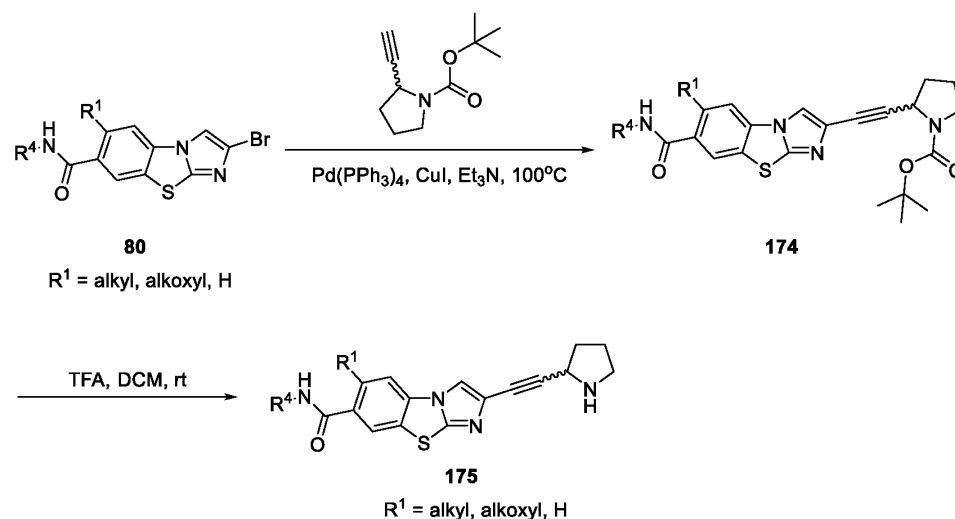
[00318] α -bromoketone analogues **8** were synthesized from building blocks **1**, following the same synthetic sequence described in **Scheme 10**. The final compounds **54** were synthesized from α -bromoketone

analogues **8** following the same synthetic sequence outlined in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt.



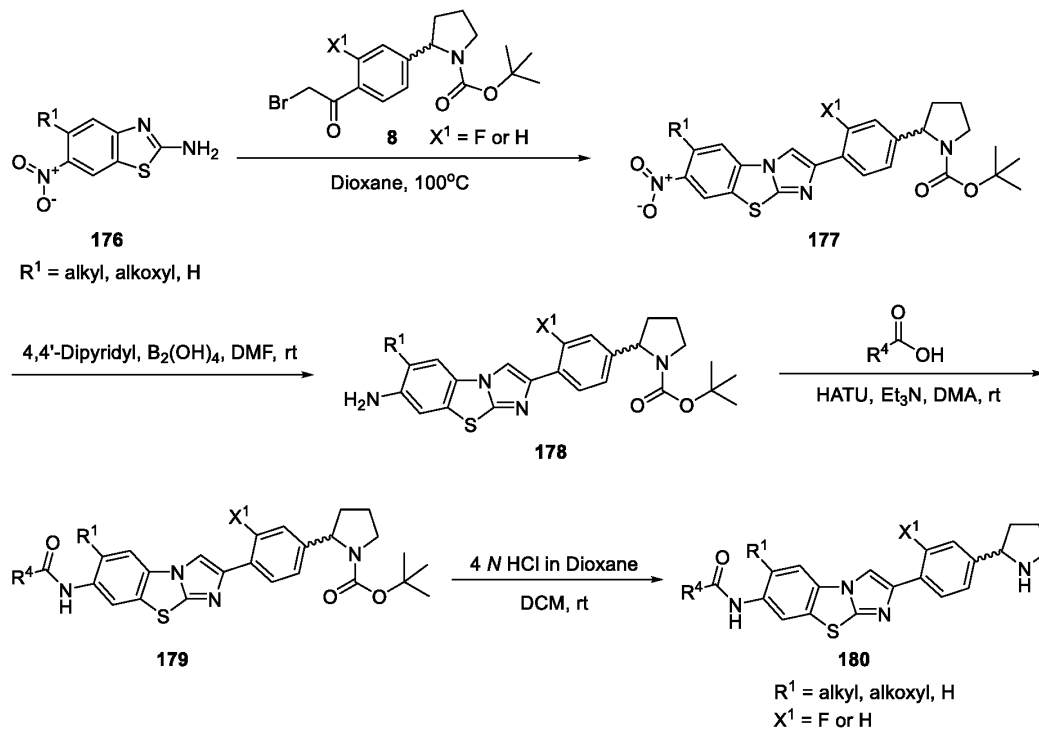
Scheme 50. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **173**.

- 5 [00319] Benzyl alcohol intermediates **170** were synthesized from building blocks **1**, following the same synthetic sequence described in **Scheme 10**. The final compounds **173** were synthesized from intermediates **170** following the same synthetic sequence outlined in **Scheme 39**. The compounds were isolated as the free base or as the hydrochloride salt.



- 10 **Scheme 51.** General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **175**.

[00320] Sonogushira cross-coupling reaction was performed between intermediates **80** and the terminal alkynyl compound shown to provide intermediates **174**. The *N*-Boc protecting group was removed using trifluoroacetic acid in dichloromethane to produce the final benzo[*d*]imidazo[2,1-*b*]oxazole analogues **175** as a free base.

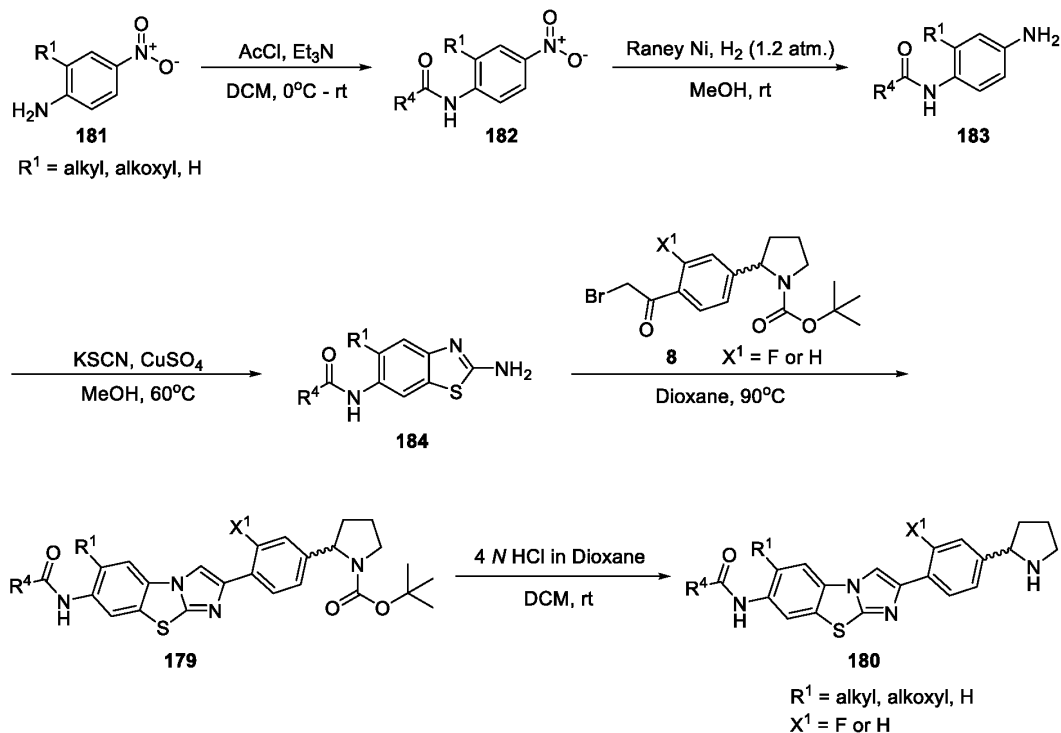


5

Scheme 52. General synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole analogues **180**.

[00321] Intermediates **177** were synthesized from 2-aminobenzothiazole building blocks **176** and α -bromoketone analogue **8** at elevated temperatures. Nitro group was reduced by using hypodiboric acid to generate aniline intermediates **178**. The final compounds **180** were synthesized from intermediates **178** following the same synthetic sequence described in **Scheme 26**. The compounds were isolated as the free base or as the hydrochloride salt. Chiral resolution was performed on amide compounds **179** if required.

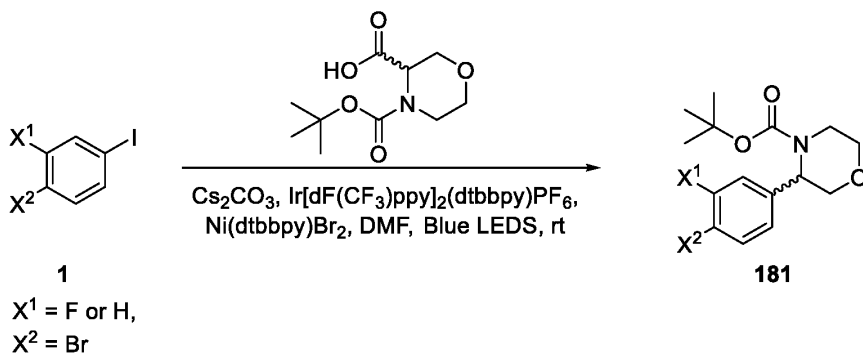
10



Scheme 53. An alternative synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **180**.

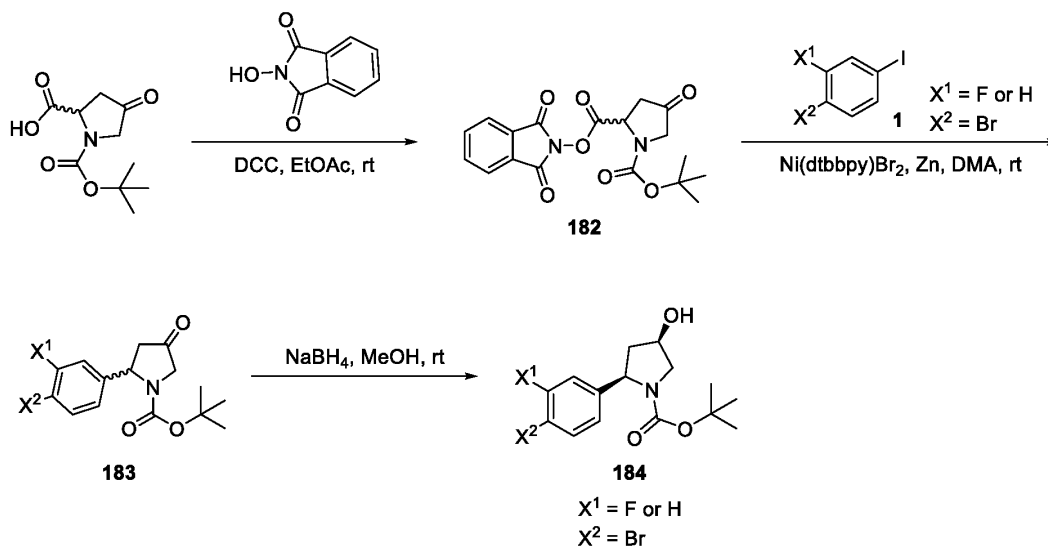
[00322] Reaction of anilines **181** with acyl chlorides gave amide intermediates **182**. Nitro group was reduced by hydrogenation to produce aniline intermediates **183**. The final compounds **180** were synthesized from intermediates **183** following the same synthetic sequence described in **Scheme 21**. The compounds were isolated as the free base or as the hydrochloride salt. Chiral resolution was performed on amide compounds **179** if required.

Synthetic Details for Additional Compounds of the Invention



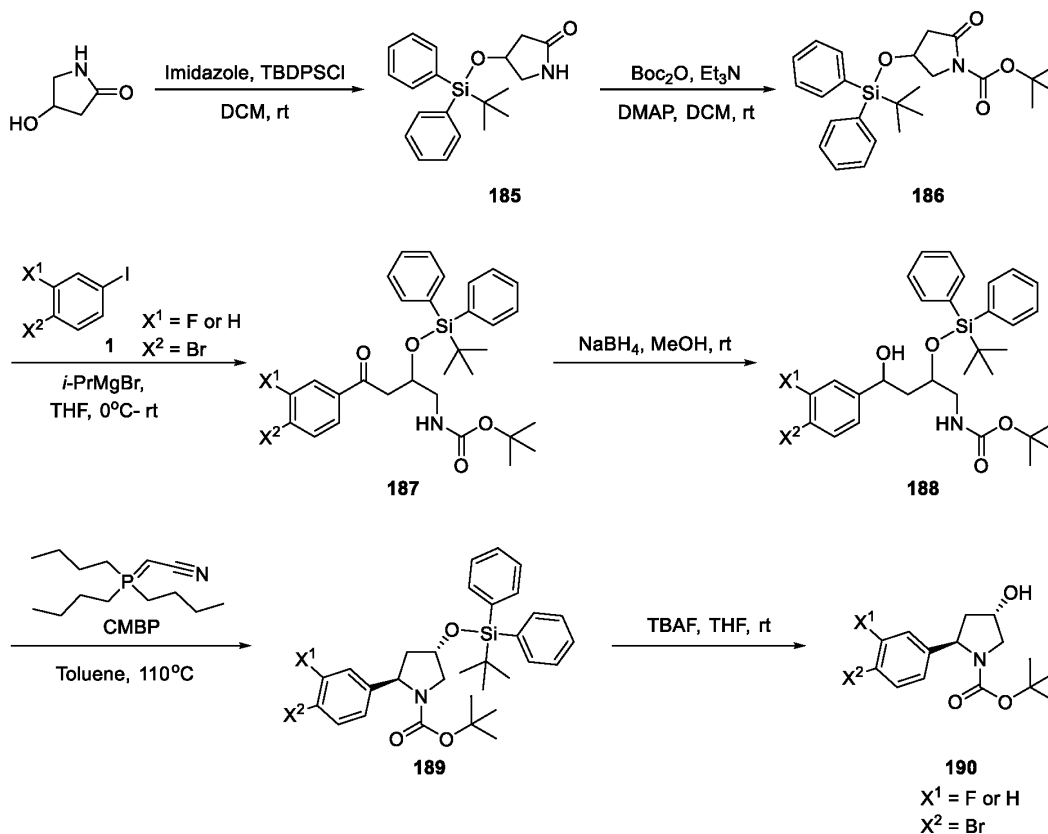
Scheme 54. General synthesis of right-hand side fragment bromobenzene analogue **181**.

[00323] Intermediate **181** was synthesized from starting material **1** and the corresponding commercial available carboxylic acids, 3*R*/3*S*-4-(1,1-Dimethylethyl)-3,4-morpholinedicarboxylate using photoredox cross-coupling reaction.



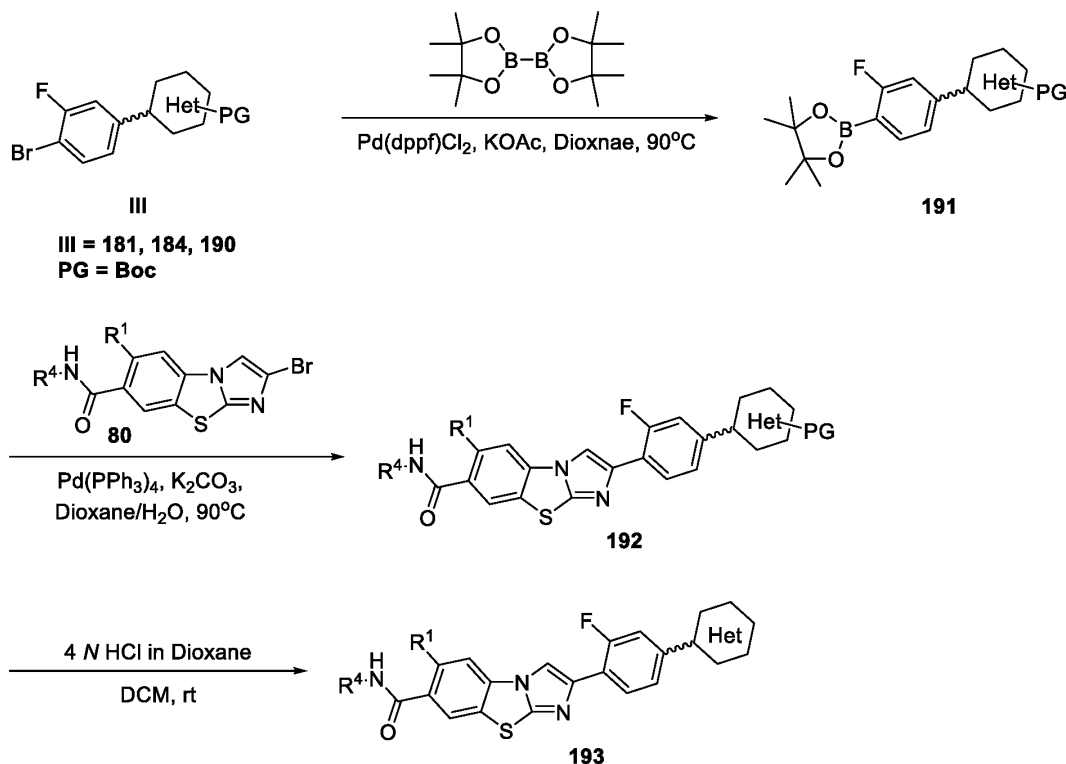
Scheme 55. General synthesis of right-hand side fragment bromobenzene analogue **184**.

[00324] Condensation reaction was performed on commercially available carboxylic acids, 2R/2S-1-(1,1-Dimethylethyl)-4-oxo-1,2-pyrrolidinedicarboxylate with 2-hydroxyisoindoline-1,3-dione to generate activated ester intermediate **182**. It was followed by a cross-coupling reaction with compound **1** to generate ketone analogue **183**. The ketone **183** was reduced to the *cis* alcohol intermediate **184**.



Scheme 56. General synthesis of right-hand side fragment bromobenzene analogue **190**.

[00325] The hydroxyl group of 4-hydroxypyrrolidin-2-one was protected with a TBDPS group to generate intermediate **185**. It was followed by Boc protection of the lactam to generate doubly protected intermediate **186**. The ketone intermediate **187** was synthesized following the same procedure described in **Scheme 10** step 1. The ketone was then reduced to alcohol intermediate **188**. A Mitsunobu reaction was performed on **188** using the reagent CMBP to selectively generate *trans* intermediate **189**. The TBDPS group was removed by TBAF to generate intermediate **190**.



Scheme 57. General synthesis of benzo[d]imidazo[2,1-b]thiazole analogues **193**.

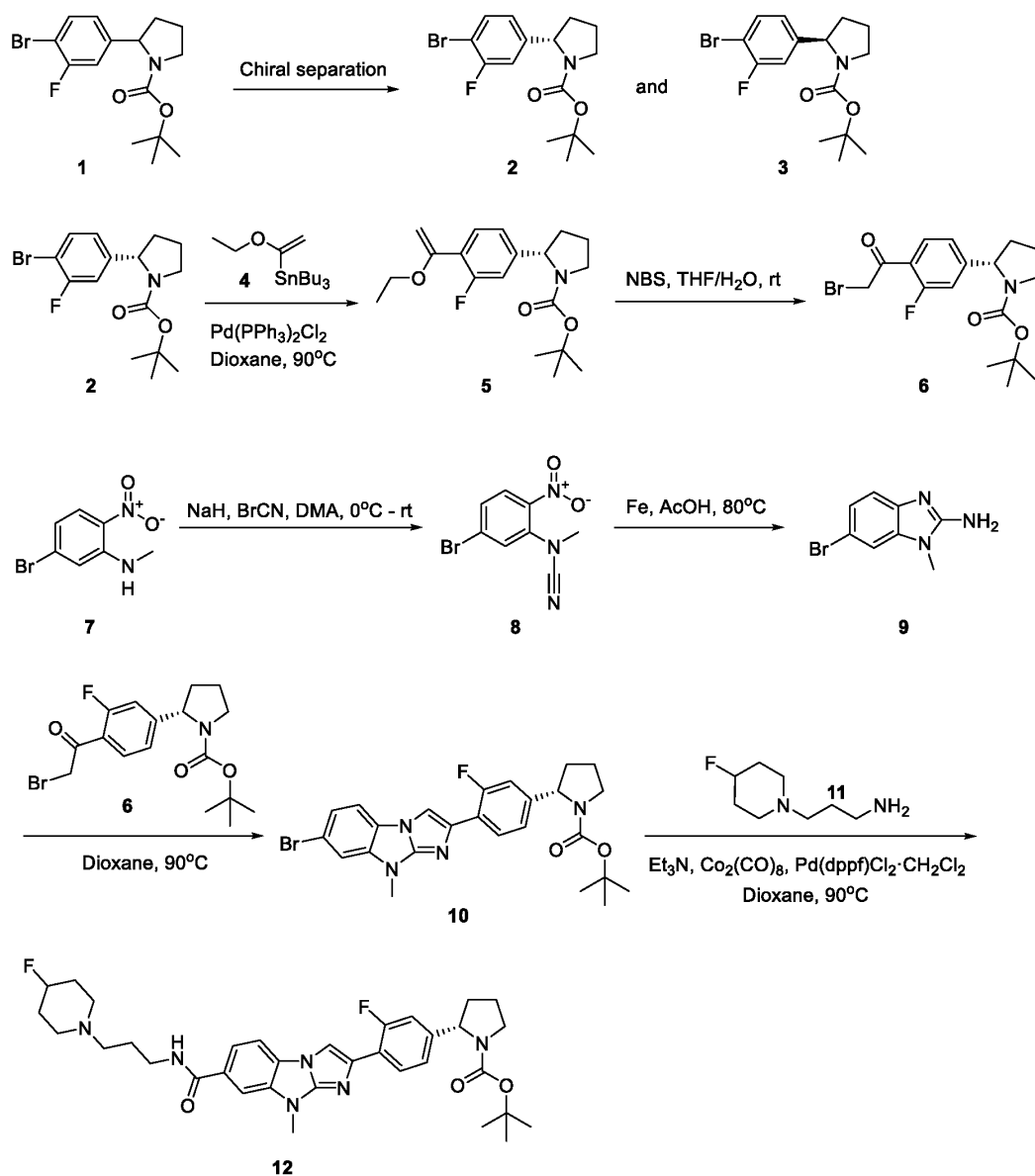
[00326] Right-hand side fragment bromobenzene analogues **III** were converted to their corresponding boronic esters/acids analogues **191** via Miyaura borylation reaction. Cross-coupling reactions with bromides **80** gave an array of protected intermediates **192** possessing differential substitution at the right-hand terminus. The *N*-Boc protecting group was removed by 4 *N* hydrochloride in 1,4-dioxane to generate benzo[d]imidazo[2,1-b]thiazole analogues **193** as a free base or as the hydrochloride salt. Chiral resolution was performed on *N*-Boc protected compounds **192** to generate final enantiomers if required.

EXAMPLE 3

Synthetic details of Specific Compounds of the Invention (Schemes 58-79)

Intermediate Preparations

Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 58

- 5 *Synthesis of tert-butyl (S)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate and tert-butyl (R)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (2, 3 Scheme 58)*

[00327] *Tert*-butyl 2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (10.46 g, 30.39 mmol) was chirally separated by Prep-SFC with the following conditions; Column: (S,S)-Whelk-O1 Kromasil, 3 x 25 cm, 5 μm; Mobile Phase A: carbon dioxide, Mobile Phase B: methanol (plus 0.1% 2 N ammonia - methanol); Flow rate: 100 mL/min; Gradient: isocratic 20% B in 6 min; Detector: UV 254 nm; The faster eluting peak at 2.7 min was collected and concentrated under reduced pressure to afford *tert*-butyl (S)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate as a pink solid.

Yield 5.00 g (48%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 7.2, 8.0 Hz, 1H), 6.97 (dd, *J* = 2.0, 9.6 Hz, 1H), 6.88 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.90-4.75 (m, 1H), 3.65-3.50 (m, 2H), 2.40-2.30 (m, 1H), 1.97-1.84 (m, 2H), 1.83-1.74 (m, 1H), 1.49-1.25 (m, 9H). m/z: [ESI⁺] 344, 346 (M+H)⁺.

The slower eluting peak at 4.35 min was collected and concentrated under reduced pressure to afford *tert*-butyl (*R*)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate as a pink solid.

Yield 5.00 g (48%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 7.2, 8.0 Hz, 1H), 6.97 (dd, *J* = 2.0, 9.6 Hz, 1H), 6.88 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.90-4.75 (m, 1H), 3.65-3.50 (m, 2H), 2.40-2.30 (m, 1H), 1.97-1.84 (m, 2H), 1.83-1.74 (m, 1H), 1.49-1.25 (m, 9H). m/z: [ESI⁺] 344, 346 (M+H)⁺.

10 *Synthesis of tert-butyl (S)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (5, Scheme 58)*

[00328] To a stirred solution of *tert*-butyl (*S*)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (4.50 g, 13.07 mmol) in 1,4-dioxane (80 mL) were added tributyl(1-ethoxyethenyl)stannane (7.12 g, 19.71 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.90 g, 1.28 mmol) in one portion sequentially at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 2 h at 90°C. The resulting mixture was cooled to room temperature and diluted with an aqueous solution of saturated sodium bicarbonate (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic phase was washed with brine (200 mL) and dried with anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give *tert*-butyl (*S*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate as a brown oil. The crude product was used in the next step directly without further purification.

Yield 4.10 g (crude). ¹H NMR not run. m/z: [ESI⁺] 336 (M+H)⁺.

25 *Synthesis of tert-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (6, Scheme 58)*

[00329] To a stirred solution of crude *tert*-butyl (*S*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (4.10 g) in tetrahydrofuran (45 mL) and water (1 mL) was added *N*-bromosuccinimide (3.28 g, 18.43 mmol) in one portion at room temperature. The reaction solution was stirred for 1 h at this temperature. The resulting solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0%-20% of ethyl acetate in petroleum ether) to afford *tert*-butyl (*S*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate as a light yellow oil.

Yield 4.42 g (88% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.11 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.00-4.76 (m, 1H), 4.52 (d, *J* = 2.4 Hz, 2H), 3.72-3.50 (m, 2H), 2.46-2.28 (m, 1H), 1.96-1.87 (m, 2H), 1.87-1.77 (m, 1H), 1.47-1.25 (m, 9H). m/z: [ESI⁺] 330, 332 (M+H-56)⁺.

Synthesis of N-(5-bromo-2-nitrophenyl)-N-methylcyanamide (8, Scheme 58)

[00330] To a stirred solution of 5-bromo-*N*-methyl-2-nitroaniline (2.00 g, 8.66 mmol) in *N,N*-dimethylacetamide (20 mL) was added sodium hydride (60% dispersion in mineral oil, 0.69 g, 17.25 mmol) portionwise over 3 min at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h. To the above solution was added a solution of cyanic bromide (1.83 g, 17.28 mmol) in *N,N*-dimethylacetamide (1 mL) dropwise over 5 min. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched by an aqueous solution of saturated ammonium chloride (20 mL) at room temperature and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (2 x 20 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1%-50% of ethyl acetate in petroleum ether) to afford *N*-(5-bromo-2-nitrophenyl)-*N*-methylcyanamide as a yellow solid.

Yield: 2.00 g (90%). ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.57 (dd, *J* = 2.1, 8.7 Hz, 1H), 3.37 (s, 3H). m/z: [ESI⁺] 256, 258 (M+H)⁺.

Synthesis of 6-bromo-1-methyl-1H-benzo[d]imidazol-2-amine (9, Scheme 58)

[00331] To a stirred solution of *N*-(5-bromo-2-nitrophenyl)-*N*-methylcyanamide (2.00 g, 7.81 mmol) in acetic acid (20 mL) was added iron powder (2.18 g, 39.03 mmol) in one portion at room temperature. The reaction mixture was stirred for 2 h at 80°C under a nitrogen atmosphere. The mixture was allowed to cool to room temperature and filtered. The filtered cake was washed with ethyl acetate (2 x 10 mL). The combined filtrates were concentrated under reduced pressure. The residue was diluted with water (40 mL), extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was triturated with dichloromethane (20 mL). The precipitated solids were collected by filtration, washed with dichloromethane (2 x 10 mL) and dried in a vacuum oven to afford 6-bromo-1-methyl-1H-benzo[d]imidazol-2-amine as an off-white solid.

Yield: 1.50 g (85%). ¹H NMR (300 MHz, CDCl₃) δ 7.35 (t, *J* = 1.2 Hz, 1H), 7.07-7.03 (m, 2H), 6.55 (br s, 2H), 3.49 (s, 3H). m/z: [ESI⁺] 226, 228 (M+H)⁺.

Synthesis of tert-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (10, Scheme 58)

[00332] To a stirred solution of 6-bromo-1-methyl-1H-benzo[d]imidazol-2-amine (702 mg, 3.105 mmol) in 1,4-dioxane (10 mL) was added *tert*-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (600 mg, 1.553 mmol) at room temperature. The reaction solution was stirred for 16 h at 90°C under a nitrogen atmosphere. The solution was cooled to room temperature and purified directly by reverse phase flash column chromatography with the following conditions; Column: Spherical C18, 20 - 40 μm, 330 g; Mobile Phase A: water (plus 10 mmol ammonium bicarbonate); Mobile Phase B: acetonitrile; Flow rate: 80 mL/min; Gradient: 65% - 85% B

in 20 min; Detector: UV 254 nm. The fractions containing desired product were collected at 82% B and concentrated under reduced pressure to afford *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate as a yellow solid.

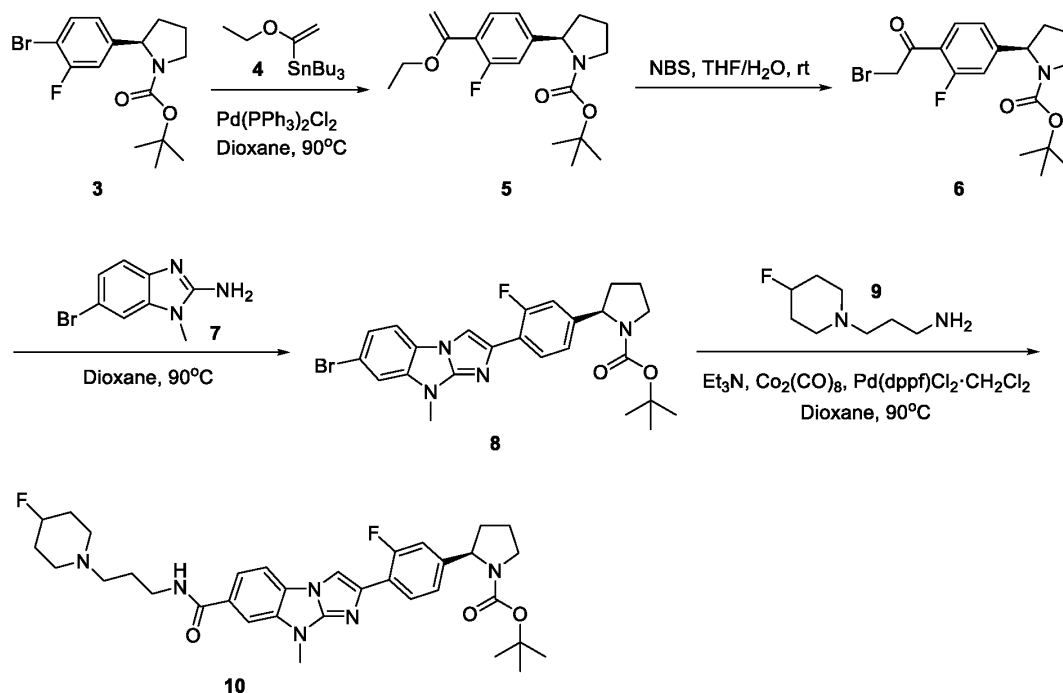
Yield 600 mg (75%). ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.82 (s, 1H), 7.47-7.41 (m, 2H), 7.34 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.07 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.03-4.77 (m, 1H), 3.84 (s, 3H), 3.73-3.49 (m, 2H), 2.43-2.26 (m, 1H), 1.99-1.82 (m, 2H), 1.82-1.60 (m, 1H), 1.49-1.25 (m, 9H). m/z: [ESI⁺] 513, 515 (M+H)⁺.

Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (12, Scheme 58)

[00333] To a stirred solution of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (300 mg, 0.584 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (187 mg, 1.167 mmol) in 1,4-dioxane (10 mL) were added triethylamine (177 mg, 1.749 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (48 mg, 0.059 mmol) and dicobalt octacarbonyl (60 mg, 0.175 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 16 h at 90°C. The mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% of methanol in dichloromethane) to afford *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a brown oil.

Yield 200 mg (55%). ¹H NMR (400 MHz, CDCl₃) δ 8.31-8.22 (m, 1H), 8.20-8.12 (m, 1H), 8.01-7.92 (m, 1H), 7.89-7.80 (m, 1H), 7.71-7.61 (m, 1H), 7.61-7.52 (m, 1H), 7.11-7.03 (m, 1H), 6.99-6.94 (m, 1H), 5.03-4.66 (m, 2H), 3.90 (s, 3H), 3.71-3.60 (m, 4H), 2.86-2.50 (m, 6H), 2.41-2.26 (m, 1H), 2.03-1.81 (m, 9H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 621 (M+H)⁺.

Synthesis of *Tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9-*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 59

5

Synthesis of *tert*-butyl (*R*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (**5**, *Scheme 59*)

[00334] Compound *tert*-butyl (*R*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl (*R*)-2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (2.35 g, 6.83 mmol) and tributyl(1-ethoxyethenyl)stannane (3.70 g, 10.24 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was extracted and concentrated under reduced pressure as a brown oil.

Yield 2.00 g (crude). ¹H NMR not run. m/z: [ESI⁺] 336 (M+H)⁺.

15 Synthesis of *tert*-butyl (*R*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (**6**, *Scheme 59*)

[00335] Compound *tert*-butyl (*R*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl (*R*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (2.00 g, crude) and *N*-bromosuccinimide (1.70 g, 9.55 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light yellow oil.

Yield 2.21 g (84% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.11 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.00-4.76 (m, 1H), 4.52 (d, *J* = 2.4 Hz, 2H),

3.72-3.50 (m, 2H), 2.46-2.28 (m, 1H), 1.96-1.87 (m, 2H), 1.87-1.77 (m, 1H), 1.47-1.25 (m, 9H). m/z: [ESI⁺] 330, 332 (M+H-56)⁺.

Synthesis of tert-butyl (R)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (8, Scheme 59)

[00336] Compound *tert*-butyl (R)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 6-bromo-1-methyl-1H-benzo[d]imidazol-2-amine (0.70 g, 3.10 mmol) and *tert*-butyl (R)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (0.60 g, 1.55 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a yellow solid.

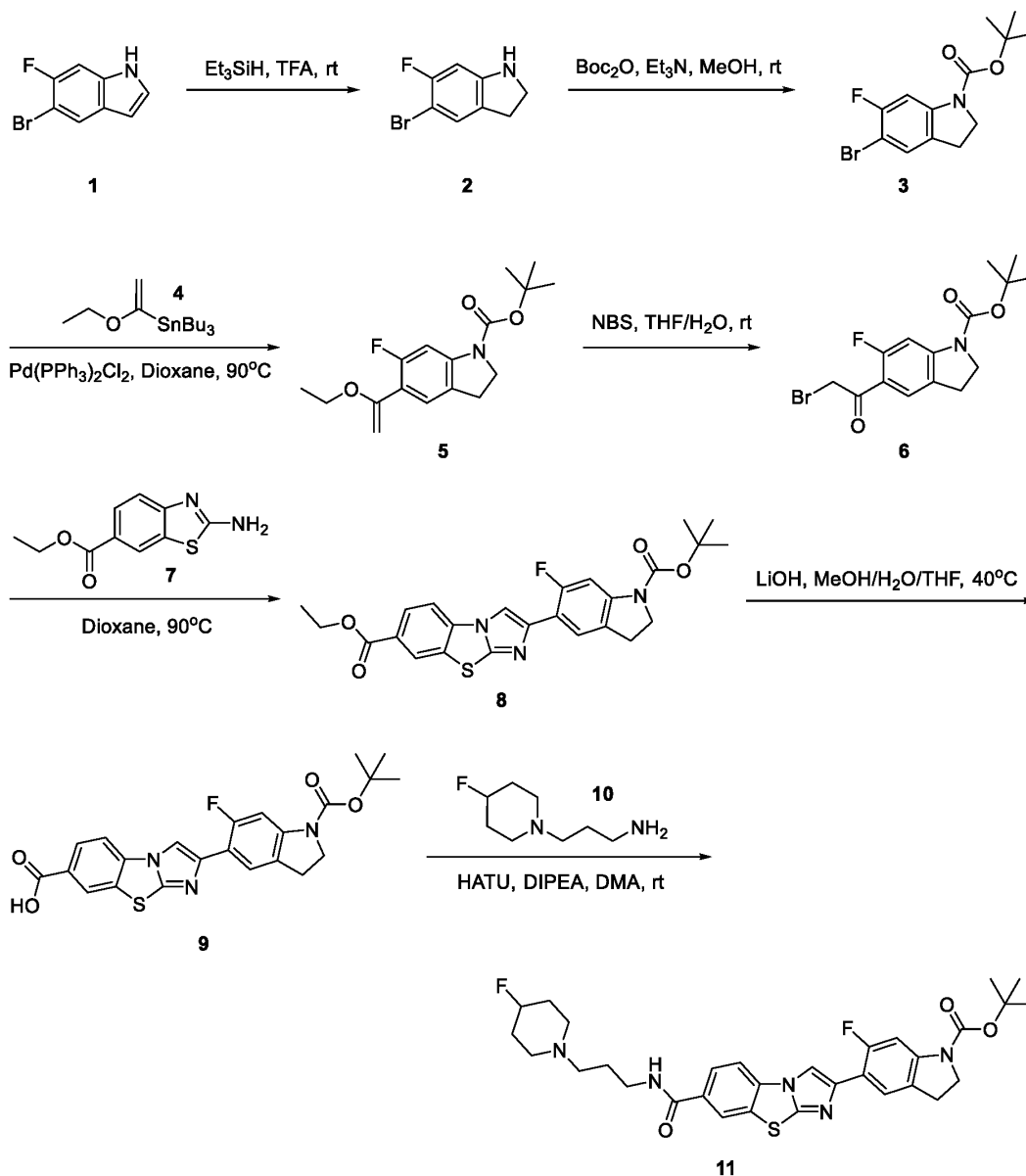
Yield 0.65 g (82%). ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.82 (s, 1H), 7.47-7.41 (m, 2H), 7.34 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.07 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.03-4.77 (m, 1H), 3.84 (s, 3H), 3.73-3.49 (m, 2H), 2.43-2.26 (m, 1H), 1.99-1.82 (m, 2H), 1.82-1.60 (m, 1H), 1.49-1.25 (m, 9H). m/z: [ESI⁺] 513, 515 (M+H)⁺.

Synthesis of tert-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (10, Scheme 59)

[00337] Compound *tert*-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl (R)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (0.30 g, 0.58 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (0.19 g, 1.18 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate, and was isolated as a brown oil.

Yield 0.20 g (55%). ¹H NMR (400 MHz, CDCl₃) δ 8.31-8.22 (m, 1H), 8.20-8.12 (m, 1H), 8.01-7.92 (m, 1H), 7.89-7.80 (m, 1H), 7.71-7.61 (m, 1H), 7.61-7.52 (m, 1H), 7.11-7.03 (m, 1H), 6.99-6.94 (m, 1H), 5.03-4.66 (m, 2H), 3.90 (s, 3H), 3.71-3.60 (m, 4H), 2.86-2.50 (m, 6H), 2.41-2.26 (m, 1H), 2.03-1.81 (m, 9H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 621 (M+H)⁺.

Synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate



Scheme 60

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*Synthesis of 5-bromo-6-fluoroindoline trifluoroacetic acid (2, **Scheme 60**)*

[00338] A solution of 5-bromo-6-fluoro-1*H*-indole (1.00 g, 4.67 mmol) and triethylsilane (1.63 g, 14.02 mmol) in trifluoroacetic acid (10 mL) was stirred for 2 h at room temperature under a nitrogen atmosphere. The resulting solution was concentrated under reduced pressure to afford 5-bromo-6-fluoroindoline trifluoroacetic acid as a brown oil, which was used in the next step directly without further purification.

10

Yield 1.50 g (crude). ¹H NMR not run. m/z: [ESI⁺] 216, 218 (M+H)⁺.

Synthesis of tert-butyl 5-bromo-6-fluoroindoline-1-carboxylate (3, Scheme 60)

[00339] To a stirred solution of the above crude 5-bromo-6-fluoroindoline trifluoroacetic acid (1.50 g) and triethylamine (1.38 g, 13.64 mmol) in dichloromethane (15 mL) was added di-*tert*-butyl dicarbonate (2.98 g, 13.65 mmol) in one portion at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% of ethyl acetate in petroleum ether) to afford *tert*-butyl 6-bromo-5-fluoroindoline-1-carboxylate as a light yellow oil.

Yield 0.40 g (27% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.71 (s, 1H), 7.26 (d, *J* = 6.8 Hz, 1H), 4.03 (t, *J* = 8.8 Hz, 2H), 3.07 (t, *J* = 8.8 Hz, 2H), 1.57 (s, 9H). LCMS mass signal not determined.

Synthesis of tert-butyl 5-(1-ethoxyvinyl)-6-fluoroindoline-1-carboxylate (5, Scheme 60)

[00340] Compound *tert*-butyl 5-(1-ethoxyvinyl)-6-fluoroindoline-1-carboxylate was prepared from *tert*-butyl 5-bromo-6-fluoroindoline-1-carboxylate (400 mg, 1.265 mmol) and tributyl(1-ethoxyvinyl)stannane (685 mg, 1.897 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was extracted and concentrated under reduced pressure as a yellow solid.

Yield 400 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 308 (M+H)⁺.

Synthesis of tert-butyl 5-(2-bromoacetyl)-6-fluoroindoline-1-carboxylate (6, Scheme 60)

[00341] Compound *tert*-butyl 5-(2-bromoacetyl)-6-fluoroindoline-1-carboxylate was prepared from *tert*-butyl 5-(1-ethoxyvinyl)-6-fluoroindoline-1-carboxylate (400 mg, crude) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light brown solid.

Yield 200 mg (44% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 4.51 (d, *J* = 2.8 Hz, 2H), 4.08 (t, *J* = 8.8 Hz, 2H), 3.11 (t, *J* = 8.8 Hz, 2H), 1.60 (s, 9H). m/z: [ESI⁺] 358, 360 (M+H)⁺.

Synthesis of ethyl 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (8, Scheme 60)

[00342] Compound ethyl 2-(1-(*tert*-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from *tert*-butyl 5-(2-bromoacetyl)-6-fluoroindoline-1-carboxylate (200 mg, 0.558 mmol) and ethyl 2-aminobenzo[d]thiazole-6-carboxylate (124 mg, 0.558 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light brown solid.

Yield 140 mg (52%). ¹H NMR (400 MHz, DMSO) δ 8.68 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 3.6 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 1.6, 8.4 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.61-7.48 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.98 (t, J = 8.8 Hz, 2H), 3.11 (t, J = 8.8 Hz, 2H), 1.53 (s, 9H), 1.37 (t, J = 7.2 Hz, 3H). m/z: [ESI⁺] 482 (M+H)⁺.

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Synthesis of 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (9, Scheme 60)

[00343] A solution of ethyl 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (140 mg, 0.291 mmol) and lithium hydroxide (35 mg, 1.461 mmol) in tetrahydrofuran:methanol:water (4:4:1, 4.5 mL) was stirred for 16 h at 40°C. The resulting mixture was concentrated under reduced pressure. The residue was acidified to pH 6 with an aqueous solution of 0.5 N hydrochloric acid. The precipitated solids were collected by filtration, washed with acetonitrile (2 x 5 mL) and dried under reduced pressure to give 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid as a white solid.

