

MYST INHIBITORS

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. provisional patent application nos. 63/585,817, filed September 27, 2023, 63/558,419, filed February 27, 2024, and 63/655,961, filed June 4, 2024, the disclosures of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] This application contains a sequence listing, which is being submitted herewith as an XML file named "ISTX104WO_SL.xml", created on September 11, 2024, size 5406 bytes, which is incorporated by reference herein in its entirety.

FIELD

[0003] Provided herein are compounds and compositions for inhibiting the MYST family of lysine acetyltransferases (KATs). In one embodiment, provided are methods of treating diseases, including hyperproliferative diseases, with the compounds and compositions provided herein. In another embodiment, the hyperproliferative disease is cancer.

BACKGROUND

[0004] The MYST family of enzymes are KATs and include KAT6A (also known as MOZ or MYST3), KAT6B (also known as MORF or MYST4), KAT5 (also known as Tip60), KAT7 (also known as, HBO1 or MYST2) and KAT8 (also known as, MOF or MYST1) (see, e.g., Wiesel-Motiuk, et al., Drug Resistance Updates 2020, 53, 100729; Wapenaar, et al., Clinical Epigenetics 2016, 8(59), 1 (DOI 10.1186/s13148-016-0225-2)). The MYST family of KATs is particularly important in regulation of the cell cycle (Carrozza, et al., Trends in Genetics 2003, 19, 321-329).

[0005] Dysregulation of the expression of KAT6 proteins supports tumor progression (see, e.g., Triscioglio et al., Stem Cells Int. 2018, Article ID 8908751 (<https://doi.org/10.1155/2018/8908751>)). Dysregulation through gene amplification, overexpression or mutation of KAT6A has been documented in multiple cancer types including breast, lung adenocarcinoma, ovarian, colon and rectal adenocarcinoma, and uterine cervix (see, e.g., Huang, et al., Molecular and Cellular Biology 2016, 63, 1900-1907; Zack, et al., Nature Genetics 2013, 45, 1134-1140). It is reported that the locus that contains the gene for KAT6A (8p11-p12 amplicon) is the 12th most commonly amplified region of the

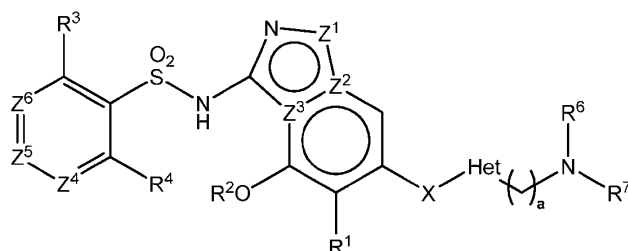
genome across all cancer types (see, e.g., Zack, et al., 2013, *supra*). In acute myeloid leukemia (AML), recurrent oncogenic fusions of KAT6A have been documented that can drive transformation to a malignant state (see, e.g., Sheikh, et al., Blood 2015, 125, 1910-1921). Translocation of KAT6A and fusion to a partner such as CBP, p300, TIF2 and NCOA3 are known to lead to aggressive forms of AML (see, e.g., Sheikh, et al., 2015, *supra*).

[0006] In addition to the role that KATs play in epigenetic regulation, KATs also acetylate non-histone proteins. Through modification of the acetylation state of non-histone proteins, KATs are involved modulating protein function and stability, protein-protein and protein-DNA interactions, and regulation of enzyme activity (see, e.g., Glozak, et al., Gene 2005, 363, 15-23; Das, et al., IUBMB Life 2005, 57, 137-148).

[0007] Thus, there is a need for MYST inhibitors for treatment of hyperproliferative diseases, including cancer.

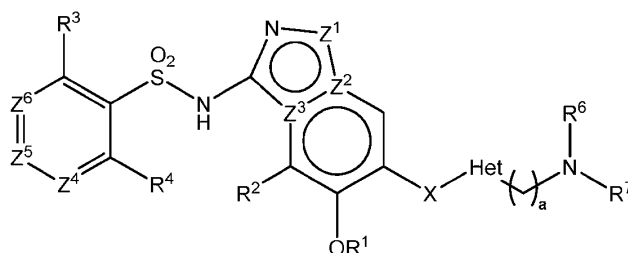
SUMMARY

[0008] Provided herein is a compound of Formula I:



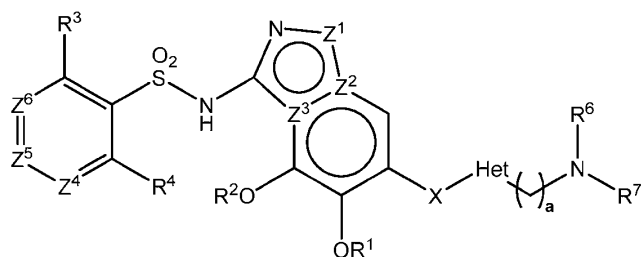
[0009] or a pharmaceutically acceptable derivative thereof, where R^1 - R^4 , R^6 , R^7 , a , Het, X and Z^1 - Z^6 are as defined elsewhere herein.

[0010] Also provided herein is a compound of Formula II:



[0011] or a pharmaceutically acceptable derivative thereof, where R^1 - R^4 , R^6 , R^7 , a , Het, X and Z^1 - Z^6 are as defined elsewhere herein.

[0012] Also provided herein is a compound of Formula III:



[0013] or a pharmaceutically acceptable derivative thereof, where R^1 - R^4 , R^6 , R^7 , a , Het, X and Z^1 - Z^6 are as defined elsewhere herein.

[0014] Pharmaceutical compositions containing a compound of Formula I, II or III and a pharmaceutically acceptable excipient are also provided.

[0015] In one embodiment, the compounds of Formula I, II or III provided herein inhibit one or more of the MYST family of lysine acetyl transferases. In another embodiment, the compounds provided herein inhibit KAT6A. In another embodiment, the compounds provided herein are covalent inhibitors of KAT6A. Without being bound by any theory, in one embodiment, the compounds provided herein inhibit KAT6A through covalent modification of a cysteine residue at or near the Ac-CoA binding site. In another embodiment, the compounds provided herein are non-covalent inhibitors of KAT6A.

[0016] In other embodiments, provided are methods of treatment of a hyperproliferative disease by administering a compound or composition provided herein. In one embodiment, the hyperproliferative disease is cancer. In another embodiment, the cancer is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, uterine/cervical cancer or leukemia. In another embodiment of the methods provided herein, the compounds of Formula I are used as single agents or in combination with a standard of care treatment for a particular cancer.

[0017] In another embodiment, provided are methods of inhibiting a MYST enzyme by contacting the MYST enzyme or a composition containing a MYST enzyme with a compound or composition provided herein. In another embodiment, provided are methods of inhibiting KAT6A by contacting KAT6A or a composition containing KAT6A with a compound or composition provided herein.

DETAILED DESCRIPTION

I. DEFINITIONS

[0018] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0020] The singular forms "a," "an," and "the" include plural references, unless the context clearly dictates otherwise.

[0021] As used herein "subject" is an animal, such as a mammal, including human, such as a patient.

[0022] As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmacokinetic behavior of such compounds, compositions and mixtures. Biological activities can be observed in in vitro systems designed to test for such activities.

[0023] As used herein, pharmaceutically acceptable derivatives of a compound include, but are not limited to, salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, clathrates, solvates or hydrates thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs.

Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and inorganic salts, such as but not limited to, sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids,

sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0024] As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a hyperproliferative disease.

[0025] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or pharmaceutical composition.

[0026] As used herein, and unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a subject who has already suffered from the disease or disorder, and/or lengthening the time that a subject who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a subject responds to the disease or disorder.

[0027] Where moieties are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical moieties that would result from writing the structure from right to left, *e.g.*, $-CH_2O-$ is equivalent to $-OCH_2-$.

[0028] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain saturated hydrocarbon radical, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbons). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0029] The term "alkenyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain hydrocarbon radical having one or more carbon-carbon double bonds, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbons).

Examples of alkenyl groups include, but are not limited to, vinyl (*i.e.*, ethenyl), 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), and the higher homologs and isomers.

[0030] The term "alkynyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain hydrocarbon radical having one or more carbon-carbon triple bonds, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Examples of alkynyl groups include, but are not limited to, ethynyl, 1- and 3-propynyl, 3-butyne, and the higher homologs and isomers.

[0031] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkyl, as exemplified, but not limited, by -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, including those groups having 10 or fewer carbon atoms. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having six or fewer carbon atoms.

[0032] The terms "alkoxy," "alkylamino," and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0033] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, consisting of a heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atom may have an alkyl substituent to fulfill valency and/or may optionally be quaternized. The heteroatom(s) O, N, P, Si and S may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)₂R' represents both -C(O)₂R' and -R'C(O)₂-.

[0034] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and

"heteroalkyl", respectively, including bicyclic, tricyclic, spirocyclic and bridged bicyclic groups. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornanyl, bicyclo[2.2.2]octanyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, 1- or 2-azabicyclo[2.2.2]octanyl, and the like.

[0035] The terms "halo," by itself or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Similarly, the terms "cycloalkenyl", "cycloalkynyl", "heterocycloalkenyl" and "heterocycloalkynyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkenyl", "alkynyl", "heteroalkenyl" and "heteroalkynyl", respectively, including bicyclic, tricyclic, spirocyclic and bridged bicyclic groups.

[0036] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (in one embodiment from 1 to 3 rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups that contain from one to four heteroatoms selected from N, O, and S in the ring(s), wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Substituent moieties for aryl and heteroaryl ring systems may be selected from the group of acceptable substituent moieties described herein. The term "heteroarylium" refers to a heteroaryl group that is positively charged on one or more of the heteroatoms.

[0037] The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom.

[0038] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Non-limiting examples of substituent moieties for each type of radical are provided below.

[0039] Substituent moieties for alkyl, heteroalkyl, alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl groups are, in one embodiment, selected from, deuterium, -OR', =O, =NR', =N-OR', -NR'R'', -SR', halo, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NRSO₂NR'R'', -CN and -NO₂ in a number ranging from zero to the number of hydrogen atoms in such radical. In one embodiment, substituent moieties for cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl groups also include substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, and substituted and unsubstituted alkynyl. R', R'', R''' and R'''' each in one embodiment independently are hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (*e.g.*, aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound provided herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituent moieties, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0040] Substituent moieties for aryl and heteroaryl groups are, in one embodiment, selected from deuterium, halo, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, and substituted and unsubstituted alkynyl, -OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and

fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of hydrogens on the aromatic ring system; and where R', R'', R''' and R'''' are, in one embodiment, independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound provided herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

[0041] Two of the substituent moieties on adjacent atoms of an aryl or heteroaryl ring may optionally form a ring of the formula -Q'-C(O)-(CRR')_q-Q'', wherein Q' and Q'' are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituent moieties on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituent moieties on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')_s-X'-(CR''R''')_d-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent moieties R, R', R'' and R''' are, in one embodiment, independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0042] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0043] As used herein, a prodrug is a compound that upon *in vivo* administration is metabolized, or otherwise undergoes chemical changes under physiological conditions, by one or more steps or processes or otherwise converted to a biologically, pharmaceutically or therapeutically active form of the compound. Additionally, prodrugs can be converted to a biologically, pharmaceutically or therapeutically active form of the compound by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

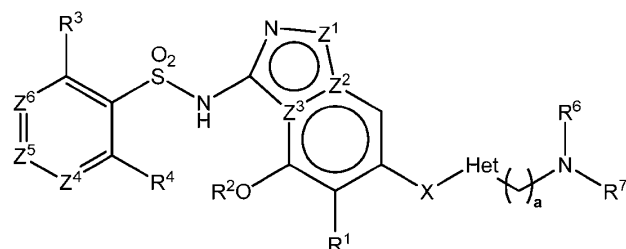
[0044] Certain compounds provided herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds provided herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure.

[0045] Certain compounds provided herein possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, tautomers, geometric isomers and individual isomers are encompassed within the scope of the present disclosure. The compounds provided herein do not include those which are known in the art to be too unstable to synthesize and/or isolate.

[0046] The compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds provided herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

II. COMPOUNDS FOR USE IN COMPOSITIONS AND METHODS

[0047] In one embodiment, provided is a compound of Formula I for use in the compositions and methods provided herein:



[0048] or a pharmaceutically acceptable derivative thereof, wherein:

[0049] a is 0-2;

[0050] R¹ and R² together form alkylene;

[0051] R³ is -O-(CH₂)_b-R⁸;

[0052] b is 1-4;

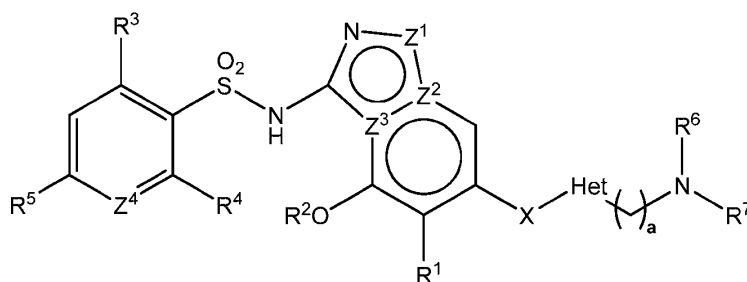
[0053] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

- [0054] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0055] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0056] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0057] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0058] R^4 is H or alkoxy;
- [0059] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0060] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0061] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0062] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0063] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0064] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0065] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0066] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0067] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0068] R^5 and R^{16} are selected from (i) or (ii):
- [0069] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0070] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0071] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0072] Het and R^6 are selected from (i) or (ii):
- [0073] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0074] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0075] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [0076] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19}

is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;
and

[0077] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.

[0078] In one embodiment, provided is a compound of Formula Ia for use in the compositions and methods provided herein:



[0079] or a pharmaceutically acceptable derivative thereof, wherein:

[0080] a is 0-2;

[0081] R^1 and R^2 together form alkylene;

[0082] R^3 is $-O-(CH_2)_b-R^8$;

[0083] b is 1-4;

[0084] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0085] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0086] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0087] R^{12} is alkyl or $NR^{14}R^{15}$;

[0088] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0089] R^4 is H or alkoxy;

[0090] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0091] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0092] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0093] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0094] Z^4 is N or CR^{16} ;

- [0095] R^5 and R^{16} are selected from (i) or (ii):
- [0096] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0097] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0098] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0099] Het and R^6 are selected from (i) or (ii):
- [0100] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0101] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0102] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0103] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0104] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.
- [0105] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:
- [0106] R^8 is H, CN, OH, alkoxy, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [0107] R^9 is H and R^{10} is H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy; and
- [0108] R^{11} is alkyl or alkoxy;
- [0109] R^5 and R^{16} are selected from (i) or (ii):
- [0110] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or
- [0111] (ii) R^5 and R^{16} together form alkylene;
- [0112] X is O or CH_2 ;

[0113] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0114] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0115] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0116] R^8 is H, CN, OH, alkoxy, aryl, NR^9R^{10} or $C(O)R^{11}$;

[0117] R^9 is H and R^{10} is $C(O)R^{13}$; where R^{13} is alkyl; and

[0118] R^{11} is alkoxy;

[0119] R^5 and R^{16} are selected from (i) or (ii):

[0120] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or

[0121] (ii) R^5 and R^{16} together form alkylene;

[0122] X is O or CH_2 ;

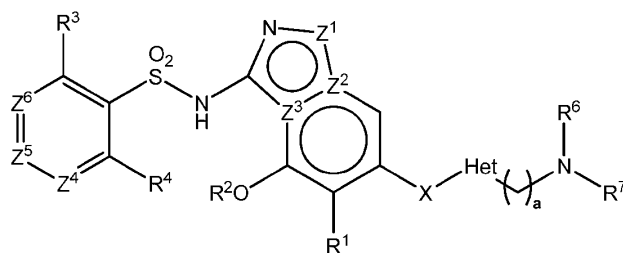
[0123] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0124] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0125] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^1 and R^2 together form C_{2-4} alkylene.

[0126] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^1 and R^2 together form propylene.

[0127] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I:



[0128] or a pharmaceutically acceptable derivative thereof, wherein:

[0129] a is 0-2;

[0130] R^1 and R^2 are selected from (i) or (ii):

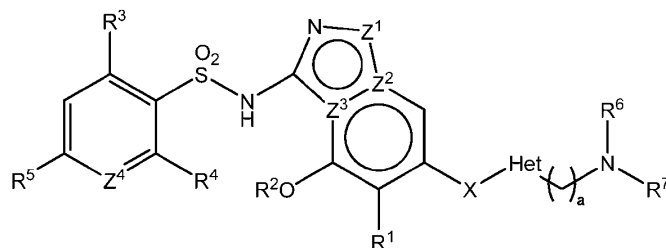
[0131] (i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

[0132] (ii) R^1 and R^2 together form alkylene;

- [0133] R^3 is $-O-(CH_2)_b-R^8$;
- [0134] b is 1-4;
- [0135] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [0136] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0137] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0138] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0139] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0140] R^4 is H or alkoxy;
- [0141] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0142] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0143] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0144] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0145] Z^4 is CR^{16} ;
- [0146] Z^5 is CR^5 ;
- [0147] Z^6 is N or CH;
- [0148] R^5 and R^{16} together form alkylene or heteroalkylene;
- [0149] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0150] Het and R^6 are selected from (i) or (ii):
- [0151] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0152] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0153] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [0154] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0155] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0156] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0157] or a pharmaceutically acceptable derivative thereof, wherein:

[0158] a is 0-2;

[0159] R^1 and R^2 are selected from (i) or (ii):

[0160] (i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

[0161] (ii) R^1 and R^2 together form alkylene;

[0162] R^3 is $-O-(CH_2)_b-R^8$;

[0163] b is 1-4;

[0164] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0165] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0166] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0167] R^{12} is alkyl or $NR^{14}R^{15}$;

[0168] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0169] R^4 is H or alkoxy;

[0170] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0171] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0172] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0173] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0174] Z^4 is CR^{16} ;

[0175] R^5 and R^{16} together form alkylene or heteroalkylene;

- [0176] X is O, S(O)_x or CH₂, where x is 0-2;
- [0177] Het and R⁶ are selected from (i) or (ii):
- [0178] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or
- [0179] (ii) Het is a 5- or 6-membered heteroaryl, R⁶ is -(CH₂)₁₋₂-, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0180] R⁷ is -C(O)R¹⁷ or -SO₂R¹⁸;
- [0181] R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, -NH-(CH₂)₂-R¹⁹, -O-(CH₂)₂-R¹⁹ or -NR²⁰R²¹; where R¹⁹ is -OR⁹ or -NR⁹R¹⁰, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0182] R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or -NR⁹R¹⁰.
- [0183] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:
- [0184] R¹ and R² are selected from (i) or (ii):
- [0185] (i) R¹ is H; and R² is alkyl, cycloalkyl or haloalkyl, or
- [0186] (ii) R¹ and R² together form alkylene;
- [0187] R⁸ is H, CN, OH, aryl, heteroaryl, NR⁹R¹⁰ or C(O)R¹¹;
- [0188] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl or alkoxy;
- [0189] R¹¹ is alkyl or alkoxy;
- [0190] R⁵ and R¹⁶ together form alkylene;
- [0191] X is O or CH₂;
- [0192] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [0193] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0194] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0195] R^1 and R^2 are selected from (i) or (ii):

[0196] (i) R^1 is H; and R^2 is alkyl or haloalkyl, or

[0197] (ii) R^1 and R^2 together form alkylene;

[0198] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

[0199] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[0200] R^{11} is alkoxy;

[0201] R^5 and R^{16} together form alkylene;

[0202] X is O or CH_2 ;

[0203] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

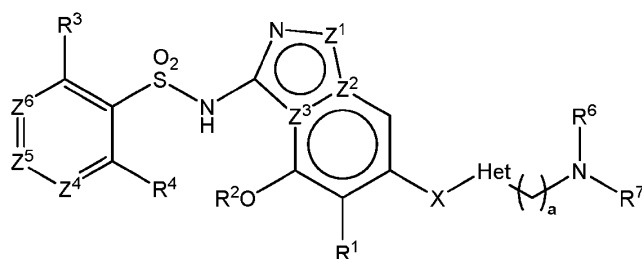
[0204] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0205] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^5 and R^{16} together form C_3 -alkylene.