15 Yield 120 mg (91%). ¹H NMR (400 MHz, DMSO) δ 13.18 (br s, 1H), 8.65 (d, J = 1.6 Hz, 1H), 8.60 (d, J = 3.6 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 1.6, 8.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.61-7.47 (m, 1H), 3.99 (t, J = 8.8 Hz, 2H), 3.11 (t, J = 8.8 Hz, 2H), 1.54 (s, 9H). m/z: [ESI⁺] 454 (M+H)⁺.

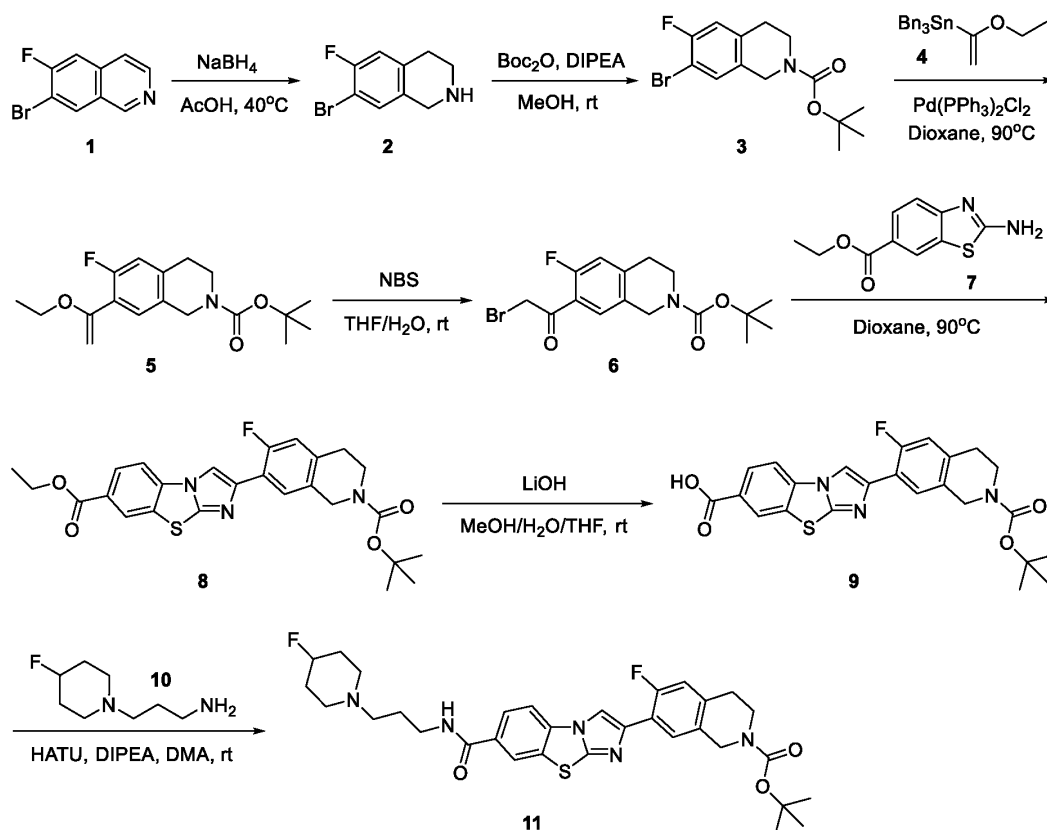
Synthesis of tert-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate (11, Scheme 60)

[00344] To a stirred solution of 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (120 mg, 0.265 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (151 mg, 0.397 mmol) in *N,N*-dimethylacetamide (5 mL) were added *N*-ethyl-*N*-isopropylpropan-2-amine (205 mg, 1.586 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (127 mg, 0.793 mmol) in one portion sequentially at room temperature under a nitrogen atmosphere. The resulting solution was stirred for 2 h. The reaction mixture was then concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with the following conditions; column, C18 silica gel, 20 - 40 μ m, 330 g; Mobile phase A: water (plus 10 mmol/L ammonium bicarbonate); Mobile phase B: acetonitrile; Flow rate: 80 mL/min; Gradient: 55% - 75% B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 68% B and concentrated under reduced pressure to afford *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate as a white solid.

25 Yield 80 mg (51%). ¹H NMR (400 MHz, DMSO) δ 8.64-8.56 (m, 2H), 8.48 (d, J = 1.6 Hz, 1H), 8.23 (dd, J = 1.6, 8.4 Hz, 1H), 8.00 (dd, J = 1.6, 8.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.64-7.48 (m, 1H), 4.67 (tdd, J = 3.6, 7.2, 49.2 Hz, 1H), 3.99 (t, J = 8.8 Hz, 2H), 3.33-3.32 (m, 2H), 3.12 (t, J = 8.8 Hz, 2H), 2.57-2.52 (m, 2H), 2.42-2.33 (m, 2H), 2.32-2.22 (m, 2H), 1.94-1.77 (m, 2H), 1.76-1.63 (m, 4H), 1.54 (s, 9H). m/z: [ESI⁺] 596 (M+H)⁺.

35

Synthesis of *tert*-butyl 6-fluoro-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate



Scheme 61

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Synthesis of 7-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline (**2**, **Scheme 61**)

[00345] A solution of 7-bromo-6-fluoroisoquinoline (1.00 g, 4.42 mmol) and sodium borohydride (0.50 g, 13.22 mmol) in acetic acid (5 mL) was stirred for 3 h at 40°C. The resulting mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford 7-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline as a colorless oil.

10

Yield 1.50 g (crude). ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 4.26 (s, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 3.03 (t, *J* = 6.4 Hz, 2H). NH proton not observed. *m/z*: [ESI⁺] 230, 232 (M+H)⁺.

15

Synthesis of *tert*-butyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**3**, **Scheme 61**)

[00346] Compound *tert*-butyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1*H*)-carboxylate was prepared from 7-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline (1.50 g, crude) following a similar procedure to that described for the synthesis of *tert*-butyl 6-bromo-5-fluoroindoline-1-carboxylate, and was isolated as a light yellow solid.

Yield 1.06 g (73% over two steps). ¹H NMR (300 MHz, CDCl₃) δ 7.31 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 4.53 (s, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 1.51 (s, 9H). m/z: [ESI⁺] 274, 276 (M+H-56)⁺.

5 *Synthesis of tert-butyl 7-(1-ethoxyvinyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (5, Scheme 61)*

[00347] Compound *tert*-butyl 7-(1-ethoxyvinyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from *tert*-butyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.06 g, 3.21 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was extracted and concentrated under reduced pressure as a brown oil.

Yield 1.30 g (crude). ¹H NMR not run. m/z: [ESI⁺] 322 (M+H)⁺.

15 *Synthesis of tert-butyl 7-(2-bromoacetyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (6, Scheme 61)*

[00348] Compound *tert*-butyl 7-(2-bromoacetyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from *tert*-butyl 7-(1-ethoxyvinyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.30 g, crude) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a white solid.

20 Yield 1.10 g (92% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 11.6 Hz, 1H), 4.60 (s, 2H), 4.51 (d, *J* = 2.4 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.90 (t, *J* = 6.0 Hz, 2H), 1.51 (s, 9H). m/z: [ESI⁺] 316, 318 (M+H-56)⁺.

25 *Synthesis of ethyl 2-(2-(tert-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (8, Scheme 61)*

[00349] Compound ethyl 2-(2-(*tert*-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from *tert*-butyl 7-(2-bromoacetyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.70 g, 1.88 mmol) and ethyl 2-aminobenzo[d]thiazole-6-carboxylate (0.42 g, 1.89 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a brown solid.

30 Yield 0.80 g (86%). ¹H NMR (300 MHz, CDCl₃) δ 8.48 (d, *J* = 1.5 Hz, 1H), 8.23 (dd, *J* = 1.5, 8.4 Hz, 1H), 8.19 (d, *J* = 3.6 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 4.66 (s, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 2.88 (t, *J* = 6.0 Hz, 2H), 1.52 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H). m/z: [ESI⁺] 496 (M+H)⁺.

Synthesis of 2-(2-(*tert*-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (**9**, *Scheme 61*)

[00350] Compound 2-(2-(*tert*-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid was prepared from ethyl 2-(2-(*tert*-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (0.80 g, 1.61 mmol) following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-5-fluoroindolin-6-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid, and was isolated as a brown solid.

Yield 0.70 g (93%). ¹H NMR (400 MHz, DMSO) δ 8.70 (d, *J* = 3.6 Hz, 1H), 8.67 (d, *J* = 1.6 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 12.0 Hz, 1H), 4.56 (s, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.82 (t, *J* = 6.0 Hz, 2H), 1.44 (s, 9H). OH proton not observed. m/z: [ESI⁺] 468 (M+H)⁺.

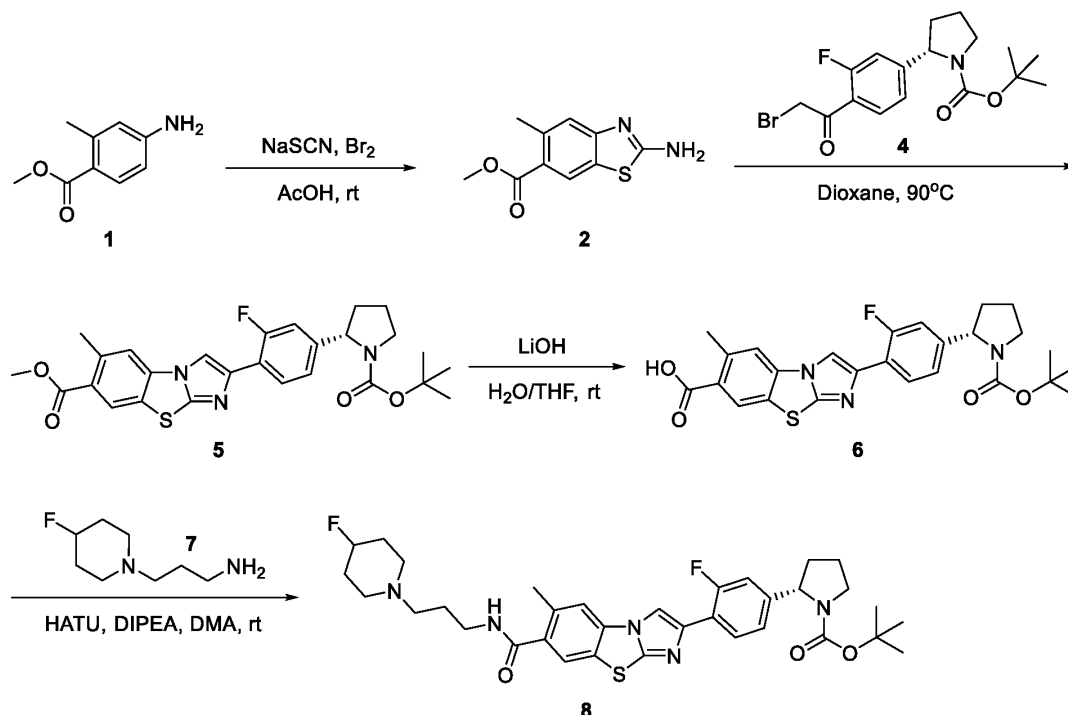
Synthesis of *tert*-butyl 6-fluoro-7-(7-((3-(4-fluoropiperidin-1-

15 *yl*)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**11**, *Scheme 61*)

[00351] Compound *tert*-butyl 6-fluoro-7-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate was prepared from 2-(2-(*tert*-butoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (0.70 g, 1.50 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (0.29 g, 1.81 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 5-fluoro-6-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a reddish brown solid.

Yield 0.60 g (66%). ¹H NMR (400 MHz, DMSO) δ 8.68 (d, *J* = 3.6 Hz, 1H), 8.65 (t, *J* = 5.6 Hz, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.01 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 12.0 Hz, 1H), 4.77-4.67 (m, 1H), 4.55 (s, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.33-3.28 (m, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.57-2.47 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.32-2.22 (m, 2H), 1.91-1.78 (m, 2H), 1.74-1.64 (m, 4H), 1.44 (s, 9H). m/z: [ESI⁺] 610 (M+H)⁺.

Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 62

5

Synthesis of methyl 2-amino-5-methylbenzo[d]thiazole-6-carboxylate (2, *Scheme 62*)

[00352] To a stirred solution of methyl 4-amino-2-methylbenzoate (5.00 g, 30.27 mmol) and sodium thiocyanate (12.27 g, 151.35 mmol) in acetic acid (70 mL) was added bromine (5.32 g, 33.29 mmol) dropwise at 0°C under a nitrogen atmosphere. The resulting solution was stirred for 16 h at room temperature. The reaction mixture was then concentrated under vacuum. The residue was purified by silica gel column chromatography (1%-50% of ethyl acetate in petroleum ether) to afford a mixture of two regioisomers. The mixture was separated by Prep-SFC using the following conditions; Column: CHIRALPAK IF, 3 x 25 cm, 5 μm ; Mobile Phase A: carbon dioxide, Mobile Phase B: methanol (plus 0.1% 2 N ammonia-methanol); Flow rate: 100 mL/min; Gradient: isocratic 20% B in 10 min; Detector: UV 220 nm. The slower eluting peak at 6.8 min was collected and concentrated under reduced pressure to afford methyl 2-amino-5-methylbenzo[d]thiazole-6-carboxylate as a white solid.

Yield 1.32 g (20%). ^1H NMR (300 MHz, CDCl_3) δ 8.25 (s, 1H), 7.42 (s, 1H), 5.76 (br s, 2H), 3.92 (s, 3H), 2.70 (s, 3H). m/z: [ESI $^+$] 223 (M+H) $^+$.

20

Synthesis of methyl (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (5, Scheme 62)

[00353] Compound methyl (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from methyl 2-amino-5-methylbenzo[d]thiazole-6-carboxylate (500 mg, 2.250 mmol) and *tert*-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (869 mg, 2.250 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate and was isolated as a light yellow solid. Yield 280 mg (24%). ¹H NMR (300 MHz, CDCl₃) δ 8.36 (s, 1H), 8.22-8.10 (m, 2H), 7.56 (s, 1H), 7.10 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.00 (dd, *J* = 1.8, 12.6 Hz, 1H), 5.04-4.74 (m, 1H), 3.96 (s, 3H), 3.72-3.60 (m, 2H), 2.79 (s, 3H), 2.46-2.27 (m, 1H), 2.00-1.82 (m, 3H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 510 (M+H)⁺.

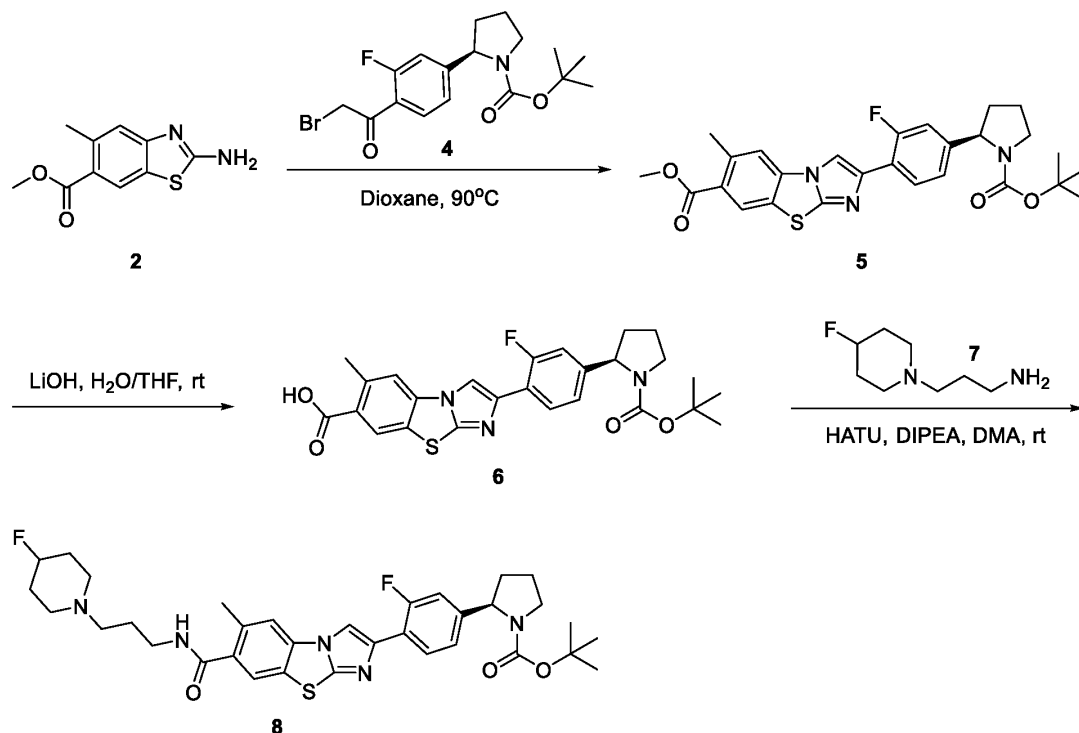
Synthesis of (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (6, Scheme 62)

[00354] Compound (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared from methyl (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (280 mg, 0.549 mmol) following a similar procedure to that described for the synthesis of 2-(1-(tert-butoxycarbonyl)-5-fluoroindolin-6-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid at room temperature, and was isolated as a light yellow solid. Yield 250 mg (92%). ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 8.08-8.00 (m, 1H), 7.59 (s, 1H), 7.34-7.21 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 4.8, 12.0 Hz, 1H), 5.06-4.76 (m, 1H), 3.74-3.53 (m, 2H), 2.73 (s, 3H), 2.45-2.28 (m, 1H), 1.98-1.83 (m, 3H), 1.57 (s, 3H, part of *t*-Bu), 1.25 (s, 6H, part of *t*-Bu). OH proton not observed. m/z: [ESI⁺] 496 (M+H)⁺.

Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (8, Scheme 62)

[00355] Compound *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from (S)-2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (250 mg, 0.504 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (97 mg, 0.605 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 5-fluoro-6-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a light yellow solid. Yield 150 mg (47%). ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.09 (m, 2H), 7.82 (s, 1H), 7.75 (s, 1H), 7.53 (s, 1H), 7.09 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.99 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.04-4.77 (m, 1H), 4.65 (d, *J* = 48.4 Hz, 1H), 3.73-3.49 (m, 4H), 2.69-2.45 (m, 7H), 2.01-1.58 (m, 1H), 1.97-1.60 (m, 11H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 638 (M+H)⁺.

Synthesis of *tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



5 Scheme 63

Synthesis of methyl (*R*)-2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (**5**, Scheme 63)

- [00356] Compound methyl (*R*)-2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate was prepared from methyl 2-amino-5-methylbenzo[d]thiazole-6-carboxylate (316 mg, 1.422 mmol) and *tert*-butyl (*R*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (500 mg, 1.294 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light yellow solid.
- Yield 200 mg (30%). ¹H NMR (300 MHz, CDCl₃) δ 8.36 (s, 1H), 8.22-8.10 (m, 2H), 7.56 (s, 1H), 7.10 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.00 (dd, *J* = 1.8, 12.6 Hz, 1H), 5.04-4.74 (m, 1H), 3.96 (s, 3H), 3.72-3.60 (m, 2H), 2.79 (s, 3H), 2.46-2.27 (m, 1H), 2.00-1.82 (m, 3H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 510 (M+H)⁺.

- Synthesis of (*R*)-2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (**6**, Scheme 63)

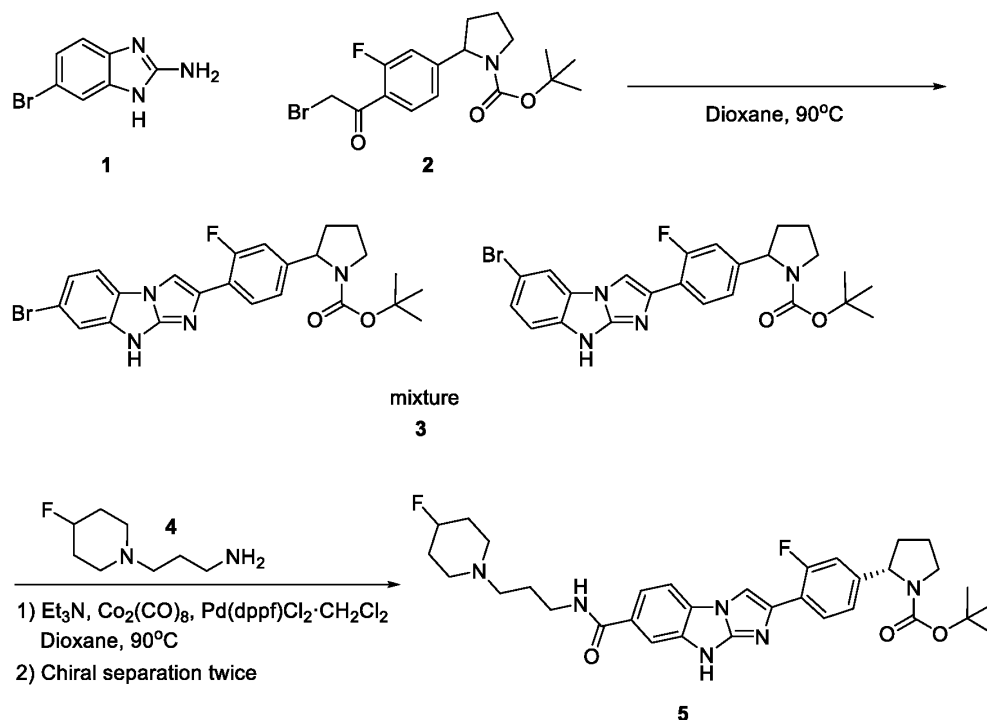
[00357] Compound (*R*)-2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid was prepared from methyl (*R*)-2-(4-(1-(*tert*-

butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (200 mg, 0.392 mmol) following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-5-fluoroindolin-6-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid at room temperature, and was isolated as a light yellow solid.

- 5 Yield 190 mg (98%). ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 8.08-8.00 (m, 1H), 7.59 (s, 1H), 7.34-7.21 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 4.8, 12.0 Hz, 1H), 5.06-4.76 (m, 1H), 3.74-3.53 (m, 2H), 2.73 (s, 3H), 2.45-2.28 (m, 1H), 1.98-1.83 (m, 3H), 1.57-1.25 (m, 9H). OH proton not observed. *m/z*: [ESI⁺] 496 (M+H)⁺.

- 10 *Synthesis of tert-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (8, Scheme 63)*
[00358] Compound *tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from (*R*)-2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methylbenzo[d]imidazo[2,1-*b*]thiazole-
15 7-carboxylic acid (190 mg, 0.383 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (78 mg, 0.487 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 5-fluoro-6-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a light yellow solid.
Yield 110 mg (45%). ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.09 (m, 2H), 7.82 (s, 1H), 7.75 (s, 1H), 7.53
20 (s, 1H), 7.09 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.99 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.04-4.77 (m, 1H), 4.65 (d, *J* = 48.4 Hz, 1H), 3.73-3.49 (m, 4H), 2.69-2.45 (m, 7H), 2.01-1.58 (m, 1H), 1.97-1.60 (m, 11H), 1.50-1.25 (m, 9H). *m/z*: [ESI⁺] 638 (M+H)⁺.

Synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 64

5

Synthesis of mixture of *tert*-butyl 2-(4-(7-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate and *tert*-butyl 2-(4-(6-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (3, **Scheme 64**)

[00359] A mixture of *tert*-butyl 2-(4-(7-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate and *tert*-butyl 2-(4-(6-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 6-bromo-1*H*-benzo[*d*]imidazol-2-amine (3.84 g, 18.11 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (3.50 g, 9.06 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a yellow solid.

Yield 3.00 g (66%). ^1H NMR (300 MHz, CDCl_3) δ 8.10-7.92 (m, 1H), 7.84-7.68 (m, 1H), 7.62-7.56 (m, 1H), 7.50-7.41 (m, 1H), 7.41-7.30 (m, 1H), 7.18-7.10 (m, 1H), 7.10-6.99 (m, 1H), 5.08-4.81 (m, 1H), 3.77-3.53 (m, 2H), 2.47-2.29 (m, 1H), 2.06-1.83 (m, 3H), 1.51-1.25 (m, 9H). NH proton not observed. m/z : $[\text{ESI}^+]$ 499, 501 ($\text{M}+\text{H}$) $^+$.

20

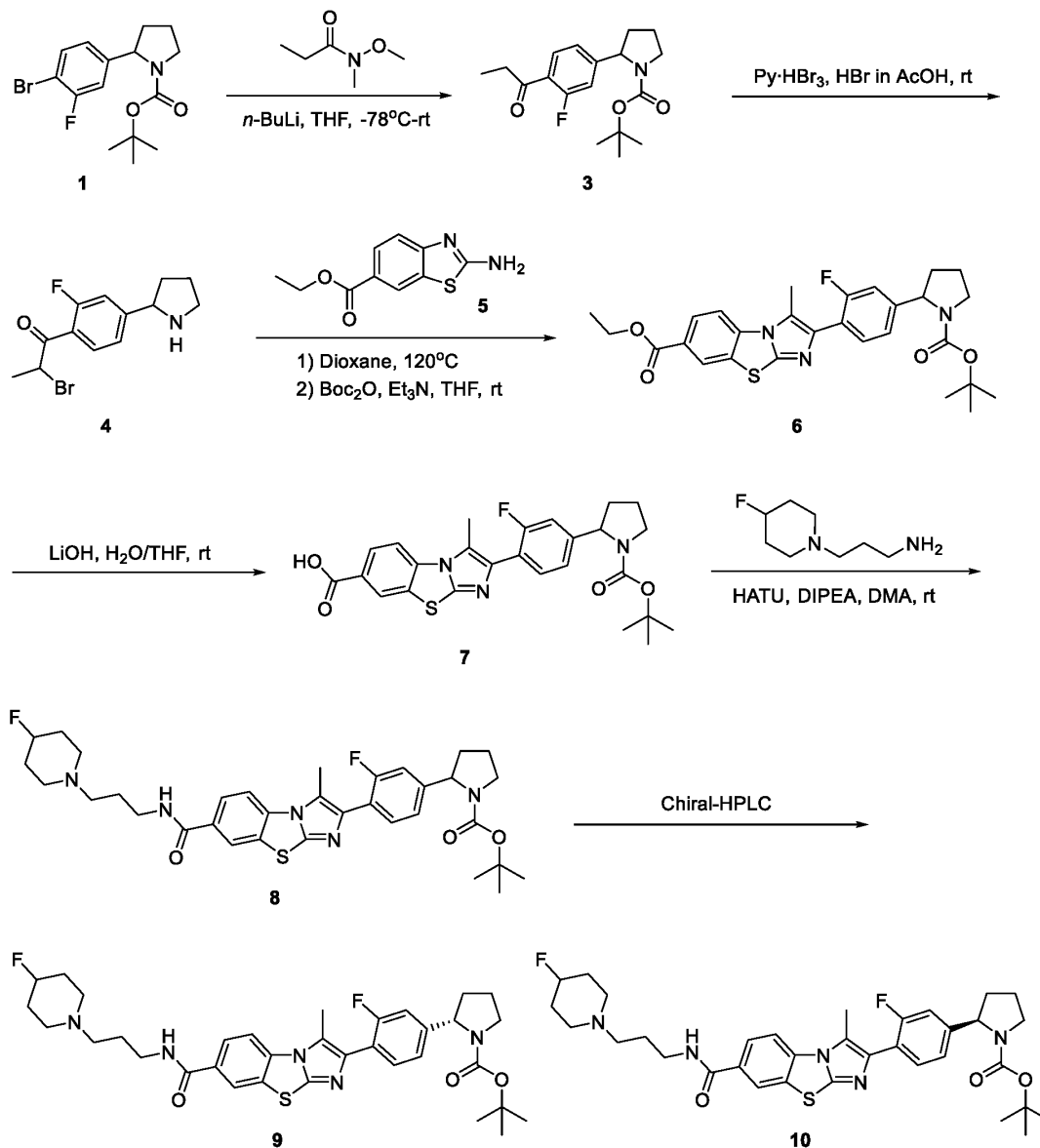
Synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (5, Scheme 64)

[00360] A mixture of *tert*-butyl 2-(3-fluoro-4-(6-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate/*tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from a mixture of *tert*-butyl 2-(4-(7-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate/*tert*-butyl 2-(4-(6-bromo-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (650 mg, 1.302 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (420 mg, 2.621 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate, and was isolated as a white solid (500 mg) *m/z*: [ESI⁺] 607 (M+H)⁺.

The two regioisomers (500 mg) were chiral separated by Prep-CHIRAL-HPLC with the following conditions; Column: CHIRALPAK IG, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane (plus 0.5% 2 *N* ammonium-methanol, Mobile Phase B: ethanol:dichloromethane = 1:1; Flow rate: 20 mL/min; Gradient: isocratic 40% B in 23 min; Detector: UV 254/220 nm. The third eluting peak at 18.72 min was collected and concentrated under reduced pressure to afford 85 mg of a mixture, which was subjected to chiral separation by Prep-CHIRAL-HPLC with the following conditions; Column: CHIRAL ART Cellulose-SC, 2 x 25 cm, 5 μm; Mobile Phase A: hexane (plus 0.5% 2 *N* ammonium-methanol), Mobile Phase B: ethanol:dichloromethane = 1:1; Flow rate: 20 mL/min; Gradient: isocratic 40% B in 11 min; Detector: UV 254/220 nm. The slower eluting peak at 9.09 min was collected and concentrated under reduced pressure to afford *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a white solid.

Yield 40 mg (5%). ¹H NMR (400 MHz, DMSO) δ 11.96 (br s, 1H), 8.54 (t, *J* = 5.6 Hz, 1H), 8.11 (d, *J* = 3.6 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.70 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.15-7.01 (m, 2H), 4.87-4.54 (m, 2H), 3.62-3.41 (m, 3H), 2.60-2.50 (m, 4H), 2.42-2.22 (m, 5H), 1.93-1.78 (m, 4H), 1.78-1.62 (m, 4H), 1.41-1.14 (m, 9H). *m/z*: [ESI⁺] 607 (M+H)⁺. [*α*]_D²⁵ = -50° (c = 1 mg/mL, methanol).

Synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate and *tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 65

Synthesis of *tert*-butyl 2-(3-fluoro-4-propionylphenyl)pyrrolidine-1-carboxylate (3, **Scheme 65**)

[00361] A solution of *tert*-butyl 2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (4.00 g, 11.62 mmol) in tetrahydrofuran (200 mL) was treated with *n*-butyllithium (2.5 *N* in hexane, 14 mL, 35.00 mmol) for 30 min at -78°C under a nitrogen atmosphere. *N*-methoxy-*N*-methylpropionamide (2.72 g, 23.22 mmol) was then added dropwise over 5 min. The resulting solution was stirred for 1 h. The

solution was allowed to warm up to 0°C and quenched with water (100 mL). The resulting mixture was concentrated under reduced pressure to remove the organic solvent. The aqueous mixture was then extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0%-50% of ethyl acetate in petroleum ether) to afford *tert*-butyl 2-(3-fluoro-4-propionylphenyl)pyrrolidine-1-carboxylate as a colorless oil.

Yield 1.20 g (32%). ¹H NMR (400 MHz, DMSO) δ 7.85-7.72 (m, 1H), 7.20-7.07 (m, 2H), 4.90-4.70 (m, 1H), 3.61-3.39 (m, 2H), 2.97 (q, J = 7.2 Hz, 2H), 2.39-2.23 (m, 1H), 1.90-1.63 (m, 3H), 1.40-1.12 (m, 9H), 1.08 (t, J = 7.2 Hz, 3H). m/z: [ESI⁺] 266 (M+H-56)⁺.

Synthesis of 2-bromo-1-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)propan-1-one hydrobromide (4, Scheme 65)

[00362] A solution of *tert*-butyl 2-(3-fluoro-4-propionylphenyl)pyrrolidine-1-carboxylate (1.20 g, 3.73 mmol) and pyridinium tribromide (1.20 g, 3.75 mmol) in 40% hydrobromide in acetic acid (12 mL) was stirred for 3 h at room temperature under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give 2-bromo-1-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)propan-1-one hydrobromide as a brown oil.

Yield 1.30 g (crude). ¹H NMR not run. m/z: [ESI⁺] 300, 302 (M+H)⁺.

*Synthesis of ethyl 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (6, Scheme 65)*

[00363] Compound ethyl 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate was prepared from 2-bromo-1-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)propan-1-one hydrobromide (1.30 g, crude) and ethyl 2-aminobenzo[d]thiazole-6-carboxylate (1.52 g, 6.84 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 120°C. Upon completion, Boc protection was carried out following a similar procedure to that described for the synthesis of *tert*-butyl 6-bromo-5-fluorindoline-1-carboxylate, and was isolated as a light brown solid.

Yield 0.92 g (47% over two steps). ¹H NMR (400 MHz, DMSO) δ 8.70 (d, J = 1.6 Hz, 1H), 8.16-8.06 (m, 2H), 7.60-7.51 (m, 1H), 7.20-7.07 (m, 2H), 4.97-4.70 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.64-3.43 (m, 2H), 2.69 (s, 3H), 2.42-2.23 (m, 1H), 1.93-1.73 (m, 3H), 1.42-1.15 (m, 12H). m/z: [ESI⁺] 524 (M+H)⁺.

Synthesis of 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (7, Scheme 65)

[00364] Compound 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared from ethyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (0.92 g, 1.76 mmol) following a similar procedure to that described for the synthesis of 2-(1-(tert-butoxycarbonyl)-5-fluoroindolin-6-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid at room temperature, and was isolated as an off-white solid.

Yield 0.57 g (65%). ¹H NMR (400 MHz, DMSO) δ 13.21 (br s, 1H), 8.63 (s, 1H), 8.16-8.06 (m, 2H), 7.62-7.51 (m, 1H), 7.19-7.06 (m, 2H), 4.95-4.69 (m, 1H), 3.66-3.40 (m, 2H), 2.69 (s, 3H), 2.42-2.23 (m, 1H), 1.92-1.72 (m, 3H), 1.42-1.15 (m, 9H). m/z: [ESI⁺] 496 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (8, Scheme 65)

[00365] Compound tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (570 mg, 1.150 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (368 mg, 2.297) following a similar procedure to that described for the synthesis of tert-butyl 5-fluoro-6-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a brown oil.

Yield 210 mg (29%). ¹H NMR (300 MHz, CD₃OD) δ 8.34 (d, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.61-7.50 (m, 1H), 7.15 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.08 (d, *J* = 11.4 Hz, 1H), 4.79-4.54 (m, 1H), 3.72-3.56 (m, 3H), 3.48 (t, *J* = 6.9 Hz, 2H), 2.75-2.62 (m, 5H), 2.60-2.36 (m, 4H), 2.05 (s, 3H), 2.01-1.79 (m, 4H), 1.69-1.56 (m, 1H), 1.55-1.42 (m, 2H), 1.30 (s, 9H). NH proton not observed. m/z: [ESI⁺] 638 (M+H)⁺.

Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate and tert-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (9, 10, Scheme 65)

[00366] Tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (240 mg, 0.376 mmol) was separated by Prep-Chiral-HPLC with the following conditions; Column: CHIRALPAK IG, 2 x 25 cm, 5 μ m; Mobile Phase A: hexane (plus 0.5% 2 *N* ammonium-methanol), Mobile Phase B: ethanol:dichloromethane = 1:1; Flow rate: 20 mL/min; Gradient: isocratic 30% B in 18 min; Detector: UV 254/220 nm. The faster eluting peak at 13.02 min was collected and concentrated under reduced

pressure to afford *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a colorless oil.

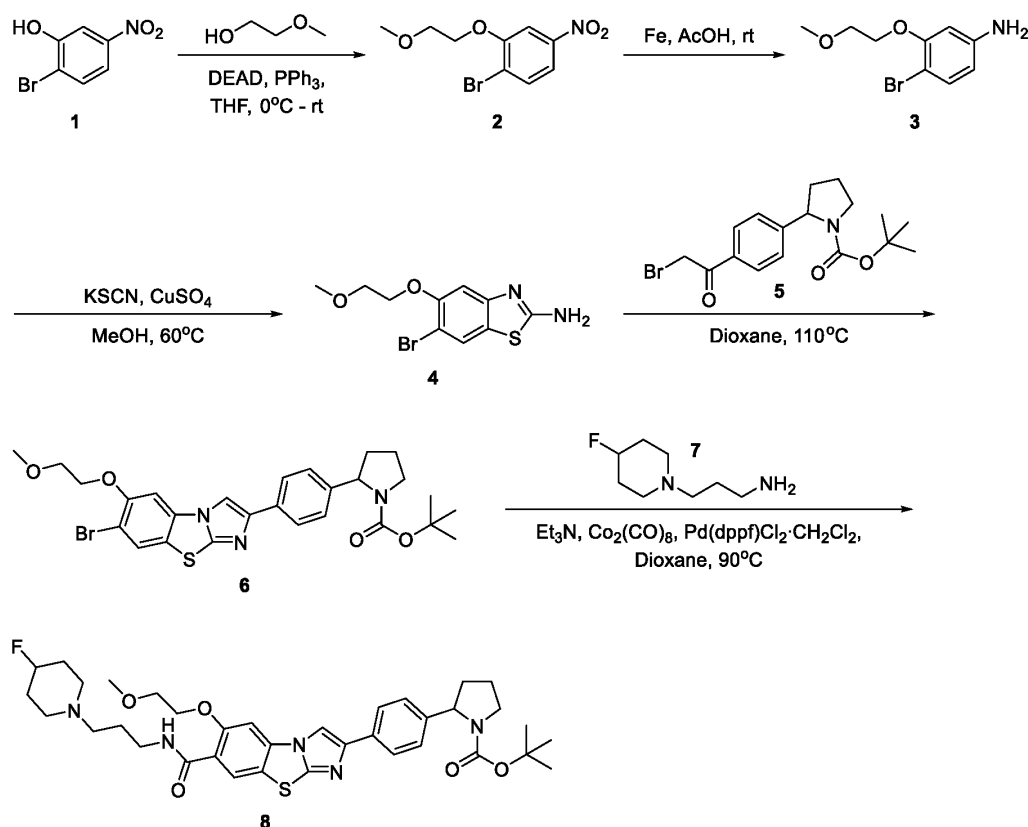
Yield 46 mg (19%). ¹H NMR (300 MHz, CD₃OD) δ 8.34 (d, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.61-7.50 (m, 1H), 7.15 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.08 (d, *J* = 11.4 Hz, 1H), 4.79-4.54 (m, 1H), 3.72-3.56 (m, 3H), 3.48 (t, *J* = 6.9 Hz, 2H), 2.75-2.62 (m, 5H), 2.60-2.36 (m, 4H), 2.05 (s, 3H), 2.01-1.79 (m, 4H), 1.69-1.56 (m, 1H), 1.55-1.42 (m, 2H), 1.30 (s, 9H). NH proton not observed. *m/z*: [ESI⁺] 638 (M+H)⁺.

The slower eluting peak at 15.78 min was collected and concentrated under reduced pressure to afford *tert*-butyl

(*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a colorless oil.

Yield 38 mg (16%). ¹H NMR (300 MHz, CD₃OD) δ 8.34 (d, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.61-7.50 (m, 1H), 7.15 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.08 (d, *J* = 11.4 Hz, 1H), 4.79-4.54 (m, 1H), 3.72-3.56 (m, 3H), 3.48 (t, *J* = 6.9 Hz, 2H), 2.75-2.62 (m, 5H), 2.60-2.36 (m, 4H), 2.05 (s, 3H), 2.01-1.79 (m, 4H), 1.69-1.56 (m, 1H), 1.55-1.42 (m, 2H), 1.30 (s, 9H). NH proton not observed. *m/z*: [ESI⁺] 638 (M+H)⁺.

*Synthesis of tert-butyl 2-(4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*



Synthesis of 1-bromo-2-(2-methoxyethoxy)-4-nitrobenzene (2, Scheme 66)

[00367] Diethyl azodicarboxylate (5.99 g, 34.39 mmol) was added dropwise over 1 min into a solution of 2-bromo-5-nitrophenol (5.00 g, 22.93 mmol), triphenylphosphine (9.02 g, 34.39 mmol) and 2-methoxyethan-1-ol (3.49 g, 45.86 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction solution was stirred for 2 h at room temperature. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% of ethyl acetate in petroleum ether) to afford 1-bromo-2-(2-methoxyethoxy)-4-nitrobenzene as a light yellow solid.

Yield 5.10 g (81%). ¹H NMR (400 MHz, CDCl₃) δ 7.80-7.79 (m, 1H), 7.75-7.73 (m, 2H), 4.32-4.28 (m, 2H), 3.89-3.85 (m, 2H), 3.51 (s, 3H). No mass ion observed.

Synthesis of 4-bromo-3-(2-methoxyethoxy)aniline (3, Scheme 66)

[00368] A mixture of 1-bromo-2-(2-methoxyethoxy)-4-nitrobenzene (3.00 g, 10.87 mmol) and iron powder (3.03 g, 54.25 mmol) in acetic acid (30 mL) was stirred for 2 h at room temperature. The resulting mixture was filtered. The filtered cake was washed with ethyl acetate (3 x 50 mL). The combined filtrate was concentrated under reduced pressure. The residue was diluted with water (50 mL) and adjusted the pH to 7 with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 4-bromo-3-(2-methoxyethoxy)aniline as an orange oil.

Yield (2.20 g, 82%). ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.13 (t, *J* = 5.7 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.50 (s, 3H). *m/z*: [ESI⁺] 246, 248 (M+H)⁺.

Synthesis of 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine (4, Scheme 66)

[00369] A mixture of 4-bromo-3-(2-methoxyethoxy)aniline (3.50 g, 14.22 mmol), potassium thiocyanate (14.10 g, 145.09 mmol) and copper(II) sulfate (11.35 g, 71.11 mmol) in methanol (40 mL) was stirred for 9 h at 60°C under a nitrogen atmosphere. The mixture was cooled to room temperature and filtered. The filtered cake was washed with methanol (3 x 100 mL). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2.5% of methanol in dichloromethane) to afford 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine as a light yellow solid.

Yield 3.80 g (88%). ¹H NMR (400 MHz, DMSO) δ 8.68 (br s, 2H), 8.00 (s, 1H), 7.12 (s, 1H), 4.23-4.15 (m, 2H), 3.76-3.68 (m, 3H), 3.36 (s, 3H). *m/z*: [ESI⁺] 303, 305 (M+H)⁺.

Synthesis of *tert*-butyl 2-(4-(7-bromo-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (**6**, *Scheme 66*)

[00370] Compound *tert*-butyl 2-(4-(7-bromo-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine (0.50 g, 1.65 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)phenyl)pyrrolidine-1-carboxylate (0.67 g, 1.82 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a yellow solid.

Yield 0.16 g (17%). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (s, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.23 (s, 1H), 5.06-4.73 (m, 1H), 4.32 (t, *J* = 4.8 Hz, 2H), 3.90 (t, *J* = 4.8 Hz, 2H), 3.76-3.59 (m, 2H), 3.54 (s, 3H), 2.44-2.26 (m, 1H), 2.02-1.81 (m, 3H), 1.47-1.22 (m, 9H). m/z: [ESI⁺] 572, 574 (M+H)⁺.

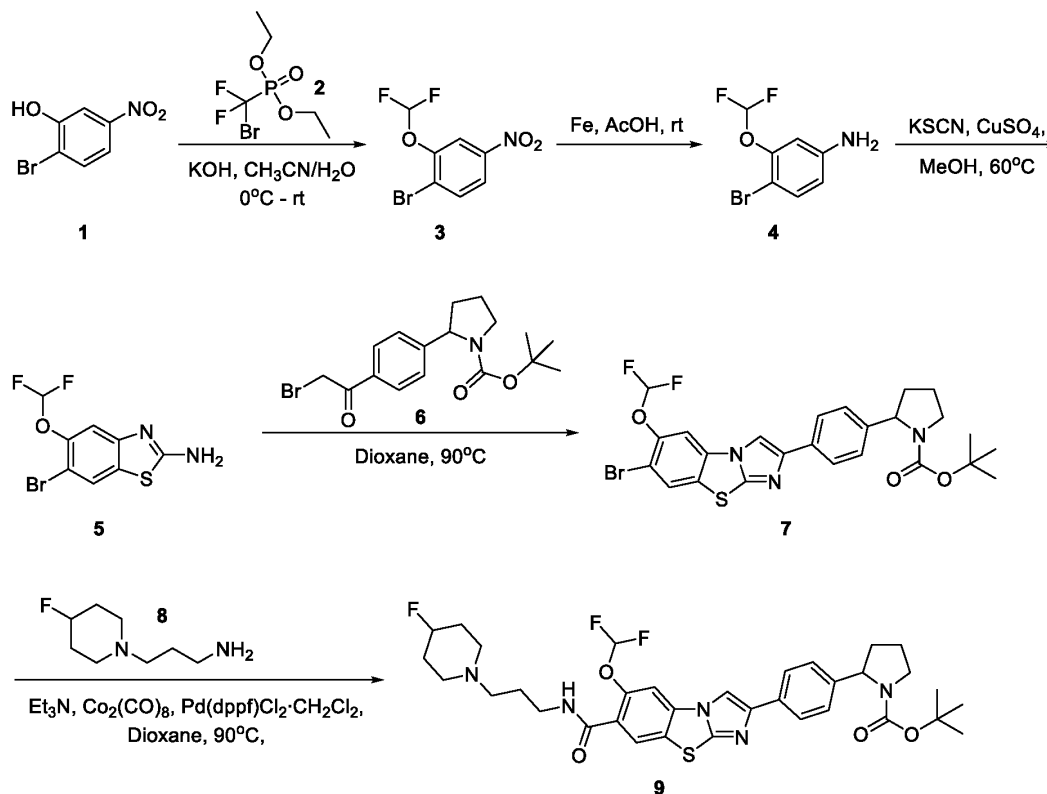
Synthesis of *tert*-butyl 2-(4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-

methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (**8**, *Scheme 66*)

[00371] Compound *tert*-butyl 2-(4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(7-bromo-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (160 mg, 0.279 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (90 mg, 0.562 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate, and was isolated as a light yellow solid.

Yield 33 mg (17%). ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 8.40 (br s, 1H), 7.95 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.27-7.24 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.20-4.74 (m, 2H), 4.48-4.35 (m, 2H), 4.02-3.84 (m, 2H), 3.73-3.63 (m, 2H), 3.63-3.56 (m, 2H), 3.55 (s, 3H), 3.04-2.63 (m, 2H), 2.41-2.29 (m, 1H), 2.11-1.84 (m, 3H), 1.69-1.53 (m, 10H), 1.49-1.23 (m, 9H). m/z: [ESI⁺] 680 (M+H)⁺.

Synthesis of tert-butyl 2-(4-(6-(difluoromethoxy)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 67

5

Synthesis of 1-bromo-2-(difluoromethoxy)-4-nitrobenzene (3, Scheme 67)

[00372] To a stirred solution of 2-bromo-5-nitrophenol (5.00 g, 22.93 mmol) and potassium hydroxide (13.00 g, 231.69 mmol) in acetonitrile:water (1:1, 60 mL) was added diethyl bromodifluoromethylphosphonate (12.00 g, 44.94 mmol) dropwise at 0°C under a nitrogen atmosphere.

10 The reaction solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with water (60 mL) and extracted with ethyl acetate (3 x 130 mL). The combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 1-bromo-2-(difluoromethoxy)-4-nitrobenzene as a brown oil.

15 Yield 6.02 g (98%). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (q, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 6.68 (t, *J* = 72.0 Hz, 1H). No mass ion observed

Synthesis of 4-bromo-3-(difluoromethoxy)aniline (4, Scheme 67)

20 [00373] Compound 4-bromo-3-(difluoromethoxy)aniline was prepared from 1-bromo-2-(difluoromethoxy)-4-nitrobenzene (6.00 g, 22.39 mmol) following a similar procedure to that described for the synthesis of 4-bromo-3-(2-methoxyethoxy)aniline, and was isolated as a brown solid.

Yield 4.50 g (crude). ¹H NMR not run. m/z: [ESI⁺] 238, 240 (M+H)⁺.

Synthesis of 6-bromo-5-(difluoromethoxy)benzo[d]thiazol-2-amine (5, Scheme 67)

[00374] Compound 6-bromo-5-(difluoromethoxy)benzo[d]thiazol-2-amine was prepared from 4-bromo-3-(difluoromethoxy)aniline (4.50 g, crude) and potassium thiocyanate (11.00 g, 113.19 mmol) following a similar procedure to that described for the synthesis of 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine, and was isolated as an off-white solid.

Yield 2.00 g (30% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 7.42 (s, 1H), 6.55 (t, *J* = 73.6 Hz, 1H), 5.44 (br s, 2H). m/z: [ESI⁺] 295, 297 (M+H)⁺.

10 *Synthesis of tert-butyl 2-(4-(7-bromo-6-(difluoromethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (7, Scheme 67)*

[00375] Compound *tert*-butyl 2-(4-(7-bromo-6-(difluoromethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 6-bromo-5-(difluoromethoxy)benzo[d]thiazol-2-amine (0.50 g, 1.69 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)phenyl)pyrrolidine-1-carboxylate (0.94 g, 2.55 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a white solid.

Yield 0.35 g (37%). ¹H NMR (400 MHz, DMSO) δ 8.79 (s, 1H), 8.51 (s, 1H), 8.10 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 72.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.90-4.66 (m, 1H), 3.62-3.43 (m, 2H), 2.39-2.21 (m, 1H), 1.91-1.65 (m, 3H), 1.41 (s, 3H), 1.12 (s, 6H). m/z: [ESI⁺] 564, 566 (M+H)⁺.

*Synthesis of tert-butyl 2-(4-(6-(difluoromethoxy)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (9, Scheme 67)*

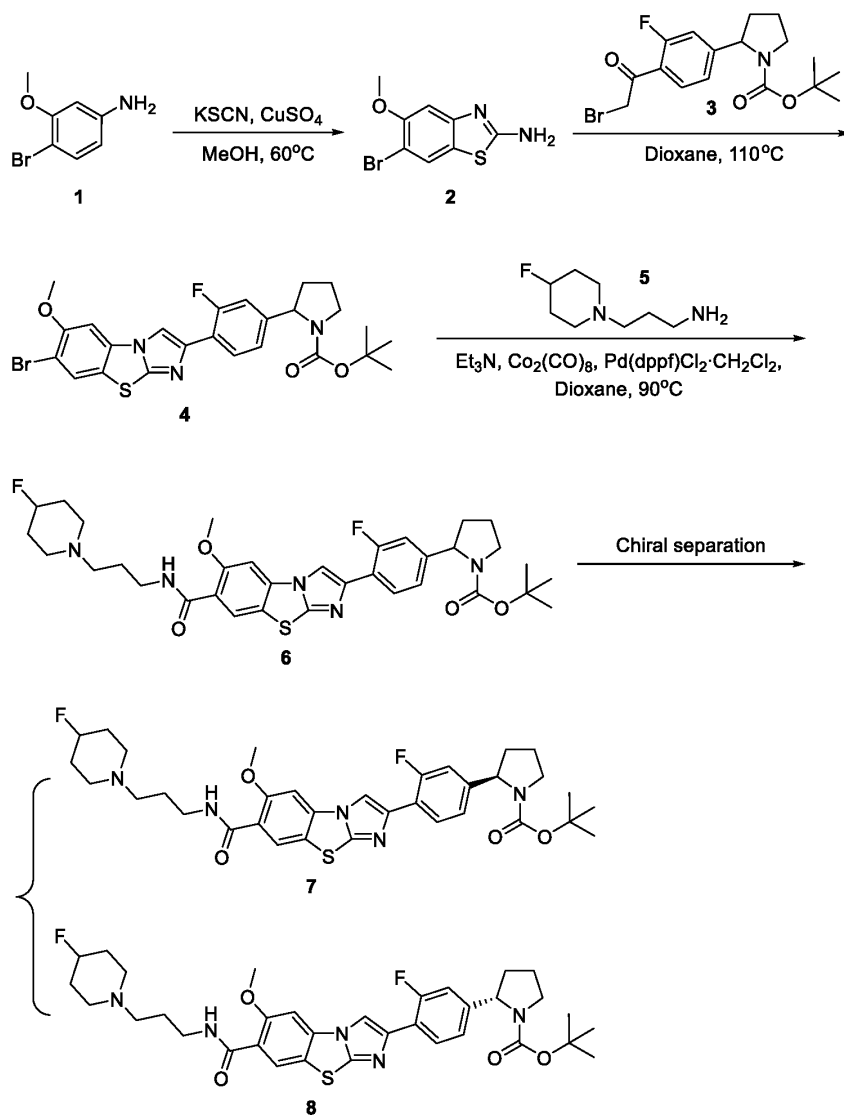
25 [00376] Compound *tert*-butyl 2-(4-(6-(difluoromethoxy)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(7-bromo-6-(difluoromethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (300 mg, 0.531 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (341 mg, 2.128 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate, and was isolated as a brown solid.

Yield 70 mg (20%). ¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.99 (s, 1H), 7.97-7.89 (br s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.47 (s, 1H), 7.28 (t, *J* = 72.8 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.05-4.54 (m, 2H), 3.78-3.55 (m, 6H), 2.76-2.23 (m, 7H), 2.06-1.73 (m, 7H), 1.49-1.22 (m, 9H). m/z: [ESI⁺] 672 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (6)

Synthesis of tert-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (7)

5 Synthesis of tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (8)



Scheme 68

10 Synthesis of 6-bromo-5-methoxybenzo[d]thiazol-2-amine (2, *Scheme 68*)

[00377] Compound 6-bromo-5-methoxybenzo[d]thiazol-2-amine was prepared from 4-bromo-3-methoxyaniline (2.00 g, 9.90 mmol) and potassium thiocyanate (9.62 g, 98.98 mmol) following a similar

procedure to that described for the synthesis of 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine, and was isolated as a yellow solid.

Yield 1.40 g (55%). ¹H NMR (400 MHz, DMSO) δ 7.84 (s, 1H), 7.58 (br s, 2H), 7.06 (s, 1H), 3.83 (s, 3H). m/z: [ESI⁺] 259, 261 (M+H)⁺.

5

Synthesis of tert-butyl 2-(4-(7-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (4, Scheme 68)

[00378] Compound *tert*-butyl 2-(4-(7-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 6-bromo-5-methoxybenzo[d]thiazol-2-amine (1.00 g, 3.86 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.49 g, 3.86 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a brown solid.

Yield 0.80 g (38%). ¹H NMR (400 MHz, DMSO) δ 8.72 (s, 1H), 8.31 (s, 1H), 8.12-8.05 (m, 2H), 7.19-7.06 (m, 2H), 4.91-4.69 (m, 1H), 4.00 (s, 3H), 3.63-3.41 (m, 2H), 2.40-2.21 (m, 1H), 1.95-1.71 (m, 3H), 1.41-1.13 (m, 9H). m/z: [ESI⁺] 546, 548 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (6, Scheme 68)

[00379] Compound *tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(7-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (200 mg, 0.366 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (120 mg, 0.749 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate, and was isolated as a yellow oil.

Yield 60 mg (25%). ¹H NMR (400 MHz, CDCl₃) δ 8.56 (s, 1H), 8.22-8.10 (m, 2H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.23 (s, 1H), 7.10 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.03-4.76 (m, 2H), 4.17 (s, 3H), 3.74-3.54 (m, 5H), 2.44-2.29 (m, 1H), 2.03-1.82 (m, 6H), 1.69-1.52 (m, 8H), 1.49-1.25 (m, 9H). m/z: [ESI⁺] 654 (M+H)⁺.

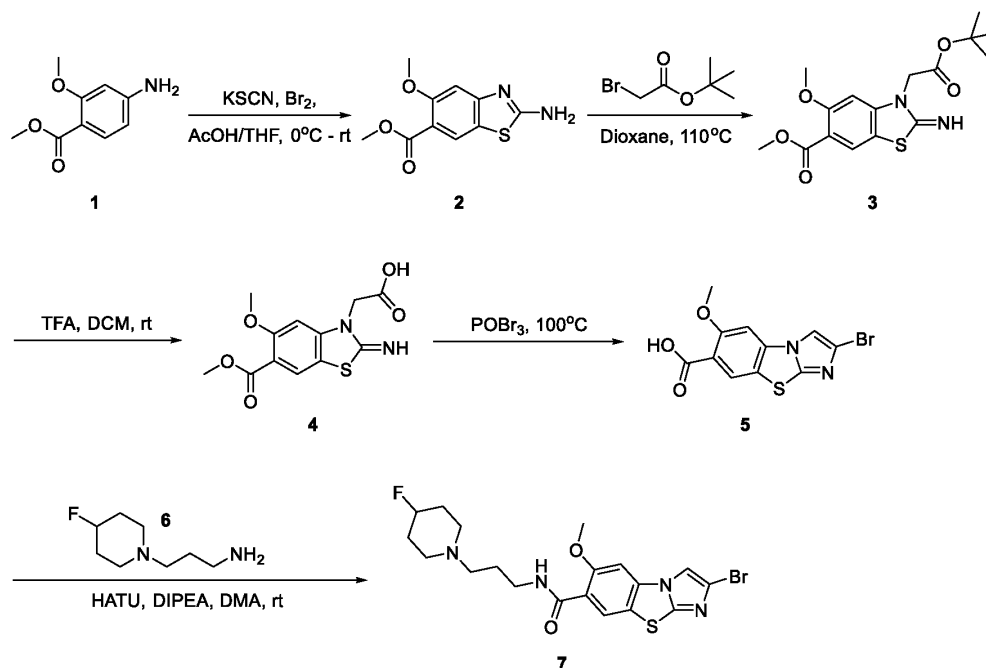
Synthesis of tert-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate and tert-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (7, 8, Scheme 68)

[00380] *tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (100 mg, 0.153 mmol) was separated by CHIRAL-HPLC with the following conditions; Column: CHIRAL ART Cellulose-

SC, 2 x 25 cm, 5 μ m; Mobile Phase A: hexane (plus 0.5% 2 *N* ammonium-methanol), Mobile Phase B: ethanol/dichloromethane = 1:1; Flow rate: 20 mL/min; Gradient: isocratic 40% B in 16 min; Detector: UV 254/220 nm. The faster eluting peak at 11.77 min was collected and concentrated under reduce pressure to afford *tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a light yellow solid. Yield 30 mg (30%). ¹H NMR (400 MHz, DMSO) δ 8.74 (s, 1H), 8.37-8.23 (m, 2H), 8.14-8.03 (m, 2H), 7.18-7.07 (m, 2H), 4.89-4.57 (m, 2H), 4.02 (s, 3H), 3.61-3.42 (m, 2H), 2.40-2.23 (m, 3H), 1.97-1.65 (m, 15H), 1.41-1.14 (m, 9H). m/z: [ESI⁺] 654 (M+H)⁺.

The slower eluting peak at 14.43 min was collected and concentrated under reduce pressure to afford *tert*-butyl (*S*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a light yellow solid. Yield 30 mg (30%). ¹H NMR (400 MHz, DMSO) δ 8.74 (s, 1H), 8.37-8.23 (m, 2H), 8.14-8.03 (m, 2H), 7.18-7.07 (m, 2H), 4.89-4.57 (m, 2H), 4.02 (s, 3H), 3.61-3.42 (m, 2H), 2.40-2.23 (m, 3H), 1.97-1.65 (m, 15H), 1.41-1.14 (m, 9H). m/z: [ESI⁺] 654 (M+H)⁺.

*Synthesis of 2-bromo-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide*



Scheme 69

Synthesis of methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (2, Scheme 69)

[00381] To a stirred solution of methyl 4-amino-2-methoxybenzoate (50.00 g, 275.95 mmol) and potassium thiocyanate (53.63 g, 551.86 mmol) in acetic acid:tetrahydrofuran (2:1, 750 mL) was added

bromine (14.14 mL, 275.95 mmol) dropwise over 5 min at 0°C. The reaction solution was stirred for 2 h at room temperature. To the above mixture was added an aqueous solution of saturated sodium thiosulfate (2000 mL). The precipitated solids were collected by filtration, washed with acetonitrile (3 x 500 mL) and dried in a vacuum oven to afford 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate as an off-white solid.

Yield 48.55 g (74%). ¹H NMR (400 MHz, DMSO) δ 7.87 (s, 1H), 6.67 (br s, 2H), 6.47 (s, 1H), 3.77 (s, 3H), 3.71 (s, 3H). m/z: [ESI⁺] 239 (M+H)⁺.

Synthesis of methyl 3-(2-(tert-butoxy)-2-oxoethyl)-2-imino-5-methoxy-2,3-dihydrobenzo[d]thiazole-6-carboxylate (3, Scheme 69)

[00382] To a stirred solution of 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (90.00 g, 377.74 mmol) in 1,4-dioxane (1000 mL) was added *tert*-butyl 2-bromoacetate (88.42 g, 453.30 mmol) at room temperature. The reaction mixture was stirred for 16 h at 110°C. The mixture was allowed to cool to room temperature. The precipitated solids were collected by filtration, washed with methanol (3 x 300 mL) and dried under reduced pressure to afford methyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2-imino-5-methoxy-2,3-dihydrobenzo[d]thiazole-6-carboxylate as a light yellow solid.

Yield 77.00 g (58%). ¹H NMR (300 MHz, CDCl₃) δ 10.68 (s, 1H), 8.11 (s, 1H), 6.76 (s, 1H), 5.45 (s, 2H), 4.00 (s, 3H), 3.93 (s, 3H), 1.52 (s, 9H). m/z: [ESI⁺] 353 (M+H)⁺.

Synthesis of 2-(2-imino-5-methoxy-6-(methoxycarbonyl)benzo[d]thiazol-3(2H)-yl)acetic acid (4, Scheme 69)

[00383] To a stirred solution of methyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2-imino-5-methoxy-2,3-dihydrobenzo[d]thiazole-6-carboxylate (3.50 g, 9.93 mmol) in dichloromethane (30 mL) was added 2,2,2-trifluoroacetic acid (10 mL) dropwise at room temperature under a nitrogen atmosphere. The resulting solution was stirred for 2 h. The precipitated solids were collected by filtration, washed with diethyl ether (2 x 30 mL) and dried under reduced pressure to afford 2-(2-imino-5-methoxy-6-(methoxycarbonyl)benzo[d]thiazol-3(2H)-yl)acetic acid as a white solid.

Yield 2.50 g (85%). ¹H NMR (300 MHz, CDCl₃) δ 10.68 (s, 1H), 8.11 (s, 1H), 6.76 (s, 1H), 5.45 (s, 2H), 4.00 (s, 3H), 3.93 (s, 3H). OH proton not observed. m/z: [ESI⁺] 297, 299 (M+H)⁺.

Synthesis of 2-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (5, Scheme 69)

[00384] A mixture of 2-(2-imino-5-methoxy-6-(methoxycarbonyl)benzo[d]thiazol-3(2H)-yl)acetic acid (2.50 g, 8.44 mmol) and phosphoryl tribromide (20.00 g, 69.76 mmol) was stirred for 3 h at 100°C under a nitrogen atmosphere. The resulting mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The precipitated solids were collected by filtration and washed sequentially with ethyl acetate (3 x 10 mL) and water (3 x 10 mL). The residue was purified by reverse phase flash column chromatography with the following conditions; Column: WelFlash TM C18-I, 20-40 μm, 330 g; Eluent A: water (plus 10 mmol/L ammonium bicarbonate); Eluent B: acetonitrile; Gradient: 45% - 65% B in

25 min; Flow rate: 80 mL/min; Detector: UV 220/254 nm. The desired fractions were collected at 62% B and concentrated under reduced pressure to afford 2-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid as a white solid.

Yield 0.50 g (18%). ¹H NMR (400 MHz, DMSO) δ 8.56 (s, 1H), 8.38 (s, 1H), 7.90 (s, 1H), 3.94 (s, 3H).

5 OH proton not observed. m/z: [ESI⁺] 327, 329 (M+H)⁺.

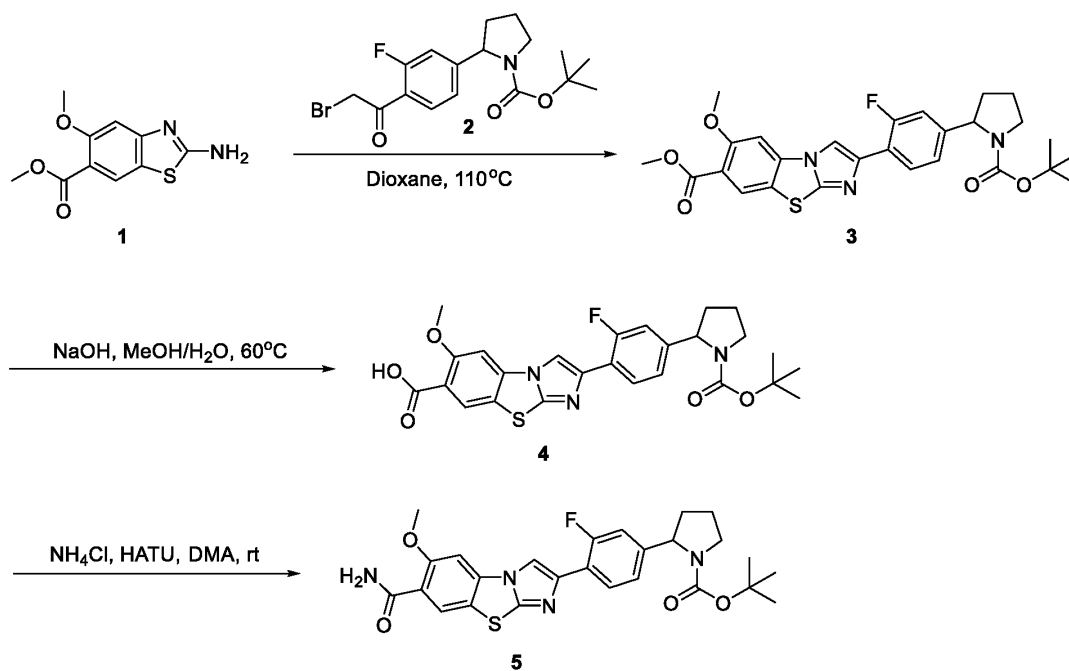
Synthesis of 2-bromo-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (7, Scheme 69)

[00385] Compound 2-bromo-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide was prepared from 2-bromo-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (300 mg, 0.917 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (220 mg, 1.373 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a white solid.

15 Yield 150 mg (35%). ¹H NMR (400 MHz, CD₃OD) δ 8.32 (s, 1H), 8.23 (s, 1H), 7.73 (s, 1H), 4.80-4.60 (m, 1H), 4.10 (s, 3H), 3.55-3.46 (m, 2H), 2.73-2.60 (m, 2H), 2.56-2.40 (m, 4H), 1.94-1.77 (m, 6H). NH proton not observed. m/z: [ESI⁺] 469, 471 (M+H)⁺.

Synthesis of tert-butyl 2-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-

20 *fluorophenyl)pyrrolidine-1-carboxylate*



Scheme 70

Synthesis of methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (3, Scheme 70)

- [00386] Compound methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (1.00 g, 4.20 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.63 g, 4.22 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a light yellow solid.
- Yield 0.55 g (25%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 8.20-8.11 (m, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 7.10 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (dd, *J* = 1.6, 12.4 Hz, 1H), 4.89-4.78 (m, 1H), 4.07 (s, 3H), 3.96 (s, 3H), 3.70-3.59 (m, 2H), 2.43-2.27 (m, 1H), 2.01-1.81 (m, 3H), 1.49-1.25 (m, 9H). *m/z*: [ESI⁺] 526 (M+H)⁺.

- Synthesis of 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (4, Scheme 70)*

- [00387] Compound 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared from methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (0.55 g, 1.05 mmol) following a similar procedure to that described for the synthesis of 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid at room temperature, and was isolated as a light yellow solid.
- Yield 0.45 g (84%). ¹H NMR (400 MHz, CDCl₃) δ 8.56 (s, 1H), 8.24-8.12 (m, 2H), 7.31-7.29 (m, 1H), 7.11 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.01 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.05-4.77 (m, 1H), 4.25 (s, 3H), 3.75-3.60 (m, 2H), 2.45-2.27 (m, 1H), 2.03-1.84 (m, 3H), 1.50-1.25 (m, 9H). OH proton not observed. *m/z*: [ESI⁺] 512 (M+H)⁺.

- Synthesis of tert-butyl 2-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (5, Scheme 70)*

- [00388] Compound *tert*-butyl 2-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (0.50 g, 0.98 mmol) and ammonium chloride (0.20 g, 3.74 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a brown solid.

Yield 0.20 g (40%). ¹H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 3.6 Hz, 1H), 8.42 (s, 1H), 8.14-8.05 (m, 2H), 7.75 (s, 1H), 7.66 (s, 1H), 7.17-7.09 (m, 2H), 4.92-4.71 (m, 1H), 4.04 (s, 3H), 3.63-3.43 (m, 2H), 2.39-2.23 (m, 1H), 1.92-1.69 (m, 3H), 1.41-1.14 (m, 9H). m/z: [ESI⁺] 511 (M+H)⁺.

5 *Synthesis of tert-butyl 2-(3-fluoro-4-(6-methoxy-7-(methylcarbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*

[00389] Compound *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(methylcarbamoyl)benzo[d]imidazo[2,1-
b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-
butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-
10 carboxylic acid (40 mg, 0.078 mmol) and methylamine (5 mg, 0.161 mmol) following a similar
procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-
yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a
light yellow solid.

Yield 25 mg (61%). ¹H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 3.6 Hz, 1H), 8.37 (s, 1H), 8.25 (q, *J* =
15 4.8 Hz, 1H), 8.14-8.03 (m, 2H), 7.19-7.07 (m, 2H), 4.91-4.68 (m, 1H), 4.03 (s, 3H), 3.63-3.43 (m, 2H),
2.84 (d, *J* = 4.8 Hz, 3H), 2.39-2.23 (m, 1H), 1.92-1.68 (m, 3H), 1.41-1.14 (m, 9H). m/z: [ESI⁺] 525
(M+H)⁺.

*Synthesis of tert-butyl 2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-
20 yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*
[00390] Compound *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-
yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from
2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-
b]thiazole-7-carboxylic acid (150 mg, 0.293 mmol) and 1-methylpiperidin-4-amine (70 mg, 0.613
25 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-
(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate,
and was isolated as a yellow solid.

Yield 100 mg (56%). ¹H NMR (400 MHz, DMSO) δ 8.74 (d, *J* = 3.6 Hz, 1H), 8.28 (s, 1H), 8.12-8.03
(m, 3H), 7.18-7.09 (m, 2H), 4.88-4.70 (m, 1H), 4.02 (s, 3H), 3.83-3.71 (m, 1H), 3.63-3.42 (m, 2H), 2.74-
30 2.65 (m, 2H), 2.40-2.26 (m, 1H), 2.18 (s, 3H), 2.09-1.98 (m, 2H), 1.91-1.72 (m, 5H), 1.65-1.50 (m, 2H),
1.41-1.13 (m, 9H). m/z: [ESI⁺] 608 (M+H)⁺.

*Synthesis of tert-butyl 2-(3-fluoro-4-(6-methoxy-7-(((*R*)-1-methylpiperidin-3-
35 yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*
[00391] Compound *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(((*R*)-1-methylpiperidin-3-
yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from
2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-
b]thiazole-7-carboxylic acid (100 mg, 0.195 mmol) and (*R*)-1-methylpiperidin-3-amine (26 mg, 0.228

mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a light yellow solid.

Yield 50 mg (42%). ¹H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 3.6 Hz, 1H), 8.36-8.30 (m, 1H), 8.26 (s, 1H), 8.14-8.05 (m, 2H), 7.17-7.10 (m, 2H), 4.91-4.67 (m, 1H), 4.01 (s, 3H), 3.68-3.28 (m, 4H), 2.89-2.74 (m, 4H), 2.70 (s, 3H), 2.42-2.23 (m, 1H), 2.01-1.72 (m, 6H), 1.41-1.13 (m, 9H). m/z: [ESI⁺] 608 (M+H)⁺.

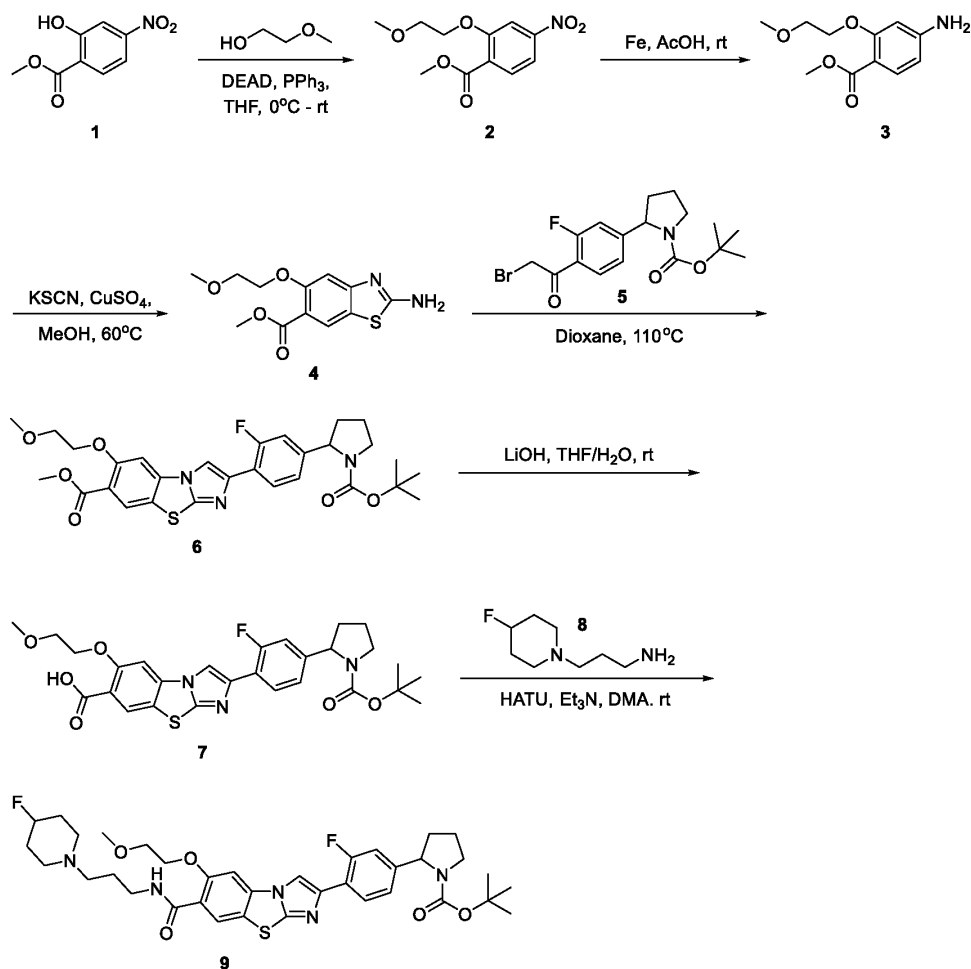
Synthesis of tert-butyl 2-(3-fluoro-4-(6-methoxy-7-(((S)-1-methylpiperidin-3-

*yl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*

[00392] Compound *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(((S)-1-methylpiperidin-3-yl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid (200 mg, 0.391 mmol) and (*S*)-1-methylpiperidin-3-amine (54 mg, 0.473 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as a light yellow solid.

Yield 100 mg (42%). ¹H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 3.6 Hz, 1H), 8.36-8.30 (m, 1H), 8.26 (s, 1H), 8.14-8.05 (m, 2H), 7.17-7.10 (m, 2H), 4.91-4.67 (m, 1H), 4.01 (s, 3H), 3.68-3.28 (m, 4H), 2.89-2.74 (m, 4H), 2.70 (s, 3H), 2.42-2.23 (m, 1H), 2.01-1.72 (m, 6H), 1.41-1.13 (m, 9H). m/z: [ESI⁺] 608 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 71

5

Synthesis of methyl 2-(2-methoxyethoxy)-4-nitrobenzoate (2, Scheme 71)

[00393] Compound methyl 2-(2-methoxyethoxy)-4-nitrobenzoate was prepared from methyl 2-hydroxy-4-nitrobenzoate (2.00 g, 10.14 mmol) and 2-methoxyethan-1-ol (1.54 g, 20.24 mmol) following a similar procedure to that described for the synthesis of 1-bromo-2-(2-methoxyethoxy)-4-nitrobenzene, and was isolated as an orange oil.

10

Yield 2.50 g (97%). ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.89-7.84 (m, 2H), 4.33-4.29 (m, 2H), 3.95 (s, 3H), 3.87-3.83 (m, 2H), 3.49 (s, 3H). No mass ion observed.

Synthesis of methyl 4-amino-2-(2-methoxyethoxy)benzoate (3, Scheme 71)

15

[00394] Compound methyl 4-amino-2-(2-methoxyethoxy)benzoate was prepared from methyl 2-(2-methoxyethoxy)-4-nitrobenzoate (2.50 g, 9.80 mmol) following a similar procedure to that described for the synthesis of 4-bromo-3-(2-methoxyethoxy)aniline, and was isolated as an orange oil.

Yield 2.50 g (crude). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.4 Hz, 1H), 6.28 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 4.14 (t, *J* = 4.8 Hz, 2H), 3.83 (s, 3H), 3.82 (t, *J* = 4.8 Hz, 2H), 3.50 (s, 3H). NH₂ protons not observed. m/z: [ESI⁺] 226 (M+H)⁺.

5 *Synthesis of methyl 2-amino-5-(2-methoxyethoxy)benzo[d]thiazole-6-carboxylate (4, Scheme 71)*

[00395] Compound methyl 2-amino-5-(2-methoxyethoxy)benzo[d]thiazole-6-carboxylate was prepared from methyl 4-amino-2-(2-methoxyethoxy)benzoate (2.50 g, crude) and potassium thiocyanate (11.01 g, 113.29 mmol) following a similar procedure to that described for the synthesis of 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine, and was isolated as tan solid.

10 Yield 1.80 g (57%). ¹H NMR (400 MHz, DMSO) δ 8.18 (br s, 2H), 8.05 (s, 1H), 7.07 (s, 1H), 4.19-4.13 (m, 2H), 3.76 (s, 3H), 3.72-3.66 (m, 2H), 3.35 (s, 3H). m/z: [ESI⁺] 283 (M+H)⁺.

Synthesis of methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (6, Scheme 71)

15 [00396] Compound methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from methyl 2-amino-5-(2-methoxyethoxy)benzo[d]thiazole-6-carboxylate (0.80 g, 2.83 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.20 g, 3.11 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a yellow solid.

20 Yield 0.30 g (19%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 8.18 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.13 (s, 1H), 7.31 (s, 1H), 7.10 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (dd, *J* = 1.6, 12.4 Hz, 1H), 5.03-4.77 (m, 1H), 4.38-4.31 (m, 2H), 3.95 (s, 3H), 3.92-3.88 (m, 2H), 3.71-3.60 (m, 2H), 3.53 (s, 3H), 2.45-2.27 (m, 1H),
25 2.01-1.81 (m, 3H), 1.50-1.25 (m, 9H). m/z: [ESI⁺] 570 (M+H)⁺.

Synthesis of 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (7, Scheme 71)

30 [00397] Compound 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared from methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (300 mg, 0.527 mmol) following a similar procedure to that described for the synthesis of 2-(1-(tert-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid at 60°C, and was isolated as a yellow solid.

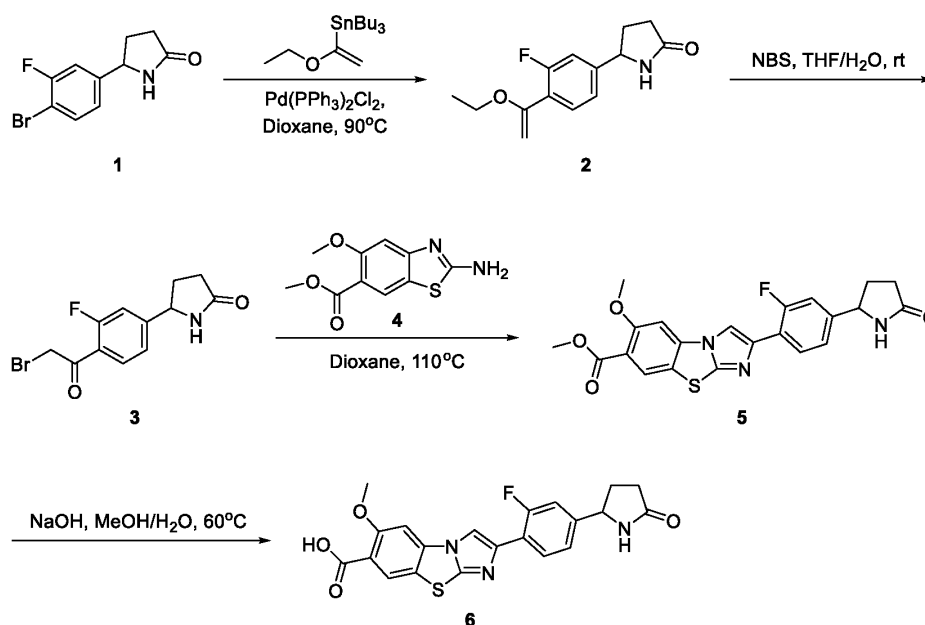
35 Yield 0.20 g (68%). ¹H NMR (400 MHz, CDCl₃) δ 8.31-8.06 (m, 2H), 8.02 (s, 1H), 7.28 (s, 1H), 7.13-7.00 (m, 1H), 7.00-6.93 (m, 1H), 5.02-4.74 (m, 1H), 4.37-4.24 (m, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.66 (t, *J* = 5.6 Hz, 2H), 3.47 (s, 3H), 2.43-2.29 (m, 1H), 2.03-1.85 (m, 3H), 1.50-1.25 (m, 9H). OH proton not observed. m/z: [ESI⁺] 556 (M+H)⁺.

Synthesis of *tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (**9**, *Scheme 71*)

[00398] Compound *tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (200 mg, 0.360 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (115 mg, 0.718 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was isolated as an orange oil.

Yield 105 mg (42%). ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H), 8.29 (br s, 1H), 8.18 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 7.10 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 (d, *J* = 12.4 Hz, 1H), 5.04-4.60 (m, 2H), 4.44-4.37 (m, 2H), 3.96-3.84 (m, 2H), 3.70-3.48 (m, 2H), 3.52 (s, 3H), 2.72-2.26 (m, 8H), 2.03-1.79 (m, 10H), 1.49-1.25 (m, 9H). *m/z*: [ESI⁺] 698 (M+H)⁺.

Synthesis of 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid



20 **Scheme 72**

Synthesis of 5-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidin-2-one (**2**, *Scheme 72*)

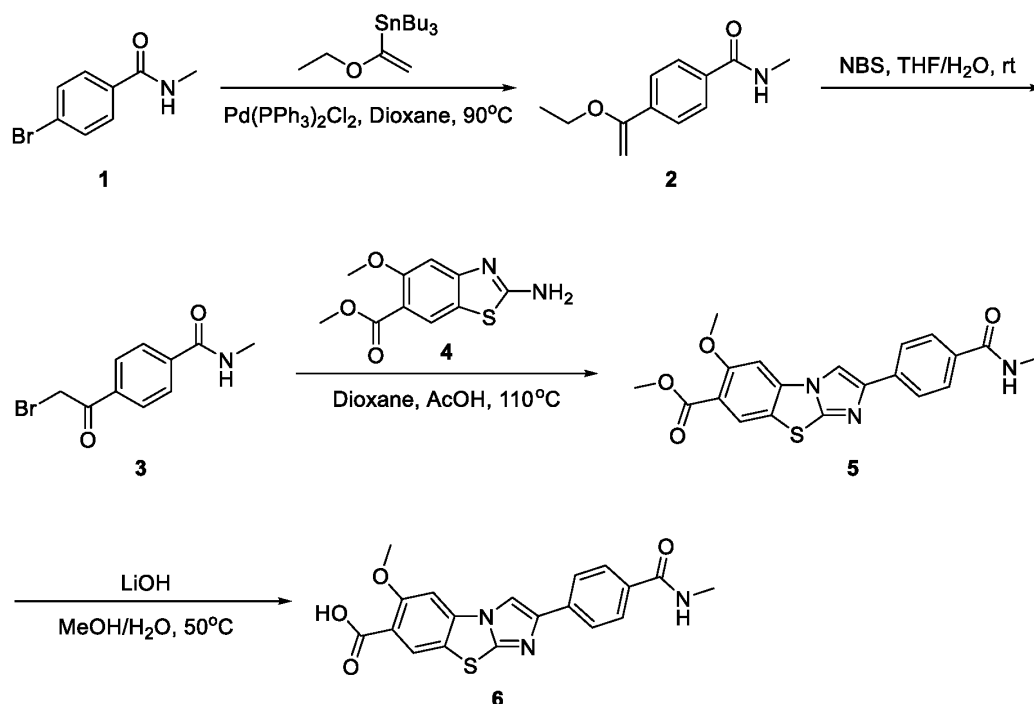
[00399] Compound 5-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidin-2-one was prepared from 5-(4-bromo-3-fluorophenyl)pyrrolidin-2-one (600 mg, 2.325 mmol) and tributyl(1-ethoxyvinyl)stannane

5 *Synthesis of 5-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidin-2-one (3, **Scheme 72**)*
 [00400] Compound 5-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidin-2-one was prepared from 5-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidin-2-one (500 mg, crude) and *N*-bromosuccinimide (370 mg, 2.079 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light yellow oil.
 10 Yield 300 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 300, 302 (M+H)⁺.

[00401] Compound methyl 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (290 mg, 1.217 mmol) and 5-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidin-2-one (330 mg, 1.100 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a brown solid. Yield 70 mg (14% over three steps). ¹H NMR (300 MHz, DMSO) δ 8.82-8.73 (m, 1H), 8.40-8.33 (m, 1H), 8.20-8.06 (m, 3H), 7.34-7.20 (m, 2H), 4.79-4.67 (m, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 2.57-2.53 (m, 1H), 2.32-2.21 (m, 2H), 1.91-1.74 (m, 1H). m/z: [ESI⁺] 440 (M+H)⁺.

[00402] Compound 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid was prepared from methyl 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylate (70 mg, 0.159 mmol) following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-5-fluoroinдолin-6-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid at 60°C, and was isolated as an off-white solid. Yield 65 mg (96%). ¹H NMR (300 MHz, DMSO) δ 12.79 (br s, 1H), 8.81-8.71 (m, 1H), 8.48 (br s, 1H), 8.40-8.29 (m, 1H), 8.18-8.04 (m, 2H), 7.32-7.21 (m, 2H), 4.79-4.68 (m, 1H), 3.97 (s, 3H), 2.58-2.43 (m, 1H), 2.33-2.13 (m, 2H), 1.93-1.74 (m, 1H). m/z: [ESI⁺] 426 (M+H)⁺.

Synthesis of 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid



Scheme 73

5

Synthesis of 4-(1-ethoxyvinyl)-N-methylbenzamide (2, Scheme 73)

[00403] Compound 4-(1-ethoxyvinyl)-N-methylbenzamide was prepared from 4-bromo-N-methylbenzamide (3.00 g, 14.01 mmol) and tributyl(1-ethoxyvinyl)stannane (6.07 g, 16.81 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a brown solid.

Yield 2.00 g (70%). ¹H NMR (400 MHz, DMSO) δ 8.45 (q, J = 4.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 4.87 (d, J = 2.8 Hz, 1H), 4.37 (d, J = 2.8 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 2.79 (d, J = 4.8 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H). m/z: [ESI⁺] 206 (M+H)⁺.