[0206] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^5 and R^{16} together form propylene.

[0207] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein X is O or $S(O)_x$, where x is 0-2. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein X is O or S.

[0208] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I:



[0209] or a pharmaceutically acceptable derivative thereof, wherein:

[0210] a is 0-2;

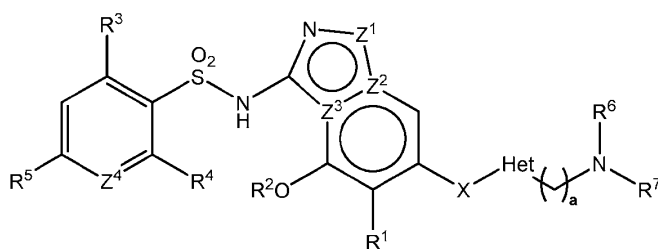
[0211] R^1 and R^2 are selected from (i) or (ii):

- [0212] (i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or
- [0213] (ii) R^1 and R^2 together form alkylene;
- [0214] R^3 is $-O-(CH_2)_b-R^8$;
- [0215] b is 1-4;
- [0216] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [0217] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0218] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0219] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0220] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0221] R^4 is H or alkoxy;
- [0222] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0223] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0224] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0225] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0226] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0227] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0228] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0229] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0230] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0231] R^5 and R^{16} are selected from (i) or (ii):
- [0232] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0233] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0234] X is O or $S(O)_x$, where x is 0-2;
- [0235] Het and R^6 are selected from (i) or (ii):
- [0236] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0237] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0238] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

[0239] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-R^{19}$, $-\text{O}-(\text{CH}_2)_2-R^{19}$ or $-\text{NR}^{20}R^{21}$, where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0240] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-\text{NR}^9R^{10}$.

[0241] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0242] or a pharmaceutically acceptable derivative thereof, wherein:

[0243] a is 0-2;

[0244] R^1 and R^2 are selected from (i) or (ii):

[0245] (i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

[0246] (ii) R^1 and R^2 together form alkylene;

[0247] R^3 is $-\text{O}-(\text{CH}_2)_b-R^8$;

[0248] b is 1-4;

[0249] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})R^{11}$, $\text{C}(\text{=NH})(R^{12})$ or $\text{C}(\text{=N-O-R}^9)(R^{12})$;

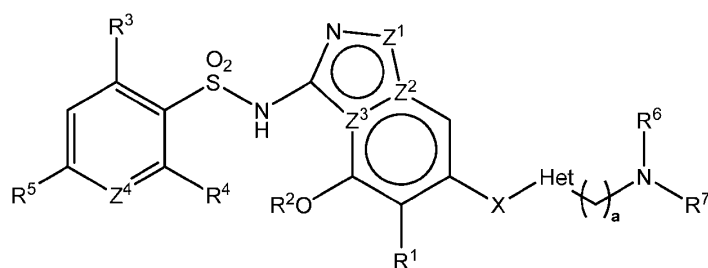
[0250] R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})R^{13}$; where R^{13} is alkyl, alkoxy or $\text{NR}^{14}R^{15}$;

[0251] R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}R^{15}$;

[0252] R^{12} is alkyl or $\text{NR}^{14}R^{15}$;

- [0253] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0254] R^4 is H or alkoxy;
- [0255] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0256] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0257] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0258] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0259] Z^4 is N or CR^{16} ;
- [0260] R^5 and R^{16} are selected from (i) or (ii):
- [0261] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0262] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0263] X is O or $S(O)_x$, where x is 0-2;
- [0264] Het and R^6 are selected from (i) or (ii):
- [0265] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0266] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0267] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0268] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0269] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [0270] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:
- [0271] R^1 and R^2 are selected from (i) or (ii):

- [0272] (i) R^1 is H; and R^2 is alkyl, cycloalkyl or haloalkyl, or
- [0273] (ii) R^1 and R^2 together form alkylene;
- [0274] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [0275] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;
- [0276] R^{11} is alkyl or alkoxy;
- [0277] R^5 and R^{16} are selected from (i) or (ii):
- [0278] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or
- [0279] (ii) R^5 and R^{16} together form alkylene;
- [0280] X is O;
- [0281] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [0282] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.
- [0283] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:
- [0284] R^1 and R^2 are selected from (i) or (ii):
- [0285] (i) R^1 is H; and R^2 is alkyl or haloalkyl, or
- [0286] (ii) R^1 and R^2 together form alkylene;
- [0287] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;
- [0288] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;
- [0289] R^{11} is alkoxy;
- [0290] R^5 and R^{16} are selected from (i) or (ii):
- [0291] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or
- [0292] (ii) R^5 and R^{16} together form alkylene;
- [0293] X is O;
- [0294] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [0295] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.
- [0296] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0297] or a pharmaceutically acceptable derivative thereof, wherein:

[0298] a is 0-2;

[0299] R^1 and R^2 are selected from (i) or (ii):

[0300] (i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

[0301] (ii) R^1 and R^2 together form alkylene;

[0302] R^3 is $-O-(CH_2)_b-R^8$;

[0303] b is 1-4;

[0304] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0305] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0306] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0307] R^{12} is alkyl or $NR^{14}R^{15}$;

[0308] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0309] R^4 is H or alkoxy;

[0310] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0311] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0312] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0313] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0314] Z^4 is N or CR^{16} , where R^{16} is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

[0315] R^5 is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

[0316] X is O, $S(O)_x$ or CH_2 , where x is 0-2;

[0317] Het and R^6 are selected from (i) or (ii):

[0318] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

[0319] (ii) Het is a 5- or 6-membered heteroaryl, R⁶ is $-(CH_2)_{1-2}-$, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0320] R⁷ is $-C(O)R^{17}$ or $-SO_2R^{18}$;

[0321] R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R¹⁹ is $-OR^9$ or $-NR^9R^{10}$, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0322] R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0323] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0324] R¹ and R² are selected from (i) or (ii):

[0325] (i) R¹ is H; and R² is alkyl, cycloalkyl or haloalkyl, or

[0326] (ii) R¹ and R² together form alkylene;

[0327] R⁵ is alkenyl or alkynyl;

[0328] R⁸ is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

[0329] R⁹ and R¹⁰ are each independently H or $C(O)R^{13}$; where R¹³ is alkyl or alkoxy;

[0330] R¹¹ is alkyl or alkoxy;

[0331] X is O or CH₂;

[0332] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0333] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0334] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0335] R¹ and R² are selected from (i) or (ii):

[0336] (i) R¹ is H; and R² is alkyl or haloalkyl, or

[0337] (ii) R¹ and R² together form alkylene;

[0338] R⁵ is alkynyl;

[0339] R⁸ is H, CN, OH, aryl, NR⁹R¹⁰ or C(O)R¹¹;

[0340] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl;

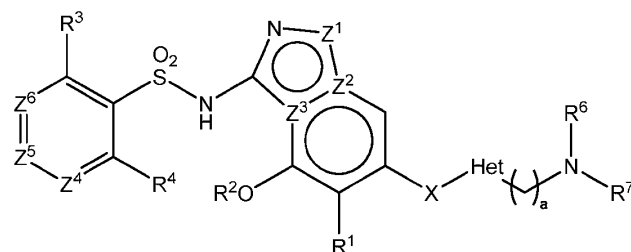
[0341] R¹¹ is alkoxy;

[0342] X is O or CH₂;

[0343] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0344] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0345] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I:



[0346] or a pharmaceutically acceptable derivative thereof, wherein:

[0347] a is 0-2;

[0348] R¹ is H, alkyl, haloalkyl or halo;

[0349] R² and R⁴ together form heteroalkylene;

[0350] R³ is -O-(CH₂)_b-R⁸;

[0351] b is 1-4;

[0352] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[0353] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[0354] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

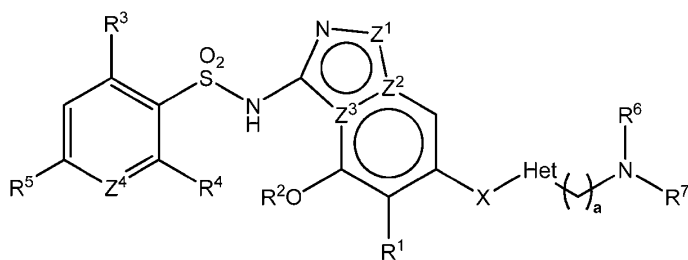
[0355] R¹² is alkyl or NR¹⁴R¹⁵;

[0356] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0357] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[0358] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

- [0359] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0360] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0361] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0362] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0363] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0364] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0365] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0366] R^5 and R^{16} are selected from (i) or (ii):
- [0367] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0368] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0369] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0370] Het and R^6 are selected from (i) or (ii):
- [0371] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0372] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0373] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [0374] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0375] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [0376] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0377] or a pharmaceutically acceptable derivative thereof, wherein:

[0378] a is 0-2;

[0379] R¹ is H, alkyl, haloalkyl or halo;

[0380] R² and R⁴ together form heteroalkylene;

[0381] R³ is -O-(CH₂)_b-R⁸;

[0382] b is 1-4;

[0383] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[0384] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[0385] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[0386] R¹² is alkyl or NR¹⁴R¹⁵;

[0387] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0388] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[0389] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[0390] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[0391] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[0392] Z⁴ is N or CR¹⁶;

[0393] R⁵ and R¹⁶ are selected from (i) or (ii):

[0394] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or

[0395] (ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

[0396] X is O, S(O)_x or CH₂, where x is 0-2;

[0397] Het and R⁶ are selected from (i) or (ii):

[0398] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

[0399] (ii) Het is a 5- or 6-membered heteroaryl, R⁶ is $-(CH_2)_{1-2}-$, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0400] R⁷ is $-C(O)R^{17}$ or $-SO_2R^{18}$;

[0401] R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R¹⁹ is $-OR^9$ or $-NR^9R^{10}$, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0402] R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0403] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0404] R¹ is H;

[0405] R² and R⁴ together form $-O-(CH_2)_r-$ or $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}-$, where r is an integer from 2 to 5 and the terminal O is attached to the R⁴ position of Formula I;

[0406] R⁸ is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

[0407] R⁹ and R¹⁰ are each independently H or $C(O)R^{13}$; where R¹³ is alkyl or alkoxy;

[0408] R¹¹ is alkyl or alkoxy;

[0409] R⁵ and R¹⁶ are selected from (i) or (ii):

[0410] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[0411] (ii) R⁵ and R¹⁶ together form alkylene;

[0412] X is O or CH₂;

[0413] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0414] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0415] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0416] R^1 is H;

[0417] R^2 and R^4 together form $-O-(CH_2)_r-$ or $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}-$, where r is an integer from 2 to 5 and the terminal O is attached to the R^4 position of Formula I;

[0418] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

[0419] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[0420] R^{11} is alkoxy;

[0421] R^5 and R^{16} are selected from (i) or (ii):

[0422] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or

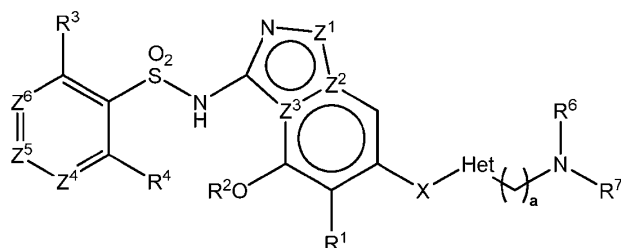
[0423] (ii) R^5 and R^{16} together form alkylene;

[0424] X is O or CH_2 ;

[0425] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0426] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0427] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I:



[0428] or a pharmaceutically acceptable derivative thereof, wherein:

[0429] a is 0-2;

[0430] R^1 is H, alkyl, haloalkyl or halo;

[0431] R^2 is alkyl, cycloalkyl or haloalkyl;

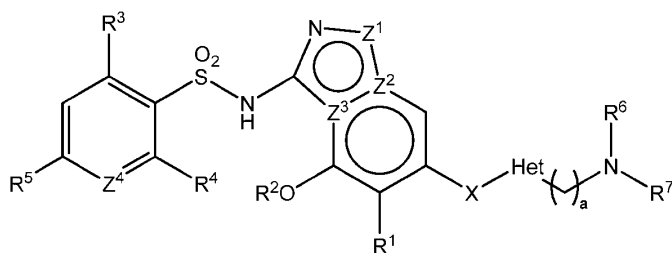
[0432] R^3 is $-O-(CH_2)_b-R^8$;

[0433] b is 1-4;

[0434] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0435] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$.

- [0436] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0437] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0438] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0439] R^4 is H or alkoxy;
- [0440] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0441] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0442] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0443] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0444] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0445] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0446] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0447] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0448] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0449] R^5 and R^{16} are selected from (i) or (ii):
- [0450] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0451] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0452] X is $CR^{22}R^{23}$, where R^{22} and R^{23} are each independently H or alkyl;
- [0453] Het and R^6 are selected from (i) or (ii):
- [0454] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0455] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0456] R^7 is $-C(O)R^{17}$; and
- [0457] R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-O-(CH_2)_2-R^{19}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$.
- [0458] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0459] or a pharmaceutically acceptable derivative thereof, wherein:

[0460] a is 0-2;

[0461] R¹ is H, alkyl, haloalkyl or halo;

[0462] R² is alkyl, cycloalkyl or haloalkyl;

[0463] R³ is -O-(CH₂)_b-R⁸;

[0464] b is 1-4;

[0465] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[0466] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[0467] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[0468] R¹² is alkyl or NR¹⁴R¹⁵;

[0469] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0470] R⁴ is H or alkoxy;

[0471] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[0472] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[0473] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[0474] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[0475] Z⁴ is N or CR¹⁶;

[0476] R⁵ and R¹⁶ are selected from (i) or (ii):

[0477] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or

[0478] (ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

[0479] X is CR²²R²³, where R²² and R²³ are each independently H or alkyl;

[0480] Het and R⁶ are selected from (i) or (ii):

[0481] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

[0482] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0483] R^7 is $-C(O)R^{17}$; and

[0484] R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-O-(CH_2)_2-R^{19}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$.

[0485] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0486] R^1 is H;

[0487] R^2 is alkyl, cycloalkyl or haloalkyl;

[0488] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

[0489] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;

[0490] R^{11} is alkyl or alkoxy;

[0491] X is CH_2 ; and

[0492] R^{17} is alkoxy.

[0493] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0494] R^1 is H;

[0495] R^2 is alkyl or haloalkyl;

[0496] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

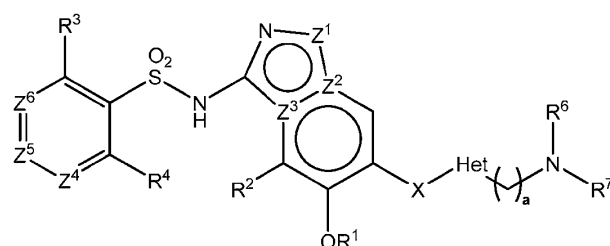
[0497] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[0498] R^{11} is alkoxy;

[0499] X is CH_2 ; and

[0500] R^{17} is alkoxy.

[0501] In one embodiment, provided is a compound of Formula II for use in the compositions and methods provided herein:



[0502] or a pharmaceutically acceptable derivative thereof, wherein:

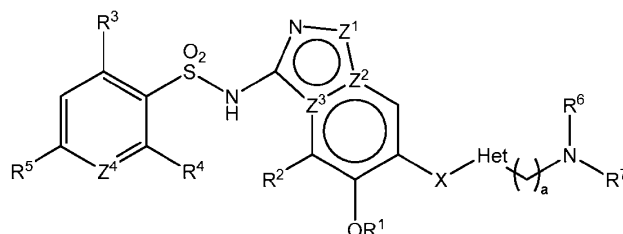
[0503] a is 0-2;

- [0504] R^1 and R^2 together form alkylene;
- [0505] R^3 is $-O-(CH_2)_b-R^8$;
- [0506] b is 1-4;
- [0507] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [0508] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0509] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0510] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0511] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0512] R^4 is H or alkoxy;
- [0513] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0514] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0515] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0516] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0517] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0518] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0519] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0520] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0521] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0522] R^5 and R^{16} are selected from (i) or (ii):
- [0523] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0524] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0525] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0526] Het and R^6 are selected from (i) or (ii):
- [0527] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0528] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0529] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [0530] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-\text{R}^{19}$, $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$ or $-\text{NR}^{20}\text{R}^{21}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0531] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-\text{NR}^{20}\text{R}^{21}$.

[0532] In one embodiment, provided is a compound of Formula IIa for use in the compositions and methods provided herein:



[0533] or a pharmaceutically acceptable derivative thereof, wherein:

[0534] a is 0-2;

[0535] R^1 and R^2 together form alkylene;

[0536] R^3 is $-\text{O}-(\text{CH}_2)_b-\text{R}^8$;

[0537] b is 1-4;

[0538] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})\text{R}^{11}$, $\text{C}(=\text{NH})(\text{R}^{12})$ or $\text{C}(=\text{N}-\text{O}-\text{R}^9)(\text{R}^{12})$;

[0539] R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[0540] R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[0541] R^{12} is alkyl or $\text{NR}^{14}\text{R}^{15}$;

[0542] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0543] R^4 is H or alkoxy;

[0544] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0545] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

- [0546] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0547] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0548] Z^4 is N or CR^{16} ;
- [0549] R^5 and R^{16} are selected from (i) or (ii):
- [0550] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0551] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0552] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0553] Het and R^6 are selected from (i) or (ii):
- [0554] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0555] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0556] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0557] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0558] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.
- [0559] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:
- [0560] R^8 is H, CN, OH, alkoxy, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [0561] R^9 is H and R^{10} is H or $C(O)R^{13}$, where R^{13} is alkyl or alkoxy; and
- [0562] R^{11} is alkyl or alkoxy;
- [0563] R^5 and R^{16} are selected from (i) or (ii):
- [0564] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[0565] (ii) R⁵ and R¹⁶ together form alkylene;

[0566] X is O or CH₂;

[0567] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0568] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0569] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0570] R⁸ is H, CN, OH, alkoxy, aryl, NR⁹R¹⁰ or C(O)R¹¹;

[0571] R⁹ is H and R¹⁰ is C(O)R¹³; where R¹³ is alkyl; and

[0572] R¹¹ is alkoxy;

[0573] R⁵ and R¹⁶ are selected from (i) or (ii):

[0574] (i) R⁵ is H, cyano, alkoxy or alkyl, and R¹⁶ is H, alkyl, alkoxy, halo or alkynyl, or

[0575] (ii) R⁵ and R¹⁶ together form alkylene;

[0576] X is O or CH₂;

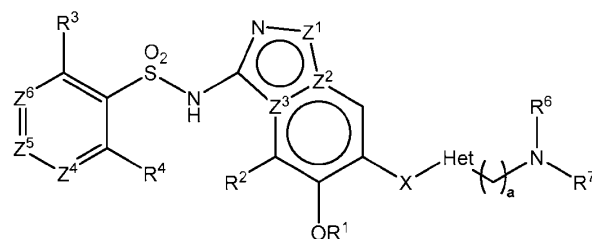
[0577] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0578] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0579] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R¹ and R² together form C₂₋₄alkylene.