15 Synthesis of 4-(2-bromoacetyl)-N-methylbenzamide (3, Scheme 73)

[00404] Compound 4-(2-bromoacetyl)-N-methylbenzamide was prepared from 4-(1-ethoxyvinyl)-N-methylbenzamide (2.00 g, 9.74 mmol) and *N*-bromosuccinimide (1.91 g, 10.73 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a light brown solid.

20 Yield 1.00 g (40%). ¹H NMR (400 MHz, DMSO) δ 8.63 (q, J = 4.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 4.82 (s, 2H), 2.81 (d, J = 4.8 Hz, 3H). m/z: [ESI⁻] 254, 256 (M-H)⁻.

Synthesis of methyl 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (5, Scheme 73)

[00405] Compound methyl 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (1.00 g, 4.20 mmol) and 4-(2-bromoacetyl)-*N*-methylbenzamide (0.90 g, 3.51 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a light yellow solid.

Yield 0.33 g (24%). ¹H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.45 (q, *J* = 4.8 Hz, 1H), 8.38 (s, 1H), 7.92 (s, 4H), 7.88 (s, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 2.81 (d, *J* = 4.8 Hz, 3H). m/z: [ESI⁺] 396 (M+H)⁺.

Synthesis of 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (6, Scheme 73)

[00406] Compound 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared from methyl 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylate (0.33 g, 0.83 mmol) following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-5-fluoroindolin-6-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid at room temperature, and was isolated as an off-white solid.

Yield 0.20 g (63%). ¹H NMR (400 MHz, DMSO) δ 12.77 (br s, 1H), 8.93 (s, 1H), 8.46 (q, *J* = 4.8 Hz, 1H), 8.36 (s, 1H), 7.93 (s, 4H), 7.87 (s, 1H), 3.97 (d, 3H), 2.81 (d, *J* = 4.8 Hz, 3H). m/z: [ESI⁺] 382 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-

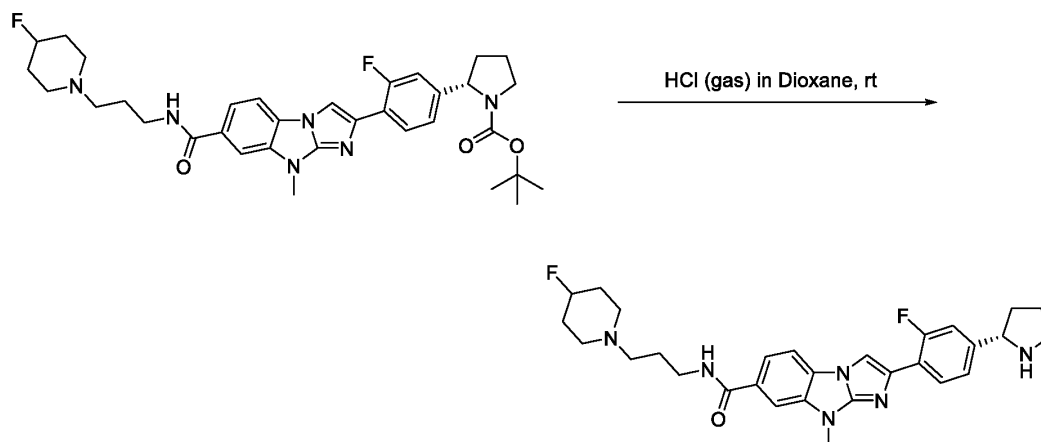
yl)phenyl)pyrrolidine-1-carboxylate

[00407] Compound *tert*-butyl 2-(3-fluoro-4-(6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 5-methoxybenzo[d]thiazol-2-amine (0.80 g, 4.44 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.89 g, 4.89 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate at 110°C, and was isolated as a yellow solid.

Yield 0.90 g (43%). ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.11 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.09 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.02-6.94 (m, 2H), 5.05-4.73 (m, 1H), 3.94 (s, 3H), 3.72-3.48 (m, 2H), 2.45-2.25 (m, 1H), 2.02-1.79 (m, 3H), 1.50-1.25 (m, 9H) m/z: [ESI⁺] 468 (M+H)⁺.

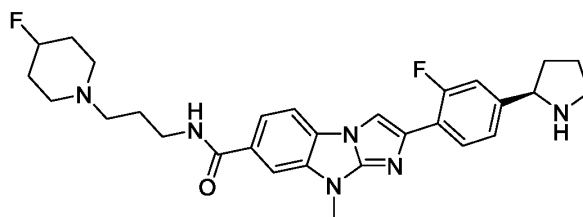
Final Compounds

Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride (**Compound 121S**)



- 5 [00408] A solution of *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (200 mg, 0.322 mmol) in HCl/1,4-dioxane (4 N, 3 mL) was stirred for 2 h at room temperature under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The solid was washed with dichloromethane (3 x 2 mL), diethyl ether (3 x 2 mL) and dried in a vacuum oven to afford (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride as a brown solid.
- 10 Yield 85 mg (44%). ¹H NMR (400 MHz, DMSO) δ 10.92 (br s, 1H), 10.39 (br s, 1H), 9.32 (brs, 1H), 8.97 (s, 1H), 8.55-8.46 (m, 1H), 8.40-8.29 (m, 2H), 8.14 (t, J = 6.8 Hz, 1H), 7.97-7.90 (m, 1H), 7.73-7.64 (m, 1H), 7.54 (d, J = 8.4 Hz, 1H), 5.12-4.71 (m, 1H), 4.66-4.55 (m, 1H), 4.10-3.97 (m, 3H), 3.57-3.47 (m, 1H),
- 15 3.45-3.39 (m, 4H), 3.35-3.24 (m, 1H), 3.22-2.97 (m, 4H), 2.47-2.37 (m, 1H), 2.35-1.96 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -111.83, -175.55, -186.58. m/z: [ESI⁺] 521 (M+H)⁺. (C₂₉H₃₆Cl₂F₂N₆O).

Synthesis of (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride (**Compound 121R**)

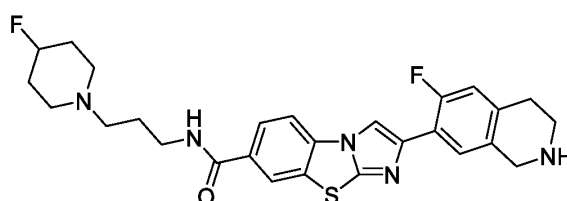


- 20 [00409] Compound (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (200 mg, 0.322 mmol)

following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a brown solid.

Yield 115 mg (60%). ¹H NMR (400 MHz, DMSO) δ 10.92 (br s, 1H), 10.39 (br s, 1H), 9.32 (brs, 1H), 8.97 (s, 1H), 8.55-8.46 (m, 1H), 8.40-8.29 (m, 2H), 8.14 (t, *J* = 6.8 Hz, 1H), 7.97-7.90 (m, 1H), 7.73-7.64 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 5.12-4.71 (m, 1H), 4.66-4.55 (m, 1H), 4.10-3.97 (m, 3H), 3.57-3.47 (m, 1H), 3.45-3.39 (m, 4H), 3.35-3.24 (m, 1H), 3.22-2.97 (m, 4H), 2.47-2.37 (m, 1H), 2.35-1.96 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -112.41, -175.61, -186.59. *m/z*: [ESI⁺] 521 (M+H)⁺. (C₂₉H₃₆Cl₂F₂N₆O).

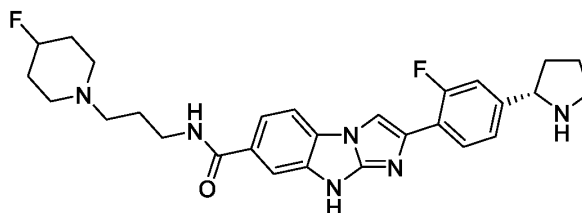
- 10 *Synthesis of 2-(6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 301)*



- [00410] Compound 2-(6-fluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 6-fluoro-7-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (580 mg, 0.951 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a pink solid.
- 20 Yield 168 mg (30%). ¹H NMR (400 MHz, DMSO) δ 10.79 (br s, 1H), 9.60 (br s, 2H), 8.94-8.87 (m, 1H), 8.74 (d, *J* = 3.6 Hz, 1H), 8.57 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.09 (dd, *J* = 1.6, 8.4 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 12.0 Hz, 1H), 5.10-4.71 (m, 1H), 4.38-4.28 (m, 2H), 3.56-3.47 (m, 1H), 3.45-3.33 (m, 5H), 3.21-2.94 (m, 6H), 2.31-1.94 (m, 6H). ¹⁹F NMR (376 MHz, DMSO) δ -115.67, -175.53, -186.62. *m/z*: [ESI⁺] 510 (M+H)⁺. (C₂₇H₃₁Cl₂F₂N₅OS).

25

*Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride (Compound 122S)*

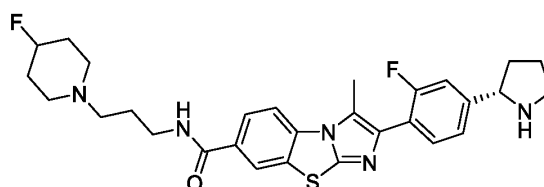


- [00411] Compound (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*S*)-

2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenyl)pyrrolidine-1-carboxylate (40 mg, 0.066 mmol) following a similar procedure to that described for the synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride, and was isolated as a yellow solid.

Yield 20 mg (52%). ¹H NMR (400 MHz, DMSO) δ 10.92 (br s, 1H), 10.47 (br s, 1H), 9.43 (br s, 1H), 8.96 (br s, 1H), 8.63-8.48 (m, 1H), 8.30-8.04 (m, 3H), 8.02-7.86 (m, 1H), 7.77-7.65 (m, 1H), 7.61-7.50 (m, 1H), 5.13-4.71 (m, 1H), 4.70-4.54 (m, 1H), 3.53-3.45 (m, 1H), 3.44-3.34 (m, 4H), 3.34-3.23 (m, 1H), 3.20-2.98 (m, 4H), 2.47-2.37 (m, 1H), 2.32-1.96 (m, 9H). One active proton not observed. ¹⁹F NMR (376 MHz, DMSO) δ -111.61, -175.54, -186.62. m/z: [ESI⁺] 507 (M+H)⁺. (C₂₈H₃₄Cl₂F₂N₆O).

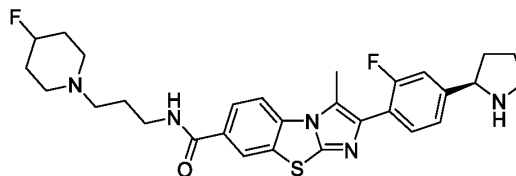
Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 103S)



[00412] Compound (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (46 mg, 0.072 mmol) following a similar procedure to that described for the synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride, and was isolated as a light yellow solid.

Yield 33 mg (75%). ¹H NMR (400 MHz, DMSO) δ 10.87 (br s, 1H), 10.36 (br s, 1H), 9.23 (br s, 1H), 8.93 (d, *J* = 7.2 Hz, 1H), 8.64-8.52 (m, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.07 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.74-7.67 (m, 1H), 7.67-7.58 (m, 1H), 7.53-7.48 (m, 1H), 5.10-4.72 (m, 1H), 4.70-4.58 (m, 1H), 3.59-3.47 (m, 1H), 3.46-3.35 (m, 4H), 3.35-3.24 (m, 1H), 3.22-2.96 (m, 4H), 2.72 (d, *J* = 2.0 Hz, 3H), 2.47-2.39 (m, 1H), 2.33-1.96 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -113.52, -175.60, -186.61. m/z: [ESI⁺] 538 (M+H)⁺. (C₂₉H₃₅Cl₂F₂N₅OS).

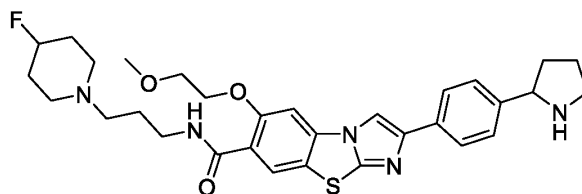
Synthesis of (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 103S)



[00413] Compound (*R*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-3-methylbenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*R*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-3-methylbenzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (38 mg, 0.060 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a light yellow solid.

Yield 26 mg (71%). ¹H NMR (400 MHz, DMSO) δ 10.73 (br s, 1H), 10.22 (br s, 1H), 9.15 (br s, 1H), 8.93 (d, *J* = 7.2 Hz, 1H), 8.64-8.52 (m, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.07 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.74-7.67 (m, 1H), 7.67-7.58 (m, 1H), 7.53-7.48 (m, 1H), 5.10-4.72 (m, 1H), 4.70-4.58 (m, 1H), 3.59-3.47 (m, 1H), 3.46-3.35 (m, 4H), 3.35-3.24 (m, 1H), 3.22-2.96 (m, 4H), 2.72 (d, *J* = 2.0 Hz, 3H), 2.47-2.39 (m, 1H), 2.33-1.96 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -113.52, -175.60, -186.61. m/z: [ESI⁺] 538 (M+H)⁺. (C₂₉H₃₅Cl₂F₂N₅OS).

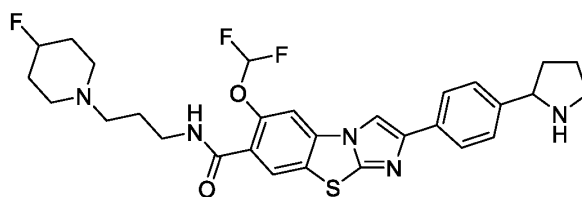
Synthesis of N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (**Compound 150**)



[00414] Compound *N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-methoxyethoxy)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (33 mg, 0.049 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a white solid.

Yield 13 mg (41%). ¹H NMR (400 MHz, DMSO) δ 11.06 (br s, 1H), 10.31 (br s, 1H), 9.08 (br s, 1H), 8.97-8.86 (m, 1H), 8.49-8.35 (m, 2H), 8.06-7.96 (m, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 5.11-4.71 (m, 1H), 4.60-4.50 (m, 1H), 4.47-4.36 (m, 2H), 3.89-3.81 (m, 2H), 3.55-3.47 (m, 1H), 3.45-3.34 (m, 7H), 3.34-3.24 (m, 1H), 3.18-2.95 (m, 4H), 2.44-2.35 (m, 1H), 2.32-1.96 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -175.55, -186.68. m/z: [ESI⁺] 580 (M+H)⁺. (C₃₁H₄₀Cl₂FN₅O₃S)

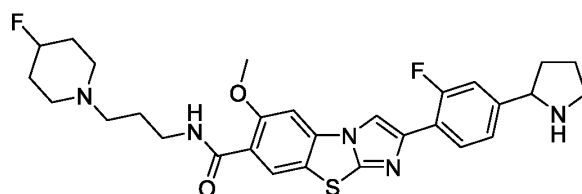
Synthesis of 6-(difluoromethoxy)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (**Compound 164**)



[00415] Compound 6-(difluoromethoxy)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide was prepared from *tert*-butyl 2-(4-(6-(difluoromethoxy)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (70 mg, 0.104 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a yellow solid.

Yield 27 mg (40%). ¹H NMR (400 MHz, DMSO) δ 11.05 (br s, 1H), 10.36 (br s, 1H), 9.11 (br s, 1H), 8.98 (s, 1H), 8.74-8.62 (m, 1H), 8.32 (s, 1H), 8.05 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 73.6 Hz, 1H), 5.13-4.72 (m, 1H), 4.64-4.46 (m, 1H), 3.55-3.21 (m, 6H), 3.21-2.95 (m, 4H), 2.45-1.92 (m, 10H). ¹⁹F NMR (376 MHz, DMSO) δ -81.40, -175.83, -186.73. m/z: [ESI⁺] 572 (M+H)⁺. (C₂₉H₃₄Cl₂F₃N₅O₂S)

Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (**Compound 144**)

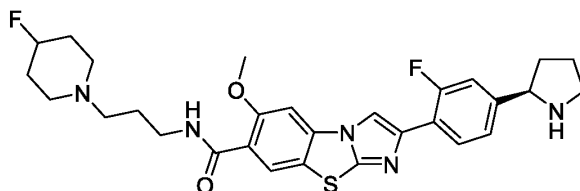


[00416] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (60 mg, 0.092 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a yellow solid.

Yield 16 mg (28%). ¹H NMR (400 MHz, DMSO) δ 10.68 (br s, 1H), 10.14 (br s, 1H), 9.09 (br s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 6.0 Hz, 1H), 8.37 (s, 1H), 8.21 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.12 (s, 1H), 7.61 (d, *J* = 12.4 Hz, 1H), 7.47 (dd, *J* = 1.6, 8.0 Hz, 1H), 5.13-4.71 (m, 1H), 4.65-4.52 (m, 1H),

4.04 (s, 3H), 3.45-3.23 (m, 6H), 3.16-2.94 (m, 4H), 2.46-2.33 (m, 1H), 2.26-1.92 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ -113.03, -175.58, -186.61. m/z: [ESI $^{+}$] 554 (M+H) $^{+}$. (C₂₉H₃₅Cl₂F₂N₅O₂S)

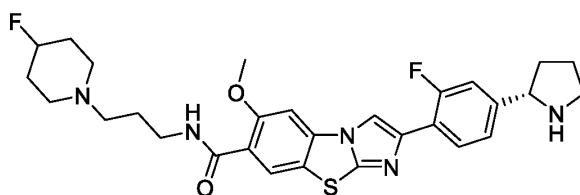
Synthesis of (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (**Compound 149R**)



[00417] Compound (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (35 mg, 0.054 mmol) following a similar procedure to that described for the synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride, and was isolated as a yellow solid.

Yield 10 mg (30%). ^1H NMR (400 MHz, DMSO) δ 10.85 (br s, 1H), 10.24 (br s, 1H), 9.14 (br s, 1H), 8.85 (d, J = 3.6 Hz, 1H), 8.50 (t, J = 6.0 Hz, 1H), 8.37 (s, 1H), 8.21 (dd, J = 8.0, 8.0 Hz, 1H), 8.12 (s, 1H), 7.61 (d, J = 12.4 Hz, 1H), 7.47 (dd, J = 1.6, 8.0 Hz, 1H), 5.13-4.71 (m, 1H), 4.65-4.52 (m, 1H), 4.04 (s, 3H), 3.45-3.23 (m, 6H), 3.16-2.94 (m, 4H), 2.46-2.33 (m, 1H), 2.26-1.92 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ -113.03. Aliphatic ^{19}F signal not observed. m/z: [ESI $^{+}$] 554 (M+H) $^{+}$. (C₂₉H₃₅Cl₂F₂N₅O₂S)

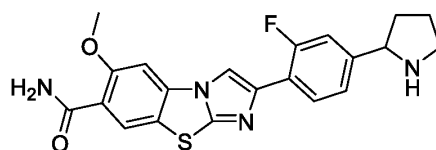
Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (**Compound 149S**)



[00418] Compound (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (35 mg, 0.054 mmol) following a similar procedure to that described for the synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride, and was isolated as a yellow solid.

Yield 12 mg (36%). ^1H NMR (400 MHz, DMSO) δ 10.85 (br s, 1H), 10.24 (br s, 1H), 9.14 (br s, 1H), 8.85 (d, J = 3.6 Hz, 1H), 8.50 (t, J = 6.0 Hz, 1H), 8.37 (s, 1H), 8.21 (dd, J = 8.0, 8.0 Hz, 1H), 8.12 (s, 1H), 7.61 (d, J = 12.4 Hz, 1H), 7.47 (dd, J = 1.6, 8.0 Hz, 1H), 5.13-4.71 (m, 1H), 4.65-4.52 (m, 1H), 4.04 (s, 3H), 3.45-3.23 (m, 6H), 3.16-2.94 (m, 4H), 2.46-2.33 (m, 1H), 2.26-1.92 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ -113.03. Aliphatic ^{19}F signal not observed. m/z : $[\text{ESI}^+]$ 554 ($\text{M}+\text{H}$) $^+$. ($\text{C}_{29}\text{H}_{35}\text{Cl}_2\text{F}_2\text{N}_5\text{O}_2\text{S}$)

Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide hydrochloride (Compound 155)



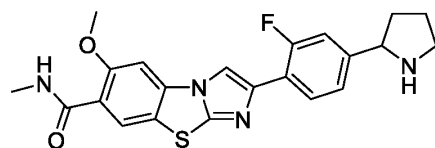
10

[00419] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide hydrochloride was prepared from *tert*-butyl 2-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (50 mg, 0.098 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a white solid.

Yield 20 mg (46%). ^1H NMR (400 MHz, DMSO) δ 10.19 (br s, 1H), 9.11 (br s, 1H), 8.85 (d, J = 3.6 Hz, 1H), 8.43 (s, 1H), 8.21 (dd, J = 8.0, 8.0 Hz, 1H), 8.12 (s, 1H), 7.75 (br s, 1H), 7.67 (br s, 1H), 7.62 (dd, J = 1.6, 12.4 Hz, 1H), 7.47 (dd, J = 1.6, 8.0 Hz, 1H), 4.66-4.55 (m, 1H), 4.04 (s, 3H), 3.45-3.23 (m, 2H), 2.47-2.36 (m, 1H), 2.19-1.98 (m, 3H). ^{19}F NMR (376 MHz, DMSO) δ -112.99. m/z : $[\text{ESI}^+]$ 411 ($\text{M}+\text{H}$) $^+$. ($\text{C}_{21}\text{H}_{20}\text{ClFN}_4\text{O}_2\text{S}$)

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Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide hydrochloride (Compound 160)



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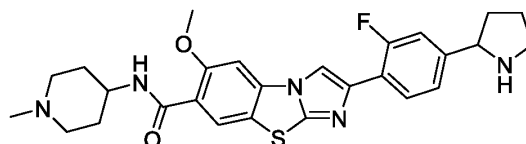
[00420] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-*N*-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide hydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(methylcarbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (20 mg, 0.038 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a light yellow solid.

30

Yield 10 mg (57%). ^1H NMR (400 MHz, DMSO) δ 10.39 (br s, 1H), 9.23 (br s, 1H), 8.85 (d, J = 3.6 Hz, 1H), 8.38 (s, 1H), 8.33-8.24 (m, 1H), 8.24-8.15 (m, 1H), 8.12 (s, 1H), 7.64 (d, J = 12.4 Hz, 1H),

7.50-4.46 (m, 1H), 4.64-4.52 (m, 1H), 4.03 (s, 3H), 3.47-3.21 (m, 2H), 2.84 (d, $J = 4.4$ Hz, 3H), 2.46-2.34 (m, 1H), 2.18-1.96 (m, 3H). ^{19}F NMR (376 MHz, DMSO) δ -112.96. m/z: $[\text{ESI}^+]$ 425 (M+H) $^+$. ($\text{C}_{22}\text{H}_{22}\text{ClFN}_4\text{O}_2\text{S}$)

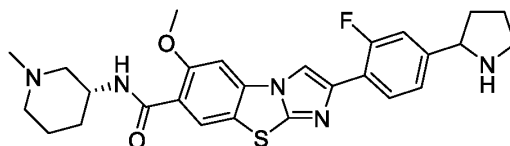
- 5 *Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 175)*



- [00421] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (100 mg, 0.165 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as an off-white solid.
- 15 Yield 30 mg (31%). ^1H NMR (400 MHz, DMSO) δ 10.65 (br s, 1H), 10.26 (br s, 1H), 9.15 (br s, 1H), 8.84 (d, $J = 3.6$ Hz, 1H), 8.36-8.28 (m, 1H), 8.24-8.18 (m, 2H), 8.14-8.09 (m, 1H), 7.63 (dd, $J = 1.6$, 12.4 Hz, 1H), 7.48 (dd, $J = 1.6$, 8.0 Hz, 1H), 4.65-4.57 (m, 1H), 4.25-3.93 (m, 4H), 3.49-3.23 (m, 4H), 3.23-3.02 (m, 2H), 2.80-2.67 (m, 3H), 2.45-2.36 (m, 1H), 2.18-1.96 (m, 5H), 1.94-1.81 (m, 2H). ^{19}F NMR (376 MHz, DMSO) δ -113.05. m/z: $[\text{ESI}^+]$ 508 (M+H) $^+$. ($\text{C}_{27}\text{H}_{32}\text{Cl}_2\text{FN}_5\text{O}_2\text{S}$)

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Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((R)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 153R)

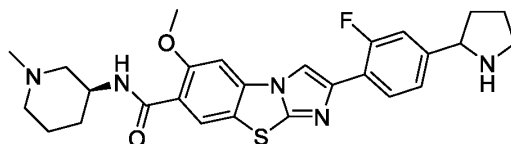


- [00422] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((R)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(((R)-1-methylpiperidin-3-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (50 mg, 0.082 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as a white solid.

Yield 20 mg (42%). ^1H NMR (400 MHz, DMSO) δ 10.95 (br s, 0.24H), 10.81 (br s, 0.76H), 10.35 (br s, 1H), 9.21 (br s, 1H), 8.85 (dd, $J = 1.2$, 3.6 Hz, 0.76H), 8.73 (d, $J = 7.6$ Hz, 0.24H), 8.35-8.31 (m, 1H), 8.27 (s, 1H), 8.21 (dd, $J = 1.6$, 8.0 Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.64 (dd, $J = 1.6$, 12.4 Hz, 1H),

7.48 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.67-4.54 (m, 1H), 4.48-4.37 (m, 0.24H), 4.37-4.19 (m, 0.76H), 4.01 (s, 3H), 3.57-3.45 (m, 1H), 3.45-3.19 (m, 4H), 3.04-2.81 (m, 2H), 2.79 (d, $J = 4.8$ Hz, 2.28H, part of NCH₃), 2.75 (d, $J = 4.8$ Hz, 0.72H, part of NCH₃), 2.45-2.35 (m, 1H), 2.21-1.72 (m, 5H), 1.60-1.44 (m, 1H). ¹⁹F NMR (376 MHz, DMSO) δ -113.03. m/z: [ESI⁺] 508 (M+H)⁺. (C₂₇H₃₂Cl₂FN₅O₂S). Isolated as 19:6 ratio of two diastereomers.

Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((S)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 153S)

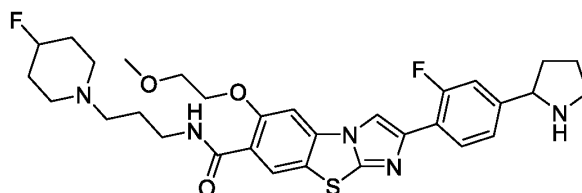


[00423] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((S)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-(((S)-1-methylpiperidin-3-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (50 mg, 0.082 mmol) following a similar procedure to that described for the synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide dihydrochloride, and was isolated as a light yellow solid.

Yield 20 mg (42%). ¹H NMR (400 MHz, DMSO) δ 10.95 (br s, 0.24H), 10.81 (br s, 0.76H), 10.35 (br s, 1H), 9.21 (br s, 1H), 8.85 (dd, $J = 1.2, 3.6$ Hz, 0.76H), 8.73 (d, $J = 7.6$ Hz, 0.24H), 8.35-8.31 (m, 1H), 8.27 (s, 1H), 8.21 (dd, $J = 1.6, 8.0$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.64 (dd, $J = 1.6, 12.4$ Hz, 1H), 7.48 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.67-4.54 (m, 1H), 4.48-4.37 (m, 0.24H), 4.37-4.19 (m, 0.76H), 4.01 (s, 3H), 3.57-3.45 (m, 1H), 3.45-3.19 (m, 4H), 3.04-2.81 (m, 2H), 2.79 (d, $J = 4.8$ Hz, 2.28H, part of NCH₃), 2.75 (d, $J = 4.8$ Hz, 0.72H, part of NCH₃), 2.45-2.35 (m, 1H), 2.21-1.72 (m, 5H), 1.60-1.44 (m, 1H). ¹⁹F NMR (376 MHz, DMSO) δ -113.03. m/z: [ESI⁺] 508 (M+H)⁺. (C₂₇H₃₂Cl₂FN₅O₂S). Isolated as 19:6 ratio of two diastereomers.

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Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 166)

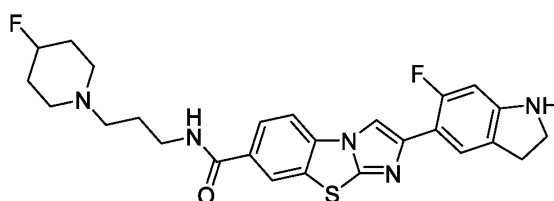


[00424] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(7-(((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-(2-

methoxyethoxy)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (105 mg, 0.150 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as an off-white solid.

- 5 Yield 96 mg (95%). ¹H NMR (400 MHz, DMSO) δ 11.02 (br s, 1H), 10.35 (br s, 1H), 9.22 (br s, 1H), 8.80 (d, *J* = 3.6 Hz, 1H), 8.42 (s, 1H), 8.25-8.14 (m, 2H), 7.64 (dd, *J* = 1.6, 12.4 Hz, 1H), 7.48 (dd, *J* = 1.6, 8.0 Hz, 1H), 5.10-4.70 (m, 1H), 4.67-4.51 (m, 1H), 4.46-4.35 (m, 2H), 3.90-3.81 (m, 2H), 3.55-3.46 (m, 1H), 3.45-3.35 (m, 8H), 3.33-3.21 (m, 1H), 3.20-2.93 (m, 4H), 2.44-2.34 (m, 1H), 2.34-1.95 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -113.05, -175.57, -186.72. m/z: [ESI⁺] 598 (M+H)⁺.
- 10 (C₃₁H₃₉Cl₂F₂N₅O₃S)

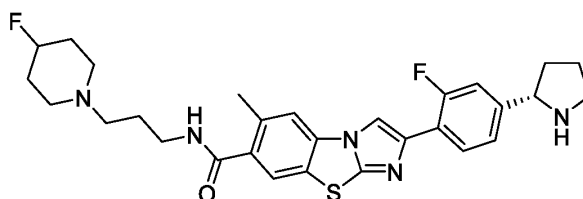
*Synthesis of 2-(6-fluoroindolin-5-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (Compound 303)*



- 15 [00425] A mixture of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate (80 mg, 0.134 mmol) in a solution of hydrochloride (gas) in 1,4-dioxane (4 mL) and dichloromethane (2 mL) was stirred for 3 h at room temperature under a nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was basified to pH 7 with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with the following conditions; column, C18 silica gel, 20-40 μ m, 120 g; Mobile phase A: water (10 mmol/L ammonium bicarbonate); Mobile phase B: acetonitrile; Gradient: 30% - 50% B in 25 min; Flow rate: 60 mL/min; Detector, UV 254 nm. The fractions containing desired product were collected at 45% B and concentrated under reduced pressure to afford 2-(6-fluoroindolin-5-yl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide as a white solid.
- 20
- 25

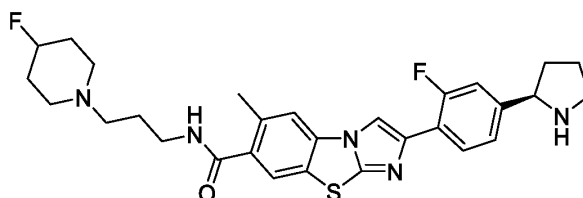
- Yield 8 mg (12%). ¹H NMR (400 MHz, DMSO) δ 8.58 (t, *J* = 5.6 Hz, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), 8.38 (d, *J* = 3.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 12.4 Hz, 1H), 5.95 (s, 1H), 4.76-4.57 (m, 1H), 3.56-3.49 (m, 2H), 3.33-3.32 (m, 2H), 2.96 (t, *J* = 8.4 Hz, 2H), 2.59-2.51 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.32-2.24 (m, 2H), 1.93-1.77 (m, 2H), 1.76-1.63 (m, 4H). ¹⁹F NMR (376 MHz, DMSO) δ -115.61, Aliphatic ¹⁹F signal not observed. m/z: [ESI⁺] 496 (M+H)⁺. (C₂₆H₂₇F₂N₅OS).
- 30

Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (Compound 102S)



- [00426] Compound (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide was prepared from *tert*-butyl (S)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (150 mg, 0.235 mmol) following a similar procedure to that described for the synthesis of 2-(6-fluoroindolin-5-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide, and was isolated as a light yellow solid.
- Yield 50 mg (40%). ¹H NMR (400 MHz, DMSO) δ 8.59 (d, J = 3.6 Hz, 1H), 8.41 (t, J = 5.6 Hz, 1H), 8.10 (d, J = 4.4 Hz, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.37-7.06 (m, 2H), 4.91-4.56 (m, 1H), 4.10 (t, J = 7.6 Hz, 1H), 3.29-3.23 (m, 2H), 3.05-2.97 (m, 1H), 2.95-2.86 (m, 1H), 2.60-2.52 (m, 2H), 2.48 (s, 3H), 2.37 (t, J = 7.2 Hz, 2H), 2.34-2.24 (m, 2H), 2.22-2.10 (m, 1H), 1.93-1.61 (m, 8H), 1.56-1.45 (m, 1H). Active NH proton of pyrrolidine not observed. ¹⁹F NMR (376 MHz, DMSO) δ -114.20.
- Aliphatic ¹⁹F signal not observed. m/z: [ESI⁺] 538 (M+H)⁺. (C₂₉H₃₃F₂N₅OS).

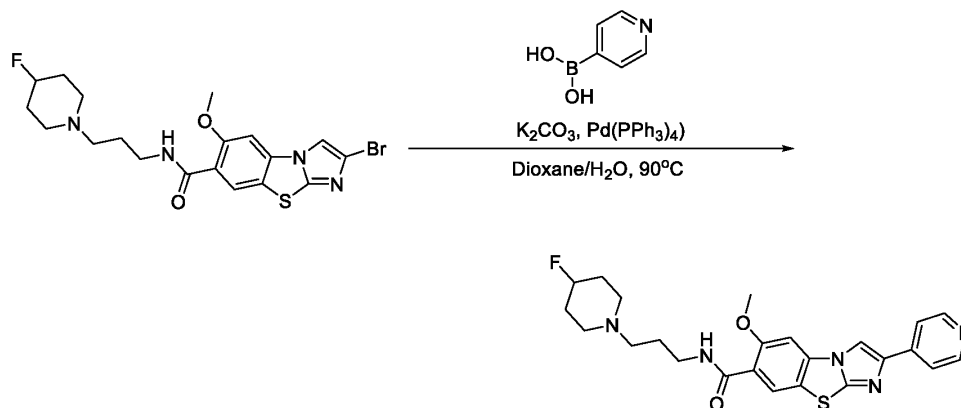
Synthesis of (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (Compound 102R)



- [00427] Compound (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide was prepared from *tert*-butyl (R)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methylbenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (110 mg, 0.172 mmol) following a similar procedure to that described for the synthesis of 2-(6-fluoroindolin-5-yl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide, and was isolated as a white solid.
- Yield 40 mg (43%). ¹H NMR (400 MHz, DMSO) δ 8.59 (d, J = 3.6 Hz, 1H), 8.41 (t, J = 5.6 Hz, 1H), 8.10 (d, J = 4.4 Hz, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.37-7.06 (m, 2H), 4.91-4.56 (m, 1H), 4.10 (t, J = 7.6 Hz, 1H), 3.29-3.23 (m, 2H), 3.05-2.97 (m, 1H), 2.95-2.86 (m, 1H), 2.60-2.52 (m, 2H), 2.48 (s, 3H), 2.37 (t, J = 7.2 Hz, 2H), 2.34-2.24 (m, 2H), 2.22-2.10 (m, 1H), 1.93-1.61 (m, 8H), 1.56-

1.45 (m, 1H). Pyrrolidine N-H not observed. ^{19}F NMR (376 MHz, DMSO) δ -114.20. Aliphatic ^{19}F signal not observed. m/z: $[\text{ESI}^+]$ 538 (M+H) $^+$. ($\text{C}_{29}\text{H}_{33}\text{F}_2\text{N}_5\text{OS}$).

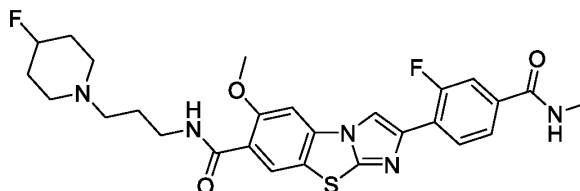
Synthesis of *N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyridin-4-yl)benzo[d]imidazo[2,1-
b]thiazole-7-carboxamide (**Compound 161**)



[00428] To a stirred mixture of 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-
b]thiazole-7-carboxamide (60 mg, 0.128 mmol) and pyridin-4-ylboronic acid (23 mg, 0.187 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL) were added potassium carbonate (34 mg, 0.246 mmol) and tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 16 h at 90°C. The mixture was cooled to room temperature and purified directly by reverse phase flash column chromatography with the following conditions; Column: WelFlash TM C18-I, 20-40 μm , 80 g; Eluent A: water (plus 10 mmol/L ammonium bicarbonate); Eluent B: acetonitrile; Gradient: 45% - 60% B in 25 min; Flow rate: 30 mL/min; Detector: UV 220/254 nm. Desired fractions were collected at 58% B, concentrated under reduced pressure and lyophilized to afford *N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyridin-4-yl)benzo[d]imidazo[2,1-
b]thiazole-7-carboxamide as a white solid.

Yield 8 mg (13%). ^1H NMR (400 MHz, DMSO) δ 9.06 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 8.34 (s, 1H), 8.28 (t, J = 5.6 Hz, 1H), 7.89 (s, 1H), 7.78 (d, J = 6.0 Hz, 2H), 4.79-4.53 (m, 1H), 4.02 (s, 3H), 3.37-3.29 (m, 2H), 2.57-2.50 (m, 2H), 2.40-2.32 (m, 2H), 2.32-2.24 (m, 2H), 1.94-1.77 (m, 2H), 1.77-1.64 (m, 4H). ^{19}F signal not observed. m/z: $[\text{ESI}^+]$ 468 (M+H) $^+$. ($\text{C}_{24}\text{H}_{26}\text{FN}_5\text{O}_2\text{S}$)

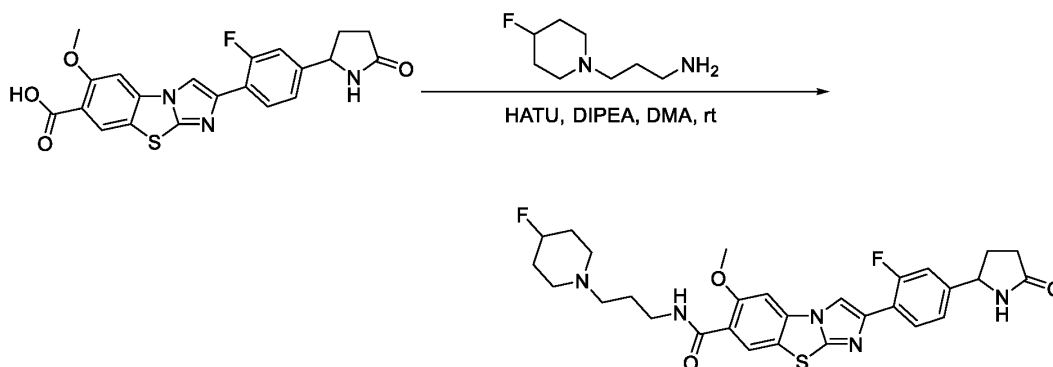
Synthesis of 2-(2-fluoro-4-(methylcarbamoyl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-
b]thiazole-7-carboxamide hydrochloride (**Compound 159**)



[00429] Compound 2-(2-fluoro-4-(methylcarbamoyl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide hydrochloride was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide (100 mg, 0.213 mmol) and (2-fluoro-4-(methylcarbamoyl)phenyl)boronic acid (60 mg, 0.305 mmol) following a similar procedure to that described for the synthesis of *N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyridin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide. After completion, the resulting solution was cooled to room temperature and purified directly by reverse phase flash column chromatography with the following conditions; Column: WelFlash TM C18-I, 20-40 μ m, 120 g; Eluent A: water (plus 10 mmol/L hydrochloric acid); Eluent B: acetonitrile; Gradient: 20% - 40% B in 25 min; Flow rate: 45 mL/min; Detector: UV 220/254 nm. Desired fractions were collected at 29% B, concentrated under reduced pressure, and lyophilized to afford 2-(2-fluoro-4-(methylcarbamoyl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide as a yellow solid.

Yield 20 mg (16%). ¹H NMR (400 MHz, DMSO) δ 10.55 (br s, 1H), 8.89 (d, *J* = 3.6 Hz, 1H), 8.66-8.55 (m, 1H), 8.55-8.45 (m, 1H), 8.37 (s, 1H), 8.24 (t, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.87-7.76 (m, 2H), 5.13-4.71 (m, 1H), 4.05 (s, 3H), 3.56-3.47 (m, 1H), 3.47-3.33 (m, 3H), 3.25-2.94 (m, 4H), 2.91-2.77 (m, 3H), 2.38-1.89 (m, 6H). ¹⁹F NMR (376 MHz, DMSO) δ -113.36, -175.87, -186.63. *m/z*: [ESI⁺] 542 (M+H)⁺. (C₂₇H₃₀ClF₂N₅O₃S)

20 *Synthesis of 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide (Compound 151)*



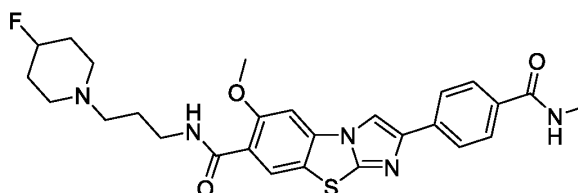
[00430] Compound 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide was prepared from 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid (70 mg, 0.165 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (40 mg, 0.250 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 5-fluoro-6-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate, and was purified by reverse phase flash column chromatography with the following conditions; Column: C18 Column 80 g; Mobile Phase A: water (10 mmol/L ammonium bicarbonate), Mobile Phase B: methanol; Flow rate: 30

mL/min; Gradient: 55% - 70% B in 30 min; Detector: UV 254/215 nm. The fractions containing the desired product were collected at 65% B, concentrated under reduced pressure and lyophilized to afford 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide as a white solid.