[0580] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R¹ and R² together form propylene.

[0581] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II:



[0582] or a pharmaceutically acceptable derivative thereof, wherein:

[0583] a is 0-2;

[0584] R¹ and R² are selected from (i) or (ii);

[0585] (i) R^1 is alkyl, cycloalkyl or haloalkyl; and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or

[0586] (ii) R^1 and R^2 together form alkylene;

[0587] R^3 is $-O-(CH_2)_b-R^8$;

[0588] b is 1-4;

[0589] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0590] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0591] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0592] R^{12} is alkyl or $NR^{14}R^{15}$;

[0593] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0594] R^4 is H or alkoxy;

[0595] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0596] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0597] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0598] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0599] Z^4 is CR^{16} ;

[0600] Z^5 is CR^5 ;

[0601] Z^6 is N or CH;

[0602] R^5 and R^{16} together form alkylene or heteroalkylene;

[0603] X is O, $S(O)_x$ or CH_2 , where x is 0-2;

[0604] Het and R^6 are selected from (i) or (ii):

[0605] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

[0606] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

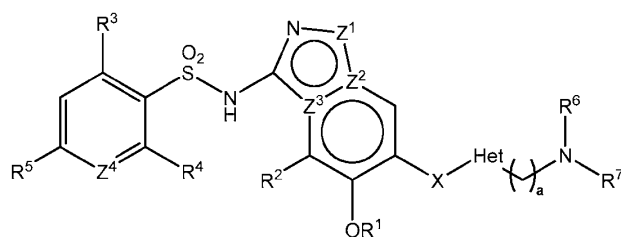
[0607] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

[0608] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-\text{R}^{19}$, $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$ or $-\text{NR}^{20}\text{R}^{21}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0609] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-\text{NR}^9\text{R}^{10}$.

[0610] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIa:



[0611] or a pharmaceutically acceptable derivative thereof, wherein:

[0612] a is 0-2;

[0613] R^1 and R^2 are selected from (i) or (ii):

[0614] (i) R^1 is alkyl, cycloalkyl or haloalkyl; and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo; or

[0615] (ii) R^1 and R^2 together form alkylene;

[0616] R^3 is $-\text{O}-(\text{CH}_2)_b-\text{R}^8$;

[0617] b is 1-4;

[0618] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})\text{R}^{11}$, $\text{C}(=\text{NH})(\text{R}^{12})$ or $\text{C}(=\text{N}-\text{O}-\text{R}^9)(\text{R}^{12})$;

[0619] R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[0620] R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[0621] R^{12} is alkyl or $\text{NR}^{14}\text{R}^{15}$;

[0622] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0623] R^4 is H or alkoxy;

[0624] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0625] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

- [0626] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0627] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0628] Z^4 is CR^{16} ;
- [0629] R^5 and R^{16} together form alkylene or heteroalkylene;
- [0630] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0631] Het and R^6 are selected from (i) or (ii):
- [0632] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0633] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0634] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0635] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0636] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [0637] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:
- [0638] R^1 and R^2 are selected from (i) or (ii):
- [0639] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H or alkoxy, or
- [0640] (ii) R^1 and R^2 together form alkylene;
- [0641] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [0642] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;
- [0643] R^{11} is alkyl or alkoxy;
- [0644] R^5 and R^{16} together form alkylene;
- [0645] X is O or CH_2 ;

[0646] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0647] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0648] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0649] R^1 and R^2 are selected from (i) or (ii):

[0650] (i) R^1 is alkyl or haloalkyl, and R^2 is H or alkoxy, or

[0651] (ii) R^1 and R^2 together form alkylene;

[0652] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

[0653] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[0654] R^{11} is alkoxy;

[0655] R^5 and R^{16} together form alkylene;

[0656] X is O or CH_2 ;

[0657] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

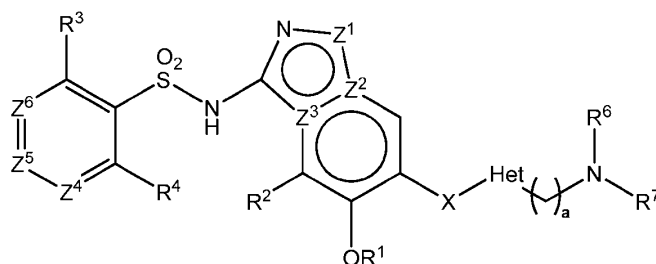
[0658] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0659] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^5 and R^{16} together form C_3 -alkylene.

[0660] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^5 and R^{16} together form propylene.

[0661] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein X is O or $S(O)_x$, where x is 0-2. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein X is O or S.

[0662] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II:



[0663] or a pharmaceutically acceptable derivative thereof, wherein:

[0664] a is 0-2;

[0665] R^1 and R^2 are selected from (i) or (ii):

[0666] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or

[0667] (ii) R^1 and R^2 together form alkylene;

[0668] R^3 is $-O-(CH_2)_b-R^8$;

[0669] b is 1-4;

[0670] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0671] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0672] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0673] R^{12} is alkyl or $NR^{14}R^{15}$;

[0674] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0675] R^4 is H or alkoxy;

[0676] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0677] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0678] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0679] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0680] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

[0681] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

[0682] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

[0683] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

[0684] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;

[0685] R^5 and R^{16} are selected from (i) or (ii):

[0686] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

[0687] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;

[0688] X is O or $S(O)_x$, where x is 0-2;

[0689] Het and R^6 are selected from (i) or (ii):

[0690] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

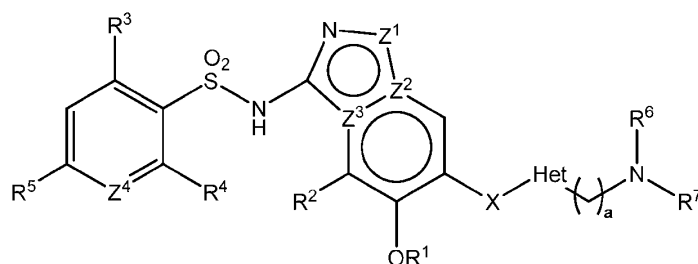
[0691] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0692] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

[0693] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0694] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0695] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIa:



[0696] or a pharmaceutically acceptable derivative thereof, wherein:

[0697] a is 0-2;

[0698] R^1 and R^2 are selected from (i) or (ii):

- [0699] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or
- [0700] (ii) R^1 and R^2 together form alkylene;
- [0701] R^3 is $-O-(CH_2)_b-R^8$;
- [0702] b is 1-4;
- [0703] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [0704] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0705] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0706] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0707] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0708] R^4 is H or alkoxy;
- [0709] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0710] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0711] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0712] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0713] Z^4 is N or CR^{16} ;
- [0714] R^5 and R^{16} are selected from (i) or (ii):
- [0715] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0716] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0717] X is O or $S(O)_x$, where x is 0-2;
- [0718] Het and R^6 are selected from (i) or (ii):
- [0719] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0720] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0721] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0722] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-\text{R}^{19}$, $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$ or $-\text{NR}^{20}\text{R}^{21}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0723] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-\text{NR}^9\text{R}^{10}$.

[0724] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0725] R^1 and R^2 are selected from (i) or (ii):

[0726] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H or alkoxy, or

[0727] (ii) R^1 and R^2 together form alkylene;

[0728] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $\text{C}(\text{O})\text{R}^{11}$;

[0729] R^9 and R^{10} are each independently H or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl or alkoxy;

[0730] R^{11} is alkyl or alkoxy;

[0731] R^5 and R^{16} are selected from (i) or (ii):

[0732] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[0733] (ii) R^5 and R^{16} together form alkylene;

[0734] X is O;

[0735] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0736] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0737] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0738] R^1 and R^2 are selected from (i) or (ii):

[0739] (i) R^1 is alkyl or haloalkyl, and R^2 is H or alkoxy, or

[0740] (ii) R^1 and R^2 together form alkylene;

[0741] R^8 is H, CN, OH, aryl, NR^9R^{10} or $\text{C}(\text{O})\text{R}^{11}$;

[0742] R^9 and R^{10} are each independently H or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl;

[0743] R^{11} is alkoxy;

[0744] R^5 and R^{16} are selected from (i) or (ii):

[0745] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or

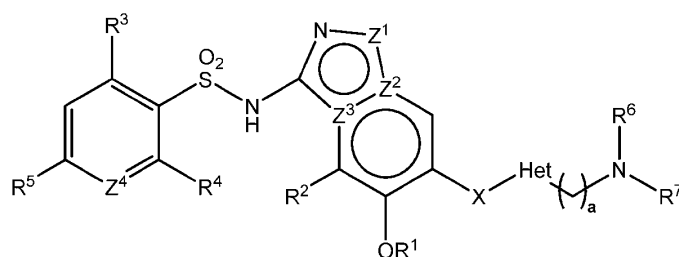
[0746] (ii) R^5 and R^{16} together form alkylene;

[0747] X is O;

[0748] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0749] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0750] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIa:



[0751] or a pharmaceutically acceptable derivative thereof, wherein:

[0752] a is 0-2;

[0753] R^1 and R^2 are selected from (i) or (ii):

[0754] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or

[0755] (ii) R^1 and R^2 together form alkylene;

[0756] R^3 is $-O-(CH_2)_b-R^8$;

[0757] b is 1-4;

[0758] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0759] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0760] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0761] R^{12} is alkyl or $NR^{14}R^{15}$;

[0762] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0763] R^4 is H or alkoxy;

[0764] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

- [0765] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0766] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0767] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0768] Z^4 is N or CR^{16} , where R^{16} is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;
- [0769] R^5 is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;
- [0770] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0771] Het and R^6 are selected from (i) or (ii):
- [0772] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0773] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0774] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [0775] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [0776] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [0777] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:
- [0778] R^1 and R^2 are selected from (i) or (ii):
- [0779] (i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H or alkoxy, or
- [0780] (ii) R^1 and R^2 together form alkylene;
- [0781] R^5 is alkenyl or alkynyl;
- [0782] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [0783] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;
- [0784] R^{11} is alkyl or alkoxy;
- [0785] X is O or CH_2 ;

[0786] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0787] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0788] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0789] R^1 and R^2 are selected from (i) or (ii):

[0790] (i) R^1 is alkyl or haloalkyl, and R^2 is H or alkoxy, or

[0791] (ii) R^1 and R^2 together form alkylene;

[0792] R^3 is alkynyl;

[0793] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

[0794] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

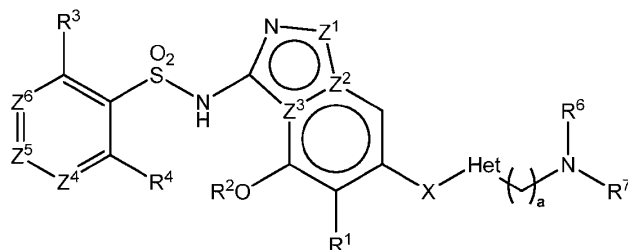
[0795] R^{11} is alkoxy;

[0796] X is O or CH_2 ;

[0797] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0798] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0799] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I:



[0800] or a pharmaceutically acceptable derivative thereof, wherein:

[0801] a is 0-2;

[0802] R^1 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

[0803] R^2 and R^4 together form heteroalkylene;

[0804] R^3 is $-O-(CH_2)_b-R^8$;

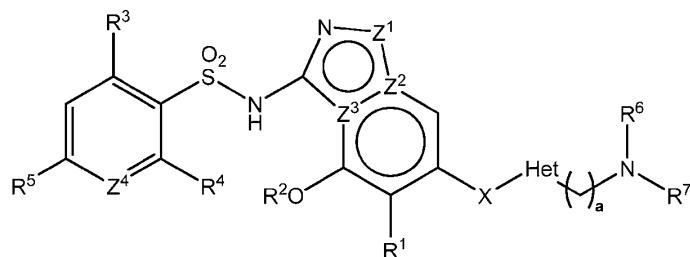
[0805] b is 1-4;

[0806] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

- [0807] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0808] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0809] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0810] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0811] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0812] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0813] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0814] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0815] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0816] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0817] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0818] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0819] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0820] R^5 and R^{16} are selected from (i) or (ii):
- [0821] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0822] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0823] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0824] Het and R^6 are selected from (i) or (ii):
- [0825] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0826] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0827] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [0828] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0829] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0830] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula Ia:



[0831] or a pharmaceutically acceptable derivative thereof, wherein:

[0832] a is 0-2;

[0833] R^1 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

[0834] R^2 and R^4 together form heteroalkylene;

[0835] R^3 is $-O-(CH_2)_b-R^8$;

[0836] b is 1-4;

[0837] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0838] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0839] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0840] R^{12} is alkyl or $NR^{14}R^{15}$;

[0841] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0842] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0843] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0844] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0845] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0846] Z^4 is N or CR^{16} ;

[0847] R^5 and R^{16} are selected from (i) or (ii):

[0848] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or

[0849] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;

[0850] X is O, $S(O)_x$ or CH_2 , where x is 0-2;

[0851] Het and R^6 are selected from (i) or (ii):

[0852] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

[0853] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0854] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;

[0855] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0856] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[0857] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0858] R^1 is H or alkoxy;

[0859] R^2 and R^4 together form $-O-(CH_2)_r-$ or $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}-$, where r is an integer from 2 to 5 and the terminal O is attached to the R^4 position of Formula I;

[0860] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

[0861] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;

[0862] R^{11} is alkyl or alkoxy;

[0863] R^5 and R^{16} are selected from (i) or (ii):

[0864] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[0865] (ii) R^5 and R^{16} together form alkylene;

[0866] X is O or CH₂;

[0867] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0868] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0869] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein:

[0870] R¹ is H or alkoxy;

[0871] R² and R⁴ together form -O-(CH₂)_r- or -O-(CH₂)₁₋₃-O-(CH₂)₁₋₃-, where r is an integer from 2 to 5 and the terminal O is attached to the R⁴ position of Formula I;

[0872] R⁸ is H, CN, OH, aryl, NR⁹R¹⁰ or C(O)R¹¹;

[0873] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl;

[0874] R¹¹ is alkoxy;

[0875] R⁵ and R¹⁶ are selected from (i) or (ii):

[0876] (i) R⁵ is H, cyano, alkoxy or alkyl, and R¹⁶ is H, alkyl, alkoxy, halo or alkynyl, or

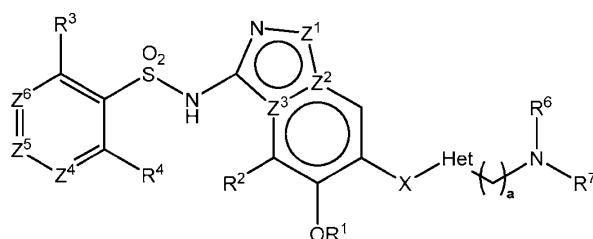
[0877] (ii) R⁵ and R¹⁶ together form alkylene;

[0878] X is O or CH₂;

[0879] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[0880] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[0881] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II:



[0882] or a pharmaceutically acceptable derivative thereof, wherein:

[0883] a is 0-2;

[0884] R¹ is alkyl, cycloalkyl or haloalkyl;

[0885] R² is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

[0886] R³ is -O-(CH₂)_b-R⁸;

[0887] b is 1-4;

[0888] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

[0889] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$, where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

[0890] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

[0891] R^{12} is alkyl or $NR^{14}R^{15}$;

[0892] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0893] R^4 is H or alkoxy;

[0894] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

[0895] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

[0896] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

[0897] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

[0898] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

[0899] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

[0900] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

[0901] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

[0902] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;

[0903] R^5 and R^{16} are selected from (i) or (ii):

[0904] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

[0905] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;

[0906] X is $CR^{22}R^{23}$, where R^{22} and R^{23} are each independently H or alkyl;

[0907] Het and R^6 are selected from (i) or (ii):

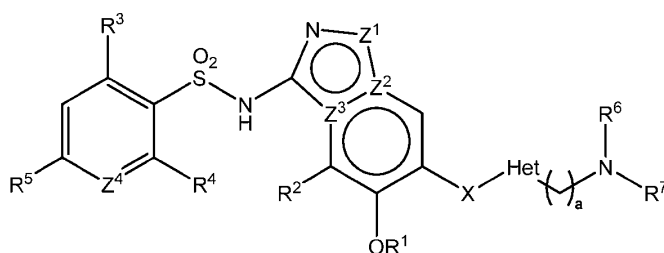
[0908] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

[0909] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0910] R^7 is $-C(O)R^{17}$; and

[0911] R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-O-(CH_2)_2-R^{19}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$.

[0912] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIa:



[0913] or a pharmaceutically acceptable derivative thereof, wherein:

[0914] a is 0-2;

[0915] R¹ is alkyl, cycloalkyl or haloalkyl;

[0916] R² is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

[0917] R³ is -O-(CH₂)_b-R⁸;

[0918] b is 1-4;

[0919] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[0920] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[0921] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[0922] R¹² is alkyl or NR¹⁴R¹⁵;

[0923] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[0924] R⁴ is H or alkoxy;

[0925] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[0926] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[0927] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[0928] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[0929] Z⁴ is N or CR¹⁶;

[0930] R⁵ and R¹⁶ are selected from (i) or (ii):

[0931] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or

[0932] (ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

[0933] X is CR²²R²³, where R²² and R²³ are each independently H or alkyl;

[0934] Het and R⁶ are selected from (i) or (ii):

[0935] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

[0936] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[0937] R^7 is $-C(O)R^{17}$; and

[0938] R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-O-(CH_2)_2-R^{19}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$.

[0939] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0940] R^1 is alkyl, cycloalkyl or haloalkyl;

[0941] R^2 is H or alkoxy;

[0942] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

[0943] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;

[0944] R^{11} is alkyl or alkoxy;

[0945] X is CH_2 ; and

[0946] R^{17} is alkoxy.

[0947] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein:

[0948] R^1 is alkyl or haloalkyl;

[0949] R^2 is H or alkoxy;

[0950] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

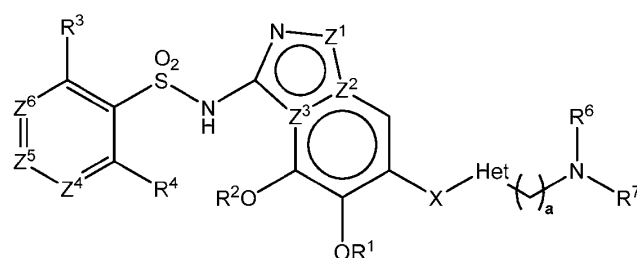
[0951] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[0952] R^{11} is alkoxy;

[0953] X is CH_2 ; and

[0954] R^{17} is alkoxy.

[0955] In one embodiment, provided is a compound of Formula III for use in the compositions and methods provided herein:



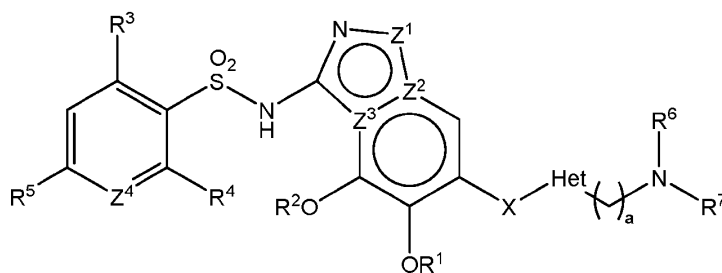
[0956] or a pharmaceutically acceptable derivative thereof, wherein:

- [0957] a is 0-2;
- [0958] R^1 and R^2 together form alkylene;
- [0959] R^3 is $-O-(CH_2)_b-R^8$;
- [0960] b is 1-4;
- [0961] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [0962] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [0963] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [0964] R^{12} is alkyl or $NR^{14}R^{15}$;
- [0965] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [0966] R^4 is H or alkoxy;
- [0967] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0968] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [0969] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [0970] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [0971] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [0972] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [0973] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [0974] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [0975] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [0976] R^5 and R^{16} are selected from (i) or (ii):
- [0977] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [0978] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [0979] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [0980] Het and R^6 are selected from (i) or (ii):
- [0981] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [0982] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [0983] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

[0984] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-R^{19}$, $-\text{O}-(\text{CH}_2)_2-R^{19}$ or $-\text{NR}^{20}R^{21}$, where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[0985] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-\text{NR}^{20}R^{21}$.

[0986] In one embodiment, provided is a compound of Formula IIIa for use in the compositions and methods provided herein:



[0987] or a pharmaceutically acceptable derivative thereof, wherein:

[0988] a is 0-2;

[0989] R^1 and R^2 together form alkylene;

[0990] R^3 is $-\text{O}-(\text{CH}_2)_b-R^8$;

[0991] b is 1-4;

[0992] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})R^{11}$, $\text{C}(=\text{NH})(R^{12})$ or $\text{C}(=\text{N}-\text{O}-R^9)(R^{12})$;

[0993] R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})R^{13}$, where R^{13} is alkyl, alkoxy or $\text{NR}^{14}R^{15}$;

[0994] R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}R^{15}$;

[0995] R^{12} is alkyl or $\text{NR}^{14}R^{15}$;

[0996] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

- [0997] R^4 is H or alkoxy;
- [0998] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [0999] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [1000] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [1001] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [1002] Z^4 is N or CR^{16} ;
- [1003] R^5 and R^{16} are selected from (i) or (ii):
- [1004] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [1005] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [1006] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [1007] Het and R^6 are selected from (i) or (ii):
- [1008] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [1009] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1010] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [1011] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [1012] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.
- [1013] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:
- [1014] R^8 is H, CN, OH, alkoxy, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [1015] R^9 is H and R^{10} is H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy; and
- [1016] R^{11} is alkyl or alkoxy;

[1017] R^5 and R^{16} are selected from (i) or (ii):

[1018] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[1019] (ii) R^5 and R^{16} together form alkylene;

[1020] X is O or CH_2 ;

[1021] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1022] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1023] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

[1024] R^8 is H, CN, OH, alkoxy, aryl, NR^9R^{10} or $C(O)R^{11}$;

[1025] R^9 is H and R^{10} is $C(O)R^{13}$; where R^{13} is alkyl; and

[1026] R^{11} is alkoxy;

[1027] R^5 and R^{16} are selected from (i) or (ii):

[1028] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or

[1029] (ii) R^5 and R^{16} together form alkylene;

[1030] X is O or CH_2 ;

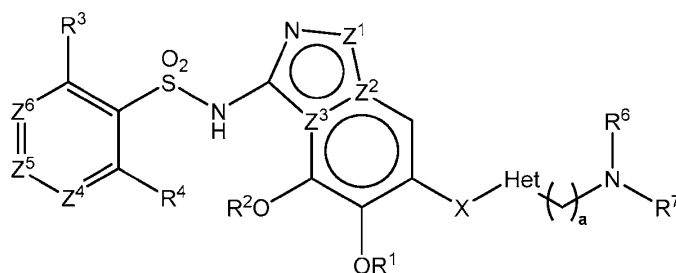
[1031] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1032] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1033] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein R^1 and R^2 together form C_{1-4} alkylene optionally substituted with one or more halo or methyl.

[1034] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein R^1 and R^2 together form methylene or ethylene each optionally substituted with one or two halo or methyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein R^1 and R^2 together form unsubstituted methylene or ethylene.

[1035] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III:



[1036] or a pharmaceutically acceptable derivative thereof, wherein:

[1037] a is 0-2;

[1038] R¹ and R² are selected from (i) or (ii):

[1039] (i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

[1040] (ii) R¹ and R² together form alkylene;

[1041] R³ is -O-(CH₂)_b-R⁸;

[1042] b is 1-4;

[1043] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[1044] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[1045] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[1046] R¹² is alkyl or NR¹⁴R¹⁵;

[1047] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[1048] R⁴ is H or alkoxy;

[1049] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[1050] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[1051] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[1052] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[1053] Z⁴ is CR¹⁶;

[1054] Z⁵ is CR⁵;

[1055] Z⁶ is N or CH;

[1056] R⁵ and R¹⁶ together form alkylene or heteroalkylene;

[1057] X is O, S(O)_x or CH₂, where x is 0-2;

[1058] Het and R⁶ are selected from (i) or (ii):

[1059] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

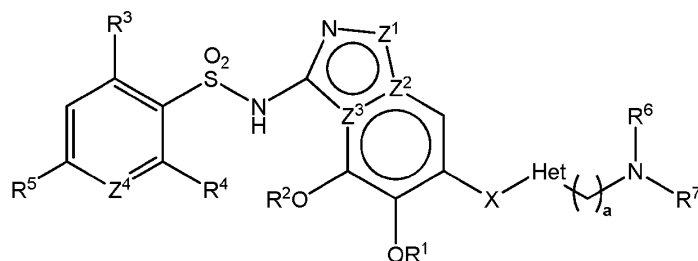
[1060] (ii) Het is a 5- or 6-membered heteroaryl, R⁶ is $-(CH_2)_{1-2}-$, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[1061] R⁷ is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

[1062] R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R¹⁹ is $-OR^9$ or $-NR^9R^{10}$, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl; and

[1063] R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

[1064] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIIa:



[1065] or a pharmaceutically acceptable derivative thereof, wherein:

[1066] a is 0-2;

[1067] R¹ and R² are selected from (i) or (ii):

[1068] (i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

[1069] (ii) R¹ and R² together form alkylene;

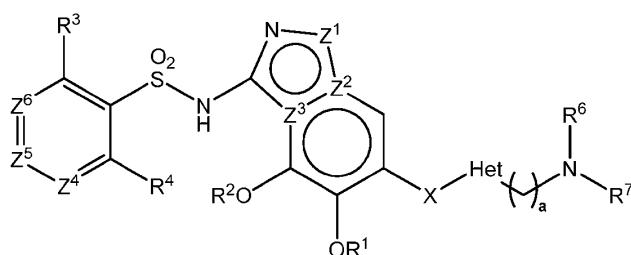
[1070] R³ is $-O-(CH_2)_b-R^8$;

[1071] b is 1-4;

[1072] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

- [1073] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [1074] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [1075] R^{12} is alkyl or $NR^{14}R^{15}$;
- [1076] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [1077] R^4 is H or alkoxy;
- [1078] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [1079] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [1080] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [1081] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [1082] Z^4 is CR^{16} ;
- [1083] R^5 and R^{16} together form alkylene or heteroalkylene;
- [1084] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [1085] Het and R^6 are selected from (i) or (ii):
- [1086] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [1087] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1088] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [1089] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [1090] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [1091] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

- [1092] R^1 and R^2 are selected from (i) or (ii):
- [1093] (i) R^1 and R^2 are each alkyl, or
- [1094] (ii) R^1 and R^2 together form alkylene optionally substituted with one or more halo or methyl;
- [1095] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [1096] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;
- [1097] R^{11} is alkyl or alkoxy;
- [1098] R^5 and R^{16} together form alkylene;
- [1099] X is O or CH_2 ;
- [1100] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [1101] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.
- [1102] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein R^5 and R^{16} together form C_3 -alkylene.
- [1103] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein R^5 and R^{16} together form propylene.
- [1104] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein X is O or $S(O)_x$, where x is 0-2. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein X is O or S.
- [1105] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III:



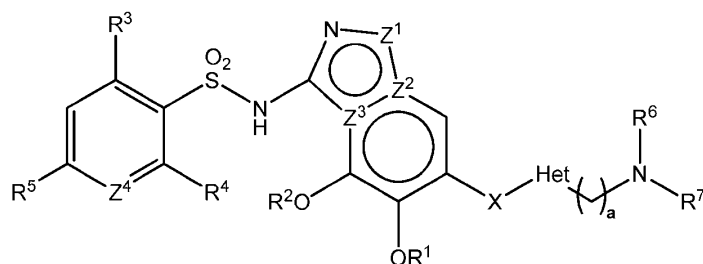
- [1106] or a pharmaceutically acceptable derivative thereof, wherein:
- [1107] a is 0-2;
- [1108] R^1 and R^2 are selected from (i) or (ii):
- [1109] (i) R^1 and R^2 are each independently alkyl, cycloalkyl or haloalkyl, or

- [1110] (ii) R^1 and R^2 together form alkylene;
- [1111] R^3 is $-O-(CH_2)_b-R^8$;
- [1112] b is 1-4;
- [1113] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [1114] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [1115] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [1116] R^{12} is alkyl or $NR^{14}R^{15}$;
- [1117] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- [1118] R^4 is H or alkoxy;
- [1119] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [1120] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [1121] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [1122] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [1123] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [1124] (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
- [1125] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [1126] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [1127] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [1128] R^5 and R^{16} are selected from (i) or (ii):
- [1129] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [1130] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [1131] X is O or $S(O)_x$, where x is 0-2;
- [1132] Het and R^6 are selected from (i) or (ii):
- [1133] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [1134] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1135] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [1136] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-\text{R}^{19}$, $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$ or $-\text{NR}^{20}\text{R}^{21}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

[1137] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-\text{NR}^9\text{R}^{10}$.

[1138] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIIa:



[1139] or a pharmaceutically acceptable derivative thereof, wherein:

[1140] a is 0-2;

[1141] R^1 and R^2 are selected from (i) or (ii):

[1142] (i) R^1 and R^2 are each independently alkyl, cycloalkyl or haloalkyl, or

[1143] (ii) R^1 and R^2 together form alkylene;

[1144] R^3 is $-\text{O}-(\text{CH}_2)_b-\text{R}^8$;

[1145] b is 1-4;

[1146] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})\text{R}^{11}$, $\text{C}(=\text{NH})(\text{R}^{12})$ or $\text{C}(=\text{N}-\text{O}-\text{R}^9)(\text{R}^{12})$;

[1147] R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[1148] R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

[1149] R^{12} is alkyl or $\text{NR}^{14}\text{R}^{15}$;

[1150] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

- [1151] R^4 is H or alkoxy;
- [1152] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [1153] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [1154] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [1155] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [1156] Z^4 is N or CR^{16} ;
- [1157] R^5 and R^{16} are selected from (i) or (ii):
- [1158] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or
- [1159] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [1160] X is O or $S(O)_x$, where x is 0-2;
- [1161] Het and R^6 are selected from (i) or (ii):
- [1162] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [1163] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1164] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [1165] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [1166] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [1167] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:
- [1168] R^1 and R^2 are selected from (i) or (ii):
- [1169] (i) R^1 and R^2 are each alkyl, or

[1170] (ii) R¹ and R² together form alkylene optionally substituted with one or more halo or methyl;

[1171] R⁸ is H, CN, OH, aryl, heteroaryl, NR⁹R¹⁰ or C(O)R¹¹;

[1172] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl or alkoxy;

[1173] R¹¹ is alkyl or alkoxy;

[1174] R⁵ and R¹⁶ are selected from (i) or (ii):

[1175] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or

[1176] (ii) R⁵ and R¹⁶ together form alkylene;

[1177] X is O;

[1178] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1179] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1180] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

[1181] R¹ and R² are selected from (i) or (ii):

[1182] (i) R¹ and R² are each alkyl, or

[1183] (ii) R¹ and R² together form alkylene optionally substituted with one or more halo or methyl;

[1184] R⁸ is H, CN, OH, aryl, NR⁹R¹⁰ or C(O)R¹¹;

[1185] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl;

[1186] R¹¹ is alkoxy;

[1187] R⁵ and R¹⁶ are selected from (i) or (ii):

[1188] (i) R⁵ is H, cyano, alkoxy or alkyl, and R¹⁶ is H, alkyl, alkoxy, halo or alkynyl, or

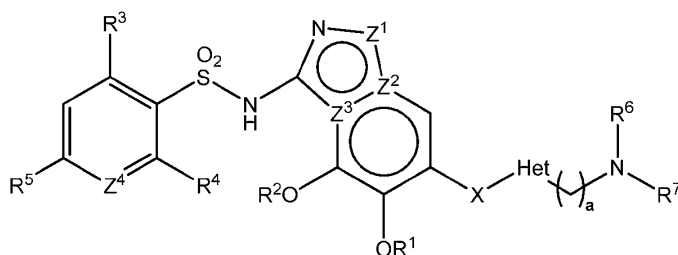
[1189] (ii) R⁵ and R¹⁶ together form alkylene;

[1190] X is O;

[1191] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1192] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1193] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIIa:



[1194] or a pharmaceutically acceptable derivative thereof, wherein:

[1195] a is 0-2;

[1196] R¹ and R² are selected from (i) or (ii):

[1197] (i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

[1198] (ii) R¹ and R² together form alkylene;

[1199] R³ is -O-(CH₂)_b-R⁸;

[1200] b is 1-4;

[1201] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[1202] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[1203] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[1204] R¹² is alkyl or NR¹⁴R¹⁵;

[1205] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[1206] R⁴ is H or alkoxy;

[1207] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[1208] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[1209] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[1210] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[1211] Z⁴ is N or CR¹⁶, where R¹⁶ is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

[1212] R⁵ is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

[1213] X is O, S(O)_x or CH₂, where x is 0-2;

[1214] Het and R⁶ are selected from (i) or (ii):

[1215] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

[1216] (ii) Het is a 5- or 6-membered heteroaryl, R⁶ is -(CH₂)₁₋₂-, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

[1217] R⁷ is -C(O)R¹⁷ or -SO₂R¹⁸;

[1218] R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, -NH-(CH₂)₂-R¹⁹, -O-(CH₂)₂-R¹⁹ or -NR²⁰R²¹; where R¹⁹ is -OR⁹ or -NR⁹R¹⁰, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl; and

[1219] R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or -NR⁹R¹⁰.

[1220] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

[1221] R¹ and R² are selected from (i) or (ii):

[1222] (i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

[1223] (ii) R¹ and R² together form alkylene optionally substituted with one or more halo or methyl;

[1224] R⁵ is alkenyl or alkynyl;

[1225] R⁸ is H, CN, OH, aryl, heteroaryl, NR⁹R¹⁰ or C(O)R¹¹;

[1226] R⁹ and R¹⁰ are each independently H or C(O)R¹³; where R¹³ is alkyl or alkoxy;

[1227] R¹¹ is alkyl or alkoxy;

[1228] X is O or CH₂;

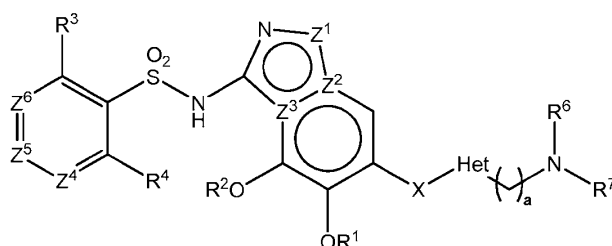
[1229] R¹⁷ is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1230] R¹⁸ is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1231] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

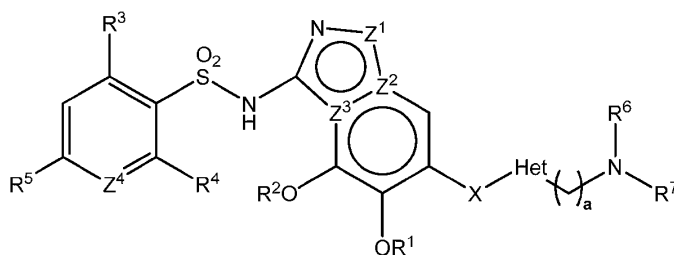
[1232] R¹ and R² are selected from (i) or (ii):

- [1233] (i) R^1 and R^2 are each independently alkyl or haloalkyl, or
- [1234] (ii) R^1 and R^2 together form alkylene optionally substituted with one or more halo or methyl;
- [1235] R^5 is alkynyl;
- [1236] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;
- [1237] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;
- [1238] R^{11} is alkoxy;
- [1239] X is O or CH_2 ;
- [1240] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [1241] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.
- [1242] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III:



- [1243] or a pharmaceutically acceptable derivative thereof, wherein:
- [1244] a is 0-2;
- [1245] R^1 is alkyl or haloalkyl;
- [1246] R^2 and R^4 together form heteroalkylene;
- [1247] R^3 is $-O-(CH_2)_b-R^8$;
- [1248] b is 1-4;
- [1249] R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- [1250] R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$, where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- [1251] R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- [1252] R^{12} is alkyl or $NR^{14}R^{15}$;
- [1253] R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

- [1254] Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- [1255] (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- [1256] (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- [1257] (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- [1258] Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
- [1259] (i) Z^4 is N, Z^5 is CR^{16} , and Z^6 is CH,
- [1260] (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
- [1261] (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
- [1262] (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
- [1263] R^5 and R^{16} are selected from (i) or (ii):
- [1264] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
- [1265] (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
- [1266] X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- [1267] Het and R^6 are selected from (i) or (ii):
- [1268] (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- [1269] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1270] R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- [1271] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [1272] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [1273] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula IIIa:



[1274] or a pharmaceutically acceptable derivative thereof, wherein:

[1275] a is 0-2;

[1276] R¹ is alkyl or haloalkyl;

[1277] R² and R⁴ together form heteroalkylene;

[1278] R³ is -O-(CH₂)_b-R⁸;

[1279] b is 1-4;

[1280] R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

[1281] R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

[1282] R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

[1283] R¹² is alkyl or NR¹⁴R¹⁵;

[1284] R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

[1285] Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

[1286] (i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

[1287] (ii) Z¹ is NH or O, and Z² and Z³ are C, or

[1288] (iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

[1289] Z⁴ is N or CR¹⁶;

[1290] R⁵ and R¹⁶ are selected from (i) or (ii):

[1291] (i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, alkyl, alkenyl, alkynyl or haloalkyl, or

[1292] (ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

[1293] X is O, S(O)_x or CH₂, where x is 0-2;

[1294] Het and R⁶ are selected from (i) or (ii):

[1295] (i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

- [1296] (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- [1297] R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;
- [1298] R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and
- [1299] R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
- [1300] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:
- [1301] R^1 is alkyl;
- [1302] R^2 and R^4 together form $-O-(CH_2)_r-$ or $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}-$, where r is an integer from 2 to 5 and the terminal O is attached to the R^4 position of Formula III or IIIa;
- [1303] R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;
- [1304] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;
- [1305] R^{11} is alkyl or alkoxy;
- [1306] R^5 and R^{16} are selected from (i) or (ii):
- [1307] (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, alkyl, alkenyl or alkynyl, or
- [1308] (ii) R^5 and R^{16} together form alkylene;
- [1309] X is O or CH_2 ;
- [1310] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and
- [1311] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1312] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula III or IIIa, wherein:

[1313] R^1 is alkyl;

[1314] R^2 and R^4 together form $-O-(CH_2)_r-$ or $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}-$, where r is an integer from 2 to 5 and the terminal O is attached to the R^4 position of Formula III or IIIa;

[1315] R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

[1316] R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

[1317] R^{11} is alkoxy;

[1318] R^5 and R^{16} are selected from (i) or (ii):

[1319] (i) R^5 is H, cyano, alkoxy or alkyl, and R^{16} is H, alkyl, alkoxy, halo or alkynyl, or

[1320] (ii) R^5 and R^{16} together form alkylene;

[1321] X is O or CH_2 ;

[1322] R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

[1323] R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

[1324] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein X is O. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein X is CH_2 .

[1325] In another embodiment, a is 0. In another embodiment, a is 1. In another embodiment, a is 2. In another embodiment, a is 0 or 1.