- 5 Yield 17 mg (18%). ¹H NMR (400 MHz, DMSO) δ 8.77 (d, *J* = 3.6 Hz, 1H), 8.33 (s, 1H), 8.27 (t, *J* = 5.6 Hz, 1H), 8.18-8.12 (m, 2H), 8.09 (s, 1H), 7.33-7.22 (m, 2H), 4.78-4.69 (m, 1H), 4.78-4.56 (m, 1H), 4.02 (s, 3H), 3.40-3.26 (m, 2H), 2.60-2.47 (m, 3H), 2.40-2.21 (m, 6H), 1.93-1.76 (m, 3H), 1.76-1.61 (m, 4H). ¹⁹F NMR (376 MHz, DMSO) δ -113.51, Aliphatic ¹⁹F signal not observed. *m/z*: [ESI⁺] 568 (M+H)⁺. (C₂₉H₃₁F₂N₅O₃S)

10

Synthesis of N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide (Compound 157)



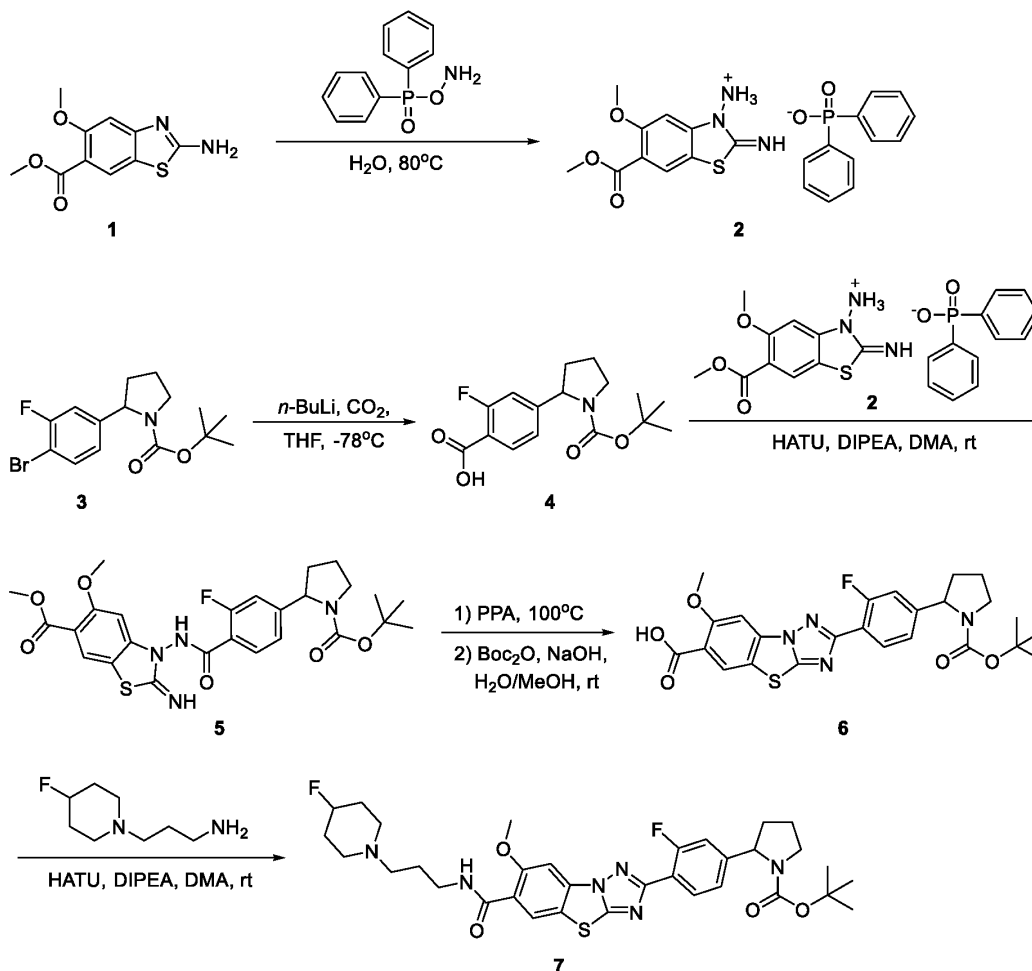
- [00431] Compound *N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide was prepared from 6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid (150 mg, 0.393 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (82 mg, 0.512 mmol) following a similar procedure to that described for the synthesis of 2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide, and was isolated as a yellow solid.

- Yield 35 mg (17%). ¹H NMR (400 MHz, DMSO) δ 8.91 (s, 1H), 8.45 (q, *J* = 4.4 Hz, 1H), 8.34 (s, 1H), 8.27 (t, *J* = 5.6 Hz, 1H), 7.93 (s, 4H), 7.87 (s, 1H), 4.77-4.57 (m, 1H), 4.02 (s, 3H), 3.38-3.26 (m, 2H), 2.81 (d, *J* = 4.4 Hz, 3H), 2.58-2.49 (m, 2H), 2.40-2.33 (m, 2H), 2.33-2.22 (m, 2H), 1.96-1.77 (m, 2H), 1.77-1.60 (m, 4H). ¹⁹F signal not observed. *m/z*: [ESI⁺] 524 (M+H)⁺. (C₂₇H₃₀FN₅O₃S)

25

Intermediate Preparations

Synthesis of tert-butyl 2-(3-fluoro-4-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-7-methoxybenzo[4,5]thiazolo[3,2-b][1,2,4]triazol-2-yl)phenyl)pyrrolidine-1-carboxylate

**5 Scheme 74.**

Synthesis of 2-imino-5-methoxy-6-(methoxycarbonyl)benzo[d]thiazol-3(2H)-aminium diphenylphosphinate (2, Scheme 74)

- [00432] A mixture of methyl 2-amino-5-methoxy-1,3-benzothiazole-6-carboxylate (5.00 g, 20.99 mmol) and amino diphenylphosphinate (10.00 g, 42.88 mmol) in water (60 mL) was stirred for 4 h at 80°C under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with water (3 x 20 mL) and the combined filtrate was concentrated under reduced pressure. The residue was triturated with acetonitrile (60 mL) for 30 min. The precipitated solids were collected by filtration, washed with acetonitrile (3 x 20 mL) and oven dried to afford 2-imino-5-methoxy-6-(methoxycarbonyl)-1,3-benzothiazol-3-aminium diphenylphosphinate as a white solid. T

Yield 4.00 g (40%). ¹H NMR (300 MHz, DMSO) δ 7.93 (s, 1H), 7.71-7.62 (m, 4H), 7.38-7.25 (m, 8H), 6.96 (s, 1H), 5.68 (br s, 2H), 3.87 (s, 3H), 3.77 (s, 3H). m/z: [ESI⁺] 254 (M+H)⁺. Observed as the ammonium cationic fragment.

5 *Synthesis of 4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzoic acid(4, Scheme 74)*

[00433] A solution of *tert*-butyl 2-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (5.60 g, 16.27 mmol) in tetrahydrofuran (70 mL) was treated with *n*-butyl lithium (2.5 N in hexane, 8.00 mL, 20.00 mmol) for 1 h at -78°C under a nitrogen atmosphere. Dry ice (5.00 g, 113.61 mmol) was added as a single portion and the reaction mixture was stirred for an additional 1 h at -78°C. The reaction was
10 quenched with saturated aqueous ammonium chloride solution (100 mL) at room temperature. The mixture was acidified to pH 5 with acetic acid and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrates were concentrated under reduced pressure to give 4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzoic acid as a colorless oil, which was used directly in the
15 next step without further purification.

Yield 4.00 g (79%). ¹H NMR (300 MHz, DMSO) δ 12.80 (br s, 1H), 7.90-7.72 (m, 1H), 7.18-6.95 (m, 2H), 4.90-4.66 (m, 1H), 3.62-3.39 (m, 2H), 2.40-2.22 (m, 1H), 1.87-1.62 (m, 3H), 1.38-1.14 (m, 9H). m/z: [ESI⁺] 254 (M+H-56)⁺.

20 *Synthesis of methyl 3-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzamido)-2-imino-5-methoxy-2,3-dihydrobenzo[d]thiazole-6-carboxylate (5, Scheme 74)*

[00434] A solution of 4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzoic acid (1.00 g, 3.23 mmol) in *N,N*-dimethylacetamide (20 mL) was treated with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (2.00 g, 5.26 mmol) for 10 min at room temperature
25 under a nitrogen atmosphere. 2-imino-5-methoxy-6-(methoxycarbonyl)benzo[d]thiazol-3(2H)-aminium diphenylphosphinate (2.40 g, 5.09 mmol) and *N,N*-diisopropylethylamine (2.50 g, 19.34 mmol) were added sequentially as a single portion. The reaction mixture was stirred for 1 h. The resulting solution was purified directly by reverse phase column chromatography with the following conditions; Column: C18 Column 330 g; Mobile Phase A: water (plus 10 mmol/L ammonium bicarbonate), Mobile Phase B:
30 acetonitrile; Flow rate: 80 mL/min; Gradient: 40% - 70% B in 25 min; Detector: 254/220 nm. The fractions containing the desired product were collected at 65% B and concentrated under reduced pressure to afford methyl 3-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzamido)-2-imino-5-methoxy-2,3-dihydrobenzo[d]thiazole-6-carboxylate as a yellow solid.

Yield 1.00 g (57%). ¹H NMR (400 MHz, DMSO) δ 8.43-8.31 (m, 1H), 7.41-7.30 (m, 2H), 7.16-6.90 (m, 4H), 4.94-4.63 (m, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.62-3.40 (m, 2H), 2.39-2.22 (m, 1H), 1.89-1.63 (m, 3H),
35 1.40-1.15 (m, 9H). m/z: [ESI⁺] 545 (M+H)⁺.

Synthesis of 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-7-

methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxylic acid (**6**, *Scheme 74*)

[00435] A mixture containing methyl 3-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzamido)-2-imino-5-methoxy-2,3-dihydrobenzo[*d*]thiazole-6-carboxylate (300 mg, 0.551 mmol) in polyphosphoric acid (5 mL) was stirred for 3 h at 100°C under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and quenched with ice/water (10 mL). The pH of the aqueous solution was adjusted to 9 with 3 *N* aqueous sodium hydroxide. Methanol (10 mL) was added, followed by di-*tert*-butyl dicarbonate (400 mg, 1.833 mmol) as a single portion. The reaction solution was stirred for an additional 2 h at room temperature. The pH was readjusted to 5 with 1 *N* aqueous hydrochloric acid. The solution was concentrated under reduced pressure to remove methanol and the resulting solid collected by vacuum filtration. After filtration, the filter cake was washed with water (1 mL) and oven dried to give 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-7-methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxylic acid as a pale solid.

Yield 80 mg (28%). ¹H NMR not run. m/z: [ESI⁺] 513 (M+H)⁺.

Synthesis of *tert*-butyl 2-(3-fluoro-4-(6-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-7-

methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazol-2-yl)phenyl)pyrrolidine-1-carboxylate (**7**, *Scheme 74*)

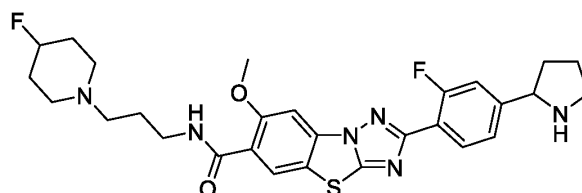
[00436] Compound *tert*-butyl 2-(3-fluoro-4-(6-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-7-methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-7-methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxylic acid (80 mg, 0.156 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (40 mg, 0.250 mmol) following a similar procedure described for the synthesis of methyl 3-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorobenzamido)-2-imino-5-methoxy-2,3-dihydrobenzo[*d*]thiazole-6-carboxylate, and was isolated as a light yellow oil.

Yield 50 mg (49%). ¹H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 8.32 (t, *J* = 5.6 Hz, 1H), 8.11 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.69 (s, 1H), 7.28-7.12 (m, 2H), 4.96-4.56 (m, 2H), 4.07 (s, 3H), 3.64-3.43 (m, 2H), 3.37-3.25 (m, 2H), 2.58-2.46 (m, 2H), 2.41-2.24 (m, 5H), 1.92-1.76 (m, 6H), 1.74-1.62 (m, 3H), 1.42-1.14 (m, 9H). m/z: [ESI⁺] 655 (M+H)⁺.

Final Compounds

Synthesis of 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-7-

methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide dihydrochloride (**Compound 178**)



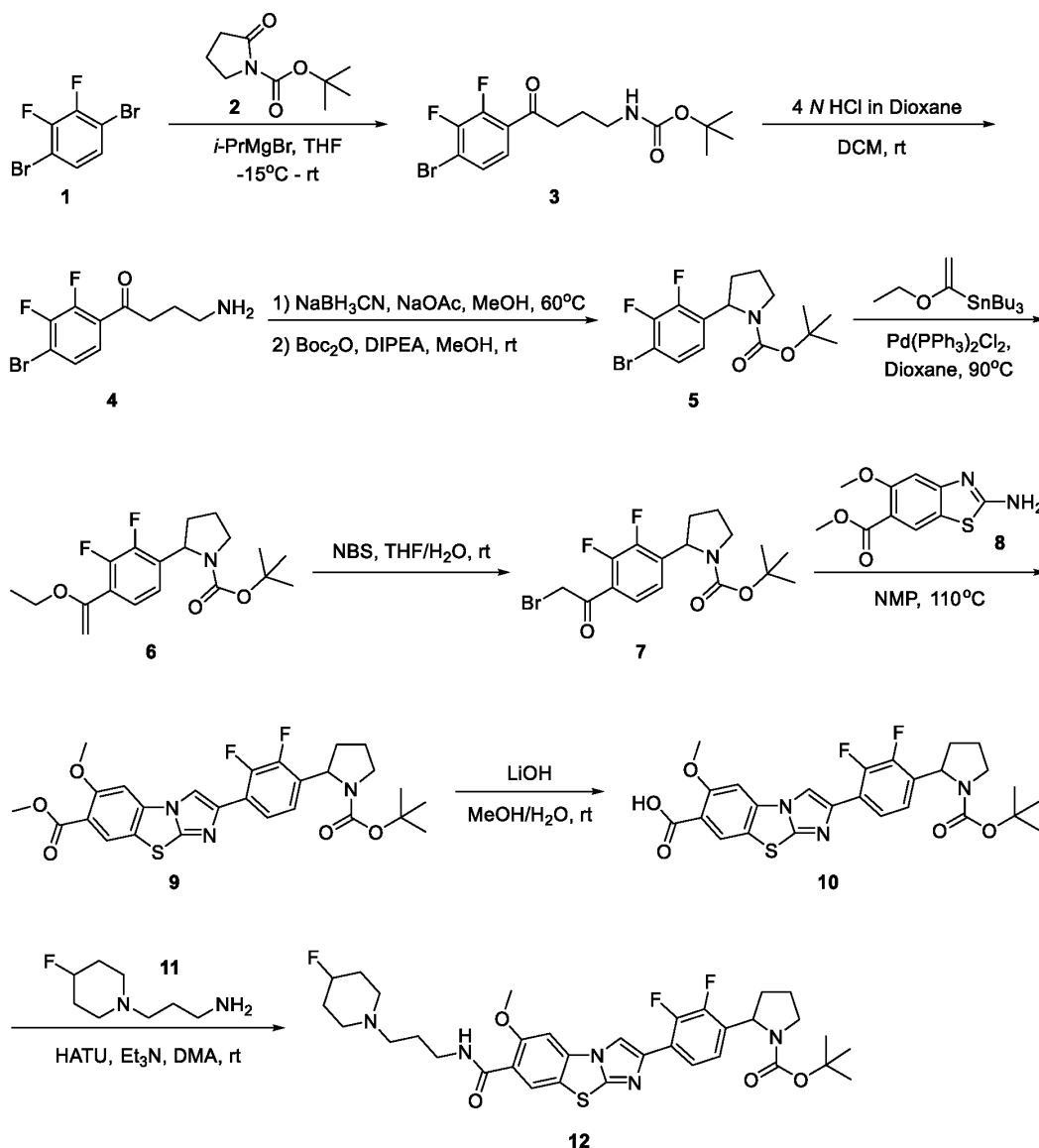
[00437] Compound 2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(3-fluoro-4-(6-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-7-

methoxybenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazol-2-yl)phenyl)pyrrolidine-1-carboxylate (50 mg, 0.076 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride, and was isolated as an off-white solid.

Yield 7 mg (15%). ¹H NMR (400 MHz, DMSO) δ 11.05 (br s, 1H), 10.48 (br s, 1H), 9.36 (br s, 1H), 8.63-8.50 (m, 2H), 8.29-8.16 (m, 1H), 7.78-7.64 (m, 2H), 7.60-7.50 (m, 1H), 5.10-4.72 (m, 1H), 4.71-4.57 (m, 1H), 4.10 (s, 3H), 3.55-3.22 (m, 6H), 3.18-2.94 (m, 4H), 2.52-2.37 (m, 1H), 2.32-1.94 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -110.54. Aliphatic ¹⁹F signal not observed. m/z: [ESI⁺] 555 (M+H)⁺. (C₂₈H₃₄Cl₂F₂N₆O₂S).

Intermediate Preparations

Synthesis of *tert*-butyl 2-(2,3-difluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate

5 **Scheme 75**

Synthesis of *tert*-butyl 4-(4-bromo-2,3-difluorophenyl)-4-oxobutyl)carbamate (3, **Scheme 75**)

[00438] Isopropylmagnesium bromide (1 N in tetrahydrofuran, 45 mL, 45.00 mmol) was added to a stirred solution of 1,4-dibromo-2,3-difluorobenzene (10.00 g, 36.78 mmol) in tetrahydrofuran (200 mL) dropwise over 5 min at -15°C under a nitrogen atmosphere. After stirring for 30 min at this temperature, *tert*-butyl 2-oxopyrrolidine-1-carboxylate (7.50 g, 40.49 mmol) was added portion wise over 5 min. The reaction solution was warmed to room temperature and stirred for an additional 16 h. The reaction was

quenched with saturated aqueous ammonium chloride (200 mL). The resulting mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% ethyl acetate in petroleum ether) to afford *tert*-butyl (4-(4-bromo-2,3-difluorophenyl)-4-oxobutyl)carbamate as a yellow oil.

Yield 9.32 g (67%). ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.52 (m, 1H), 7.48-7.40 (m, 1H), 4.61 (br s, 1H), 3.28-3.17 (m, 2H), 3.07-2.97 (m, 2H), 2.00-1.88 (m, 2H), 1.45 (s, 9H). m/z: [ESI⁺] 378, 380 (M+H)⁺.

10 *Synthesis of 4-amino-1-(4-bromo-2,3-difluorophenyl)butan-1-one hydrochloride (4, Scheme 75)*

[00439] *tert*-butyl (4-(4-bromo-2,3-difluorophenyl)-4-oxobutyl)carbamate (9.32 g, 24.64 mmol) in a solution of hydrochloride acid in 1,4-dioxane (4 N, 50 mL) and dichloromethane (50 mL) was stirred for 1 h at room temperature. The precipitated solids were collected by filtration, washed with dichloromethane (3 × 10 mL) and dried in a vacuum oven to afford 4-amino-1-(4-bromo-2,3-difluorophenyl)butan-1-one hydrochloride as a white solid.

Yield 6.00 g (77%). ¹H NMR (300 MHz, DMSO) δ 8.00 (br s, 3H), 7.75-7.60 (m, 2H), 3.20-3.10 (m, 2H), 2.91-2.78 (m, 2H), 1.98-1.86 (m, 2H). m/z: [ESI⁺] 260, 262 (M+H-18)⁺.

Synthesis of tert-butyl 2-(4-bromo-2,3-difluorophenyl)pyrrolidine-1-carboxylate (5, Scheme 75)

20 [00440] A solution of 4-amino-1-(4-bromo-2,3-difluorophenyl)butan-1-one hydrochloride (5.89 g, 18.73 mmol) in methanol (150 mL) was treated with sodium acetate (5.20 g, 63.39 mmol) for 16 h at 60°C. The reaction mixture was cooled to room temperature and treated with sodium cyanoborohydride (2.66 g, 42.33 mmol), which was added portion wise over 2 min. The reaction mixture was heated to 60°C and stirred for an additional 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was triturated with ethyl acetate (200 mL) for 30 min. After filtration, the filtrate was concentrated under reduced pressure again. The residue was dissolved in methanol (100 mL). To the above solution were added *N,N*-diisopropylethylamine (12 mL, 68.89 mmol) and di-*tert*-butyl dicarbonate (7.00 g, 32.07 mmol) sequentially at 0°C. The reaction solution was stirred for an additional 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was triturated with ethyl acetate (100 mL) for 10 min. After filtration, the filtered cake was washed with dichloromethane (3 × 10 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-30% ethyl acetate in petroleum ether) to afford *tert*-butyl 2-(4-bromo-2,3-difluorophenyl)pyrrolidine-1-carboxylate as a light yellow oil.

35 Yield 6.60 g (97%). ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.18 (m, 1H), 6.89-6.74 (m, 1H), 5.18-5.00 (m, 1H), 3.72-3.48 (m, 2H), 2.47-2.28 (m, 1H), 1.97-1.79 (m, 3H), 1.52-1.19 (m, 9H). m/z: [ESI⁺] 306, 308 (M+H-56)⁺.

Synthesis of tert-butyl 2-(4-(1-ethoxyvinyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate (6, Scheme 75)

[00441] Compound *tert*-butyl 2-(4-(1-ethoxyvinyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-bromo-2,3-difluorophenyl)pyrrolidine-1-carboxylate (3.00 g, 8.28 mmol) and tributyl(1-ethoxyvinyl)stannane (3.60 g, 9.97 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a brown oil. The crude product was used directly in the next step without further purification.

Yield 2.90 g (crude). ¹H NMR not run. m/z: [ESI⁺] 298 (M+H-56)⁺.

Synthesis of tert-butyl 2-(4-(2-bromoacetyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate (7, Scheme 75)

Compound *tert*-butyl 2-(4-(2-bromoacetyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(1-ethoxyvinyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate (2.90 g, crude) and *N*-bromosuccinimide (1.45 g, 8.15 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a yellow oil.

Yield 2.85 g (85% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.62 (m, 1H), 7.13-6.99 (m, 1H), 5.25-5.05 (m, 1H), 4.51 (s, 2H), 3.72-3.52 (m, 2H), 2.52-2.34 (m, 1H), 2.01-1.79 (m, 3H), 1.51-1.18 (m, 9H). m/z: [ESI⁺] 404, 406 (M+H-56)⁺.

Synthesis of methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (9, Scheme 75)

[00442] Compound methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate was prepared from *tert*-butyl 2-(4-(2-bromoacetyl)-2,3-difluorophenyl)pyrrolidine-1-carboxylate (1.00 g, 2.47 mmol) and methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (0.59 g, 2.48 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate, and was isolated as a yellow solid.

Yield 0.60 g (45%). ¹H NMR (400 MHz, DMSO) δ 8.85 (d, *J* = 3.6 Hz, 1H), 8.59 (s, 1H), 8.11 (s, 1H), 7.92-7.81 (m, 1H), 7.25-7.10 (m, 1H), 5.13-4.94 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.62-3.43 (m, 2H), 2.46-2.28 (m, 1H), 1.95-1.70 (m, 3H), 1.43-1.12 (m, 9H). m/z: [ESI⁺] 544 (M+H)⁺.

Synthesis of 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (10, Scheme 75)

[00443] Compound 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid was prepared at room temperature from methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-

methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (0.60 g, 1.10 mmol) following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid and was isolated as a yellow solid.

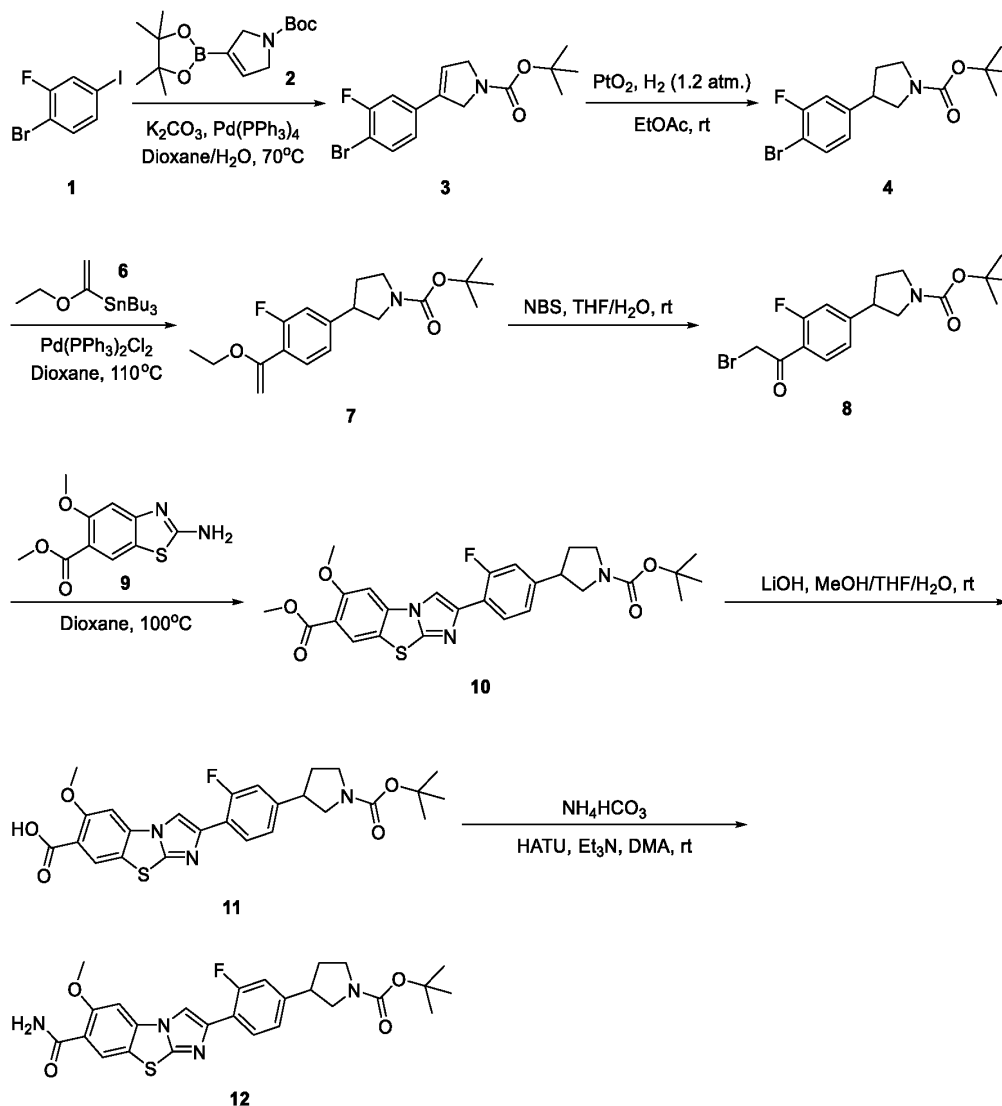
Yield 0.45 g (77%). ¹H NMR (400 MHz, CDCl₃) δ 8.87 (s, 1H), 8.51 (s, 1H), 7.96-7.85 (m, 1H), 7.81 (s, 1H), 7.18-7.07 (m, 1H), 5.33-5.02 (m, 1H), 4.19 (s, 3H), 3.73-3.46 (m, 2H), 2.56-2.29 (m, 1H), 1.99-1.77 (m, 3H), 1.56-1.16 (m, 9H). OH proton not observed. m/z: [ESI⁺] 530 (M+H)⁺.

*Synthesis of tert-butyl 2-(2,3-difluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (12, Scheme 75)*

[00444] Compound *tert*-butyl 2-(2,3-difluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2,3-difluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (0.45 g, 0.85 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (0.30 g, 1.87 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as a yellow solid.

Yield 0.10 g (18%). ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H), 8.20 – 8.13 (m, 1H), 7.98-7.89 (m, 1H), 7.25 (s, 1H), 7.09-6.92 (m, 1H), 5.28-5.05 (m, 1H), 4.95 – 4.74 (m, 1H), 4.19 (s, 3H), 3.72-3.57 (m, 6H), 3.03 – 2.53 (m, 4H), 2.51-2.30 (m, 1H), 2.02-1.86 (m, 9H), 1.50-1.22 (m, 9H). NH not observed. m/z: [ESI⁺] 672 (M+H)⁺.

Synthesis of *tert*-butyl 3-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate



Scheme 76

5

Synthesis of *tert*-butyl 3-(4-bromo-3-fluorophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**3**, *Scheme 76*)

[00445] Compound *tert*-butyl 3-(4-bromo-3-fluorophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate was prepared from 1-bromo-2-fluoro-4-iodobenzene (10.19 g, 33.87 mmol) and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (10.00 g, 33.88 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a yellow solid.

10

Yield 6.50 g (56%). ¹H NMR (300 MHz, CDCl₃) δ 7.54 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.15 (dd, *J* = 2.1, 9.6 Hz, 1H), 7.05 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.26-6.15 (m, 1H), 4.53-4.40 (m, 2H), 4.38-4.26 (m, 2H), 1.53 (s, 9H). m/z: [ESI⁺] 286, 288 (M+H-56)⁺.

5 *Synthesis of tert-butyl 3-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (4, Scheme 76)*

[00446] Compound *tert*-butyl 3-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 3-(4-bromo-3-fluorophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (6.50 g, 18.99 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate and was isolated as a colorless oil.

10 Yield 2.60 g (40%). ¹H NMR (300 MHz, CDCl₃) δ 7.50 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.03 (dd, *J* = 2.1, 9.6 Hz, 1H), 6.93 (dd, *J* = 2.1, 8.4 Hz, 1H), 3.87-3.78 (m, 1H), 3.67-3.55 (m, 1H), 3.52-3.18 (m, 3H), 2.35-2.22 (m, 1H), 2.04-1.89 (m, 1H), 1.50 (s, 9H). m/z: [ESI⁺] 288, 290 (M+H-56)⁺.

Synthesis of tert-butyl 3-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (7, Scheme 76)

15 [00447] Compound *tert*-butyl 3-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 3-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (1.00 g, 2.91 mmol) and tributyl(1-ethoxyvinyl)stannane (1.50 g, 4.15 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate and was isolated as a brown oil. The crude product was used directly in the next step without further purification.

20 Yield 1.00 g (crude). ¹H NMR not run. m/z: [ESI⁺] 336 (M+H)⁺.

Synthesis of tert-butyl 3-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (8, Scheme 76)

[00448] Compound *tert*-butyl 3-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 3-(4-(1-ethoxyvinyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.00 g, crude) and *N*-bromosuccinimide (0.60 g, 3.37 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate and was isolated as a yellow oil.

25 Yield 1.00 g (89% over two steps). ¹H NMR (300 MHz, DMSO) δ 7.91-7.82 (m, 1H), 7.39-7.28 (m, 2H), 4.80 (s, 2H), 3.77-3.68 (m, 1H), 3.53-3.40 (m, 2H), 3.38-3.26 (m, 1H), 3.26-3.14 (m, 1H), 2.31-2.16 (m, 1H), 2.09-1.91 (m, 1H), 1.42 (s, 9H). m/z: [ESI⁺] 330, 332 (M+H-56)⁺.

*Synthesis of methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (10, Scheme 76)*

[00449] Compound methyl 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate was prepared from *tert*-butyl 3-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (1.00 g, 2.59 mmol) and methyl 2-amino-5-methoxybenzo[d]thiazole-6-carboxylate (1.00 g, 4.20 mmol) following a similar procedure to that

Yield 0.70 g (51%). ¹H NMR not run. m/z: [ESI⁺] 526 (M+H)⁺.

[00450] Compound 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid was prepared from methyl 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-

Yield 0.60 g (88%). ¹H NMR (400 MHz, DMSO) δ 8.65 (d, *J* = 3.6 Hz, 1H), 8.13-8.04 (m, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.31-7.25 (m, 1H), 7.25-7.20 (m, 1H), 3.85 (s, 3H), 3.78-3.69 (m, 1H), 3.53-3.44 (m, 1H), 3.44-3.35 (m, 1H), 3.34-3.26 (m, 1H), 3.24-3.19 (m, 1H), 2.30-2.16 (m, 1H), 2.07-1.95 (m, 1H), 1.43 (s, 9H). OH proton not observed. m/z: [ESI⁺] 512 (M+H)⁺.

20 [00451] Compound *tert*-butyl 3-(4-(7-carbamoyl-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (150 mg, 0.293 mmol) and ammonium bicarbonate (40 mg, 0.506 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as an off-white solid

Yield 70 mg (47%). ¹H NMR (300 MHz, DMSO) δ 8.74 (d, *J* = 3.6 Hz, 1H), 8.42 (s, 1H), 8.15-8.04 (m, 2H), 7.74 (br s, 1H), 7.64 (br s, 1H), 7.35-7.21 (m, 2H), 4.04 (s, 3H), 3.81-3.69 (m, 1H), 3.59-3.34 (m, 3H), 3.27-3.16 (m, 1H), 2.31-2.16 (m, 1H), 2.09-1.92 (m, 1H), 1.43 (s, 9H). m/z: [ESI⁺] 511 (M+H)⁺.

[00452] Compound *tert*-butyl 3-(3-fluoro-4-(6-methoxy-7-(methylcarbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-

260

1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate and was isolated as a brown solid.

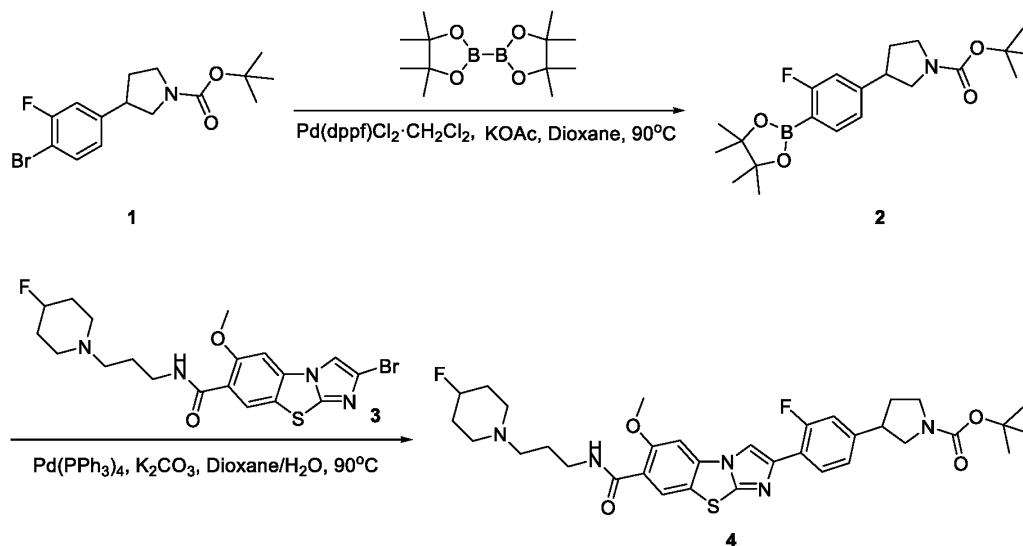
Yield 80 mg (52%). ¹H NMR (300 MHz, DMSO) δ 8.72 (d, *J* = 3.6 Hz, 1H), 8.37 (s, 1H), 8.23 (q, *J* = 4.8 Hz, 1H), 8.14-8.03 (m, 2H), 7.35-7.18 (m, 2H), 4.03 (s, 3H), 3.80-3.67 (m, 1H), 3.55-3.26 (m, 3H), 3.25-3.15 (m, 1H), 2.84 (d, *J* = 4.8 Hz, 3H), 2.32-2.17 (m, 1H), 2.11-1.94 (m, 1H), 1.43 (s, 9H). *m/z*: [ESI⁺] 525 (M+H)⁺.

Synthesis of tert-butyl 3-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate

[00453] Compound *tert*-butyl 3-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (150 mg, 0.293 mmol) and 1-methylpiperidin-4-amine (50 mg, 0.438 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate and was isolated as an orange solid.

Yield 100 mg (56%). ¹H NMR (300 MHz, DMSO) δ 8.72 (d, *J* = 3.6 Hz, 1H), 8.28 (s, 1H), 8.13-8.02 (m, 3H), 7.31-7.20 (m, 2H), 4.02 (s, 3H), 3.83-3.69 (m, 2H), 3.56-3.26 (m, 4H), 3.26-3.16 (m, 1H), 2.75-2.64 (m, 2H), 2.31-2.17 (m, 4H), 2.11-1.93 (m, 3H), 1.90-1.76 (m, 2H), 1.65-1.48 (m, 1H), 1.43 (s, 9H). *m/z*: [ESI⁺] 608 (M+H)⁺.

Synthesis of tert-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate



Scheme 77

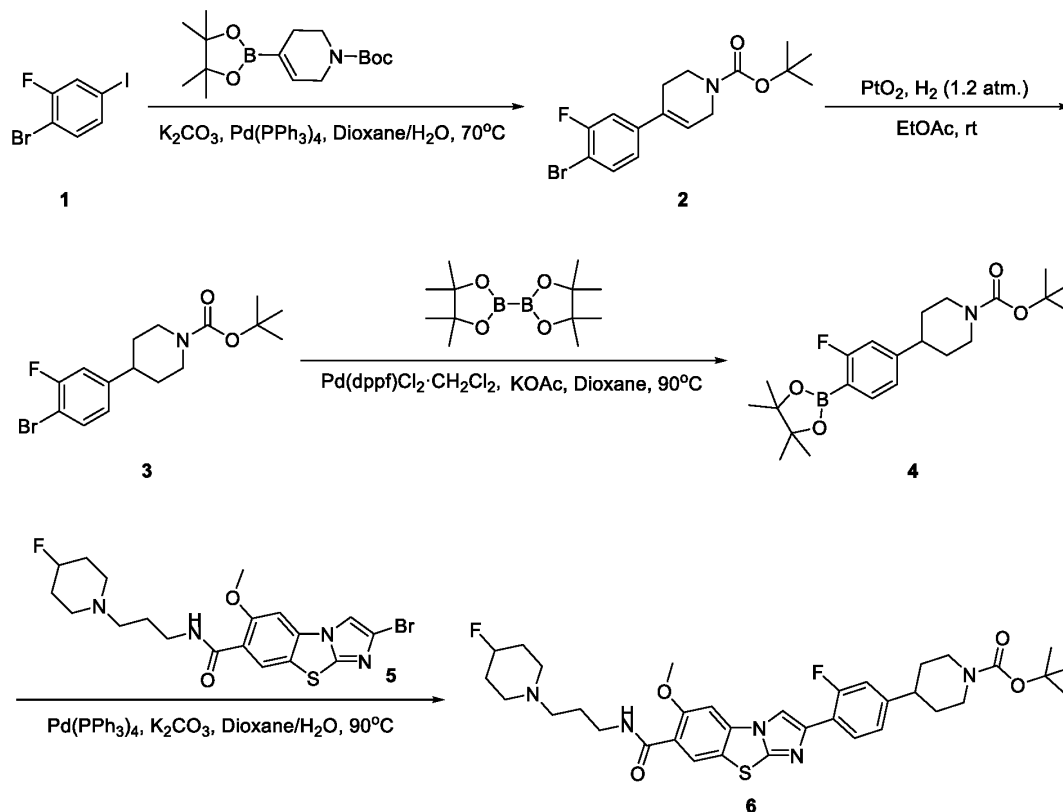
Synthesis of tert-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate (2, Scheme 77)

[00454] To a stirred mixture of *tert*-butyl 3-(4-bromo-3-fluorophenyl)pyrrolidine-1-carboxylate (300 mg, 0.872 mmol) and bis(pinacolato)diboron (330 mg, 1.300 mmol) in 1,4-dioxane (10 mL), were added
5 potassium acetate (260 mg, 2.649 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (70 mg, 0.086 mmol) sequentially as a single portion at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 16 h at 90°C. The mixture was cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were concentrated under reduced pressure to afford
10 *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate as a brown solid, which was used directly in the next step without further purification.
Yield 250 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 336 (M+H-56)⁺.

Synthesis of tert-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (4, Scheme 77)

[00455] Compound *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
20 (200 mg, 0.426 mmol) and *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate (250 mg, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a yellow solid.
Yield 80 mg (29%). ¹H NMR (400 MHz, DMSO) δ 8.74 (d, *J* = 3.6 Hz, 1H), 8.33 (s, 1H), 8.28 (t, *J* = 5.6 Hz, 1H), 8.15-8.03 (m, 2H), 7.36-7.27 (m, 1H), 7.27-7.20 (m, 1H), 4.78-4.57 (m, 1H), 4.02 (s, 3H),
25 3.80-3.68 (m, 1H), 3.55-3.26 (m, 6H), 3.25-3.14 (m, 1H), 2.42-2.14 (m, 6H), 2.07-1.94 (m, 1H), 1.92-1.76 (m, 2H), 1.76-1.60 (m, 4H), 1.43 (s, 9H). m/z: [ESI⁺] 654 (M+H)⁺.

Synthesis of *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate



Scheme 78

5

Synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**2**, **Scheme 78**)

[00456] To a stirred mixture of 1-bromo-2-fluoro-4-iodobenzene (15.00 g, 49.85 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (18.00 g, 58.21 mmol) in 1,4-dioxane:water (7:1, 170 mL), were added potassium carbonate (21.00 g, 151.95 mmol) and tetrakis(triphenylphosphine)palladium (0) (5.70 g, 4.93 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 4 h at 70°C. The mixture was cooled to room temperature, diluted with water (500 mL) and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate as a white oil.

Yield 16.00 g (90%). ¹H NMR (400 MHz, CD₃OD) δ 7.56 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.28 (dd, *J* = 2.0, 10.4 Hz, 1H), 7.18 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.25-6.15 (m, 1H), 4.12-4.01 (m, 2H), 3.67-3.59 (m, 2H), 2.55-2.48 (m, 2H), 1.50 (s, 9H). *m/z*: [ESI⁺] 300, 302 (M+H-56)⁺.

Synthesis of tert-butyl 4-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate (3, Scheme 78)

[00457] A mixture of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (10.00 g, 28.07 mmol) and platinum dioxide (1.00 g, 4.40 mmol) in ethyl acetate (15 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere (1.2 atm.). After filtration, the filter cake was washed with ethyl acetate (3 × 50 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate as a colorless oil. Yield 8.00 g (80%). ¹H NMR (400 MHz, DMSO) δ 7.61 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.30 (dd, *J* = 2.0, 10.4 Hz, 1H), 7.08 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.12-4.01 (m, 2H), 2.86-2.65 (m, 3H), 1.79-1.69 (m, 2H), 1.53-1.43 (m, 2H), 1.42 (s, 9H). m/z: [ESI⁺] 302, 304 (M+H-56)⁺.

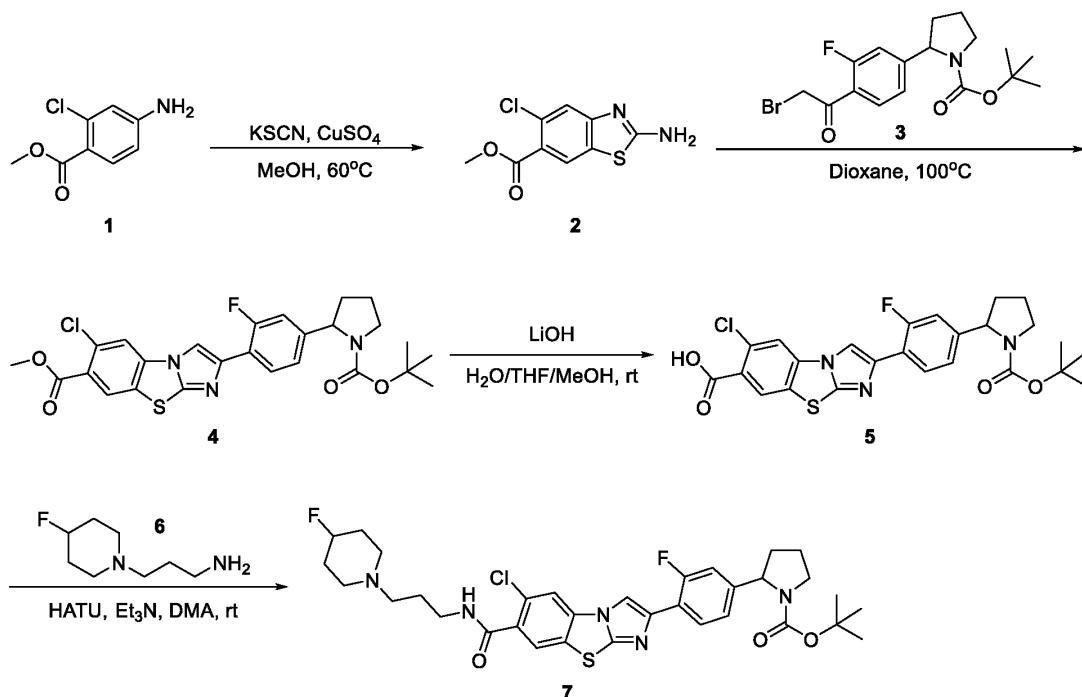
Synthesis of tert-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (4, Scheme 78)

[00458] Compound *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate was prepared from *tert*-butyl 4-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate (1.00 g, 2.79 mmol) and bis(pinacolato)diboron (1.00 g, 3.94 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate and was isolated as a brown oil. The crude product was used directly in the next step without further purification. Yield 1.00 g (crude). ¹H NMR not run. m/z: [ESI⁺] 350 (M+H-56)⁺.