[1326] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^2 is alkyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^2 is methyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^2 is haloalkyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^2 is fluoromethyl, difluoromethyl or trifluoromethyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I or Ia, wherein R^2 is difluoromethyl.

[1327] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^2 is H. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa,

wherein R^2 is alkoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^2 is methoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^2 is haloalkoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^2 is fluoromethoxy, difluoromethoxy or trifluoromethoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula II or IIa, wherein R^2 is difluoromethoxy.

[1328] In another embodiment, b is 1. In another embodiment, b is 2. In another embodiment, b is 3. In another embodiment, b is 4. In another embodiment, b is 1 or 2.

[1329] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^8 is H, phenyl, 4-fluorophenyl, morpholinyl, COOH, COOMe, C(=NH)NHOH, tetrazolyl, oxadiazolyl, triazolyl, pyridyl, imidazolyl, oxazolidinyl, NHC(O)OMe, cyano, hydroxy, amino or acetylamino. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^8 is H, phenyl, COOMe, hydroxy, cyano, amino or acetylamino. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^8 is hydrogen. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein b is 1 and R^8 is hydrogen.

[1330] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^4 is alkoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^4 is methoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^4 is H.

[1331] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Z^1 is NH or O, and Z^2 and Z^3 are C. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Z^1 is O, and Z^2 and Z^3 are C.

[1332] In another embodiment, Z^4 is N. In another embodiment, Z^4 is CR¹⁶.

[1333] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^5 is H, cyano, alkoxy or alkyl,

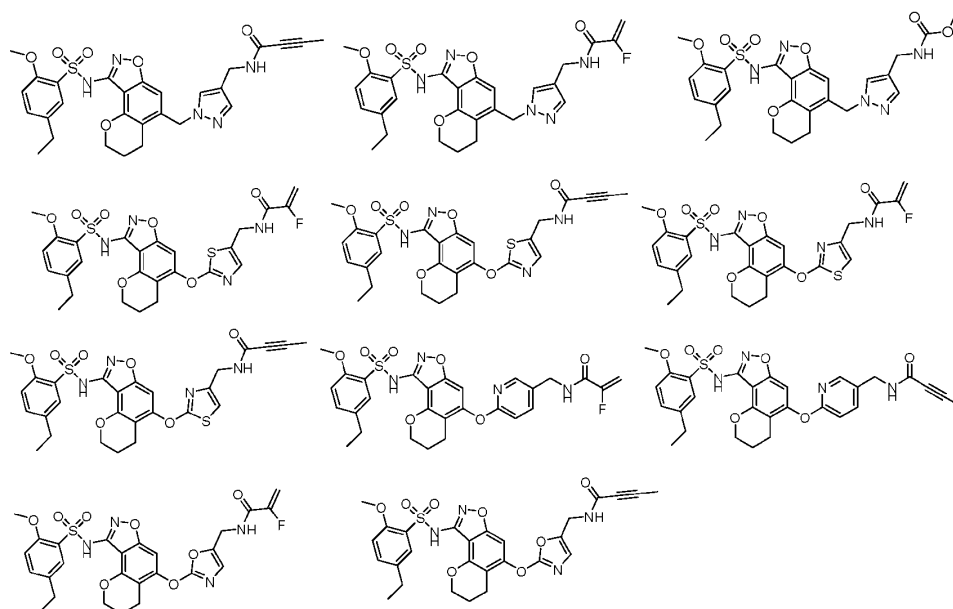
and R^{16} is H, alkyl, alkoxy, halo or alkynyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^5 is H, cyano, methoxy or methyl, and R^{16} is H, methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, fluoro, ethynyl or propynyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^5 is H, cyano, methoxy or methyl, and R^{16} is H, methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, ethynyl or propynyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^5 is H and R^{16} is H, methyl, ethyl, isopropyl, tert-butyl or methoxy.

[1334] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is a 5- or 6-membered heteroaryl, and R^6 is H or alkyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is a 5-membered heteroaryl, and R^6 is H or methyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is pyrazolyl, oxazolyl, thiazolyl or pyridyl, and R^6 is H or methyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is pyrazolyl, and R^6 is H or methyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is a 5-membered heteroaryl, R^6 is $-(CH_2)-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-bicyclic ring system. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein Het is a pyrazolyl, R^6 is $-(CH_2)-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-bicyclic ring system.

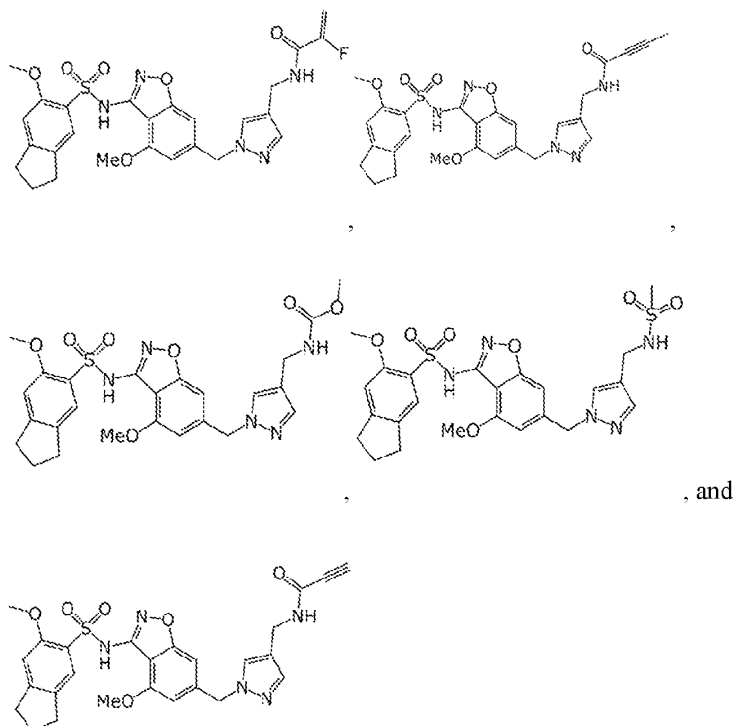
[1335] In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^7 is $-C(O)R^{17}$. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^7 is $-S(O)R^{18}$. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R^7 is $-SO_2R^{18}$. In another embodiment, the compounds for use in the

compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is alkyl, alkoxy, alkenyl, haloalkenyl, alkynyl, NR²⁰R²¹ or hydroxyalkynyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is alkyl, alkoxy, alkenyl, haloalkenyl, alkynyl or hydroxyalkynyl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is methyl, methoxy, NHMe, ethenyl, 1-fluoro-1-ethenyl, ethynyl or 1-propyn-1-yl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is methyl, methoxy, ethenyl, 1-fluoro-1-ethenyl, ethynyl or 1-propyn-1-yl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is methyl or methoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is methoxy. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁷ is ethenyl, 1-fluoro-1-ethenyl, ethynyl or 1-propyn-1-yl. In another embodiment, the compounds for use in the compositions and methods provided herein have Formula I, Ia, II, IIa, III or IIIa, wherein R¹⁸ is methyl or tert-butyl.

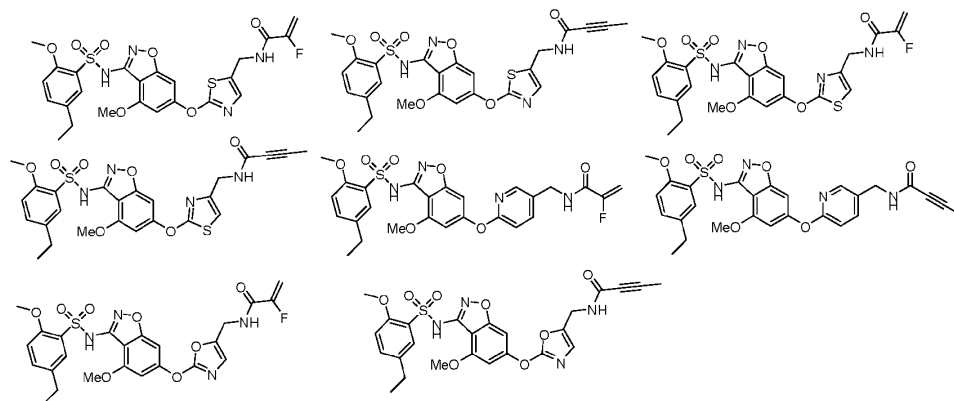
[1336] In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

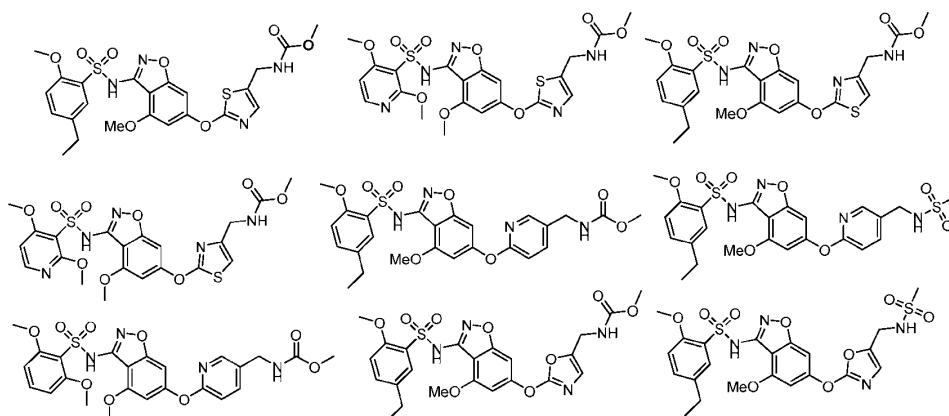


[1337] In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

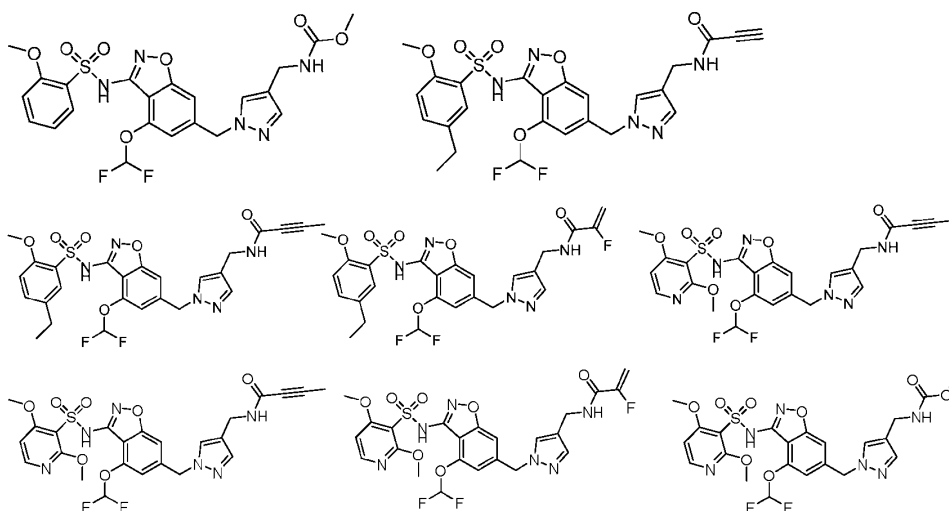


[1338] In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

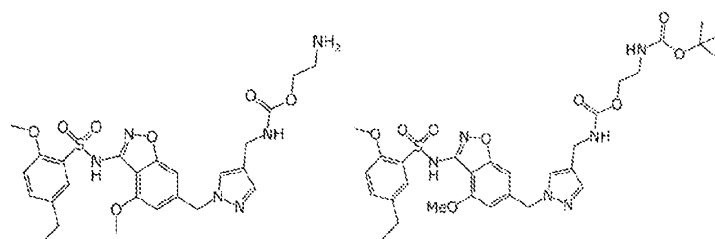
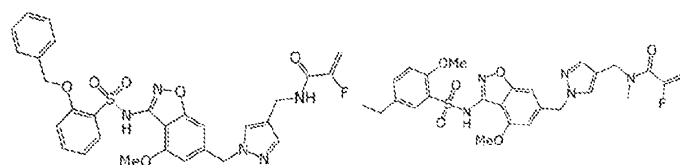
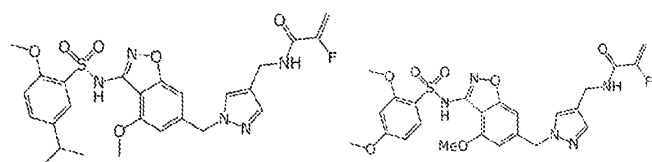
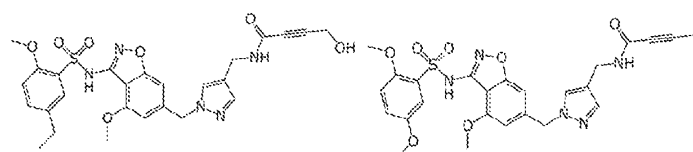
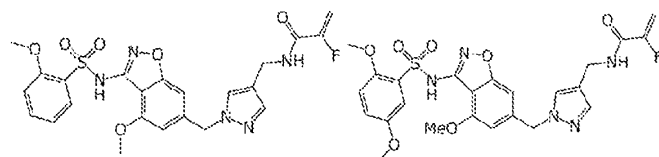


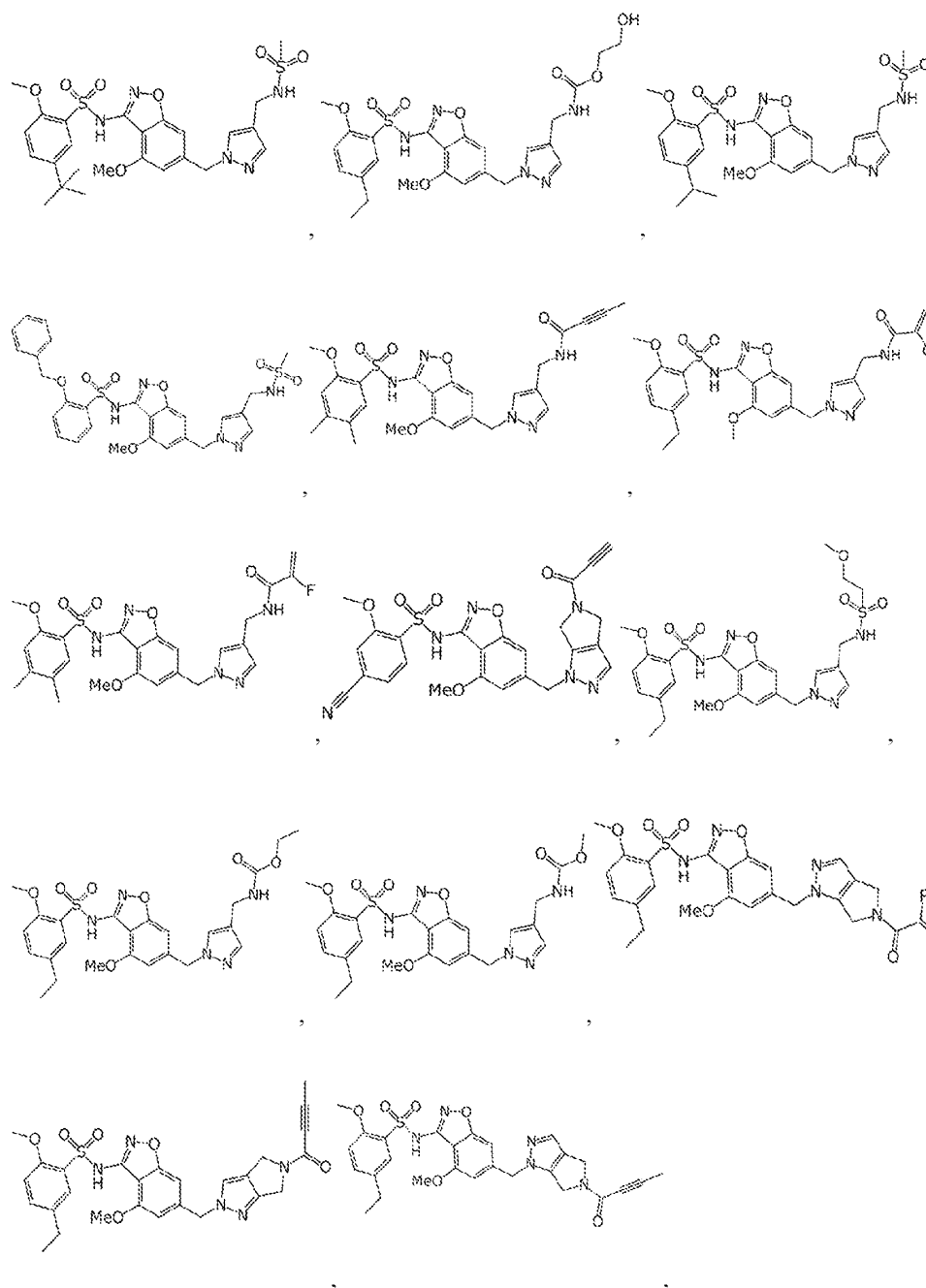


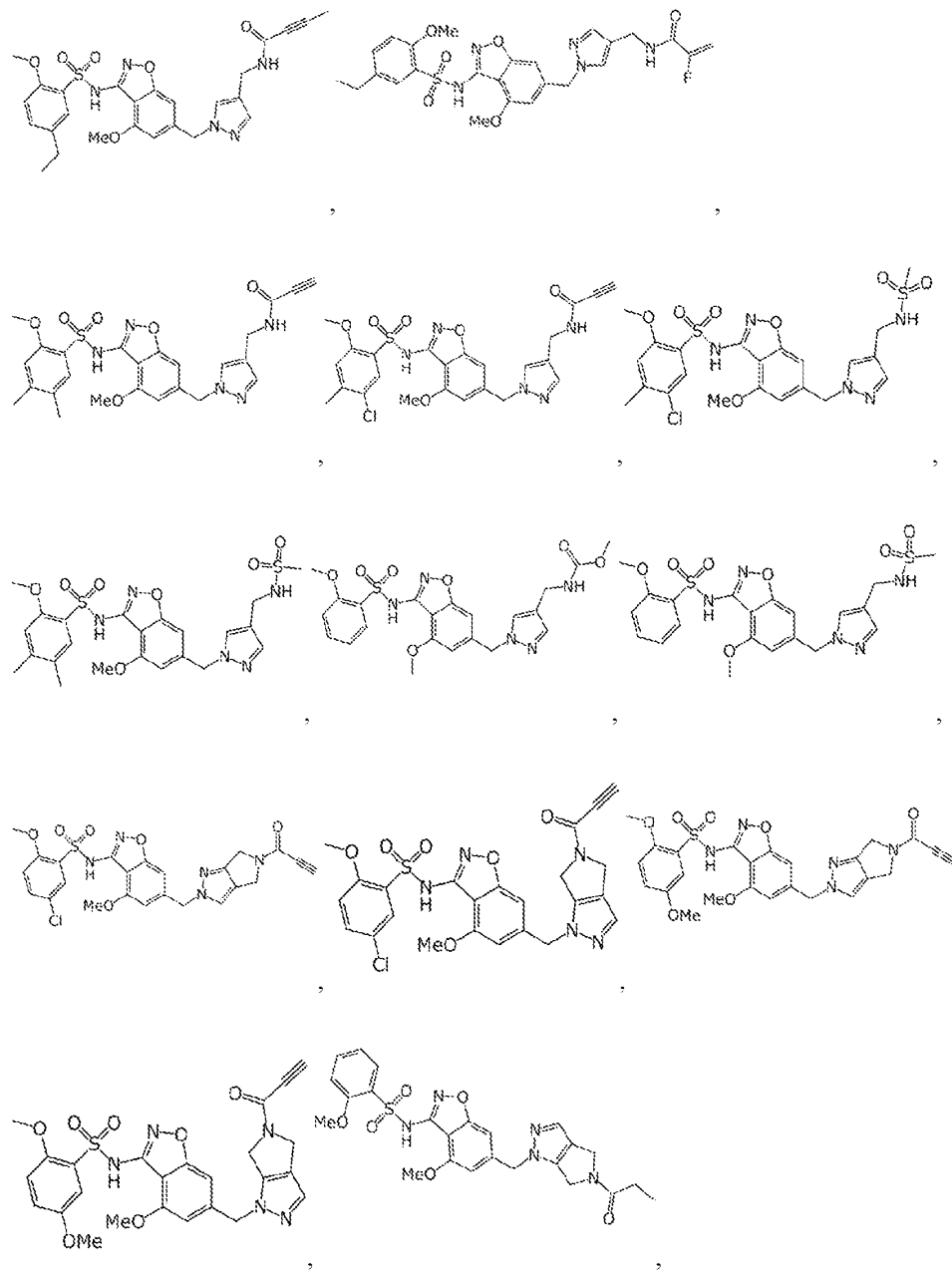
[1339] In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