*Synthesis of tert-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate (6, Scheme 78)*

[00459] Compound *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (300 mg, 0.639 mmol) and *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (300 mg, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a brown solid. Yield 200 mg (47%). ¹H NMR (400 MHz, DMSO) δ 8.72 (d, *J* = 3.6 Hz, 1H), 8.32 (s, 1H), 8.26 (t, *J* = 5.6 Hz, 1H), 8.11-8.05 (m, 2H), 7.27-7.17 (m, 2H), 4.78-4.55 (m, 1H), 4.13-4.05 (m, 2H), 4.02 (s, 3H), 3.36-3.29 (m, 2H), 2.88-2.70 (m, 3H), 2.60-2.51 (m, 2H), 2.40-2.33 (m, 2H), 2.33-2.23 (m, 4H), 1.92-1.76 (m, 2H), 1.74-1.63 (m, 4H), 1.59-1.47 (m, 2H), 1.43 (s, 9H). m/z: [ESI⁺] 668 (M+H)⁺.

Synthesis of *tert*-butyl 2-(4-(6-chloro-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate



Scheme 79

5

Synthesis of methyl 2-amino-5-chlorobenzo[d]thiazole-6-carboxylate (2, Scheme 79)

[00460] Compound methyl 2-amino-5-chlorobenzo[d]thiazole-6-carboxylate was prepared from methyl 4-amino-2-chlorobenzoate (8.00 g, 43.10 mmol) and potassium thiocyanate (44.00 g, 452.77 mmol) following a similar procedure to that described for the synthesis of 6-bromo-5-(2-methoxyethoxy)benzo[d]thiazol-2-amine and was isolated as a purple solid.

10

Yield 4.00 g (38%). ¹H NMR (300 MHz, DMSO) δ 8.23 (s, 1H), 8.05 (br s, 2H), 7.42 (s, 1H), 3.83 (s, 3H). m/z: [ESI⁺] 243, 245 (M+H)⁺.

Synthesis of methyl 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-chlorobenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (4, Scheme 79)

15

[00461] Compound methyl 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-chlorobenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate was prepared from methyl 2-amino-5-chlorobenzo[d]thiazole-6-carboxylate (1.50 g, 6.18 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (3.00 g, 7.77 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (S)-2-(4-(7-bromo-9-methyl-9H-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate and was isolated as a brown solid.

20

5 *Synthesis of 2-(4-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-chlorobenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (5, **Scheme 79**)*

10 carboxylate (1.00 g, 1.89 mmol) at room temperature, following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid and was isolated as a red solid.

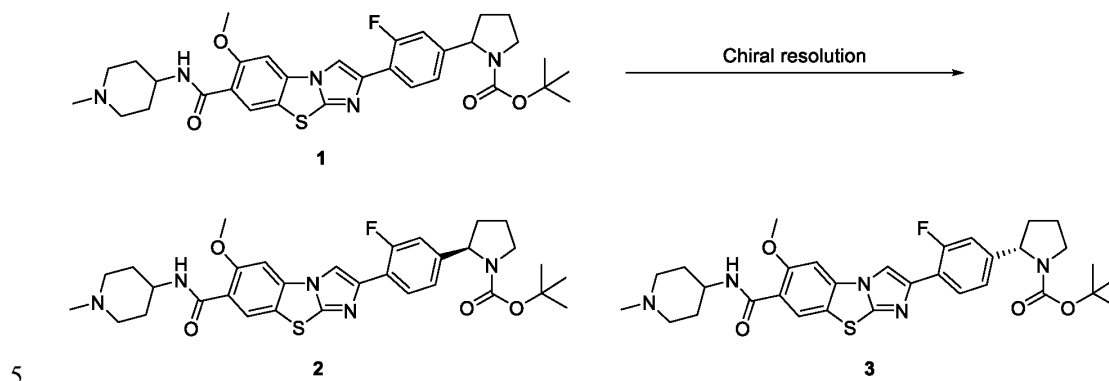
15 1.66 (m, 3H), 1.45-1.08 (m, 9H). OH proton not observed. m/z: [ESI⁺] 516, 518 (M+H)⁺.

20 [00463] Compound *tert*-butyl 2-(4-(6-chloro-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate was prepared from 2-(4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-fluorophenyl)-6-chlorobenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxylic acid (0.30 g, 0.58 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (0.15 g, 0.94 mmol) following a similar procedure to that described for the

25 synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as an off-white solid.

Yield 0.30 g (78%). ¹H NMR (300 MHz, DMSO) δ 8.73 (d, *J* = 3.6 Hz, 1H), 8.62 (t, *J* = 5.7 Hz, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.13-8.03 (m, 1H), 7.18-7.08 (m, 2H), 4.92-4.63 (m, 2H), 3.64-3.41 (m, 2H), 3.36-3.27 (m, 2H), 2.90-2.60 (m, 6H), 2.41-2.22 (m, 1H), 1.91-1.72 (m, 9H), 1.45-1.10 (m, 9H). m/z: [ESI]⁺ 658, 660 (M+H)⁺.

Synthesis of *tert*-butyl (*R*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate and *tert*-butyl (*S*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate

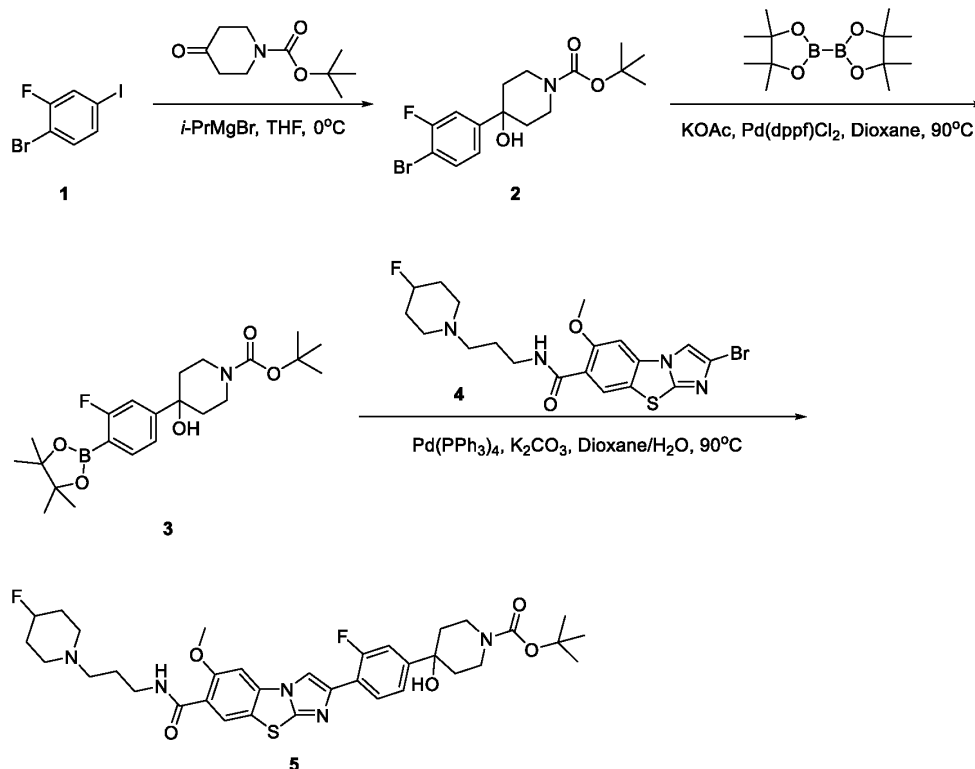


Scheme 80

[00464] *Tert*-butyl 2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (450 mg, 0.740 mmol) was separated by Prep-CHIRAL-HPLC using the following conditions; Column: CHIRAL ART Cellulose-SC, 2 × 25 cm, 5 μm; Mobile Phase A: hexane (plus 0.5% 2 *N* ammonia-methanol), Mobile Phase B: ethanol:dichloromethane = 1:1; Flow rate: 20 mL/min; Gradient: 35% B in 24 min; UV detector: 220/254 nm. The faster eluting peak at 16.33 min was collected and concentrated under reduced pressure to afford *tert*-butyl (*R*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a yellow solid. Yield 100 mg (22%). ¹H NMR (400 MHz, CD₃OD) δ 8.55 (d, *J* = 3.6 Hz, 1H), 8.30 (s, 1H), 8.12-8.01 (m, 1H), 7.86 (s, 1H), 7.18-7.11 (m, 1H), 7.11-7.04 (m, 1H), 5.00-4.85 (m, 1H), 4.13 (s, 3H), 4.13-4.02 (m, 1H), 3.72-3.54 (m, 2H), 3.25-3.12 (m, 2H), 2.80-2.66 (m, 2H), 2.62 (s, 3H), 2.49-2.31 (m, 1H), 2.23-2.11 (m, 2H), 2.01-1.72 (m, 5H), 1.53-1.22 (m, 9H). NH proton not observed. *m/z*: [ESI⁺] 608 (M+H)⁺. [α]_D²⁵ = +38° (c = 1 mg/mL, methanol).

The slower eluting peak at 19.85 min was collected and concentrated under reduced pressure to afford *tert*-butyl (*S*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate as a yellow solid. Yield 110 mg (24%). ¹H NMR (400 MHz, CD₃OD) δ 8.55 (d, *J* = 3.6 Hz, 1H), 8.30 (s, 1H), 8.12-8.01 (m, 1H), 7.86 (s, 1H), 7.18-7.11 (m, 1H), 7.11-7.04 (m, 1H), 5.00-4.85 (m, 1H), 4.13 (s, 3H), 4.13-4.02 (m, 1H), 3.72-3.54 (m, 2H), 3.25-3.12 (m, 2H), 2.80-2.66 (m, 2H), 2.62 (s, 3H), 2.49-2.31 (m, 1H), 2.23-2.11 (m, 2H), 2.01-1.72 (m, 5H), 1.53-1.22 (m, 9H). NH proton not observed. *m/z*: [ESI⁺] 608 (M+H)⁺. [α]_D²⁵ = -42° (c = 1 mg/mL, methanol).

Synthesis of *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate



Scheme 81

- 5 Synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (**2**, **Scheme 81**) [00465] Compound *tert*-butyl 4-(4-bromo-3-fluorophenyl)-4-hydroxypiperidine-1-carboxylate was prepared from 1-bromo-2-fluoro-4-iodobenzene (4.53 g, 15.05 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (3.00 g, 15.06 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-2,3-difluorophenyl)-4-oxobutyl)carbamate and was isolated as a colorless oil.
- 10 Yield 3.51 g (62%). ¹H NMR (400 MHz, CDCl₃) δ 7.55 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.30 (dd, *J* = 2.0 10.4 Hz, 1H), 7.14 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.12-4.03 (m, 2H), 3.26-3.16 (m, 2H), 2.02-1.90 (m, 2H), 1.75-1.66 (m, 2H), 1.51 (s, 9H). OH proton not observed. *m/z*: [ESI⁺] 372, 374 (M-H)⁺.

Synthesis of *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-

- 15 hydroxypiperidine-1-carboxylate (**3**, **Scheme 81**) [00466] Compound *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate was prepared from *tert*-butyl 4-(4-bromo-3-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (300 mg, 0.802 mmol) and bis(pinacolato)diboron (300 mg, 1.181 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate and was isolated as a
- 20 brown solid. The compound was used directly in the next step without further purification.

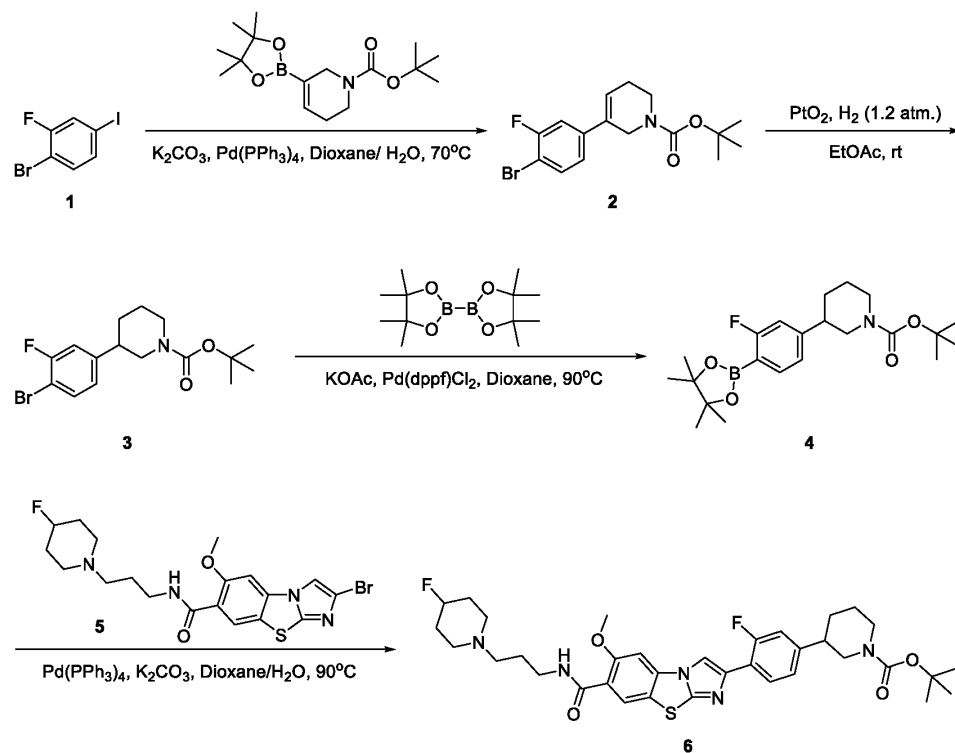
Yield 340 mg (crude). ^1H NMR not run. m/z : $[\text{ESI}]^-$ 420 (M-H).

Synthesis of *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate (**5**, *Scheme 81*)

[00467] Compound *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (200 mg, 0.426 mmol) and *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate (340 mg, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a brown solid.

Yield 135 mg (46%). ^1H NMR (300 MHz, CDCl_3) δ 8.38 (s, 1H), 8.14-8.05 (m, 1H), 8.00 (d, $J = 3.6$ Hz, 1H), 7.30-7.28 (m, 1H), 7.26-7.23 (m, 1H), 7.16-7.13 (m, 1H), 4.86-4.60 (m, 1H), 4.19-3.98 (m, 5H), 3.62-3.53 (m, 2H), 3.38-3.23 (m, 2H), 2.76-2.63 (m, 2H), 2.63-2.42 (m, 4H), 2.12-1.83 (m, 8H), 1.83-1.72 (m, 2H), 1.52 (s, 9H). OH and NH protons not observed. m/z : $[\text{ESI}]^+$ 684 (M+H) $^+$.

Synthesis of *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate



20

Scheme 82

Synthesis of tert-butyl 5-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2, Scheme 82)

[00468] Compound *tert*-butyl 5-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate was prepared from 1-bromo-2-fluoro-4-iodobenzene (3.30 g, 10.97 mmol) and *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (4.00 g, 12.94 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate and was isolated as an off-white solid.

Yield 3.00 g (77%). ¹H NMR (400 MHz, DMSO) δ 7.68 (dd, J = 7.2, 8.4 Hz, 1H), 7.44 (dd, J = 2.0, 10.4 Hz, 1H), 7.21 (dd, J = 2.0, 8.4 Hz, 1H), 6.48-6.40 (m, 1H), 4.23-4.16 (m, 2H), 3.50-3.42 (m, 2H), 2.31-2.21 (m, 2H), 1.43 (s, 9H). m/z: [ESI⁺] 300, 302 (M+H-56)⁺.

Synthesis of tert-butyl 3-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate (3, Scheme 82)

[00469] Compound *tert*-butyl 3-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate was prepared from *tert*-butyl 5-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (1.90 g, 5.33 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate and was isolated as a colorless oil.

Yield 0.61 g (32%). ¹H NMR (300 MHz, DMSO) δ 7.69-7.59 (m, 1H), 7.38-7.29 (m, 1H), 7.16-7.06 (m, 1H), 4.02-3.86 (m, 2H), 3.75-3.52 (m, 2H), 3.00-2.57 (m, 3H), 1.76-1.57 (m, 2H), 1.41 (s, 9H). m/z: [ESI⁺] 302, 304 (M+H-56)⁺.

Synthesis of tert-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (4, Scheme 82)

[00470] Compound *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate was prepared from *tert*-butyl 3-(4-bromo-3-fluorophenyl)piperidine-1-carboxylate (200 mg, 0.558 mmol) and bis(pinacolato)diboron (213 mg, 0.839 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate and was isolated as a brown solid. The compound was used directly in the next step without further purification.

Yield 200 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 350 (M+H-56)⁺.

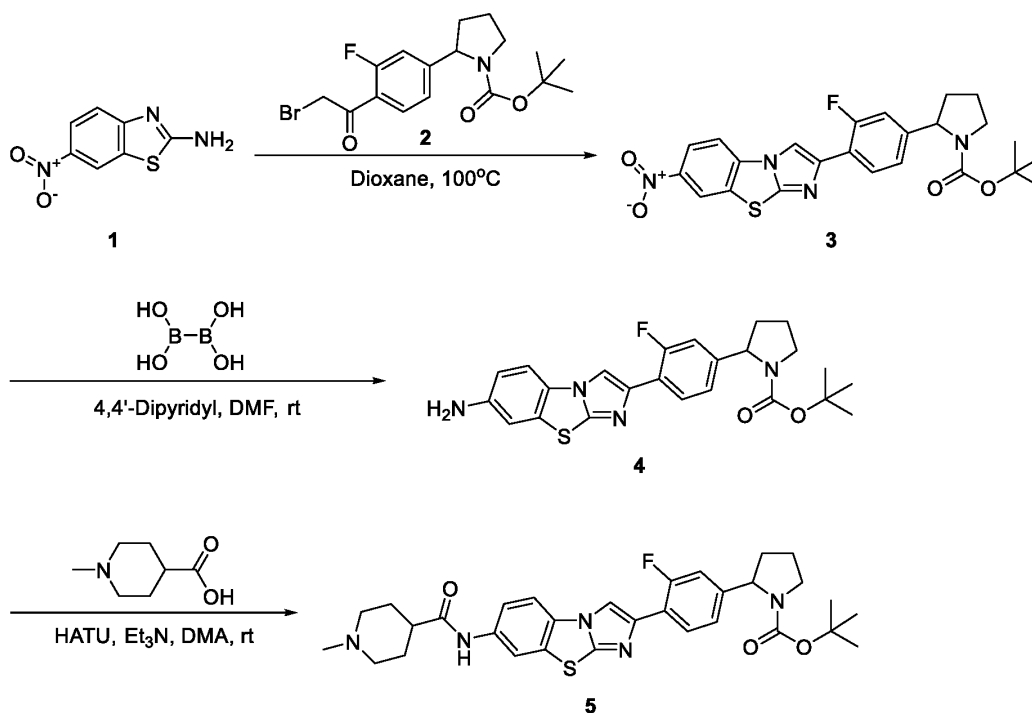
Synthesis of tert-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)piperidine-1-carboxylate (6, Scheme 82)

[00471] Compound *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)piperidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (200 mg, 0.426 mmol) and *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (200 mg, crude) at 90°C, following a similar procedure to that

described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a yellow solid.

Yield 80 mg (28%). ¹H NMR (400 MHz, DMSO) δ 8.73 (d, *J* = 3.6 Hz, 1H), 8.32 (s, 1H), 8.26 (t, *J* = 5.6 Hz, 1H), 8.13-8.05 (m, 2H), 7.31-7.25 (m, 1H), 7.25-7.20 (m, 1H), 4.77-4.56 (m, 1H), 4.02 (s, 3H), 3.99-3.92 (m, 1H), 3.35-3.23 (m, 2H), 2.88-2.75 (m, 1H), 2.75-2.62 (m, 1H), 2.59-2.42 (m, 2H), 2.40-2.21 (m, 6H), 1.97-1.77 (m, 2H), 1.77-1.56 (m, 8H), 1.43 (s, 9H). *m/z*: [ESI⁺] 668 (M+H)⁺.

*Synthesis of tert-butyl 2-(3-fluoro-4-(7-(1-methylpiperidine-4-carboxamido)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate*



Scheme 83

*Synthesis of tert-butyl 2-(3-fluoro-4-(7-nitrobenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate ((3, **Scheme 83**))*

[00472] Compound *tert*-butyl 2-(3-fluoro-4-(7-nitrobenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from 6-nitrobenzo[d]thiazol-2-amine (1.00 g, 5.12 mmol) and *tert*-butyl 2-(4-(2-bromoacetyl)-3-fluorophenyl)pyrrolidine-1-carboxylate (2.18 g, 5.64 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl (*S*)-2-(4-(7-bromo-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate and was isolated as an orange solid.

Yield 0.90 g (36%). ¹H NMR (400 MHz, CD₃OD) δ 8.93 (d, *J* = 2.0 Hz, 1H), 8.54 (s, 1H), 8.46 (dd, *J* = 2.0, 8.8 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.12-8.05 (m, 1H), 7.17-7.13 (m, 1H), 7.10-7.04 (m, 1H),

4.97-4.76 (m, 1H), 3.70-3.55 (m, 2H), 2.49-2.31 (m, 1H), 2.06-1.79 (m, 3H), 1.52-1.18 (m, 9H). m/z: [ESI⁺] 483 (M+H)⁺.

Synthesis of tert-butyl 2-(4-(7-aminobenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (4, Scheme 83)

[00473] To a stirred solution of *tert*-butyl 2-(3-fluoro-4-(7-nitrobenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (900 mg, 1.865 mmol) in *N,N*-dimethylformamide (9 mL) were added hypodiboric acid (334 mg, 3.726 mmol) and 4,4'-bipyridine (58 mg, 0.371 mmol) sequentially as single portions at room temperature. The reaction mixture was stirred for an additional 30 min. The reaction solution was purified directly by reverse phase flash chromatography using the following conditions; Column: Spherical C18, 20 - 40 μ m, 330 g; Mobile Phase A: water (plus 10 mM ammonium bicarbonate); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient: 60% - 80% B in 20 min; UV Detector: 254 nm. The fractions containing desired product were collected at 76% B and concentrated under reduced pressure to afford *tert*-butyl 2-(4-(7-aminobenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate as an orange solid.

Yield 450 mg (53%). ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.12 (m, 1H), 8.05 (s, 1H), 7.48-7.38 (m, 1H), 7.11-7.05 (m, 1H), 7.02-6.94 (m, 2H), 6.82-6.73 (m, 1H), 5.04-4.75 (m, 1H), 3.96 (br s, 2H), 3.73-3.54 (m, 2H), 2.47-2.25 (m, 1H), 2.04-1.82 (m, 3H), 1.54-1.21 (m, 9H). m/z: [ESI⁺] 453 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-(1-methylpiperidine-4-carboxamido)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (5, Scheme 83)

[00474] Compound *tert*-butyl 2-(3-fluoro-4-(7-(1-methylpiperidine-4-carboxamido)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(7-aminobenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (100 mg, 0.221 mmol) and 1-methylpiperidine-4-carboxylic acid (63 mg, 0.440 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbonyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate and was isolated as an off-white solid.

Yield 105 mg (82%). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (br s, 1H), 8.27-8.06 (m, 1H), 7.92-7.78 (m, 1H), 7.73-7.62 (m, 1H), 7.62-7.52 (m, 1H), 7.27-7.12 (m, 1H), 6.94-6.85 (m, 1H), 6.85-6.72 (m, 1H), 4.94-4.76 (m, 1H), 3.74-3.53 (m, 2H), 3.08-2.90 (m, 2H), 2.47-2.25 (m, 5H), 2.16-1.77 (m, 9H), 1.61-1.27 (m, 9H). m/z: [ESI⁺] 578 (M+H)⁺.

Synthesis of tert-butyl 2-(3-fluoro-4-(7-(tetrahydro-2H-pyran-4-carboxamido)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate

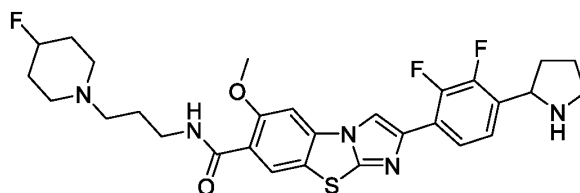
[00475] Compound *tert*-butyl 2-(3-fluoro-4-(7-(tetrahydro-2H-pyran-4-carboxamido)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate was prepared from *tert*-butyl 2-(4-(7-aminobenzo[d]imidazo[2,1-b]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate

(100 mg, 0.221 mmol) and tetrahydro-2H-pyran-4-carboxylic acid (58 mg, 0.446 mmol) following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as an off-white solid.

- 5 Yield 103 mg (83%). ¹H NMR (400 MHz, CDCl₃) δ 9.10 (br s, 1H), 8.31-8.04 (m, 1H), 7.87-7.75 (m, 1H), 7.75-7.66 (m, 1H), 7.66-7.54 (m, 1H), 7.28-7.17 (m, 1H), 6.92-6.81 (m, 1H), 6.81-6.70 (m, 1H), 4.93-4.74 (m, 1H), 4.17-4.02 (m, 2H), 3.76-3.57 (m, 2H), 3.56-3.41 (m, 2H), 2.71-2.52 (m, 1H), 2.42-2.26 (m, 1H), 2.10-1.74 (m, 7H), 1.67-1.24 (m, 9H). m/z: [ESI⁺] 565 (M+H)⁺.

10 Final Compounds

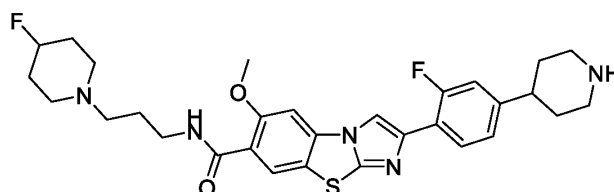
*Synthesis of 2-(2,3-difluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 187)*



- [00476] Compound 2-(2,3-difluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(2,3-difluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (100 mg, 0.149 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.

- Yield 20 mg (21%). ¹H NMR (400 MHz, DMSO) δ 10.65 (br s, 1H), 10.05 (br s, 1H), 9.21 (br s, 1H), 8.94 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 5.6 Hz, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 8.06-7.98 (m, 1H), 7.60-7.53 (m, 1H), 5.13-4.72 (m, 2H), 4.05 (s, 3H), 3.45-3.30 (m, 6H), 3.19-2.95 (m, 4H), 2.49-2.35 (m, 1H), 2.30-1.93 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -140.12, -140.17, -140.58, -140.64, -175.67, -186.62. m/z: [ESI⁺] 572 (M+H)⁺. (C₂₉H₃₄Cl₂F₃N₅O₂S).

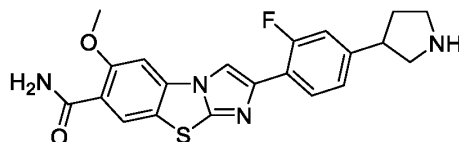
*Synthesis of 2-(2-fluoro-4-(piperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 186)*



[00477] Compound 2-(2-fluoro-4-(piperidin-4-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate (100 mg, 0.150 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.

Yield 15 mg (16%). ¹H NMR (400 MHz, DMSO) δ 10.69 (br s, 1H), 8.94 (br s, 2H), 8.76 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 5.6 Hz, 1H), 8.36 (s, 1H), 8.17-8.06 (m, 2H), 7.27-7.13 (m, 2H), 5.11-4.72 (m, 1H), 4.04 (s, 3H), 3.55-3.28 (m, 6H), 3.17-2.84 (m, 7H), 2.28-1.77 (m, 10H). ¹⁹F NMR (376 MHz, DMSO) δ -113.60, -175.56, -186.61. m/z: [ESI⁺] 568 (M+H)⁺. (C₃₀H₃₇Cl₂F₂N₅O₂S).

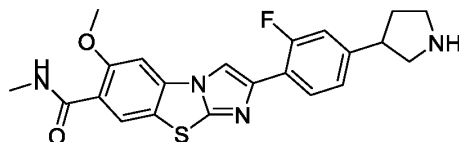
*Synthesis of 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide hydrochloride (Compound 183)*



[00478] Compound 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide hydrochloride was prepared from *tert*-butyl 3-(4-(7-carbamoyl-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (70 mg, 0.137 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a brown solid.

Yield 14 mg (23%). ¹H NMR (400 MHz, DMSO) δ 9.62 (br s, 2H), 8.79 (d, *J* = 3.6 Hz, 1H), 8.42 (s, 1H), 8.15-8.07 (m, 2H), 7.74 (br s, 1H), 7.65 (br s, 1H), 7.47-7.38 (m, 1H), 7.36-7.25 (m, 1H), 4.03 (s, 3H), 3.68-3.57 (m, 1H), 3.57-3.46 (m, 1H), 3.46-3.34 (m, 1H), 3.27-3.17 (m, 1H), 3.17-3.04 (m, 1H), 2.45-2.34 (m, 1H), 2.05-1.92 (m, 1H). ¹⁹F NMR (376 MHz, DMSO) δ -113.32. m/z: [ESI⁺] 411 (M+H)⁺. (C₂₁H₂₀ClFN₄O₂S).

*Synthesis of 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-*N*-methylbenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide hydrochloride (Compound 184)*

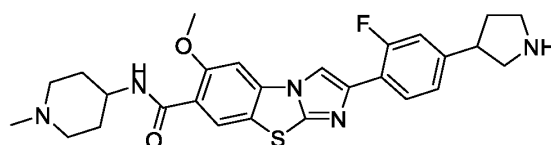


[00479] Compound 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-*N*-methylbenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide hydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(6-methoxy-7-(methylcarbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (80 mg, 0.152

mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a brown solid.

Yield 20 mg (28%). ¹H NMR (400 MHz, DMSO) δ 9.68 (br s, 2H), 8.79 (d, *J* = 3.6 Hz, 1H), 8.38 (s, 1H), 8.25 (q, *J* = 4.8 Hz, 1H), 8.15-8.04 (m, 2H), 7.42 (dd, *J* = 1.6, 12.8 Hz, 1H), 7.30 (dd, *J* = 1.6, 8.0 Hz, 1H), 4.02 (s, 3H), 3.68-3.59 (m, 1H), 3.58-3.45 (m, 1H), 3.45-3.37 (m, 1H), 3.27-3.18 (m, 1H), 3.18-3.06 (m, 1H), 2.83 (d, *J* = 4.8 Hz, 3H), 2.45-2.33 (m, 1H), 2.04-1.93 (m, 1H). ¹⁹F NMR (376 MHz, DMSO) δ -113.24. m/z: [ESI⁺] 425 (M+H)⁺. (C₂₂H₂₂ClF₄N₄O₂S).

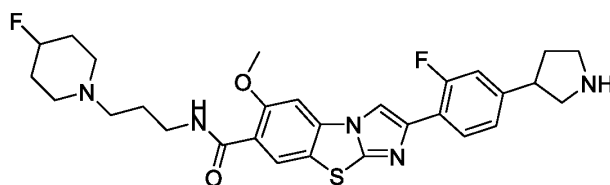
- 10 *Synthesis of 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 185)*



- [00480] Compound 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (100 mg, 0.165 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.
- 20 Yield 31 mg (32%). ¹H NMR (400 MHz, DMSO) δ 11.08 (br s, 1H), 9.86 (br s, 2H), 8.82 (d, *J* = 3.6 Hz, 1H), 8.42-8.28 (m, 1H), 8.23 (s, 1H), 8.16-8.05 (m, 2H), 7.46-7.36 (m, 1H), 7.34-7.25 (m, 1H), 3.99 (s, 3H), 3.69-3.58 (m, 1H), 3.58-3.46 (m, 1H), 3.46-3.35 (m, 3H), 3.35-3.04 (m, 4H), 2.73 (s, 3H), 2.44-2.34 (m, 1H), 2.18-1.84 (m, 6H). ¹⁹F NMR (376 MHz, DMSO) δ -113.01. m/z: [ESI⁺] 508 (M+H)⁺. (C₂₇H₃₂Cl₂FN₅O₂S).

25

*Synthesis of 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 182)*

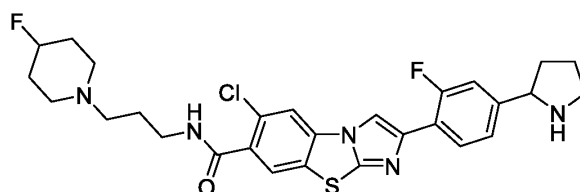


- [00481] Compound 2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (80 mg, 0.122 mmol) following a similar procedure to that described

for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.

Yield 12 mg (16%). ¹H NMR (400 MHz, DMSO) δ 10.97 (br s, 1H), 9.57 (br s, 2H), 8.80 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 6.4 Hz, 1H), 8.37 (s, 1H), 8.18-8.07 (m, 2H), 7.45-7.39 (m, 1H), 7.36-7.25 (m, 1H), 5.12-4.70 (m, 1H), 4.05 (s, 3H), 3.70-3.58 (m, 1H), 3.58-3.46 (m, 2H), 3.46-3.32 (m, 4H), 3.30-2.95 (m, 5H), 2.45-2.34 (m, 1H), 2.34-1.93 (m, 8H). ¹⁹F NMR (376 MHz, DMSO) δ -113.38, -175.83, -186.63. m/z: [ESI⁺] 554 (M+H)⁺. (C₂₉H₃₅ClF₂N₅O₂S).

- 10 *Synthesis of 6-chloro-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 188)*

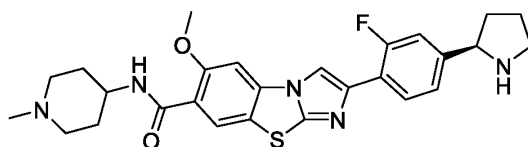


- [00482] Compound 6-chloro-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 2-(4-(6-chloro-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)-3-fluorophenyl)pyrrolidine-1-carboxylate (300 mg, 0.456 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.

- 20 Yield 66 mg (23%). ¹H NMR (400 MHz, DMSO) δ 11.18 (br s, 1H), 10.49 (br s, 1H), 9.33 (br s, 1H), 8.82 (d, *J* = 3.6 Hz, 1H), 8.78 (t, *J* = 5.6 Hz, 1H), 8.54 (s, 1H), 8.26 (s, 1H), 8.20-8.15 (m, 1H), 7.65 (dd, *J* = 1.6, 12.4 Hz, 1H), 7.49 (dd, *J* = 1.6, 8.0 Hz, 1H), 5.16-4.72 (m, 1H), 4.65-4.51 (m, 1H), 3.53-3.44 (m, 1H), 3.44-3.23 (m, 6H), 3.20-2.98 (m, 3H), 2.45-2.35 (m, 1H), 2.33-1.92 (m, 9H). ¹⁹F NMR (376 MHz, DMSO) δ -112.82, -175.67, -186.59. m/z: [ESI⁺] 558, 560 (M+H)⁺. (C₂₈H₃₂ClF₂N₅OS).

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*Synthesis of (R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 189)*

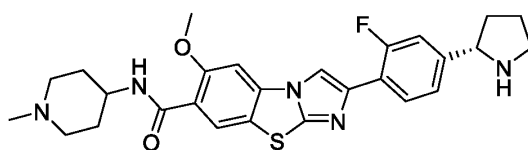


- [00483] Compound (*R*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*R*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (100 mg, 0.165 mmol) following a similar procedure to that described

for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.

Yield 45 mg (47%). ¹H NMR (400 MHz, DMSO) δ 10.69 (br s, 1H), 10.28 (br s, 1H), 9.16 (br s, 1H), 8.84 (d, *J* = 3.6 Hz, 1H), 8.36-8.28 (m, 1H), 8.24-8.18 (m, 2H), 8.14-8.09 (m, 1H), 7.63 (dd, *J* = 2.0, 12.4 Hz, 1H), 7.48 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.67-4.55 (m, 1H), 4.21-3.96 (m, 4H), 3.47-3.22 (m, 4H), 3.22-2.99 (m, 2H), 2.78-2.68 (m, 3H), 2.46-2.37 (m, 1H), 2.20-1.80 (m, 7H). ¹⁹F NMR (376 MHz, DMSO) δ -113.05. *m/z*: [ESI⁺] 508 (M+H)⁺. (C₂₇H₃₂Cl₂FN₅O₂S). [α]_D²⁵ = +8° (c = 1 mg/mL, methanol).

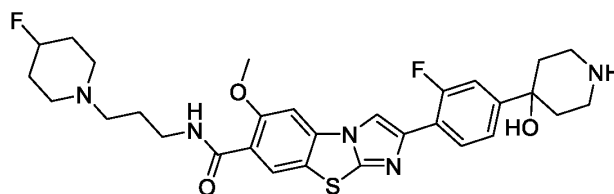
- 10 *Synthesis of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 190)*



- [00484] Compound (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*S*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)pyrrolidine-1-carboxylate (110 mg, 0.181 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.
- 20 Yield 47 mg (45%). ¹H NMR (400 MHz, DMSO) δ 10.30 (br s, 1H), 10.05 (br s, 1H), 9.02 (br s, 1H), 8.83 (d, *J* = 3.6 Hz, 1H), 8.35-8.27 (m, 1H), 8.25-8.19 (m, 2H), 8.14-8.09 (m, 1H), 7.66-7.55 (m, 1H), 7.51-7.43 (m, 1H), 4.69-4.54 (m, 1H), 4.22-3.95 (m, 4H), 3.51-3.23 (m, 4H), 3.21-2.99 (m, 2H), 2.81-2.70 (m, 3H), 2.45-2.36 (m, 1H), 2.18-1.93 (m, 5H), 1.93-1.75 (m, 2H). ¹⁹F NMR (376 MHz, DMSO) δ -113.05. *m/z*: [ESI⁺] 508 (M+H)⁺. (C₂₇H₃₂Cl₂FN₅O₂S). [α]_D²⁵ = -2° (c = 1 mg/mL, methanol).

25

*Synthesis of 2-(2-fluoro-4-(4-hydroxypiperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 191)*



- 30 [00485] Compound 2-(2-fluoro-4-(4-hydroxypiperidin-4-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from

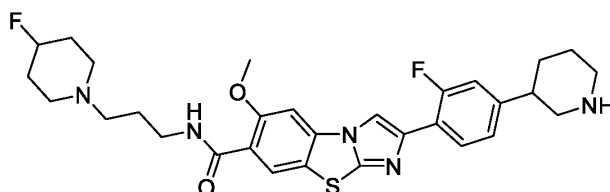
tert-butyl 4-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypiperidine-1-carboxylate (140 mg, 0.205 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide

5 dihydrochloride and was isolated as a grey solid.

Yield 115 mg (86%). ¹H NMR (400 MHz, DMSO) δ 10.80 (br s, 1H), 9.12 (br s, 1H), 8.95 (br s, 1H), 8.79 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 5.6 Hz, 1H), 8.37 (s, 1H), 8.18-8.13 (m, 1H), 8.12 (s, 1H), 7.42-7.36 (m, 2H), 5.11-4.71 (m, 1H), 4.04 (s, 3H), 3.55-3.45 (m, 1H), 3.45-3.33 (m, 3H), 3.26-2.95 (m, 8H), 2.36-1.93 (m, 8H), 1.86-1.73 (m, 2H). OH proton not observed. ¹⁹F NMR (376 MHz, DMSO) δ -113.49, -175.54, -

10 186.61. m/z: [ESI⁺] 584 (M+H)⁺. (C₃₀H₃₇Cl₂F₂N₅O₃S).

*Synthesis of 2-(2-fluoro-4-(piperidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (Compound 192)*

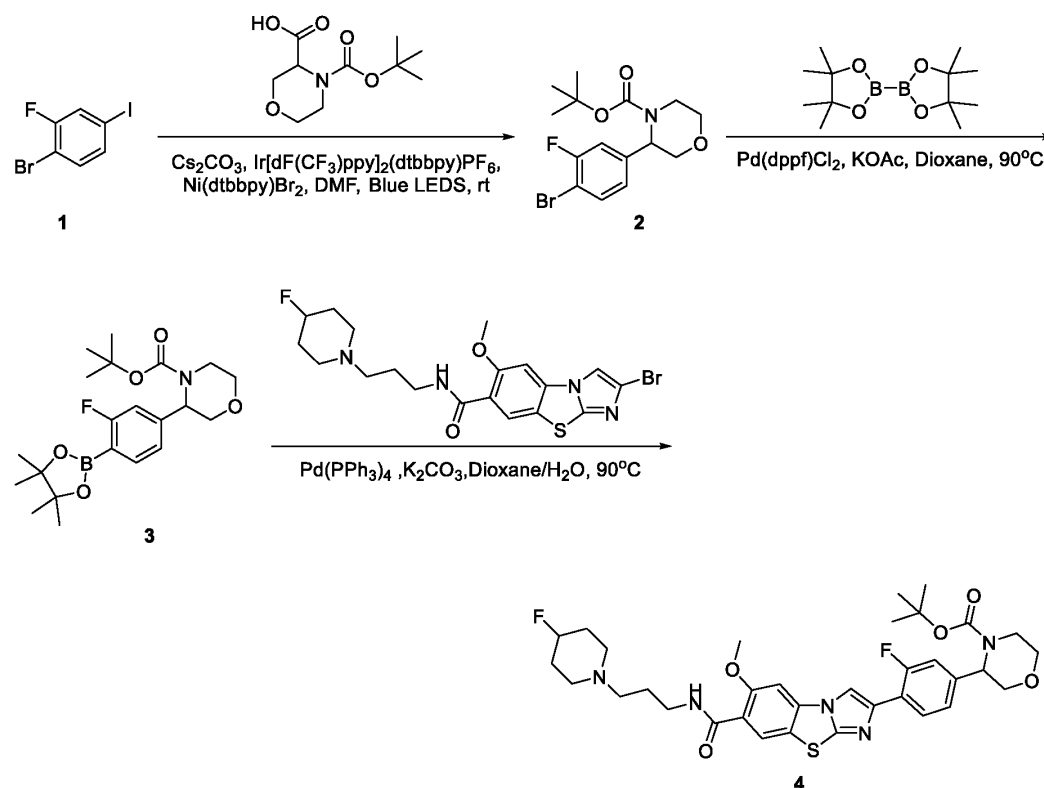


15 [00486] Compound 2-(2-fluoro-4-(piperidin-3-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)piperidine-1-carboxylate (80 mg, 0.120 mmol) following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a white solid.

Yield 35 mg (46%). ¹H NMR (400 MHz, DMSO) δ 10.81 (br s, 1H), 9.26 (br s, 1H), 9.03 (br s, 1H), 8.78 (d, *J* = 3.6 Hz, 1H), 8.49 (t, *J* = 5.6 Hz, 1H), 8.36 (s, 1H), 8.17-8.06 (m, 2H), 7.39-7.30 (m, 1H), 7.30-7.19 (m, 1H), 5.11-4.70 (m, 1H), 3.88 (s, 3H), 3.56-3.46 (m, 1H), 3.45-3.25 (m, 5H), 3.19-2.94 (m, 6H), 2.94-2.79 (m, 1H), 2.36-1.65 (m, 10H). ¹⁹F NMR (376 MHz, DMSO) δ -113.58, -175.55, -186.61. m/z: [ESI⁺] 568 (M+H)⁺. (C₃₀H₃₇Cl₂F₂N₅O₂S).