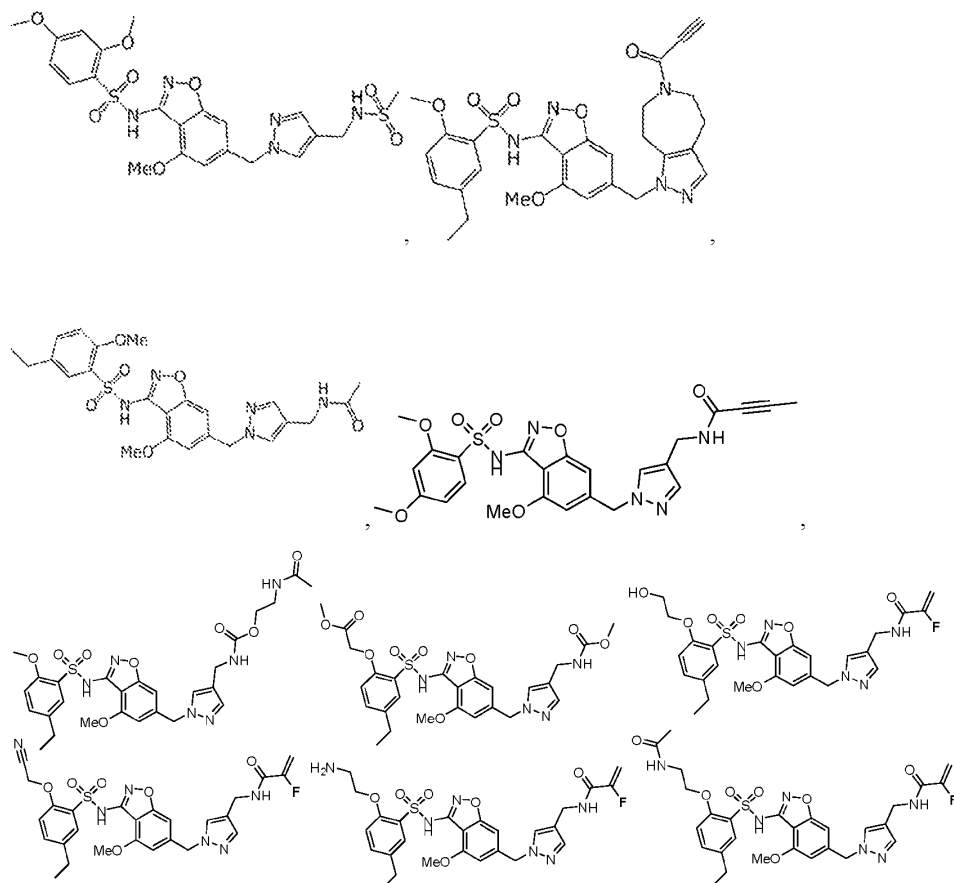


[1340] In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

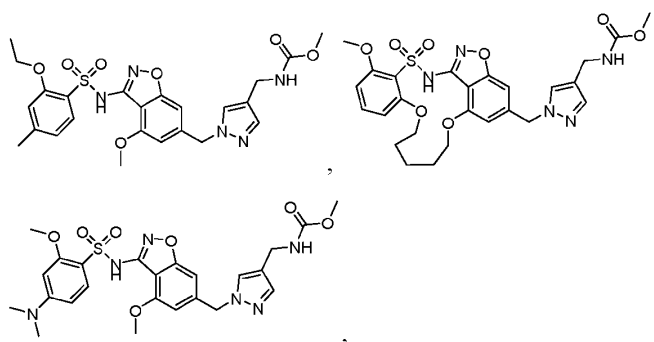


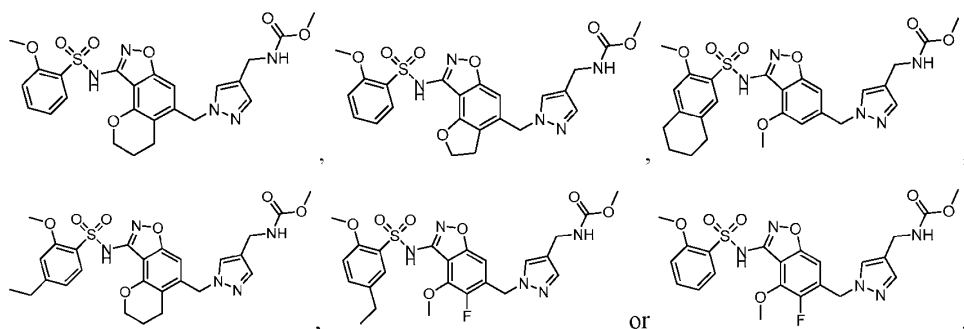




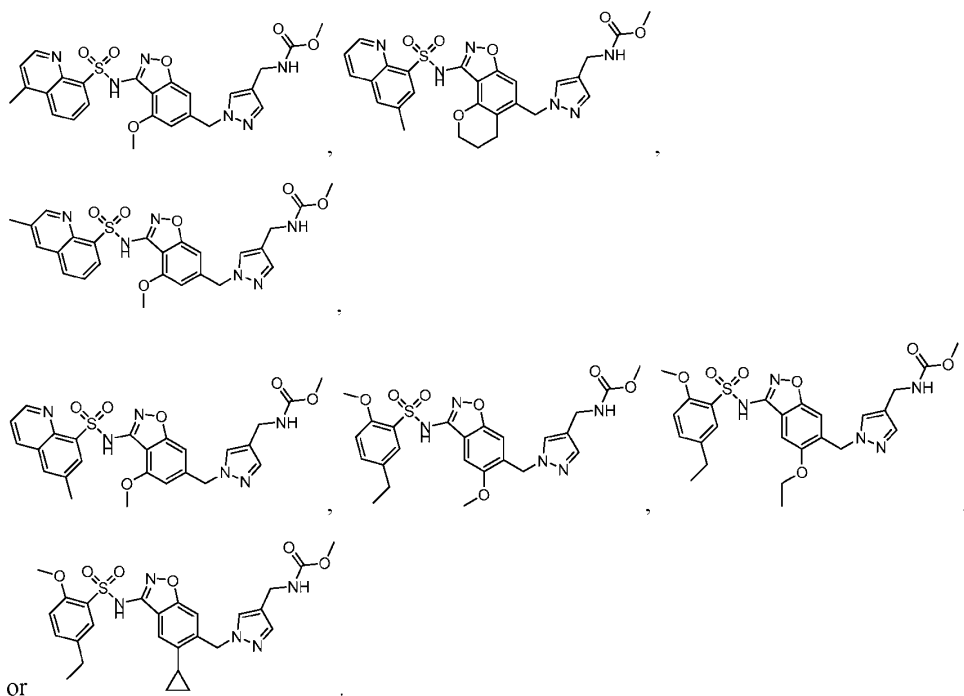


[1341] In another embodiment, the compound for use in the compositions and methods provided herein is:

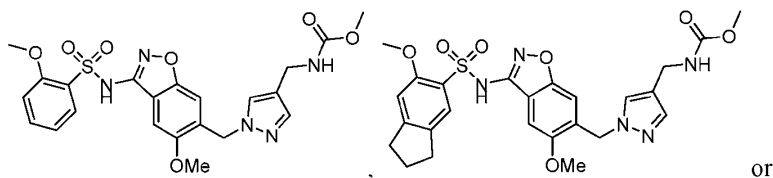


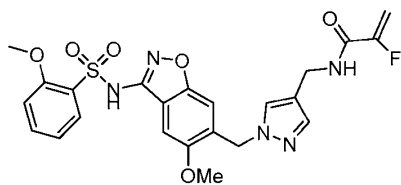


[1342] In another embodiment, the compound for use in the compositions and methods provided herein is:

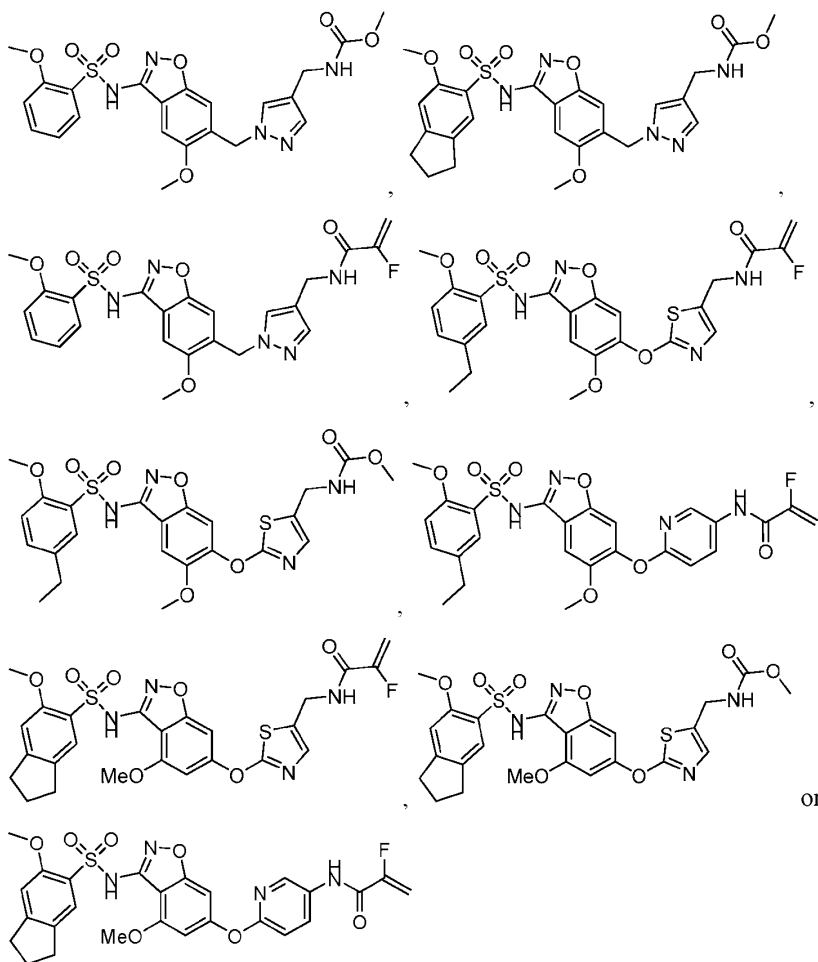


[1343] In another embodiment, the compound for use in the compositions and methods provided herein is:

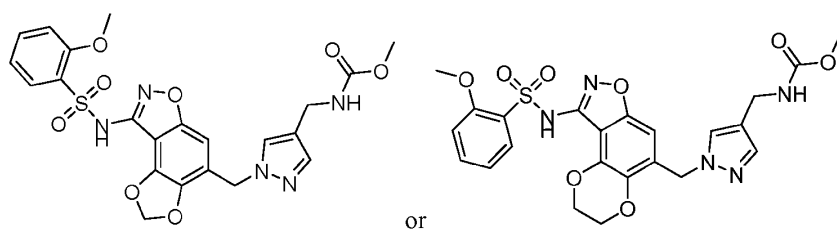




[1344] In another embodiment, the compound for use in the compositions and methods provided herein is:



[1345] In another embodiment, the compound for use in the compositions and methods provided herein is:



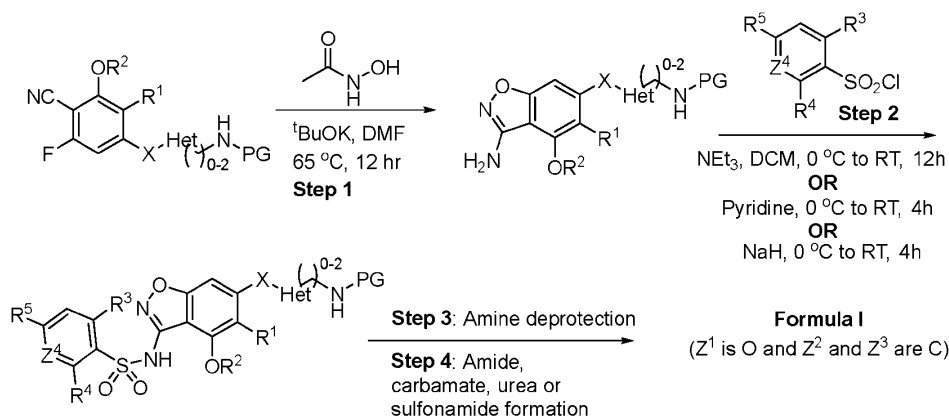
III. SYNTHESIS OF THE COMPOUNDS

[1346] The compounds provided herein can be prepared, isolated or obtained by any method apparent to those of skill in the art. Compounds provided herein can be prepared according to the Exemplary Preparation Schemes provided below. Reaction conditions, steps, and reactants not provided in the Exemplary Preparation Schemes would be apparent to, and known by, those skilled in the art.

[1347] Additional steps and reagents not provided in the Exemplary Preparation Schemes would be known to those of skill in the art. Exemplary methods of preparation are described in detail in the Examples herein.

[1348] **General Scheme 1** describes the preparation of a compound of Formula I where Z^1 is O and Z^2 and Z^3 are C; and all other groups are as defined in the Summary or in any embodiments described herein.

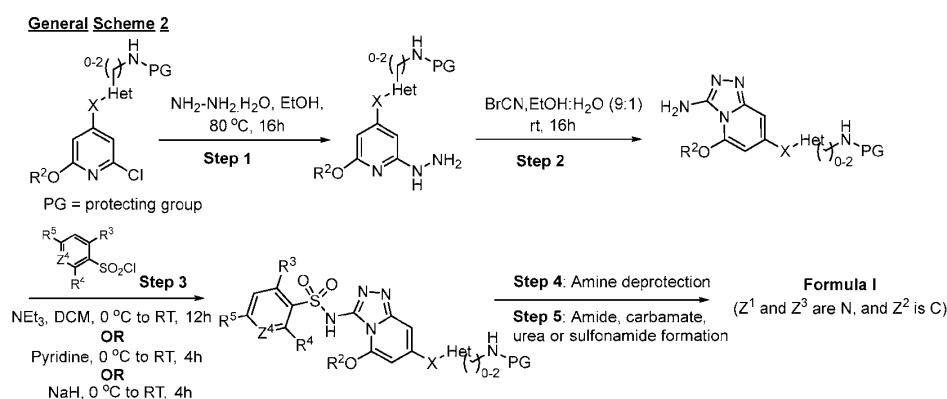
General Scheme 1



[1349] **General Scheme 1** outlines a way to prepare the appropriately substituted benzo[d]isoxazole compounds provided herein where in Step 1, an appropriately substituted 2-fluorobenzonitrile is converted to a benzo[d]isoxazol-3-amine scaffold by reacting with N-hydroxyacetamide in presence of a base such as potassium t-butoxide. In Step 2, the free amine is reacted with an aryl or heteroaryl sulfonyl chloride in presence of a base such as sodium tert-pentoxide, triethylamine, pyridine or sodium hydride. This can be accomplished

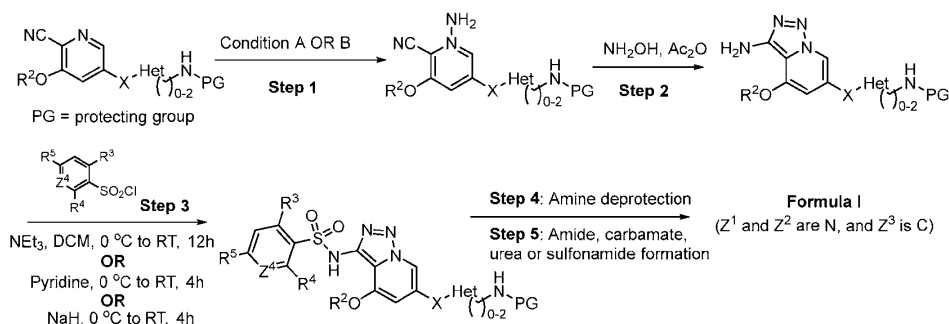
at 0 °C, but may need to be done at room temperature or at an elevated temperature such as 60 °C. The final steps involve deprotection of the amine (Step 3) followed by amide formation (either via a reaction with an appropriately substituted acid chloride or via activation of an acid using a coupling agent such as HATU, HBTU, T₃P, EDCI/HOBt or other agents known to those skilled in the art) or sulfonamide formation with a sulfonyl chloride in the presence of a base such as triethyl amine in Step 4. For preparing a carbamate or a urea derivative, an appropriately substituted carbonochloridate or isocyanate can be reacted with the free amine, in the presence of a base such as triethyl amine.

[1350] General Scheme 2 describes the preparation of a compound of Formula I where Z¹ and Z³ are N and Z² is C; and all other groups are as defined in the Summary or in any embodiments described herein.



[1351] As shown, the [1,2,4]triazolo[4,3-a]pyridine compounds provided herein can be prepared by starting with an appropriately substituted 2-chloropyridine which can be converted to the corresponding 2-hydrazinopyridine by heating in presence of hydrazine hydrate (Step 1). In Step 2, reaction with cyanogen bromide leads to the assembly of the [1,2,4]triazolo[4,3-a]pyridin-3-amine scaffold. Steps 3, 4 and 5 follow protocols detailed above for General Scheme 1 (steps 2, 3 and 4) leading to the synthesis of compounds of Formula I, where Z¹ and Z³ are N and Z² is C.

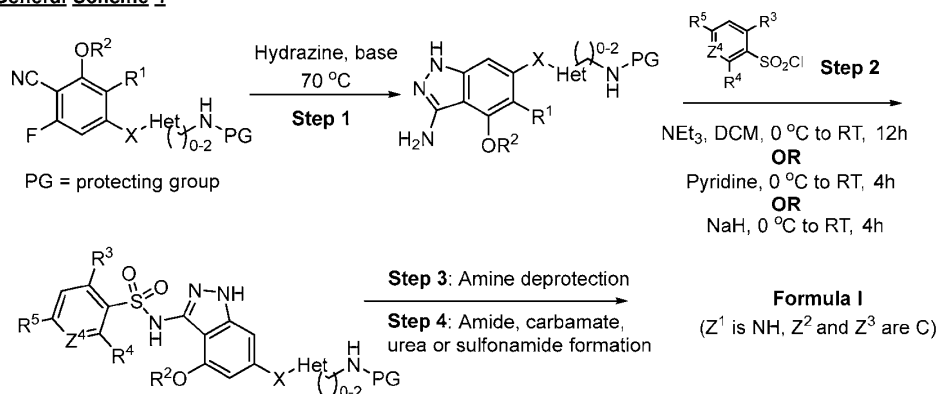
[1352] General Scheme 3 describes the preparation of a compound of Formula I where Z¹ and Z² are N and Z³ is C; and all other groups are as defined in the Summary or in any embodiments described herein.