Intermediate Preparations

Synthesis of *tert*-butyl 3-(3-fluoro-4-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)morpholine-4-carboxylate

**5 Scheme 84**

Synthesis of *tert*-butyl 3-(4-bromo-3-fluorophenyl)morpholine-4-carboxylate (**2**, **Scheme 84**)

[00487] A mixture of 1-bromo-2-fluoro-4-iodobenzene (1.00 g, 3.32 mmol), 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (1.00 g, 4.32 mmol), cesium carbonate (2.10 g, 6.45 mmol), (4,4'-di-*tert*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl- κN]phenyl- κC]iridium(I) hexafluorophosphate ($\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$) (20 mg, 0.018 mmol) and (SP-4-2)-[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- $\kappa N1, \kappa N1'$]dibromo-nickel ($\text{Ni}(\text{dtbbpy})\text{Br}_2$) (250 mg, 0.513 mmol) in *N,N*-dimethylformamide (20 mL) was stirred for 4 h at room temperature under a nitrogen atmosphere with irradiation by Blue LED light. The resulting mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 $\times$ 200 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 0-10% ethyl acetate in petroleum ether) to afford *tert*-butyl 3-(4-bromo-3-fluorophenyl)morpholine-4-carboxylate as a colorless oil.

Yield 320 mg (27%). ¹H NMR (400 MHz, CDCl₃) δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.31-7.27 (m, 1H), 7.19-7.10 (m, 1H), 5.10-4.94 (m, 1H), 4.33-4.22 (m, 1H), 3.93-3.85 (m, 2H), 3.85-3.75 (m, 1H), 3.62-3.53 (m, 1H), 3.12-3.02 (m, 1H), 1.48 (s, 9H). m/z: [ESI⁺] 304, 306 (M+H-56)⁺.

5 *Synthesis of tert-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine-4-carboxylate (3, Scheme 84)*

[00488] Compound *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine-4-carboxylate was prepared from *tert*-butyl 3-(4-bromo-3-fluorophenyl)morpholine-4-carboxylate (470 mg, 1.305 mmol) and bis(pinacolato)diboron (500 mg, 1.969 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate and was isolated as a brown solid. The compound was used directly in the next step without further purification.
10 Yield 450 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 352 (M+H-56)⁺.

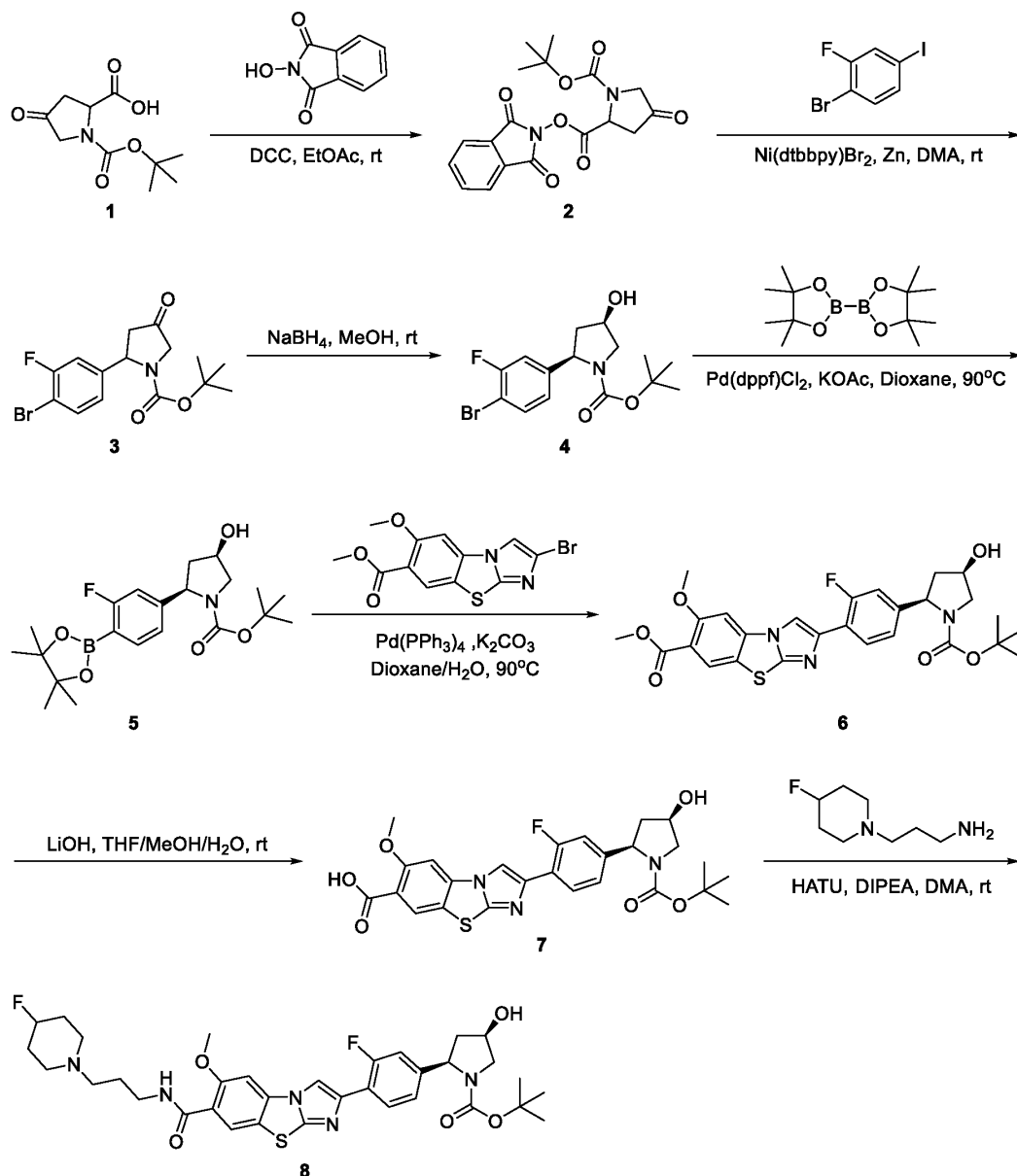
15 *Synthesis of tert-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)morpholine-4-carboxylate (4, Scheme 84)*

[00489] Compound *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)morpholine-4-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide
20 (200 mg, 0.426 mmol) and *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine-4-carboxylate (450 mg, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a yellow solid.

Yield 60 mg (21%). ¹H NMR (400 MHz, DMSO) δ 8.59-8.54 (m, 1H), 8.25-8.19 (m, 1H), 8.18-8.09 (m, 1H), 8.08-7.97 (m, 1H), 7.39-7.30 (m, 1H), 7.24-7.21 (m, 1H), 7.12-7.02 (m, 1H), 5.19-5.06 (m, 1H), 4.89-4.73 (m, 1H), 4.75-4.59 (m, 1H), 4.40-4.34 (m, 1H), 4.18-4.10 (m, 4H), 4.00-3.80 (m, 2H), 3.63-3.54 (m, 3H), 2.83-2.52 (m, 4H), 2.06 (d, *J* = 3.2 Hz, 2H), 2.00-1.90 (m, 6H), 1.52 (s, 9H). m/z: [ESI⁺] 670 (M+H)⁺.

30

Synthesis of *tert*-butyl (cis)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate



Scheme 85

5

Synthesis of 1-(*tert*-butyl) 2-(1,3-dioxoisindolin-2-yl) 4-oxopyrrolidine-1,2-dicarboxylate (**2**, *Scheme 85*)

[00490] To a stirred solution of 2-hydroxyisoindoline-1,3-dione (35.60 g, 218.23 mmol) and dicyclohexylmethanediimine (45.00 g, 218.09 mmol) in ethyl acetate (1000 mL) was added a solution of 1-(*tert*-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid (50.00 g, 218.12 mmol) in ethyl acetate (1000 mL) dropwise over 30 min at room temperature under a nitrogen atmosphere. The reaction

solution was stirred for 16 h at room temperature. The resulting mixture was filtered. The filter cake was washed with ethyl acetate (3 × 300 mL). The combined filtrates were washed with saturated aqueous sodium bicarbonate solution (5 × 200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 1-(*tert*-butyl) 2-(1,3-dioxoisindolin-2-yl) 4-oxopyrrolidine-1,2-dicarboxylate as a white solid.

Yield 30.00 g (37%). ¹H NMR (400 MHz, CDCl₃) δ 7.94-7.88 (m, 2H), 7.88-7.78 (m, 2H), 5.33-5.00 (m, 1H), 4.03-3.91 (m, 2H), 3.30-3.07 (m, 1H), 3.07-2.93 (m, 1H), 1.56 (s, 9H). m/z: [ESI⁺] 397 (M+Na)⁺.

Synthesis of tert-butyl 2-(4-bromo-3-fluorophenyl)-4-oxopyrrolidine-1-carboxylate (3, Scheme 85)

[00491] A mixture of 1-(*tert*-butyl) 2-(1,3-dioxoisindolin-2-yl) 4-oxopyrrolidine-1,2-dicarboxylate (30.00 g, 80.14 mmol), 1-bromo-2-fluoro-4-iodobenzene (22.00 g, 73.11 mmol), (SP-4-2)-[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-κN1,κN1']dibromo-nickel (Ni(dtbbpy)Br₂) (7.80 g, 16.02 mmol) and zinc powder (10.48 g, 160.29 mmol) in *N,N*-dimethylaniline (240 mL) was stirred for 4 h at room temperature under a nitrogen atmosphere. The reaction mixture was diluted with brine (800 mL) and extracted with ethyl acetate (4 × 600 mL). The combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 1%-20% ethyl acetate in petroleum ether) to afford *tert*-butyl 2-(4-bromo-3-fluorophenyl)-4-oxopyrrolidine-1-carboxylate as a yellow oil.

Yield 8.50 g (32%). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (dd, *J* = 7.2, 8.0 Hz, 1H), 6.98 (dd, *J* = 2.0, 7.2 Hz, 1H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.42-5.22 (m, 1H), 4.14-4.06 (m, 1H), 3.94-3.84 (m, 1H), 3.30-3.07 (m, 1H), 2.59-2.49 (m, 1H), 1.42 (s, 9H). m/z: [ESI⁺] 302, 304 (M+H-56)⁺.

Synthesis of tert-butyl (cis)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (4, Scheme 85)

[00492] Sodium borohydride (1.06 g, 28.02 mmol) was added to a stirred solution of *tert*-butyl 2-(4-bromo-3-fluorophenyl)-4-oxopyrrolidine-1-carboxylate (5.00 g, 13.96 mmol) in methanol (50 mL) portionwise over 1 min at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of acetone (20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 12% ethyl acetate in petroleum ether) to afford *tert*-butyl (*cis*)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate as a colorless oil.

Yield 2.50 g (50%). ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.11 (dd, *J* = 2.0, 9.6 Hz, 1H), 6.99 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.01-4.75 (m, 1H), 4.56-4.45 (m, 1H), 3.94-3.76 (m, 1H), 3.65-3.53 (m, 1H), 2.65-2.54 (m, 1H), 2.01-1.92 (m, 1H), 1.48-1.21 (m, 9H). OH proton not observed. m/z: [ESI⁺] 304, 306 (M+H-56)⁺.

Synthesis of tert-butyl (cis)-2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (5, Scheme 85)

[00493] Compound *tert*-butyl (*cis*)-2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate was prepared from *tert*-butyl (*cis*)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (900 mg, 2.498 mmol) and bis(pinacolato)diboron (950 mg, 3.741 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate and was isolated as a yellow solid.

Yield 750 mg (crude). ¹H NMR not run. m/z: [ESI⁺] 352 (M+H)⁺.

Synthesis of methyl 2-(4-((cis)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylate (6, Scheme 85)

[00494] Compound methyl 2-(4-((*cis*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate was prepared from methyl 2-bromo-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (1.68 g, 4.92 mmol) and *tert*-butyl (*cis*)-2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (2.00 g, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a yellow solid.

Yield 1.50 g (56%). ¹H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H), 8.19-8.14 (m, 2H), 7.24-7.16 (m, 1H), 7.15-7.10 (m, 2H), 4.66-4.44 (m, 1H), 4.12-4.00 (m, 3H), 4.01-3.93 (m, 4H), 3.67-3.56 (m, 1H), 2.80-2.49 (m, 2H), 2.16-1.98 (m, 1H), 1.49-1.30 (m, 9H). OH proton not observed. m/z: [ESI⁺] 542 (M+H)⁺.

Synthesis of 2-(4-((cis)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid (7, Scheme 85)

[00495] Compound 2-(4-((*cis*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid was prepared from methyl 2-(4-((*cis*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylate (240 mg, 0.443 mmol) at room temperature, following a similar procedure to that described for the synthesis of 2-(1-(*tert*-butoxycarbonyl)-6-fluoroindolin-5-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid and was isolated as a white solid.

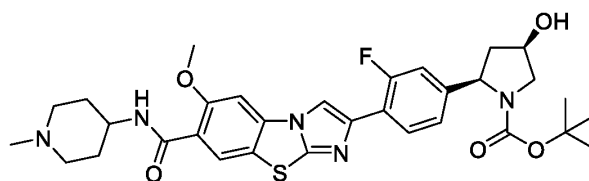
Yield 200 mg (86%). ¹H NMR (400 MHz, DMSO) δ 12.90 (br s, 1H), 8.87-8.45 (m, 1H), 8.34-8.15 (m, 1H), 8.17-7.94 (m, 2H), 7.30-7.04 (m, 2H), 5.18-5.00 (m, 1H), 4.89-4.63 (m, 1H), 4.35-4.17 (m, 1H), 3.97-3.90 (m, 3H), 3.72-3.57 (m, 1H), 3.32-3.28 (m, 1H), 1.80-1.70 (m, 1H), 1.40-1.11 (m, 9H). OH proton not observed. m/z: [ESI⁺] 528 (M+H)⁺.

Synthesis of *tert*-butyl (*cis*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (8, *Scheme 85*)

[00496] Compound *tert*-butyl (*cis*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate was prepared from 2-(4-((*cis*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (50 mg, 0.095 mmol) and 3-(4-fluoropiperidin-1-yl)propan-1-amine (30 mg, 0.187 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as a yellow solid.

Yield 30 mg (47%). ¹H NMR (400 MHz, DMSO) δ 8.75-8.72 (m, 1H), 8.34-8.31 (m, 1H), 8.26 (t, *J* = 5.6 Hz, 1H), 8.12-8.03 (m, 2H), 7.26-7.16 (m, 2H), 5.18-4.95 (m, 1H), 4.78-4.50 (m, 2H), 4.32-4.23 (m, 1H), 4.14-4.05 (m, 1H), 4.02 (s, 3H), 3.74-3.60 (m, 1H), 3.21-3.13 (m, 4H), 2.82-2.69 (m, 1H), 2.41-2.17 (m, 6H), 1.75-1.63 (m, 4H), 1.40-1.11 (m, 9H). OH proton not observed. *m/z*: [ESI⁺] 670 (M+H)⁺.

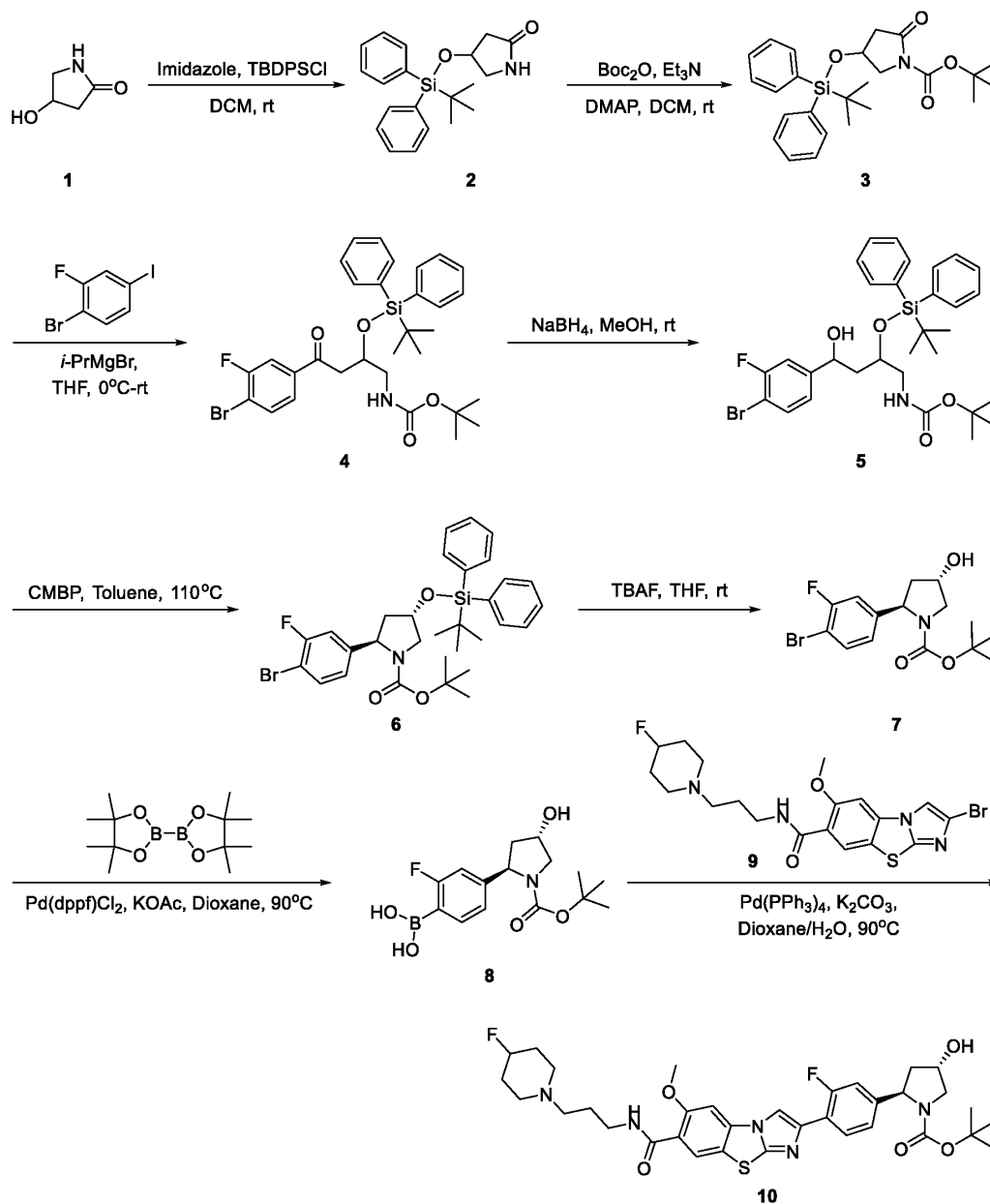
Synthesis of *tert*-butyl (*cis*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate



[00497] Compound *tert*-butyl (*cis*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate was prepared from 2-(4-((*cis*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxylic acid (50 mg, 0.095 mmol) and 1-methylpiperidin-4-amine (22 mg, 0.193 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)indoline-1-carboxylate and was isolated as a white solid.

Yield 30 mg (51%). ¹H NMR not run. *m/z*: [ESI⁺] 624 (M+H)⁺.

Synthesis of *tert*-butyl (trans)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate



Scheme 86

5

Synthesis of 4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidin-2-one (2, *Scheme 86*)

[00498] To a stirred solution of 4-hydroxypyrrolidin-2-one (15.00 g, 148.35 mmol) in dichloromethane (200 mL) were added imidazole (15.00 g, 220.33 mmol) and *tert*-butylchlorodiphenylsilane (53.00 g, 192.83 mmol) sequentially as single portions at 0°C under a nitrogen atmosphere. The reaction solution was stirred for 2 h at room temperature. The resulting mixture was diluted with water (400 mL) and

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extracted with dichloromethane (2 × 200 mL). The combined organic layers were washed with water (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 30% ethyl acetate in petroleum ether) to afford 4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidin-2-one as a white solid.

- 5 Yield 38.00 g (75%). ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.60 (m, 4H), 7.50-7.38 (m, 6H), 5.99 (br s, 1H), 4.62-4.50 (m, 1H), 3.44-3.36 (m, 1H), 3.36-3.27 (m, 1H), 2.47-2.34 (m, 2H), 1.09 (s, 9H). m/z: [ESI⁺] 340 (M+H)⁺.

Synthesis of tert-butyl 4-((tert-butyldiphenylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate (3, Scheme 86)

- 10 [00499] To a stirred solution of 4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidin-2-one (20.00 g, 58.91 mmol) and *N,N*-diisopropylethylamine (15.00 g, 116.05 mmol) in dichloromethane (400 mL) were added 4-dimethylaminopyridine (0.70 g, 5.73 mmol) and di-*tert*-butyl dicarbonate (20.00 g, 91.64 mmol) sequentially as single portions at room temperature under a nitrogen atmosphere. The reaction solution was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 30% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-((*tert*-butyldiphenylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate as a colorless oil.

Yield 25.00 g (97%). ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.61 (m, 4H), 7.51-7.38 (m, 6H), 4.43-4.34 (m, 1H), 3.73-3.66 (m, 2H), 2.58-2.52 (m, 2H), 1.54 (s, 9H), 1.08 (s, 9H). m/z: [ESI⁺] 384 (M+H-56)⁺.

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Synthesis of tert-butyl (4-(4-bromo-3-fluorophenyl)-2-((tert-butyldiphenylsilyl)oxy)-4-oxobutyl)carbamate (4, Scheme 86)

- [00500] Compound *tert*-butyl (4-(4-bromo-3-fluorophenyl)-2-((*tert*-butyldiphenylsilyl)oxy)-4-oxobutyl)carbamate was prepared from 1-bromo-2-fluoro-4-iodobenzene (13.00 g, 43.20 mmol) and *tert*-butyl 4-((*tert*-butyldiphenylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate (25.00 g, 56.87 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl (4-(4-bromo-2,3-difluorophenyl)-4-oxobutyl)carbamate and was isolated as a colorless oil.

- Yield 11.00 g (41%). ¹H NMR (400 MHz, DMSO) δ 7.84-7.79 (m, 1H), 7.67-7.62 (m, 1H), 7.62-7.49 (m, 4H), 7.47-7.29 (m, 7H), 6.83-6.77 (m, 1H), 4.43-4.34 (m, 1H), 3.22-3.02 (m, 4H), 1.32 (s, 9H), 0.93 (s, 9H). m/z: [ESI⁺] 636, 638 (M+Na)⁺.

30

Synthesis of tert-butyl (4-(4-bromo-3-fluorophenyl)-2-((tert-butyldiphenylsilyl)oxy)-4-hydroxybutyl)carbamate (5, Scheme 86)

- [00501] Compound *tert*-butyl (4-(4-bromo-3-fluorophenyl)-2-((*tert*-butyldiphenylsilyl)oxy)-4-hydroxybutyl)carbamate was prepared from *tert*-butyl (4-(4-bromo-3-fluorophenyl)-2-((*tert*-butyldiphenylsilyl)oxy)-4-oxobutyl)carbamate (90.00 g, 146.43 mmol) and sodium tetrahydroborate (8.31 g, 219.67 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl

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(*cis*)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate and was isolated as a colorless oil.

Yield 80.00 g (89%). ¹H NMR (400 MHz, CDCl₃) δ 7.75-7.70 (m, 1H), 7.70-7.62 (m, 4H), 7.52-7.37 (m, 6H), 7.02-6.95 (m, 1H), 6.86-6.80 (m, 1H), 4.90-4.82 (m, 1H), 4.78-4.69 (m, 1H), 4.06-4.00 (m, 1H), 3.42-3.32 (m, 2H), 3.29-3.19 (m, 1H), 1.92-1.75 (m, 2H), 1.44 (s, 9H), 1.10 (s, 9H). m/z: [ESI⁺] 616, 618 (M+1)⁺.

Synthesis of tert-butyl (trans)-2-(4-bromo-3-fluorophenyl)-4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (6, Scheme 86)

[00502] To a stirred solution of *tert*-butyl (4-(4-bromo-3-fluorophenyl)-2-((*tert*-butyldiphenylsilyl)oxy)-4-hydroxybutyl)carbamate (30.00 g, 48.65 mmol) in toluene (300 mL) was added cyanomethylenetriethylphosphorane (25.00 g, 103.58 mmol) dropwise over 5 min at room temperature under a nitrogen atmosphere. The reaction solution was stirred for 16 h at 110°C. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 5% ethyl acetate in petroleum ether) to afford *tert*-butyl (*trans*)-2-(4-bromo-3-fluorophenyl)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate as a colorless oil.

Yield 17.00 g (58%). ¹H NMR (400 MHz, DMSO) δ 7.69-7.63 (m, 1H), 7.56-7.33 (m, 10H), 7.30-7.18 (m, 1H), 7.13-7.05 (m, 1H), 4.91-4.75 (m, 1H), 4.42-4.33 (m, 1H), 3.63-3.50 (m, 1H), 3.50-3.39 (m, 1H), 2.50-2.35 (m, 1H), 1.93-1.83 (m, 1H), 1.40-1.13 (m, 9H), 0.87 (s, 9H). m/z: [ESI⁺] 598, 600 (M+1)⁺.

Synthesis of tert-butyl (trans)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (7, Scheme 86)

[00503] Tetrabutylammonium fluoride (8.74 g, 33.43 mmol) was added to a stirred solution of *tert*-butyl (*trans*)-2-(4-bromo-3-fluorophenyl)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (10.00 g, 16.70 mmol) in tetrahydrofuran (100 mL) portionwise over 2 min at room temperature. The reaction solution was stirred for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 15% ethyl acetate in petroleum ether) to afford *tert*-butyl (*trans*)-2-(4-bromo-3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate as a white solid.

Yield 3.00 g (50%). ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.63 (m, 1H), 7.10-7.02 (m, 1H), 7.00-6.95 (m, 1H), 5.05-4.78 (m, 1H), 4.54-4.41 (m, 1H), 3.95-3.81 (m, 1H), 3.64-3.55 (m, 1H), 2.66-2.54 (m, 1H), 2.03-1.93 (m, 1H), 1.41-1.22 (m, 9H). OH proton not observed. m/z: [ESI⁺] 304, 306 (M+1-56)⁺.

Synthesis of 4-((trans)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenylboronic acid (8, Scheme 86)

[00504] Compound 4-((*trans*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenylboronic acid was prepared from *tert*-butyl (*trans*)-2-(4-bromo-3-fluorophenyl)-4-

hydroxypyrrolidine-1-carboxylate (200 mg, 0.555 mmol) and bis(pinacolato)diboron (210 mg, 0.827 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate and was isolated as an off-white solid.

- 5 Yield 130 mg (72%). ¹H NMR (400 MHz, DMSO) δ 7.62-7.54 (m, 1H), 7.09-7.02 (m, 1H), 7.02-6.95 (m, 1H), 5.09-4.97 (m, 1H), 4.86-4.73 (m, 1H), 4.33-4.19 (m, 1H), 3.67-3.53 (m, 1H), 3.51-3.41 (m, 1H), 2.29-2.18 (m, 1H), 1.82-1.68 (m, 1H), 1.31-1.09 (m, 9H). Two OH protons of boronic acid not observed. m/z: [ESI⁺] 270 (M+1-56)⁺.

- 10 *Synthesis of tert-butyl (trans)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (10, Scheme 86)*

- [00505] Compound *tert*-butyl (trans)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (70 mg, 0.149 mmol) and (4-((trans)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)boronic acid (80 mg, 0.246 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate and was isolated as a brown solid.

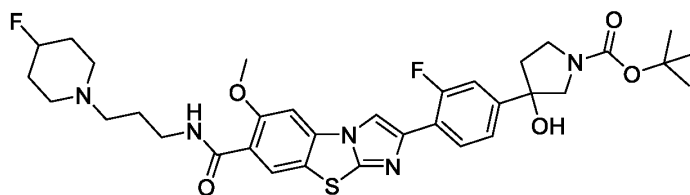
- 20 Yield 50 mg (50%). ¹H NMR (300 MHz, DMSO) δ 8.80-8.64 (m, 1H), 8.37-8.29 (m, 1H), 8.26 (t, *J* = 5.7 Hz, 1H), 8.19-8.03 (m, 2H), 7.62-7.45 (m, 1H), 7.23-7.11 (m, 1H), 5.15-4.95 (m, 1H), 4.93-4.67 (m, 2H), 4.65-4.46 (m, 1H), 4.33-4.25 (m, 1H), 4.02 (s, 3H), 3.71-3.41 (m, 2H), 2.41-2.22 (m, 6H), 2.00-1.60 (m, 8H), 1.39-1.10 (m, 9H). OH proton not observed. m/z: [ESI⁺] 670 (M+H)⁺.

- 25 *Synthesis of tert-butyl (trans)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate*

- [00506] Compound *tert*-butyl (trans)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate was prepared from 2-bromo-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide (50 mg, 0.118 mmol) and (4-((trans)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)-2-fluorophenyl)boronic acid (60 mg, 0.185 mmol), following a similar procedure to that described for the synthesis of *tert*-butyl 6-fluoro-5-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)benzo[d]imidazo[2,1-b]thiazol-2-yl)indoline-1-carboxylate and was isolated as a brown solid.

- 35 Yield 50 mg (68%). ¹H NMR not run. m/z: [ESI⁺] 624 (M+H)⁺.

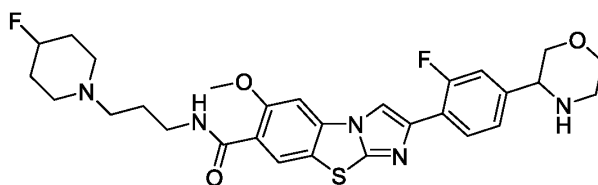
Synthesis of *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-3-hydroxypyrrolidine-1-carboxylate



[00507] Compound *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-3-hydroxypyrrolidine-1-carboxylate was prepared from 2-bromo-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (200 mg, 0.426 mmol) and *tert*-butyl 3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-hydroxypyrrolidine-1-carboxylate (350 mg, crude) at 90°C, following a similar procedure to that described for the synthesis of *tert*-butyl 4-(4-bromo-3-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and was isolated as a brown yellow solid. Yield 180 mg (63%). ¹H NMR (300 MHz, CDCl₃) δ 8.38-8.20 (m, 1H), 8.02 (t, *J* = 5.7 Hz, 1H), 7.96-7.84 (m, 2H), 7.26-7.16 (m, 2H), 7.11-7.06 (m, 1H), 4.95-4.61 (m, 1H), 4.11 (s, 3H), 3.80-3.48 (m, 6H), 2.81-2.51 (m, 6H), 2.13-1.84 (m, 8H), 1.51 (s, 9H). OH proton not observed. *m/z*: [ESI⁺] 670 (M+H)⁺.

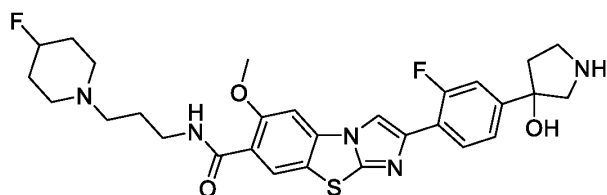
15 Final Compounds

Synthesis of 2-(2-fluoro-4-(morpholin-3-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride (**Compound 195**)



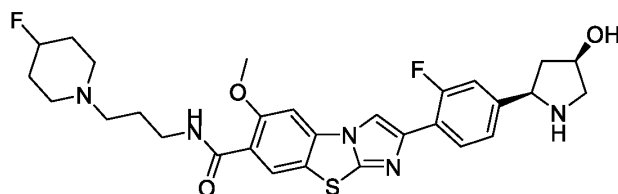
[00508] Compound 2-(2-fluoro-4-(morpholin-3-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)morpholine-4-carboxylate (60 mg, 0.090 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a white solid. Yield 19 mg (33%). ¹H NMR (400 MHz, DMSO) δ 10.86 (br s, 1H), 10.31 (br s, 1H), 9.98 (br s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.50 (t, *J* = 5.6 Hz, 1H), 8.37 (s, 1H), 8.25-8.16 (m, 1H), 8.13 (s, 1H), 7.77 (d, *J* = 12.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 5.18-4.67 (m, 1H), 4.60-4.49 (m, 1H), 4.02-3.93 (m, 6H), 3.94-3.81 (m, 2H), 3.59-3.20 (m, 5H), 3.14-2.99 (m, 4H), 2.33-1.89 (m, 6H). ¹⁹F NMR (376 MHz, DMSO) δ -112.27, -175.52, -186.58. *m/z*: [ESI⁺] 570 (M+H)⁺. (C₂₉H₃₅Cl₂F₂N₅O₃S).

Synthesis of 2-(2-fluoro-4-(3-hydroxypyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride (Compound 197)



- 5 [00509] Compound 2-(2-fluoro-4-(3-hydroxypyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl 3-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-3-hydroxypyrrolidine-1-carboxylate (180 mg, 0.269 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-
10 *a*]imidazole-7-carboxamide dihydrochloride and was isolated as a brown yellow solid.
Yield 140 mg (81%). ¹H NMR (400 MHz, DMSO) δ 11.01 (br s, 1H), 9.84 (br s, 1H), 9.46 (br s, 1H), 8.94-8.68 (m, 1H), 8.66-8.46 (m, 1H), 8.37 (d, *J* = 1.6 Hz, 1H), 8.20-8.05 (m, 2H), 7.64-7.31 (m, 2H), 5.17-4.67 (m, 1H), 4.05 (s, 3H), 3.57-3.32 (m, 8H), 3.22-3.00 (m, 4H), 2.41-1.89 (m, 8H). OH proton not observed.
15 ¹⁹F NMR (376 MHz, DMSO) δ -113.45, -175.53, -186.56. *m/z*: [ESI⁺] 570 (M+H)⁺. (C₂₉H₃₅Cl₂F₂N₅O₃S).

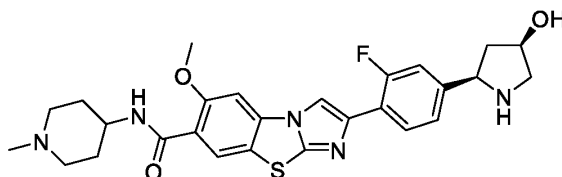
Synthesis of 2-(2-fluoro-4-((*cis*,4*S*)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide (Compound 200*S*)



- 20 [00510] Compound 2-(2-fluoro-4-((*cis*,4*S*)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*cis*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (30 mg, 0.045 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-
25 *a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid.
Yield 5 mg (17%). ¹H NMR (400 MHz, DMSO) δ 10.89 (br s, 1H), 10.45 (br s, 1H), 9.18 (br s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.56-8.46 (m, 1H), 8.37 (s, 1H), 8.21 (t, *J* = 5.6 Hz, 1H), 8.13 (s, 1H), 7.61 (d, *J* = 12.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 5.17-4.81 (m, 1H), 4.83-4.66 (m, 1H), 4.64-4.45 (m, 1H), 4.04 (s, 3H),

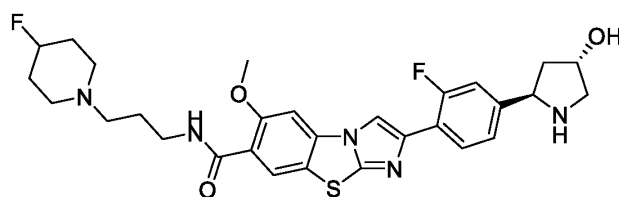
3.51-3.45 (m, 5H), 3.24-2.94 (m, 5H), 2.78-2.64 (m, 1H), 2.34-1.88 (m, 7H). OH proton not observed. ^{19}F NMR (376 MHz, DMSO) δ -112.95, -175.53, -186.58. m/z: [ESI $^{+}$] 570 (M+H) $^{+}$. (C₂₉H₃₅Cl₂F₂N₅O₃S).

Synthesis of 2-(2-fluoro-4-((2*S*,4*S*)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (Compound 203*S*)



[00511] Compound 2-(2-fluoro-4-((*cis*)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*cis*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (30 mg, 0.048 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as an off-white solid. Yield 5 mg (17%). ^1H NMR (400 MHz, DMSO) δ 10.42 (br s, 2H), 9.17 (br s, 1H), 8.84 (t, J = 3.6 Hz, 1H), 8.37-8.27 (m, 1H), 8.27-8.17 (m, 2H), 8.15-8.06 (m, 1H), 7.67-7.51 (m, 1H), 7.52-7.38 (m, 1H), 4.71 (s, 1H), 4.56 (s, 1H), 4.08-3.93 (m, 4H), 3.40-3.35 (m, 2H), 3.23-3.00 (m, 4H), 2.83-2.61 (m, 4H), 2.17-1.97 (m, 3H), 1.97-1.78 (m, 2H). OH proton not observed. ^{19}F NMR (376 MHz, DMSO) δ -113.02. m/z: [ESI $^{+}$] 524 (M+H) $^{+}$. (C₂₇H₃₂Cl₂FN₅O₃S).

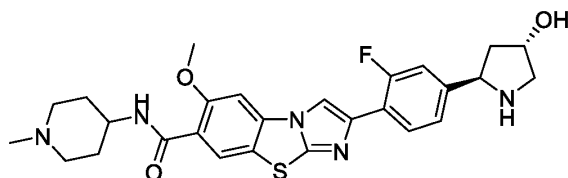
20 Synthesis of 2-(2-fluoro-4-((2*S*,4*R*)-4-hydroxypyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide (Compound 200*R*)



[00512] Compound 2-(2-fluoro-4-((*trans*)-4-hydroxypyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*trans*)-2-(3-fluoro-4-(7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-6-methoxybenzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (100 mg, 0.149 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a white solid. Yield 12 mg (13%). ^1H NMR (400 MHz, DMSO) δ 11.04 (br s, 1H), 10.57 (br s, 1H), 9.37 (br s, 1H), 8.96-8.76 (m, 1H), 8.51 (t, J = 5.6 Hz, 1H), 8.36 (s, 1H), 8.21-8.07 (m, 2H), 7.66 (d, J = 12.4 Hz, 1H), 7.50 (d, J

= 8.0 Hz, 1H), 5.23-4.64 (m, 2H), 4.61-4.50 (m, 1H), 4.04 (s, 3H), 3.68-3.34 (m, 5H), 3.28-2.96 (m, 5H), 2.38-1.95 (m, 8H). OH proton not observed. ^{19}F NMR (376 MHz, DMSO) δ -113.02. Aliphatic ^{19}F not observed. m/z: $[\text{ESI}^+]$ 570 (M+H) $^+$. ($\text{C}_{29}\text{H}_{35}\text{Cl}_2\text{F}_2\text{N}_5\text{O}_3\text{S}$).

- 5 *Synthesis of 2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide (Compound 203R)*



- [00513] Compound 2-(2-fluoro-4-((*trans*)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-*N*-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-*b*]thiazole-7-carboxamide dihydrochloride was prepared from *tert*-butyl (*trans*)-2-(3-fluoro-4-(6-methoxy-7-((1-methylpiperidin-4-yl)carbamoyl)benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-4-hydroxypyrrolidine-1-carboxylate (50 mg, 0.080 mmol), following a similar procedure to that described for the synthesis of (*S*)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-*N*-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9*H*-benzo[d]imidazo[1,2-*a*]imidazole-7-carboxamide dihydrochloride and was isolated as a yellow green solid.
- 15 Yield 8 mg (17%). ^1H NMR (400 MHz, DMSO) δ 10.84 (br s, 1H), 10.49 (br s, 1H), 9.29 (br s, 1H), 8.86 (d, J = 3.6 Hz, 1H), 8.38-8.29 (m, 1H), 8.26-8.15 (m, 2H), 8.11 (s, 1H), 7.66 (d, J = 12.4 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.89-4.77 (m, 1H), 4.60-4.52 (m, 1H), 4.00-3.95 (m, 4H), 3.65-3.53 (m, 1H), 3.46-3.24 (m, 2H), 3.22-3.02 (m, 3H), 2.71 (s, 3H), 2.36-2.19 (m, 2H), 2.14-1.80 (m, 4H). OH proton not observed. ^{19}F NMR (376 MHz, DMSO) δ -112.97. m/z: $[\text{ESI}^+]$ 524 (M+H) $^+$. ($\text{C}_{27}\text{H}_{32}\text{Cl}_2\text{FN}_5\text{O}_3\text{S}$).

20

EXAMPLE 4

Biological activity of compounds of the invention

[00514] The biological activity results of compounds of the invention are summarized in Table 2.

Table 2. Cellular -LogEC₅₀ values of compounds of the invention in the immunofluorescence assay.

Compound No.	Myc Efficacy (-LogEC ₅₀)
102R	+++
102S	+++
103R	+++
103S	+++
121R	+++
121S	+++
122R	++
122S	++
137R	++
137S	++

138	+++
139	++
140	++
141	++
142	++
143	+
144	+++
145	++
146	++
147	++
148	+
149R	+++
149S	+++
150	+++
151	+++
152	+
153R	+++
153S	+++
154	+
155	+++
156	++
157	++
158	++
159	+++
160	+++
161	+++
162	++
163	++
164	+++
165	+++
166	+++
167	++
168	+++
169	+++
170	++
171	+
172	++
173	+
174	+
175	+++
176	+++
177	++
178	+++
179	++
180	++

181	++
182	+++
183	+++
184	+++
185	+++
186	+++
187	+++
188	+++
189	+++
190	+++
191	+++
192	+++
195	+++
196	+++
197	+++
198	+++
199	++
200R	+++
200S	++
201R	++
201S	++
202R	++
202S	++
203R	+++
203S	+++
204	++
205	+
300	+++
301	+++
302	+++
303	+++
400R	+
400S	+
401	+
402	+
403	+
404	+
408	+
409	+
410	+

Activity (-LogEC₅₀):

- ≤3
+ >3 and <5
++ ≥5 and <6
+++ ≥6

[00515] Compounds activity is tested in tumor cell lines expressing c-Myc by using high content image analysis. c-Myc mRNA rate of translation is assayed using PSM assay, c-Myc protein levels and intracellular localization are assayed by immunofluorescence using a c-Myc specific antibody and c-Myc mRNA levels and intracellular localization is tested using specific fluorescent probes, as detailed in the Experimental Methods below (Example 6). The di-tRNA translation rate measurement specificity to c-Myc is shown by co-transfecting c-Myc specific siRNA. Transfection of labelled di-tRNA with c-Myc specific siRNA reduce the FRET signal originating from ribosome translating c-Myc, relative to cells transfected with nonrelevant siRNA.

[00516] A549 cells are incubated with active compounds and metabolically labelled with fluorescent methionine for a 4 hour pulse (click-chemistry modified methionine). Cells are fixed and newly synthesized proteins detected by using click-chemistry with a fluorescent detector.

[00517] A549 cells are incubated with compounds for 24 hours and c-Myc protein is detected by immunofluorescence. In parallel, A549 cells are incubated with compounds for 4 hours and c-Myc mRNA is visualized by microscopy using c-Myc mRNA specific fluorescent-tagged probes.

[00518] A549 human non-small cell lung carcinoma cells are treated for 24 hours with increasing compound concentration, cells are fixed and stained with a nuclei stain (DAPI) and anti-c-Myc fluorescent antibody. The c-Myc signal is quantified by image analysis, and data is exported and analyzed using TIBCO Spotfire® (TIBCO Corporation). Dose response curves are generated and fitted with logistic regression to calculate potency (EC₅₀ values).

EXAMPLE 5

In vivo activity of compounds of the invention

A549 xenograft model in nude mice.

[00519] NMRI nude female mice of 6-8 weeks of age are acclimated after shipping for > 4 days. A549 cells, 5 x 10⁶ in 100 ul Matrigel:PBS (50:50), are subcutaneously injected into flanks of mice. When the tumor size reaches 80 to 200 mm³, mice are grouped with similar average tumor size in each group, 10 animals per group. Compounds are dissolved in 10% DMSO, 10% Solutol, 80% water. Compounds are given i.p. for 49 days at 3 mg/kg twice a week. Caliper measurement of tumor size are done twice a week.

EXAMPLE 6

Experimental Methods

High content screen for the identification of c-Myc modulators

[00520] Compound effect on translation of c-Myc in A549, human non-small cell lung carcinoma cell line, is conducted using specific PSM assay using tRNA^{Gln} and tRNA^{Ser} isoacceptors, as described below. A library of diverse small molecules, 90,000 compounds, is used at a final concentration of 30 μM. Image and data analyses are conducted using Anima's proprietary algorithms. False positive and toxic compounds

are eliminated. Compounds are identified as hits, compounds which increase or decrease the FRET signal generated by ribosomes during c-Myc translation.