General Scheme 3

Condition A: O-Mesitylenesulfonylhydroxylamine in 10-40% H₂O, DCM, 0 °C, 3h
Condition B: NH₂OSO₃H, K₂CO₃, HI, H₂O, 90 °C, 3h

[1353] An appropriately substituted 2-cyano pyridine is converted to a 1-amino 2-cyano pyridine by reacting with a sulfonylated hydroxyl amine or (aminooxy)sulfonic acid (Step 1, condition A or B), followed by cyclization in the presence of hydroxylamine and acetic anhydride (Step 2). Steps 3, 4 and 5 follow protocols detailed above for General Scheme 1 (steps 2, 3 and 4) leading to the synthesis of compounds of Formula I, where Z¹ and Z² are N and Z³ is C.

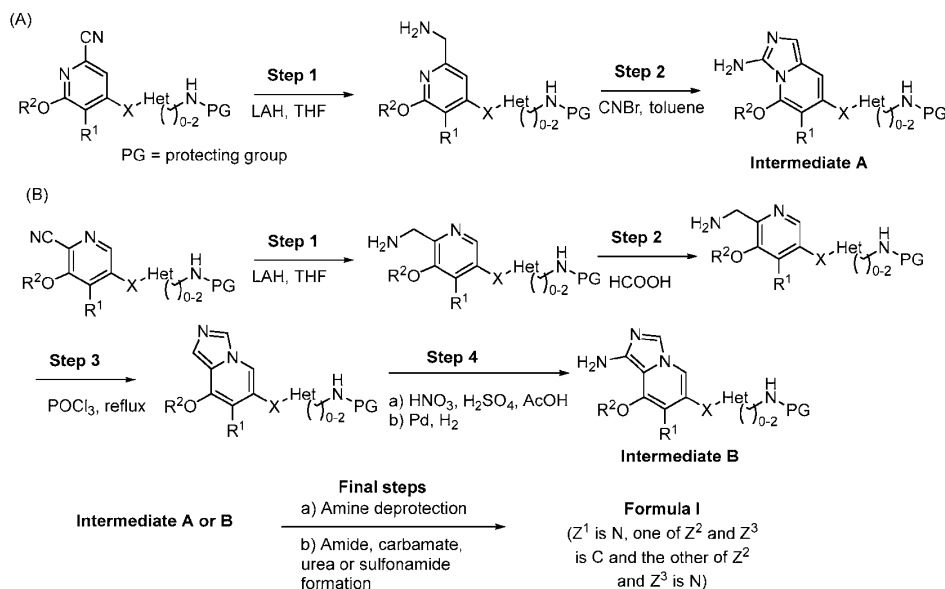
[1354] **General Scheme 4** describes the preparation of a compound of Formula I where Z¹ is NH and Z² and Z³ are C; and all other groups are as defined in the Summary or in any embodiments described herein.

General Scheme 4

[1355] An appropriately substituted 2-fluorobenzonitrile starting material is converted to the 3-aminobenzopyrazole (Step 1), using hydrazine in the presence of a base such as potassium carbonate, as shown above. Steps 2, 3 and 4 follow protocols detailed above for General Scheme 1 (steps 2, 3 and 4) leading to the synthesis of compounds of Formula I, where Z¹ is NH and Z² and Z³ are C.

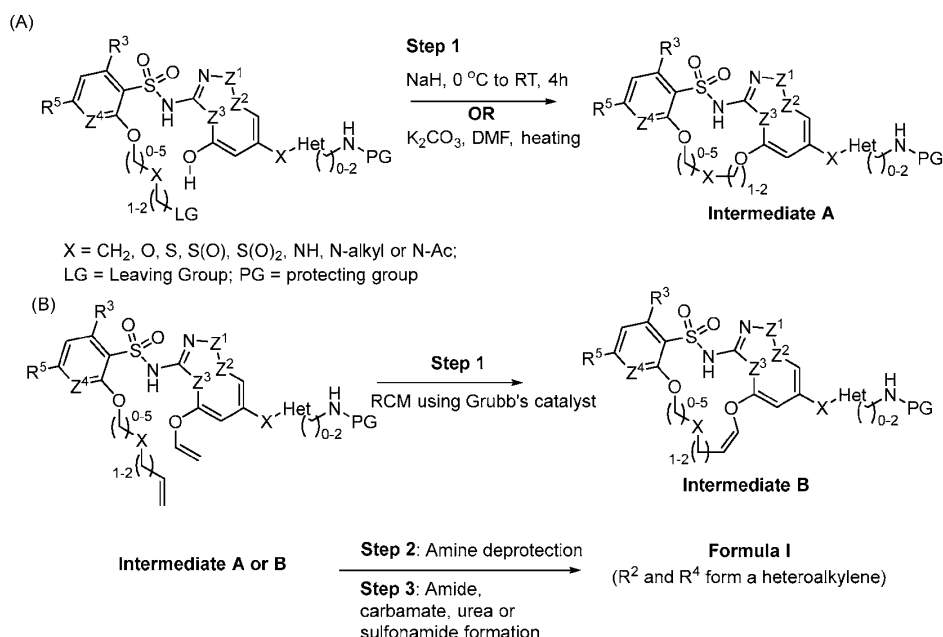
[1356] **General Scheme 5** describes the preparation of a compound of Formula I where Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N; and all other groups are as defined in the Summary or in any embodiments described herein.

General Scheme 5



[1357] General scheme 5(A) shows that an appropriately substituted picolinonitrile is reduced in Step 1 with LAH in a solvent such as THF. Treatment of the resulting 2-aminomethyl pyridine intermediate with cyanogen bromide in toluene (Step 2) affords the imidazo[1,5-a]pyridin-3-amine **Intermediate A**. In General scheme 5(B), an appropriately substituted 2-cyanopyridine is reduced to the corresponding 2-aminomethyl pyridine (Step 1 as in Scheme 5A above), then subjected to Steps 2 and 3 which involve N-formylation followed by refluxing in phosphorus oxychloride to construct the imidazo[1,5-a]pyridine ring. Nitration and reduction with the reagents in Step 4 leads to the substituted imidazo[1,5-a]pyridin-1-amine, **Intermediate B**. In the final steps, **Intermediate A** and **B** follow protocols detailed above for General Scheme 1 (steps 2, 3 and 4) leading to the synthesis of compounds of Formula I, where Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N.

[1358] **General Scheme 6** describes the preparation of a compound of Formula I where R^2 and R^4 together form heteroalkylene; and all other groups are as defined in the Summary or in any embodiments described herein.

General Scheme 6

[1359] The synthesis of the macrocyclic compounds is accomplished by assembling starting materials using general methods described above. In General Scheme 6(A), R⁴ is a phenoxy or heteroaryloxy group with a terminal leaving group which reacts with a hydroxy group at R² in the presence of a base such as NaH or K₂CO₃. Alternatively, in General Scheme 6(B), R⁴ is a phenoxy or heteroaryloxy group with a terminal alkene which reacts with a terminal alkene at R² in a ring closing metathesis (RCM) reaction in the presence of Grubb's catalyst. The resulting alkene is a feature of the final molecule or is reduced to a saturated heterocycle. Steps 2 and 3 follow protocols detailed above for General Scheme 1 (steps 2, 3 and 4) leading to the synthesis of compounds of Formula I, where R² and R⁴ form a heteroalkylene.

IV. PHARMACEUTICAL COMPOSITIONS

[1360] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of compounds provided herein and a pharmaceutically acceptable carrier, diluent or excipient.

[1361] The compounds can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for ophthalmic or parenteral administration, as well as transdermal patch preparation and dry

powder inhalers. Typically, the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, e.g., Ansel Introduction to Pharmaceutical Dosage Forms, Seventh Edition 1999).

[1362] In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable salts is (are) mixed with a suitable pharmaceutical carrier or vehicle. In certain embodiments, the concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms and/or progression of a disease or disorder disclosed herein.

[1363] Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[1364] In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as known in the art. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

[1365] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the subject treated. The therapeutically effective concentration may be determined empirically by testing the compounds in in vitro and in vivo systems described herein and then extrapolated therefrom for dosages for humans. In some embodiments, the active compound is administered in a method to achieve a therapeutically effective concentration of the drug. In some embodiments, a companion diagnostic (see, e.g., Olsen D and Jorgensen J T, Front. Oncol., 2014 May 16, 4:105, doi: 10.3389/fonc.2014.00105) is used to determine

the therapeutic concentration and safety profile of the active compound in specific subjects or subject populations.

[1366] The concentration of active compound in the pharmaceutical composition will depend on absorption, tissue distribution, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of a disease or disorder disclosed herein.

[1367] In certain embodiments, a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/mL to about 50-100 µg/mL. In one embodiment, the pharmaceutical compositions provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and in certain embodiments, from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

[1368] The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[1369] Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable salts thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating, retarding progression, or preventing. The concentration of active compound in the composition will depend on absorption, tissue distribution, inactivation, excretion rates of the active compound, the dosage schedule,

amount administered, particular formulation as well as other factors known to those of skill in the art.

[1370] The compositions are intended to be administered by a suitable route, including but not limited to oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, mucosal, dermal, transdermal, buccal, rectal, topical, local, nasal or inhalation. For oral administration, capsules and tablets can be formulated. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.

[1371] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol, dimethyl acetamide or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, pens, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[1372] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[1373] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[1374] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable salts thereof. The pharmaceutically therapeutically active compounds and salts thereof are formulated and administered in unit dosage forms or multiple dosage forms. Unit dose forms as used herein refer to physically discrete units suitable for human and animal subjects and

packaged individually as is known in the art. Each unit dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampules and syringes and individually packaged tablets or capsules. Unit dose forms may be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses which are not segregated in packaging.

[1375] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compound provided herein, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include iontophoresis patches, polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated compound remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in their structure. Rational strategies can be devised for stabilization depending on the mechanism of action involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[1376] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium croscarmellose, glucose, sucrose, magnesium carbonate or sodium

saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001%-100% active ingredient, in certain embodiments, about 0.1-85% active ingredient, or, in other embodiments, about 75-95% active ingredient.

[1377] The active compounds or pharmaceutically acceptable salts may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

[1378] The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable salts thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases related to oxidative stress. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

[1379] Lactose-free compositions provided herein can contain excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions contain an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose-free dosage forms contain an active ingredient, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate.

[1380] Further encompassed are anhydrous pharmaceutical compositions and dosage forms containing a compound provided herein. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment and use of formulations.

[1381] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[1382] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs and strip packs.

A. ORAL DOSAGE FORMS

[1383] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[1384] In certain embodiments, the formulations are solid dosage forms, such as capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[1385] Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water-soluble FD and C dyes, mixtures thereof, and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant

sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Emetic coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[1386] If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[1387] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[1388] The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H₂ blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable salt thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[1389] Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric coated tablets, because of the enteric coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar coated, multiple compressed and

chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[1390] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil in-water or water in oil. In some embodiments, the suspension is a suspension of microparticles or nanoparticles. In some embodiments, the emulsion is an emulsion of microparticles or nanoparticles.

[1391] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[1392] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water-soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[1393] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

[1394] Alternatively, liquid or semi solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxyethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[1395] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[1396] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

B. INJECTABLES, SOLUTIONS AND EMULSIONS

[1397] Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. In some

embodiments, the suspension is a suspension of microparticles or nanoparticles. In some embodiments, the emulsion is an emulsion of microparticles or nanoparticles. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow release or sustained release system, such that a constant level of dosage is maintained is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[1398] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[1399] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[1400] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[1401] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[1402] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the subject or animal as is known in the art.

[1403] The unit dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[1404] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[1405] Injectables are designed for local and systemic administration. Typically, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

[1406] The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

C. LYOPHILIZED POWDERS

[1407] Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[1408] The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable salt thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (including but not limited to 10-1000

mg or 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4° C. to room temperature.

[1409] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, about 5-35 mg, or about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

D. TOPICAL ADMINISTRATION

[1410] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsion or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[1411] The compounds or pharmaceutically acceptable salts thereof may be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will have diameters of less than 50 microns or less than 10 microns.

[1412] The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[1413] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts.

E. COMPOSITIONS FOR OTHER ROUTES OF ADMINISTRATION

[1414] Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

[1415] For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients.

Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono, di and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. An exemplary weight of a rectal suppository is about 2 to 3 grams.

[1416] Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

F. SUSTAINED RELEASE COMPOSITIONS

[1417] Active ingredients provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and U.S. Pat. Nos. 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, 5,639,480, 5,733,566, 5,739,108, 5,891,474, 5,922,356, 5,972,891, 5,980,945, 5,993,855, 6,045,830, 6,087,324, 6,113,943, 6,197,350, 6,248,363, 6,264,970, 6,267,981, 6,376,461, 6,419,961, 6,589,548, 6,613,358, 6,699,500 and 6,740,634, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein.

[1418] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. In one embodiment, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. In certain embodiments, advantages of controlled-

release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[1419] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[1420] In certain embodiments, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see, Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., thus requiring only a fraction of the systemic dose (see, e.g., Goodson, Medical Applications of Controlled Release, vol. 2, pp. 115-138 (1984).

[1421] In some embodiments, a controlled release device is introduced into a subject in proximity of the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990). The active ingredient can be dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene,

ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

G. TARGETED FORMULATIONS

[1422] The compounds provided herein, or pharmaceutically acceptable salts thereof, may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, e.g., U.S. Pat. Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874.

[1423] In one embodiment, the antibody-based delivery system is an antibody-drug conjugate ("ADC"), e.g., as described in Hamilton G S, *Biologicals*, 2015 September, 43(5):318-32; Kim E G and Kim K M, *Biomol. Ther. (Seoul)*, 2015 November, 23(6):493-509; and Peters C and Brown S, *Biosci. Rep.*, 2015 Jun. 12, 35(4) pii: e00225, each of which is incorporated herein by reference.

[1424] In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Pat. No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

H. ARTICLES OF MANUFACTURE

[1425] The compounds or pharmaceutically acceptable salts can be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable salt thereof provided herein, which is used for treatment, prevention or amelioration of one or

more symptoms or progression of a disease or disorder disclosed herein, and a label that indicates that the compound or pharmaceutically acceptable salt thereof is used for treatment, prevention or amelioration of one or more symptoms or progression of a disease or disorder disclosed herein.

[1426] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, pens, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated.

[1427] In certain embodiments, provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kit provided herein includes a container and a dosage form of a compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[1428] In certain embodiments, the kit includes a container comprising a dosage form of the compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a container comprising one or more other therapeutic agent(s) described herein.

[1429] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[1430] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection,

and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

V. DOSING

[1431] The compounds and pharmaceutical compositions provided herein may be dosed in certain therapeutically or prophylactically effective amounts, certain time intervals, certain dosage forms, and certain dosage administration methods as described below.

[1432] In certain embodiments, a therapeutically or prophylactically effective amount of the compound is from about 0.005 to about 1,000 mg per day, from about 0.01 to about 500 mg per day, from about 0.01 to about 250 mg per day, from about 0.01 to about 100 mg per day, from about 0.1 to about 100 mg per day, from about 0.5 to about 100 mg per day, from about 1 to about 100 mg per day, from about 0.01 to about 50 mg per day, from about 0.1 to about 50 mg per day, from about 0.5 to about 50 mg per day, from about 1 to about 50 mg per day, from about 0.02 to about 25 mg per day, from about 0.05 to about 10 mg per day, from about 0.05 to about 5 mg per day, from about 0.1 to about 5 mg per day, or from about 0.5 to about 5 mg per day.

[1433] In certain embodiments, the therapeutically or prophylactically effective amount is about 0.1, about 0.2, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 15, about 20, about 25, about 30, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, or about 150 mg per day.

[1434] In one embodiment, the recommended daily dose range of the compound provided herein, or a derivative thereof, for the conditions described herein lie within the range of from about 0.5 mg to about 50 mg per day, in one embodiment given as a single once-a-day dose, or in divided doses throughout a day. In some embodiments, the dosage ranges from about 1 mg to about 50 mg per day. In other embodiments, the dosage ranges from about 0.5 to about 5 mg per day. Specific doses per day include 0.1, 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg per day.

[1435] In a specific embodiment, the recommended starting dosage may be 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25 or 50 mg per day. In another embodiment, the recommended starting dosage may be 0.5, 1, 2, 3, 4, or 5 mg per day. The dose may be escalated to 15, 20, 25, 30, 35, 40, 45 and 50 mg/day. In a specific embodiment, the compound can be administered in an amount of about 25 mg/day. In a particular embodiment, the compound can be administered

in an amount of about 10 mg/day. In a particular embodiment, the compound can be administered in an amount of about 5 mg/day. In a particular embodiment, the compound can be administered in an amount of about 4 mg/day. In a particular embodiment, the compound can be administered in an amount of about 3 mg/day.

[1436] In certain embodiments, the therapeutically or prophylactically effective amount is from about 0.001 to about 100 mg/kg/day, from about 0.01 to about 50 mg/kg/day, from about 0.01 to about 25 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.01 to about 9 mg/kg/day, 0.01 to about 8 mg/kg/day, from about 0.01 to about 7 mg/kg/day, from about 0.01 to about 6 mg/kg/day, from about 0.01 to about 5 mg/kg/day, from about 0.01 to about 4 mg/kg/day, from about 0.01 to about 3 mg/kg/day, from about 0.01 to about 2 mg/kg/day, from about 0.01 to about 1 mg/kg/day, or from about 0.01 to about 0.05 mg/kg/day.

[1437] The administered dose can also be expressed in units other than mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both (see, www.fda.gov/cder/cancer/animalframe.htm). For example, a dose of 1 mg/kg/day for a 65 kg human is approximately equal to 38 mg/m²/day.

[1438] In certain embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 0.001 to about 500 µM, about 0.002 to about 200 µM, about 0.005 to about 100 µM, about 0.01 to about 50 µM, from about 1 to about 50 µM, about 0.02 to about 25 µM, from about 0.05 to about 20 µM, from about 0.1 to about 20 µM, from about 0.5 to about 20 µM, or from about 1 to about 20 µM.

[1439] In other embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 5 to about 100 nM, about 5 to about 50 nM, about 10 to about 100 nM, about 10 to about 50 nM or from about 50 to about 100 nM.

[1440] As used herein, the term "plasma concentration at steady state" is the concentration reached after a period of administration of a compound provided herein, or a derivative thereof. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the plasma concentration of the compound.

[1441] In certain embodiments, the amount of the compound administered is sufficient to provide a maximum plasma concentration (peak concentration) of the compound, ranging

from about 0.001 to about 50 μM , about 0.002 to about 200 μM , about 0.005 to about 100 μM , about 0.01 to about 50 μM , from about 1 to about 50 μM , about 0.02 to about 25 μM , from about 0.05 to about 20 μM , from about 0.1 to about 20 μM , from about 0.5 to about 20 μM , or from about 1 to about 20 μM .

[1442] In certain embodiments, the amount of the compound administered is sufficient to provide a minimum plasma concentration (trough concentration) of the compound, ranging from about 0.001 to about 500 μM , about 0.002 to about 200 μM , about 0.005 to about 100 μM , about 0.01 to about 50 μM , from about 1 to about 50 μM , about 0.01 to about 25 μM , from about 0.01 to about 20 μM , from about 0.02 to about 20 μM , from about 0.02 to about 20 μM , or from about 0.01 to about 20 μM .