[00521] Positive hits are re-screened in the specific PSM assay, using tRNA^{gln} and tRNA^{ser}. Hits are scored using Anima's proprietary algorithms, and compounds, which selectively inhibit c-Myc synthesis in specific PSM assay, are selected as confirmed hits. These compounds are purchased as powder to confirm activity. Re-purchased hits are tested in the specific PSM assay (tRNA^{gln}-tRNA^{ser}) and anti-c-Myc immunofluorescence, and in counter assays to eliminate global translation modulators: (1) bulk tRNA and (2) metabolic labeling using Click-IT™ AHA (L-Azidohomoalanine).

10 *Cell culture*

[00522] A549 cells (ATCC® CCL-185™) are maintained in DMEM low glucose medium (Biological Industries, Cat. 01-050-1A), containing 10% fetal bovine serum, 1% L-glutamine and 1% penicillin-streptomycin solution.

[00523] SK-N-F1 cells (ATCC® CRL-2142™) are maintained in DMEM high glucose medium (Biological Industries, Cat. 01-055-1A), containing 10% fetal bovine serum, 2% L-glutamine, 1% penicillin-streptomycin solution, 1% sodium pyruvate and 1% non-essential amino acids.

Specific tRNA (tRNA isoacceptor) isolation and labeling

[00524] The specific tRNA^{gln} (TTG) and tRNA^{ser} (CGA) are isolated from baker's yeast (Roche) using biotinylated oligos complementary to sequences encompassing the D-loop and anti-codon. The biotinylated oligos are mixed with total yeast tRNA and heat up to 82°C for 10 min, followed by addition of TMA buffer (20mM Tris, pH 7.6, 1.8M tetramethylammonium chloride, 0.2mM EDTA). The mixture is incubated at 68°C for 10 min, and annealed by slow cooling to 37°C. tRNA:DNA oligo mixture then is incubated with streptavidin linked agarose beads at room temperature for 30 min while shaking. Unbound tRNA and tRNA:DNA complexes are removed by centrifugation and beads are washed with 10mM Tris-HCl (pH 7.6). The target tRNA is eluted from the resin by incubation at 45°C or 55°C for 7 min followed by centrifugation and collection of the supernatant to clean tubes.

[00525] The purity of the isolated tRNA isoacceptors is confirmed using fluorescent polarization assay. Purified tRNA is annealed to a complementary oligo tagged at the 3'-end with Cy3. The annealed purified tRNA isoacceptor FP signal is compared to the signal derived from annealing of a tRNA isoacceptor oligo annealed to the same Cy3-oligo. Samples with more than 80% purity are selected for labeling.

[00526] The dihydrouridines of the target tRNAs or total yeast tRNA are labeled as described in U.S. Pat. No. 8,785,119. Labeled tRNAs are purified by reverse phase HPLC and eluted with an ethanol gradient.

35 *Protein synthesis monitoring (PSM) Assays*

[00527] Cy3 and Cy5 Labeled tRNA, bulk or specific, are transfected with 0.4 µl HiPerFect (Qiagen) per 384 well. First, HiPerFect is mixed with DMEM and incubated for 5 min; next, 6 nanograms Cy3-labeled tRNA^{gln} and 6 ng Cy5-labeled tRNA^{ser} (or 9 ng each Cy3 and Cy5-labelled bulk tRNA) are diluted

in 1xPBS and then added to the HiPerFect:DMEM cocktail and incubated at room temperature for 10 min. The transfection mixture is dispersed automatically into 384-well black plates. Cells are then seeded at 3,500 cells per well in complete culture medium and incubated at 37°C, 5% CO₂. Forty-eight hours after transfection compounds are added at a final concentration of 30 µM. Four hours post-treatment, cells are fixed with 4% paraformaldehyde and images are captured with Operetta microscope (Perkin Elmer) using x20 high NA objective lens.

Metabolic labeling assay

[00528] A549 cells are seeded at 3,200 cells per well in complete culture medium. Plates are incubated at 37°C, 5% CO₂ overnight. After 48 hours of incubation, the growth medium is aspirated, and cells are washed three times with HBSS. Metabolic labeling medium DMEM (-Cys -Met), containing 10% dialyzed FBS, 1% penicillin-streptomycin and 1% L-glutamine is added to the cells for 30 min. Then medium is replaced by metabolic labeling medium containing 25 µM L-Azidohomoalanine (AHA, ThermoFisher) and tested compounds at a final concentration of 30 µM, and cells are incubated for 4 hours at 37°C, 5% CO₂. Cells are washed by HBSS at 37°C for 15 min before fixing with 4% paraformaldehyde. Cells are washed twice with 3% BSA in PBS before permeabilization with 0.5% Triton X-100 in PBS for 20 min. The AHA staining with Alexa Fluor™ 555 alkyne is performed according to the manufacturer protocol. Images are captured with Operetta microscope (Perkin Elmer) using x20 high NA objective lens.

c-Myc immunofluorescence assay

[00529] A549 cells are grown in 384-wells plates (Perkin Elmer, Cat. 6057300) for 48 hours, treated with compounds and then fixed for 20 min in 4% paraformaldehyde. After that permeabilization is done using 0.1% Triton X-100 in PBS for 20 min. Primary anti-c-Myc antibody (Abcam, ab32072) staining is performed for 90 min at room temperature. Cells then are washed twice with PBS and incubated with secondary antibody (Abcam, ab150075) for 90 min at room temperature. Nuclei are stained with DAPI for 10 min and washed twice with PBS.

[00530] Cell images are taken with Operetta (Perkin Elmer, USA), a wide-field fluorescence microscope at 20x magnification. After acquisition, the images are transferred to Columbus software (Perkin-Elmer) for image analysis. In Columbus, cells are identified by their nucleus, using the "Find Nuclei" module and cytoplasm is detected based on the secondary antibody channel. Subsequently, the fluorescent signal is enumerated in the identified cell region. Then data is exported to a data analysis and visualization software, Tibco Spotfire, USA.

Fluorescent In Situ Hybridization (FISH) assay

[00531] A549 cells are grown in 384-wells plates (Perkin Elmer, Cat. 6057300) for 48 hours, treated with compounds for 4 hours and then fixed for 20 min in 4% paraformaldehyde. Next day, permeabilization is done for 90 min at 4°C, using 70% ethanol. Then, the cells are incubated for 10 min with 10% formamide in 10% saline-sodium citrate. Fluorescently labeled custom DNA probes that target c-Myc (Cy3,

BioSearch Technologies, Cat. SMF-1063-5) and GAPDH (Cy5, BioSearch Technologies, Cat. SMF-2019-1) mRNAs are hybridized overnight at 37°C in a dark chamber in 10% formamide. The next day, cells are washed twice with 10% formamide for 30 min. Next, nuclei are counterstained with DAPI (SIGMA, Cat. 5MG-D9542) and then cells are washed twice with PBS. FISH experiments are performed according to the probes manufacturer's protocol for adherent cells.

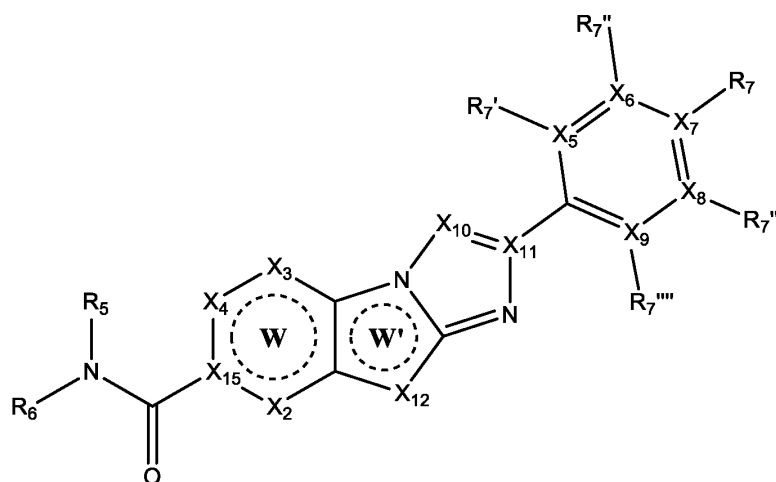
[00532] Following RNA FISH experiments, images of cells are taken with Operetta (Perkin Elmer, USA), a wide-field fluorescence microscope at x63 magnification. After acquisition, the images are transferred to Columbus software for image analysis. In Columbus, cells are identified by their nucleus, using the "Find Nuclei" module, cytoplasm is detected based on the FISH-channel, and single mRNAs in the cytoplasm and transcription sites in the nucleus are detected using "Find Spots" module. Subsequently, fluorescent signals are collected for each channel in the identified regions: nucleus, cytoplasm and spots. Data is exported to a data analysis and visualization software, Tibco Spotfire, USA.

A549 xenograft model in nude mice.

[00533] NMRI nude female mice of 6-8 weeks of age are acclimated after shipping for > 4 days. A549 cells, 5×10^6 in 100 μ l Matrigel:PBS (50:50), are subcutaneously injected into flanks of mice. When the tumor size reached 80 to 200 mm^3 , mice are grouped with similar average tumor size in each group, 10 animals per group. Compounds are dissolved in 10% DMSO, 10% Solutol, 80% water. Compounds are given i.p. for 49 days at 3 mg/kg twice a week. Caliper measurement of tumor size is done twice a week.

WHAT IS CLAIMED:

1. A compound represented by the structure of formula **I(k)**:



I(k)

5 wherein

Ring W may be either aromatic or non-aromatic ring,

wherein if **ring W** is aromatic then

10 X₂, X₃, and X₄, are each independently CH, C(R) or N (e.g., C(CH₃), C(O-CH₂-cyclopropyl), C(O-CH₂-methylcyclobutyl), C(O-CH₂-3-methyloxetane), C(NH-CH₂-cyclopropyl), C(isopropoxy), C(O-CH(CH₃)-CH₂-O-CH₃), C(CH₂CH₃), C-iPr, C-CH₂-cyclopropyl, C(OCH₃), C(OCH₂CH₃), C(O-(CH₂)₂-O-CH₃), C(OCHF₂), C(Cl), C(C(O)CH₃), C(O-CH₂CH₂-O-CH₃), C(OH));

X₁₅ is C; and

wherein if **ring W** is non-aromatic then

15 X₂, X₃, and X₄, are each independently CH₂, CH(R), C(R)₂, NH, N(R), O, S, S=O or SO₂ (e.g., CH₂);

X₁₅ is CH, C(R) or N (e.g., CH, N);

X₅, X₆, X₇, X₈ and X₉ are each independently nitrogen or carbon atoms;

wherein if either one of X₅, X₆, X₇, X₈ and X₉ is nitrogen, then the respective R₇', R₇'',

20 R₇, R₇'', and R₇'''' substitution is absent;

X₁₀ is N, CH, C(R), or C=O; wherein if X₁₀ is C=O then X₁₁ is N (e.g., C(CH₂-OH), C(CH₂-CH₂-OH), C(NH-CH₂-cyclopropyl), C(COOH), C(CH₃), C(cyclopropyl), C(isopropoxy));

X₁₁ is N or C; wherein if X₁₁ is N then X₁₀ is C=O;

Ring W' may be either aromatic or non-aromatic ring,

25 wherein if **ring W'** is aromatic then

X_{12} is S, SO_2 , O, NH, N(R), N-OH, $CH=CH$, $CH=CH(R)$, $C(R)=CH$, $N=CH$, $N=C(R)$, $CH=N$ or $C(R)=N$ (e.g., $N-CH_2-COOH$, $N-CH_2-CH_2-OH$, $N-CH_3$, $N-CH_2CH_3$, $N-iPr$, $N-cyclopropyl$, $N-CH_2-cyclopropyl$);

wherein if **ring W'** is non-aromatic then

5 X_{12} is $CH=CH$, $CH=CH(R)$, $C(R)=CH$, OCH_2 , SCH_2 , $CH=N$, $C(R)=N$, $N=CH$, $N=C(R)$;

wherein if both **Ring W** and **Ring W'** are aromatic, then at least one of X_2 , X_3 , and X_4 is C(R); X_{11} is N; or X_{12} is not S;

R_5 is H or C_1-C_5 linear or branched alkyl (e.g. methyl);

10 R_6 is H, F, Cl, Br, I, OH, SH, R_8-OH , R_8-SH , $-R_8-O-R_{10}$ (e.g., CH_2-O-CH_3 , $(CH_2)_2-O-CH_3$, $(CH_2)_3-O-CH_3$, $(CH_2)_2-O-CH(CH_3)_2$), R_8-S-R_{10} (e.g., $(CH_2)_3-S-(CH_2)_2CH_3$), $R_8-NHC(O)-R_{10}$, $-O-R_8-R_{10}$, R_8 -(substituted or unsubstituted C_3-C_8 cycloalkyl) (e.g., $CH_2-cyclopropyl$, $CH_2-cyclobutanol$, CH_2 -difluorocyclopropyl, $CH_2-methylcyclopropyl$, $CH_2-dimethylamino-cyclohexyl$, $(CH_2)_2-cyclopentanol$, $CH_2-cyclohexanol$), R_8 -(substituted or unsubstituted, saturated, unsaturated or aromatic, single, fused or

15 spiro 3-10 membered heterocyclic ring) (e.g., $(CH_2)_3$ -piperidine, $(CH_2)_3$ -4-fluoro-piperidine, $(CH_2)_3$ -pyran, $(CH_2)_2$ -pyrazole, $(CH_2)_2$ -imidazole, CH_2 -tetrahydrofuran, CH_2 -dioxane, CH_2 -oxetane, CH_2 -piperidine, CH_2 -triazole, CH_2 -1-oxa-8-azaspiro[4.5]decane, $(CH_2)_3$ -diazabicyclo[2.2.1]heptane, CH_2 -methyl-THF, CH_2 -ethyl-piperidine, CH_2 -oxa-azaspirodecane, $(CH_2)_3$ -dimethylpyrazole, CH_2 -2-oxo-methylpyrrolidine, CH_2 -methyl-azetidine, CH_2 -azaspiroheptane), CF_3 , CD_3 , OCD_3 , CN, NO_2 , $-CH_2CN$,

20 $-R_8CN$, NH_2 , NHR , $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, $R_8-N(R_{10})(R_{11})$ (e.g., $(CH_2)_2-NH_2$, $(CH_2)_3-N(CH_2CH_3)_2$, $(CH_2)_3-N(CH(CH_3)_2)_2$, $(CH_2)_3$ -piperidine, $(CH_2)_3$ -4-fluoro-piperidine, $(CH_2)_3$ -4-cyano-piperidine, $(CH_2)_4-NH(CH_3)$, $(CH_2)_3-NH-CH_3$, $(CH_2)_3-NH-CH_2CH_3$, $(CH_2)_3-N(CH_2CH_3)_2$, $(CH_2)_3-NH_2$, $(CH_2)_3-N(CH_2CH_3)(CH_2CF_3)$), $R_9-R_8-N(R_{10})(R_{11})$ (e.g., $(CH_2)_2-C(O)$ -piperidine), $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$, $NHCO-N(R_{10})(R_{11})$, $COOH$, $-C(O)Ph$, $C(O)O-R_{10}$, $R_8-C(O)-R_{10}$, $C(O)H$, $C(O)-$

25 R_{10} (e.g., $C(O)CH_3$), C_1-C_5 linear or branched $C(O)$ -haloalkyl, $-C(O)NH_2$, $C(O)NHR$, $C(O)N(R_{10})(R_{11})$, SO_2R , $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH-R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., $CH(CH_3)CH_2OCH_3$, $CH(CH_3)CH_2NH_2$, $CH(CH_3)C(O)N(CH_3)_2$, $CH_2-CH(OH)Ph$, $(CH_2)_3N(H)CH_2CH_3$, $CH(CH_3)(CH_2)_2OH$, $CH(CH_2OH)(CH_2CH_3)$, $(CH_2)_3-OCH_3$, $(CH_2)_2-OCH_3$, $(CH_2)_2-OCH(CH_3)_2$, $CH(CH_2OH)(CH_2CH(CH_3)_2)$, $CH_2CH(CH_3)(OCH_3)$, $CH_2CH(N(CH_3)_2)(CH_2CH_3)$,

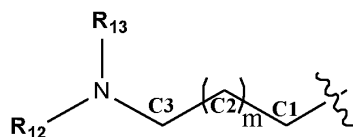
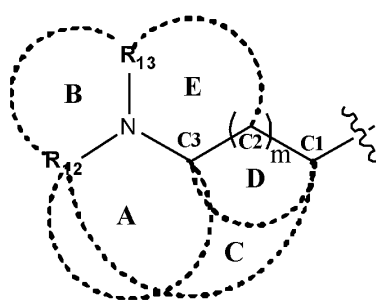
30 benzyl, methyl, ethyl, $CH_2-OCH_2-CH_2-O-CH_3$, $CH(CH_3)C(O)N(CH_3)_2$, C_1-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear or branched, or C_3-C_8 cyclic haloalkyl, substituted or unsubstituted C_1-C_5 linear or branched, or C_3-C_8 cyclic alkoxy (e.g. methoxy, $O-(CH_2)_2-O-CH_3$), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched

35 alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl, methoxycyclopropyl, methylcyclobutyl, aminomethyl-cyclobutyl, methoxycyclobutyl, 2,3-dihydro-1H-indenol), R_8 -(substituted or unsubstituted C_3-C_8 cycloalkyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperidine, 1-methyl-piperidine, azetidine, pyrrolidine, pyrrolidinone,

quinuclidine, tetrahydropyran, azaspiro[3.3]heptane, imidazole, trifluoromethyl-oxetane, hydroxy-tetrahydrofuran, azepan-2-one, azabicyclohexane), substituted or unsubstituted aryl, substituted or unsubstituted R_8 -aryl (e.g., benzyl), substituted or unsubstituted benzyl;

or R_6 and R_5 are joined to form a substituted or unsubstituted 5-8 membered heterocyclic ring (e.g., azepane, piperazine, 2-(piperazin-1-yl)acetamide;

or R_6 is represented by the structure of formula **B** or **Bi**:

**B****Bi**

wherein

m is 0 or 1; and

R_{12} is R_{20} or C_1 - C_5 $C(O)$ -alkyl, and R_{13} is R_{30} ; or

R_{12} and R_{13} are both H;

R_{12} and R_{13} are each independently H or substituted or unsubstituted C_1 - C_5 alkyl (e.g., ethyl, trifluoroethyl);

R_{12} and C_3 are joined to form ring **A** and R_{13} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B**; or

R_{12} and C_1 are joined to form ring **C** and R_{13} is R_{30} ; or

C_1 and C_3 are joined to form ring **D** and R_{12} and R_{13} are each independently R_{30} ; or

R_{13} and C_2 are joined to form ring **E**, m is 1, and R_{12} is R_{30} ; or

R_{12} and R_{13} are joined to form ring **B** and C_1 and C_3 are joined to form ring **D**;

wherein

Ring **A**, **C** and **E** are each independently a substituted or unsubstituted single spiro or fused 3-8 membered heterocyclic ring (e.g., **A**: pyrrolidine, methylpyrrolidine, ethylpyrrolidine); **C**: piperidine, pyrrolidine, methyl-2-oxopyrrolidine, pyran-pyrrolidine, methyl-azetidine, azabicyclooctane, 2-azabicyclo[2.1.1]hexane, 2-azaspiro[3.3]heptane; **E**: pyrrolidine, azetidine, ethylpyrrolidine, oxopyrrolidine, methylpiperidine;

Ring **B** is a substituted or unsubstituted single, spiro or fused 3-8 membered heterocyclic ring (**B**: piperidine, piperidin-2-one, 4-fluoropiperidin-2-one, piperidine-4-carbonitrile, 4-fluoropiperidine, 4-fluoro-2-methylpiperidine, methyl-piperidin, fluoropiperidine, difluoropiperidine, pyrrolidine, piperazine, methylpyrrolidine, thiomorpholine 1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane, methyl-piperazine, dimethyl-pyrazole, imidazole, 2-methyl-2,5-diazabicyclo[2.2.1]heptane, hydroxymethyl-pyrrolidine, diazabicyclo[2.2.1]heptane, 6-fluoro-3-azabicyclo[3.1.1]heptane; and

Ring **D** is a substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclobutane, cyclohexane);

R₇ is H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, SR₁₀, -R₈-O-R₁₀, -R₈-S-R₁₀, R₈-(C₃-C₈ cycloalkyl), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)NH(CH₃), C(O)NH(CH₂CH₂OCH₃), C(O)NH(CH₂CH₂OH)), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methylimidazole, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy, ethoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom, C₁-C₅ linear or branched thioalkyl, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopropanol, cyclohexyl), substituted or unsubstituted 4-7 membered heterocyclic ring (e.g., morpholine (e.g., 2 or 3-morpholine), tetrahydrofuran, tetrahydropyran, oxetane, oxetan-3-ol, pyrrolidine, pyrrolidine-3-ol, 1-methylpyrrolidine, pyrrolidin-2-one, pyrrolidinone, imidazole, pyrazole, piperazine, piperidine, piperidine-4-ol, piperidine-4-carbonitrile, 4-fluoropiperidine, oxadiazole, triazole, 2-oxopyrrolidine, pyridine, 1-methylpyridine), R₈-(substituted or unsubstituted single, fused or spiro 3-8 membered heterocyclic ring), substituted or unsubstituted aryl, substituted or unsubstituted benzyl;

R₇', **R₇''**, **R₇'''** and **R₇''''** are each independently H, F, Cl, Br, I, OH, O-R₂₀, SH, R₈-OH, R₈-SH, -R₈-O-R₁₀, R₈-(C₃-C₈ cycloalkyl), R₈-(3-8 membered heterocyclic ring), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), R₈-N(R₁₀)(R₁₁), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀, NHCO-N(R₁₀)(R₁₁), COOH, -C(O)Ph, C(O)O-R₁₀, R₈-C(O)-R₁₀, C(O)H, C(O)-R₁₀, C₁-C₅ linear or branched C(O)-haloalkyl, -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁), SO₂R, SO₂N(R₁₀)(R₁₁), CH(CF₃)(NH-R₁₀), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., isopropyl, methyl, ethyl), C₁-C₅ linear or branched, substituted or unsubstituted alkenyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl (e.g., CHF₂), C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced

with an oxygen atom, C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclohexyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, pyran, oxetane, pyrrolidine, imidazole, piperazine, piperidine, dioxazole, 2-oxopyrrolidine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

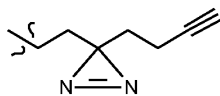
or R₇' and R₇' are joined to form a 3-8 membered substituted or unsubstituted, saturated, unsaturated or aromatic, carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇' and R₇ are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇ and R₇' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

or R₇' and R₇' are joined to form a 3-8 membered substituted or unsubstituted carbocyclic or heterocyclic ring (e.g., cyclopentyl, cyclohexyl, piperidine, tetrahydrofuran, tetrahydropyran, pyrrolidine);

R₂₀ is represented by the following structure:



R₃₀ is H, R₂₀, F, Cl, Br, I, OH, SH, alkoxy, N(R)₂, NH(R₁₀), N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, -R₈-R₁₀ (e.g., (CH₂)₂-O-CH₃), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));

R is H, F, Cl, Br, I, OH, SH, COOH, CO(R₁₀), C(O)CH₃, NH(R₁₀), NH-CH₂-cyclopropyl, N(R₁₀)(R₁₁), CF₃, CN, NO₂, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, iPr, CH₂-cyclopropyl, CH₂-OH, CH₂-CH₂-OH, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-O-CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl, cyclopropyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, (e.g., methoxy, ethoxy, O-(CH₂CH₃), OCHF₂, O-(CH₂)₂-O-CH₃, isopropoxy, O-(CH₂)-cyclopropyl, O-CH₂-methylcyclobutyl, O-CH₂-3-methyloxetane, O-CH(CH₃)-CH₂-O-CH₃), C₁-C₅ linear or branched haloalkyl (e.g., CHF₂, CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), -R₈-O-R₈-O-R₁₀ (e.g., (CH₂)₂-O-(CH₂)₂-O-CH₃), -R₈-O-R₁₀, O-R₈-R₁₀ (e.g., O-(CH₂)₂-O-CH₃, O-(CH₂CH₃), O-(CH₂)-cyclopropyl), -R₈-R₁₀ (e.g.,

(CH₂)-cyclopropyl, (CH₂)₂-O-CH₃, (CH₂)-OH, (CH₂)₂-OH, (CH₂)-COOH, substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

each **R**₈ is independently [CH₂]_p

wherein **p** is between 1 and 10 (e.g., 1, 2);

5 **R**₉ is [CH]_q, [C]_q

wherein **q** is between 2 and 10;

R₁₀ and **R**₁₁ are each independently H, OH, COOH, C₁-C₅ substituted or unsubstituted linear or branched alkyl (e.g., methyl, ethyl, CH₂-cyclopropyl, CH₂-CH₂-O-CH₃), C₃-C₈ substituted or unsubstituted cycloalkyl (e.g., cyclopropyl), C₁-C₅ substituted or unsubstituted linear or branched

10 haloalkyl (e.g., CH₂CF₃), C₁-C₅ linear or branched alkoxy (e.g., O-CH₃), **R**₂₀, C(O)**R**, or S(O)₂**R**;

or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., piperazine, piperidine),

n is an integer between 0 and 4 (e.g., 1, 2);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse

15 amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

2. The compound of claim 1, wherein **R**₅ is H or CH₃.

3. The compound of claims 1 or 2, wherein **R**₆ is H, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (preferably methyl), substituted or unsubstituted 3-8 membered heterocyclic ring (preferably substituted or unsubstituted piperidine or tetrahydropyran), **R**₈-N(**R**₁₀)(**R**₁₁) (preferably (CH₂)₂-NH₂, (CH₂)₃-NH₂, (CH₂)₃-piperidine or (CH₂)₃-4-fluoro-piperidine), or **R**₆ is represented by the structure of formula **Bi**.

4. The compound of claim 3, wherein **R**₁₂ and **R**₁₃ of formula **Bi** are joined to form a substituted or unsubstituted piperidine ring, or wherein **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted

25 3-8 membered heterocyclic ring (e.g., piperidine or 4-fluoro-piperidine).

5. The compound of any one of the preceding claims, wherein **R**₇ is H, C(O)N(**R**₁₀)(**R**₁₁) (preferably C(O)NH(CH₃)), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (preferably methyl), substituted or unsubstituted C₃-C₈ cycloalkyl (preferably cyclopropanol), substituted or unsubstituted 4-7 membered heterocyclic ring (preferably morpholine, pyrrolidine, pyrrolidine-3-ol, piperidine, piperidine-4-ol, tetrahydrofuran, oxetane, oxetan-3-ol, pyridine, or 1-methylpyridine), or substituted or

30 unsubstituted aryl.

6. The compound of any one of the preceding claims, wherein **R**₇' is H or F.

7. The compound of any one of the preceding claims, wherein **Ring W** is aromatic and one of **X**₂, **X**₃ and **X**₄ is C(**R**); preferably wherein **R** is alkoxy, more preferably methoxy.

35 8. The compounds of any one of the preceding claims, wherein **X**₁₂ is O, NH, N(**R**), CH=N, N=CH, CH=CH, OCH₂, or N-OH; preferably wherein **R** is C₁-C₅ linear or branched, substituted or

unsubstituted alkyl, substituted or unsubstituted C₁-C₅ linear or branched alkoxy, O-R₈-R₁₀, OH, NH(R₁₀), haloalkoxy or cycloalkyl.

9. The compound of any one of the preceding claims, wherein R is CH₂-COOH, CH₂-CH₂-OH, CH₃, CH₂CH₃, iPr, cyclopropyl or CH₂-cyclopropyl.
- 5 10. The compound of any one of the preceding claims, wherein X₄ is C(R) and R is alkoxy, preferably methoxy.
11. The compound of any one of the preceding claims, selected from the following:

Compound No.	Compound Name
100R	(R)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
100S	(S)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
101R	6-(((R)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
101S	6-(((S)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(tetrahydrofuran-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
102S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
102R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
104S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
104R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-((3-methyloxetan-3-yl)oxy)-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
105R	6-(((R)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
105S	6-(((S)-1-methoxypropan-2-yl)oxy)-N-(3-(piperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
106S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
106R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
107S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
107R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
108S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-8-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
108R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-8-isopropoxy-N-(3-(piperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
110S	(S)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-((3-methyloxetan-3-yl)methoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
110R	(R)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-((3-methyloxetan-3-yl)methoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
111S	(S)-6-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
111R	(R)-6-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
112	6-(cyclopropylmethoxy)-2-(2-fluoro-4-(1-hydroxycyclopropyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
113	6-(cyclopropylmethoxy)-2-(2-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
118S	(S)-6-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

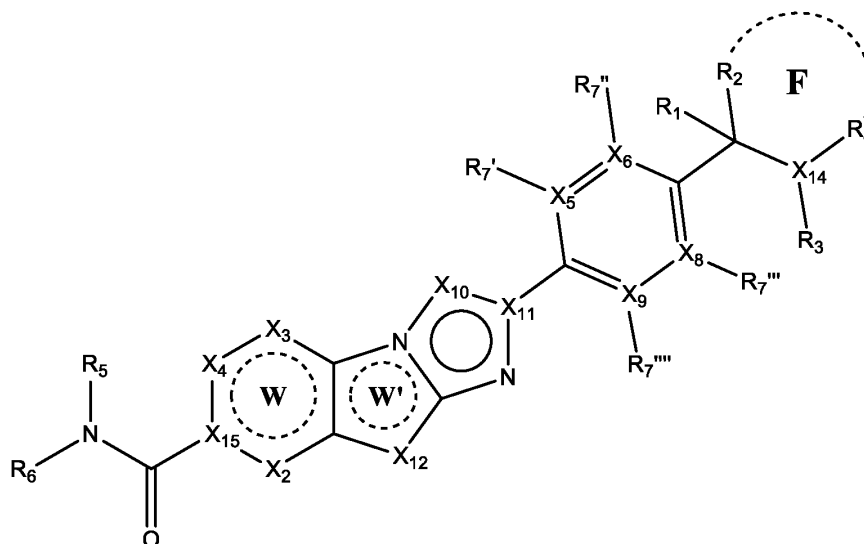
118R	(R)-6-((cyclopropylmethyl)amino)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
119S	(S)-5-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
119R	(R)-5-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
120S	(S)-8-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
120R	(R)-8-(cyclopropylmethoxy)-2-(2-fluoro-4-(tetrahydrofuran-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
121S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
121R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-methyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
122S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
122R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
123S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]oxazole-7-carboxamide
123R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]oxazole-7-carboxamide
124S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-hydroxy-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
124R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-hydroxy-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
125S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-(2-hydroxyethyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
125R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-(2-hydroxyethyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
126S	(S)-2-(2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)acetic acid
126R	(R)-2-(2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-((3-(4-fluoropiperidin-1-yl)propyl)carbamoyl)-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)acetic acid
131S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-oxo-2,3-dihydrobenzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
131R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-3-oxo-2,3-dihydrobenzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
135	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinoxaline-7-carboxamide
136	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinazoline-7-carboxamide
137S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-8-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
137R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-8-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
138	9-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
139	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9-isopropyl-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
140	9-cyclopropyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
141	9-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-7-carboxamide
142	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-5,8-dihydroimidazo[2',1':2,3]thiazolo[5,4-c]pyridine-7(6H)-carboxamide
143	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-isopropylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
144	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

145	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6,9-dimethyl-9H-benzo[d]imidazo[1,2-a]thiazole-7-carboxamide
146	6-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
147	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-isopropoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
148	8-ethyl-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
149S	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
149R	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
150	N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
151	2-(2-fluoro-4-(5-oxopyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
152	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
153S	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((S)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
153R	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-((R)-1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
154	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
155	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
156	6-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
157	N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(4-(methylcarbamoyl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
158	8-(cyclopropylmethyl)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
159	2-(2-fluoro-4-(methylcarbamoyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
160	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
161	N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
162	N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
163	6-methoxy-N-(1-methylpiperidin-3-yl)-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
164	6-(difluoromethoxy)-N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(4-(pyrrolidin-2-yl)phenyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
165	N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(2-methylpyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
166	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-(2-methoxyethoxy)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
167	2-(2-fluoro-5-methylphenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
168	2-(2-fluoro-4-(methylcarbamoyl)phenyl)-6-methoxy-N-(1-methylpiperidin-3-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
169	6-methoxy-N-(1-methylpiperidin-3-yl)-2-(pyridin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
170	6-methoxy-N-(piperidin-4-yl)-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
171	N-(2-aminoethyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
172	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]oxazole-7-carboxamide
173	N-(3-aminopropyl)-6-methoxy-2-(m-tolyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
174	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N,N-dimethylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide

175	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
176	N-(2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazol-7-yl)acetamide
177	N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxy-2-(m-tolyl)benzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
178	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxybenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
179	2-(2-fluoro-4-(methylcarbamoyl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-7-methoxybenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
180	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-hydroxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
181	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-7-methoxy-N-methylbenzo[4,5]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide
182	2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
183	2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
184	2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
185	2-(2-fluoro-4-(pyrrolidin-3-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
186	2-(2-fluoro-4-(piperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
187	2-(2,3-difluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
188	6-chloro-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
189	(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
190	(S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
191	2-(2-fluoro-4-(4-hydroxypiperidin-4-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
192	2-(2-fluoro-4-(piperidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
195	2-(2-fluoro-4-(morpholin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
196	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)imidazo[1,2-a]quinoline-7-carboxamide
197	2-(2-fluoro-4-(3-hydroxypyrrolidin-3-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
198	6-ethoxy-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide
199	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-4H-benzo[b]imidazo[1,2-d][1,4]oxazine-7-carboxamide
200S	2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
200R	2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
201S	2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
201R	2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
202S	2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
202R	2-(2-fluoro-4-((2S,4R)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-methylbenzo[d]imidazo[2,1-b]thiazole-7-carboxamide
203S	2-(2-fluoro-4-((2S,4S)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy-N-(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide

203R	2-(2-fluoro-4-((2 <i>S</i> ,4 <i>R</i>)-4-hydroxypyrrolidin-2-yl)phenyl)-6-methoxy- <i>N</i> -(1-methylpiperidin-4-yl)benzo[d]imidazo[2,1- <i>b</i>]thiazole-7-carboxamide
204	2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)- <i>N</i> -(1-methylpiperidin-4-yl)-4 <i>H</i> -benzo[<i>b</i>]imidazo[1,2- <i>d</i>][1,4]oxazine-7-carboxamide
205	<i>N</i> -(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyrrolidin-2-yl)benzo[d]imidazo[2,1- <i>b</i>]thiazole-7-carboxamide

12. The compound according to claim 1, represented by the structure of formula **I(l)**:



wherein

5 **Ring F** is absent or is a substituted or unsubstituted, saturated or unsaturated, 3-8 membered heterocyclic or carbocyclic ring (e.g., pyrrolidine, 1-methylpyrrolidine, pyrrolidine-3-ol, pyrrolidin-2-one, pyridine, piperidine, piperidine-4-ol, tetrahydrofurane, morpholine, tetrahydrothiophene, cyclopropyl, oxetane, oxetan-3-ol, imidazole, pyrimidine, triazole, oxadiazole, pyrazole);

10 **R₁** and **R₂** are each independently H, F, Cl, Br, I, OH, SH, or CF₃, substituted or unsubstituted C₁-C₅ alkyl, C₁-C₅ linear or branched, or C₃-C₈ cyclic haloalkyl, substituted or unsubstituted C₁-C₅ linear or branched, or C₃-C₈ cyclic alkoxy;

 or **R₁** and **R₂** are joined to form a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, oxetane);

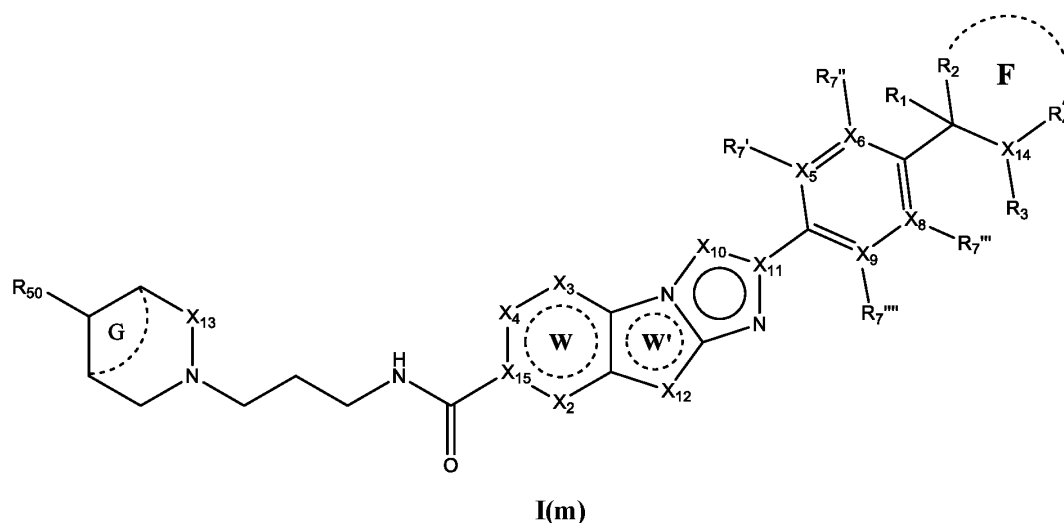
15 or **R₂** and **R₄** are joined to form **Ring F** as defined above (e.g., pyrrolidine, pyrrolidin-2-one, piperidine, morpholine, pyridine, pyrimidine, triazole, oxadiazole, pyrazole, tetrahydrofurane), wherein if **Ring F** is aromatic, then **R₁** and/or **R₃** are absent;

20 **R₃** and **R₄** are each independently H, Me, substituted or unsubstituted C₁-C₅ alkyl (e.g., methoxyethylene, methylaminoethyl, aminoethyl), -R₈-O-R₁₀ (e.g., (CH₂)₂-O-CH₃), R₈-N(R₁₀)(R₁₁) (e.g., (CH₂)₂-NH(CH₃)), substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 5-7 membered heterocyclic ring (e.g., pyrrolidine, methylpyrrolidine, piperidine), or R₂₀;

 or **R₃** and **R₄** are joined to form a 3-8 membered heterocyclic ring (e.g., pyrrolidine, , pyrrolidone, 2-oxopyrrolidine, piperidine, morpholine, piperazine, imidazole); and

X_{14} is S, O, N or CH, wherein if X_{14} is CH then Ring **F** is not absent and if X_{14} is S or O then R_3 is absent.

13. The compound of claims 1 or 12, represented by the structure of formula **I(m)**:



5

wherein

X_{13} is CH_2 , $CH(R)$ (e.g., $CH-CH_3$), $C(R)_2$, or $C=O$;

Ring **G** is absent or is a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclobutane, cyclopentane, cyclohexane);

10 R_{50} is H, R_{20} , F, Cl, Br, I, OH, SH, $N(R)_2$, $NH(R_{10})$, $N(R_{10})(R_{11})$, CF_3 , CN, NO_2 , C_1-C_5 linear or branched, substituted or unsubstituted alkyl C_1-C_5 linear or branched alkoxy, C_1-C_5 linear or branched haloalkyl, $-R_8-R_{10}$ (e.g., $(CH_2)_2-O-CH_3$), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine)).

14. The compound of any one of claims 12 or 13, wherein X_{14} is O or N.

15. The compound of any one of claims 12-14, wherein R_1 is H, or wherein R_1 and R_2 are joined to form a 3-8 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, oxetane, pyrrolidine).

16. The compound of any one of claims 12-15, wherein R_3 is H, substituted or unsubstituted C_1-C_5 alkyl or absent.

17. The compound of any one of claims 12-16, wherein R_2 and R_4 are joined to form Ring **F** (preferably pyrrolidine, piperidine, tetrahydrofurane, pyrrolidin-2-one, pyrrolidin-3-ol, morpholine).

20

18. A compound represented by any one of the following structures:

Compound No.	Compound Name
130R	<i>(R)</i> -3-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
130S	<i>(S)</i> -3-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)benzo[4,5]thiazolo[2,3-c][1,2,4]triazole-7-carboxamide
400S	<i>(S)</i> -2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-6-carboxamide

400R	<i>(R)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-N-(3-(4-fluoropiperidin-1-yl)propyl)-9H-benzo[d]imidazo[1,2-a]imidazole-6-carboxamide</i>
401	<i>7-bromo-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-isopropoxybenzo[d]imidazo[2,1-b]thiazole</i>
402	<i>2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-5,6,7,8-tetrahydrobenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid</i>
403	<i>2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxylic acid</i>
404	<i>2-bromo-N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxybenzo[d]imidazo[2,1-b]thiazole-7-carboxamide</i>
408	<i>N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(pyrrolidin-2-ylethynyl)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide</i>
409	<i>N-(3-(4-fluoropiperidin-1-yl)propyl)-2-(pyrrolidine-2-carboxamido)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide</i>
410	<i>N-(3-(4-fluoropiperidin-1-yl)propyl)-6-methoxy-2-(pyrrolidine-2-carboxamido)benzo[d]imidazo[2,1-b]thiazole-7-carboxamide</i>

19. The compound of any one of the preceding claims, wherein the compound is a substantially pure single stereoisomer.
20. The compound according to any one of the preceding claims, wherein the compound is a c-MYC
5 mRNA translation modulator, a c-MYC mRNA transcription regulator, a c-MYC inhibitor or any combination thereof.
21. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable carrier.
22. The compound according to any one of claims 1-21, for use in treating, suppressing, reducing the
10 severity, reducing the risk of developing or inhibiting cancer in a subject.
23. The compound of claim 22,
 wherein the cancer is selected from the list of: breast cancer, ovarian carcinoma, acute myeloid leukemia, chronic myelogenous leukemia, Hodgkin's and Burkitt's lymphoma, diffuse large Bcell lymphoma, prostate cancer, colon cancer, gastric cancer, primary central nervous system lymphoma,
 15 glioblastoma, medulloblastoma, melanoma, non-small cell lung carcinoma, germinal center-derived lymphomas, esophageal squamous cell carcinoma, osteosarcoma, bladder cancer, pancreatic cancer, lung adenocarcinoma, BRAF V600E thyroid cancer, choroid plexus carcinoma, colitis-associated cancer, epithelial ovarian cancer, colorectal cancer, pancreatic cancer and uterine cancer;
 wherein the cancer is early cancer, advanced cancer, invasive cancer, metastatic cancer, drug
 20 resistant cancer or any combination thereof;
 wherein the subject has been previously treated with chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof;
 wherein the compound is administered in combination with an anti-cancer therapy;
 or any combination thereof.
24. The compound of claim 23, wherein the anti-cancer therapy is chemotherapy, immunotherapy,
 25 radiotherapy, biological therapy, surgical intervention, or any combination thereof.

25. The compound according to any one of claims 1-21, for use in suppressing, reducing or inhibiting tumor growth in a subject.
26. A method of modulating c-MYC mRNA translation, or regulating c-MYC mRNA transcription in a cell, comprising contacting a compound according to any one of claims 1-22 with a cell, thereby
5 modulating c-MYC mRNA translation, or regulating c-MYC mRNA transcription in said cell.
27. The method of claim 26, wherein said method is carried out
- (a) by regulating c-MYC mRNA splicing (inclusion or exclusion of untranslated region or alternative usage of exons);
 - (b) by regulation of c-MYC mRNA modifications;
 - 10 (c) by regulation of the interaction of RNA binding protein with c-MYC mRNA thereby changing mRNA localization;
 - (d) by regulating c-MYC mRNA localization in the cytoplasm;
 - (e) by regulating ribosomes or ribosome accessory factor to c-MYC mRNA;
 - (f) by reducing the amount of c-MYC protein in the cell;
 - 15 or any combination thereof.