[1443] In certain embodiments, the amount of the compound administered is sufficient to provide an area under the curve (AUC) of the compound, ranging from about 100 to about 100,000 $\text{ng}\cdot\text{hr}/\text{mL}$, from about 1,000 to about 50,000 $\text{ng}\cdot\text{hr}/\text{mL}$, from about 5,000 to about 25,000 $\text{ng}\cdot\text{hr}/\text{mL}$, or from about 5,000 to about 10,000 $\text{ng}\cdot\text{hr}/\text{mL}$.

[1444] The methods provided herein encompass treating a patient regardless of subject's age, although some diseases or disorders are more common in certain age groups.

[1445] Depending on the disease to be treated and the subject's condition, the compound provided herein, or a derivative thereof, may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, CIV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration. The compound provided herein, or a derivative thereof, may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration.

[1446] In one embodiment, the compound provided herein, or a derivative thereof, is administered orally. In another embodiment, the compound provided herein, or a derivative thereof, is administered parenterally. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered intravenously.

[1447] The compound provided herein, or a derivative thereof, can be delivered as a single dose such as, e.g., a single bolus injection, or oral tablets or pills; or over time, such as, e.g., continuous infusion over time or divided bolus doses over time. The compound can be administered repeatedly if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter

of measurable lesions has not increased by 25% or more from the last measurement.

Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, Journal of the National Cancer Institute 92(3): 205-216 (2000). Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

[1448] The compound provided herein, or a derivative thereof, can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (i.e., daily for consecutive days or every day), intermittent, e.g., in cycles (i.e., including days, weeks, or months of rest without drug). As used herein, the term "daily" is intended to mean that a therapeutic compound, such as the compound provided herein, or a derivative thereof, is administered once or more than once each day, for example, for a period of time. The term "continuous" is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of the compound provided herein or a derivative thereof is administration for one to six days per week, administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days. The term "cycling" as used herein is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily or continuously but with a rest period. In some such embodiments, administration is once a day for two to six days, then a rest period with no administration for five to seven days.

[1449] In some embodiments, the frequency of administration is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks. In one embodiment, the compound provided herein, or a derivative thereof, is administered once a day. In another embodiment, the compound provided herein, or a derivative thereof, is administered twice a day. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered three times a day. In still another embodiment, the compound provided herein, or a derivative thereof, is administered four times a day.

[1450] In certain embodiments, the compound provided herein, or a derivative thereof, is administered once per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, the compound provided herein, or a derivative thereof, is administered once per day for one week, two weeks, three weeks, or four weeks. In one embodiment, the compound provided herein, or a derivative thereof, is administered once per day for 4 days. In one embodiment, the compound provided herein, or a derivative thereof, is administered once per day for 5 days. In one embodiment, the compound provided herein, or a derivative thereof, is administered once per day for 6 days. In one embodiment, the compound provided herein, or a derivative thereof, is administered once per day for one week. In another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for two weeks. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for three weeks. In still another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for four weeks.

VI. METHODS OF TREATMENT

[1451] Inhibitors of post-translational lysine acetylation mediated by KATs of the MYST family are promising anti-neoplastic agents and therefore are useful therapeutic agents, e.g., for use in the treatment of cancer. Such agents are also useful as therapeutic agents for the treatment of cancers which exhibit overexpression of MYST proteins.

[1452] In another embodiment, provided is a method of treating a subject with cancer by administering a compound or composition provided herein. In another embodiment, provided herein is a method of treating a condition, disease, or disorder by inhibiting MYST family of lysine acetyl transferases, including KAT6A and KAT6B, comprising administering a therapeutically effective amount of a compound or composition provided herein.

[1453] In another embodiment, provided is a method of treating a condition, disease, or disorder, where the condition, disease, or disorder is a hyperproliferative disease, such as cancer. In some embodiments, the cancer is selected from: lymphoma, melanoma, carcinoma (e.g. adenocarcinoma, hepatocellular carcinoma, medullary carcinoma, papillary carcinoma, squamous cell carcinoma), astrocytoma, glioma, medulloblastoma, myeloma, meningioma, neuroblastoma, and sarcoma (e.g. angiosarcoma, chondrosarcoma, osteosarcoma). In some embodiments, the cancer is a MYST overexpressing cancer. In another embodiment, the cancer over-expresses MYST protein relative to non-cancerous tissue. In some embodiments, the cancer overproduces MYST mRNA relative to non-cancerous tissue. In another

embodiment, the cancer is a MYST overexpressing cancer where the overexpressed MYST protein or MYST mRNA is any one of KATs of the MYST family, e.g., KAT6A. In some embodiments, the cancer is leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), non-Hodgkin's lymphoma, Hodgkin's disease, prostate cancer, lung cancer, melanoma, breast cancer, breast ductal carcinoma, colon and rectal cancer, colon cancer, squamous cell carcinoma, gastric cancer, adrenocortical cancer, anal cancer, bladder cancer, blood cancer, bone cancer, brain tumor, cancer of the female genital system, cancer of the male genital system (including testicular cancer and penile cancer), central nervous system lymphoma, cervical cancer, childhood rhabdomyosarcoma, childhood sarcoma, endometrial cancer, endometrial sarcoma, esophageal cancer, eye cancer, gallbladder cancer, gastrointestinal tract cancer, hairy cell leukemia, head and neck cancer, hepatocellular cancer, hypopharyngeal cancer, Kaposi's sarcoma, kidney cancer, laryngeal cancer, liver cancer, malignant fibrous histiocytoma, malignant thymoma, mesothelioma, multiple myeloma, myeloma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, nervous system cancer, neuroblastoma, oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, parathyroid cancer, pharyngeal cancer, pituitary tumor, plasma cell neoplasm, primary CNS lymphoma, rectal cancer, respiratory system, retinoblastoma, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thyroid cancer, urinary system cancer, uterine cancer, uterine sarcoma, vaginal cancer, endocrine, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, glioblastoma, brain stem glioma, pituitary adenoma, vascular system, Waldenstrom's macroglobulinemia or Wilms' tumor. In some embodiments, the cancer is breast cancer, including ER positive breast cancer, non-small cell lung cancer, prostate cancer, pancreatic cancer, ovarian cancer, or blood cancer (including a leukemia or lymphoma). In one embodiment, the cancer is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, uterine/cervical cancer or leukemia.

[1454] In another embodiment, provided is a method of inhibiting the activity of a MYST KAT by contacting the MYST KAT or a composition comprising the MYST KAT with a compound or composition provided herein. In one embodiment, the MYST KAT is a KAT6 lysine acetyl transferase. In another embodiment, the MYST KAT is KAT6A.

[1455] Without wishing to be bound by any theory, one aspect of the catalytic mechanism of the KAT family of enzymes is the acetylation of lysine residues using the cofactor Ac-CoA as an acetyl donor. One possible catalytic mechanism is the stepwise transfer of the

acetyl group from acetyl co-enzyme A (Ac-CoA) to transiently form an acetyl-enzyme intermediate. This acetyl-enzyme intermediate subsequently is the source of the acetyl group that is transferred to the substrate, typically a lysine on a histone (Wapenaar et al., 2016, *supra*). In the MYST family of KATs there is a conserved cysteine that is acylated transiently as part of the catalytic cycle, as indicated by the bold C in the sequences below.

Amino Acid Sequence Alignment near the Ac-CoA binding site
of the MYST Family of KATs

KAT5	ESTEDYNV AC ILTLPPYQRR (SEQ ID NO: 1)
KAT8	ESPDGNNV AC ILTLPPYQRR (SEQ ID NO: 2)
KAT7	NSFLNYNV SC ILTMPQYMRQ (SEQ ID NO: 3)
KAT6A	HCQKYNV SC IMILPQYQRK (SEQ ID NO: 4)
KAT6B	LCQKYNV SC IMIMPQHQRQ (SEQ ID NO: 5)

[1456] Thus, in one embodiment, provided is a method of inhibiting a MYST KAT by covalent modification of this conserved cysteine residue with a compound or composition provided herein. In another embodiment, provided is a method of covalent modification of this conserved MYST KAT cysteine residue by contacting the MYST KAT or a composition containing the MYST KAT with a compound or composition provided herein.

[1457] In another embodiment, it is known in the art that histone acetyltransferases or HATs, including KAT6, have a key role in facilitating myc-driven transcriptional regulation. Myc is a transcriptional regulator that is known to recruit HATs to target chromatin facilitating chromatin remodeling, resulting in transcription, proliferation, and tumor growth. Myc is a transcriptional regulator with many protein interactors in a series of complexes, which mediate this transcriptional activity. One such interacting protein known as transformation/transcription domain associated protein or TRRAP, is a member of several HAT containing protein complexes where it serves as bridging protein between transcription factors like myc and HATs. Myc has been documented to recruit histone acetylation through a TRRAP complex facilitating acetylation of nucleosomes at histone H4 through HATs that include but may not be limited to KAT2A and KAT5 and Tip60/p400. This myc-associated HAT activity enables the opening of chromatin structurally facilitating transcription (see, e.g., Laurenco, et al. Nature Reviews Cancer 2021, 21, 579-591). Myc recruits HATs to target chromatin and locally promote acetylation of multiple specific lysines on both H3 and H4 some of which are known targets of KAT6A acetylation, resulting in transcriptional activation (see, e.g., Martinato et al. PLoS ONE 2008, 3(11), e3650, doi:10.1371/journal.pone.0003650). KAT6A, as a recruitable HAT, plays a role in specific

cancers and cell types and may be a key mediator of HAT activity recruited to myc-driven transcriptional activation sites in some tumors.

[1458] Furthermore, hallmark targets of myc-induced transcriptional regulation (myc pathway targets) are reduced through the use of KAT6A inhibitors. This includes the myc pathway in KAT6A-amplified breast cancer cell lines following administration of a KAT6 inhibitor (See, e.g., Sharma et al. Cell Chemical Biology 2023, doi.org/10.1016/j.chembiol.2023.07.005).

[1459] Indeed, there is direct evidence that KAT6 may be a HAT that has a key role in myc-driven transcriptional regulation and that loss of KAT6 activity could disrupt myc-driven transcriptional programming. Myc-driven growth of a lymphoma cell line in vivo is inhibited by systemic administration of KAT6 inhibitors. Specifically, two small molecule inhibitors of KAT6A and KAT6B lead to anti-tumor activity in MYC-driven models of lymphoma (see, e.g., Baell, et al. Nature 2018, 560, 253–257; Priebbenow et al. J. Med. Chem. 2020, 63, 4655–4684)

[1460] Finally, MYC is amplified in approximately 30% of solid tumors, including lung, ovarian, esophagus, breast, stomach, pancreas and liver cancer. There are a number of overlapping solid tumor types with characterized myc activity which also contain KAT6 genomic amplifications. Therefore, inhibition of KAT6A activity is expected to reduce transcriptional activity and tumorigenicity in solid tumors in which myc is a key transcriptional regulator.

[1461] Thus, in another embodiment, provided is a method of treating a myc-driven cancer in a subject by administering a compound or composition provided herein to the subject. In another embodiment, the myc-driven cancer is lung, ovarian, esophageal, breast, stomach, pancreatic or liver cancer. In another embodiment, the myc-driven cancer is a cancer in which myc is amplified. In another embodiment, provided is a method of treating a cancer in which myc is amplified in a subject by administering a compound or composition provided herein to the subject.

[1462] KAT6A is an acetyltransferase of p53 at K120 and K382 and colocalizes with p53 in promyelocytic leukemia (PML) nuclear bodies following cellular stress (Rokudai, et al. PNAS 2013, 110(10), 3895-3900). This ternary complex enhances p53-dependent p21 expression. KAT6A acetylation of p53, affecting complex formation or stability and altering its downstream activity, is thus involved in pathogenesis of tumors and leukemia. Therefore, KAT6A inhibitors can be used in the treatment of hematological cancers. Thus, in another

embodiment, provided is a method of treating a hematological cancer in a subject by administering a compound or composition provided herein to the subject.

[1463] KAT6A acetylation of SMAD3 regulates myeloid-derived suppressor cell recruitment, metastasis, and immunotherapy in triple-negative breast cancer (TNBC) (Yu, et al. Adv. Sci. 2021, 8, 2100014). Therefore, KAT6A inhibitors can be used in the treatment of TNBC. In another embodiment, provided is a method of treating TNBC in a subject by administering a compound or composition provided herein to the subject.

VII. COMBINATION THERAPY WITH OTHER ACTIVE AGENT(S)

[1464] The compound provided herein, or a derivative thereof, can also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of hyperproliferative diseases including cancer.

[1465] In one embodiment, provided herein is a method of treating, preventing, or managing hyperproliferative diseases including cancer, comprising administering to a subject a compound provided herein, or a derivative thereof, in combination with one or more second active agents.

[1466] As used herein, the term "in combination" includes the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (e.g., a prophylactic or therapeutic agent such as a compound provided herein, or a derivative thereof) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

[1467] Administration of the compound provided herein, or a derivative thereof and one or more other active agents to a subject can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease or disorder being treated.

[1468] The route of administration of the compound provided herein, or a derivative thereof, is independent of the route of administration of a second therapy. In one embodiment, the compound provided herein, or a derivative thereof, is administered orally. In another embodiment, the compound provided herein, or a derivative thereof, is administered intravenously. Thus, in accordance with these embodiments, the compound provided herein, or a derivative thereof, is administered orally or intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, the compound provided herein, or a derivative thereof, and a second therapy are administered by the same mode of administration, orally or by IV. In another embodiment, the compound provided herein, or a derivative thereof, is administered by one mode of administration, e.g., by IV, whereas the second agent is administered by another mode of administration, e.g., orally.

[1469] In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount of the compound provided herein, or a derivative thereof, and any optional additional active agents concurrently administered to the subject.

[1470] One or more other active ingredients or agents can be used together with the compound provided herein, or a derivative thereof, in the methods and compositions provided herein. Other active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules).

[1471] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies, immune-based therapeutic agents in classification known as immunoncology which improve immune-mediated recognition of tumors, particularly, therapeutic antibodies to cancer antigens. Typical large molecule active agents are biological molecules, such as naturally occurring or synthetic or recombinant proteins.

[1472] In one embodiment, the compound provided herein, or a derivative thereof, are administered in an amount ranging from about 0.1 to about 150 mg, from about 1 to about 25

mg, or from about 2 to about 10 mg orally and daily alone, or in combination with a second active agent, prior to, during, or after the use of conventional therapy.

[1473] In another embodiment, the choice of other active agent depends on the disease to be treated. Examples of second active agents for a particular cancer are well known to those of skill in the art. For example, if the disease is breast cancer, then the second active agent may be an aromatase inhibitor, a CDK4/6 inhibitor or an ER antagonist. Other examples of agents that can be used in combination with a KAT6 inhibitor for treatment of breast cancer are selective inhibitors of Cyclin Dependent Kinases such as CDK2 or CDK4 inhibitors and Selective Estrogen Receptor Degraders (SERDs). PIK3CA is a frequently mutated oncogene in breast cancer. The H1047R mutation of PIK3CA is highly prevalent in breast cancers and other solid tumors. KAT6 inhibitors can be combined with mutant-selective PI3K α inhibitors for the treatment of breast and other cancers.

[1474] Another example of a solid tumor type which harbors KAT6A genomic and mRNA amplifications is ovarian cancer. Ovarian cancers are treated with platinum-based chemotherapeutics such as cisplatin, which have a high level of toxicity that often limits dosing and achieving maximal efficacious exposures. In some cases, PARP inhibitors or CDK2 inhibitors are used to treat ovarian cancers. KAT6 inhibitors can be used in combination with these agents, but not limited to these agents, to treat ovarian cancers.

[1475] KAT6 epigenetic activity has been shown to be involved in the development of resistance to menin pathway inhibitors and has been demonstrated to play a role in chromatin remodeling by the menin-MLL/KMT2 complex in solid tumors as well as AML. KAT6 inhibitors can be applied in the treatment of hematological cancers such as AML and in tumors where the menin-MLL/KMT2 complex drives tumors growth, alone and in combination with menin and menin pathway inhibitors.

VIII. EXAMPLES

[1476] The examples below are meant to illustrate certain embodiments provided herein, and not to limit the scope of this disclosure.

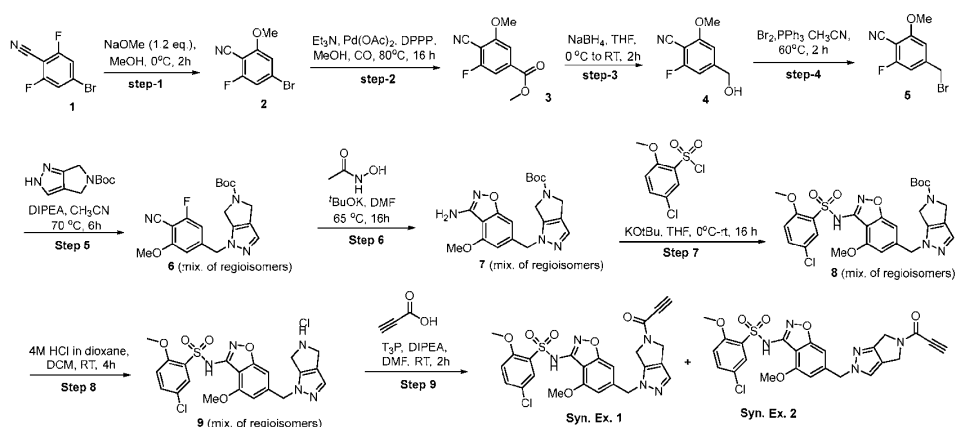
[1477] As used herein, the symbols and conventions used in these processes, schemes, and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μ L (microliters); mM (millimolar); μ M (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); h, hr or

hrs (hours); min (minutes); MS (mass spectrometry); ESI (electrospray ionization); rt (room temperature); Rf (retention factor); TLC (thin-layer chromatography); LCMS (liquid chromatography-mass spectrometry); HPLC (high performance liquid chromatography); AcOH (acetic acid); n-BuLi (n-Butyl lithium); tBuOK (potassium tert butoxide); CDCl₃ (Chloroform-d); CH₃CN (acetonitrile); Cs₂CO₃ (cesium carbonate); DMF (N,N-Dimethylformamide); DCM (dichloromethane); DEA (diethylamine); DIPEA (diisopropyl ethylamine); DMSO (dimethylsulfoxide); DMSO-d₆ (dimethyl sulfoxide-d₆); EtOAc or EA (ethyl acetate); Et₃N (triethylamine); EtOH (ethanol); HCl (hydrochloric acid); H₂SO₄ (sulphuric acid); K₂CO₃ (potassium carbonate); LiOH (lithium hydroxide); MsCl (methane sulphonyl chloride); MeI (methyl iodide); MeOH (Methanol); MeOH-d₄ (Methanol-d₄); NaBH₄ (sodium borohydride); NaH (sodium hydride); NaHCO₃ (sodium bicarbonate); NaNO₂ (sodium nitrite); NaOH (sodium hydroxide); NaOMe (sodium methoxide); Na₂SO₄ (sodium sulphate); K₃FeCN₆ (potassium ferricyanide); Pd(PPh₃)₄ (tetrakis(triphenylphosphine)palladium(0)); SO₂ (sulphur dioxide); SO₂Cl₂ (sulfuryl chloride); T₃P (propanephosphonic acid anhydride); THF (tetrahydrofuran); TMEDA (1,2 bis(dimethylamino)ethane); Zn (zinc); ZnCN₂ (zinc cyanide).

[1478] For all the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in °C (degrees Celsius). All reactions are conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

EXAMPLES 1-2

[1479] **Scheme 1: Synthesis of 5-chloro-2-methoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 1) and 5-chloro-2-methoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 2)**



[1480] Synthesis of 4-bromo-2-fluoro-6-methoxybenzonitrile (2)

[1481] To a stirred solution of compound **1** (50 g, 229.35 mmol) in MeOH (500 mL) was added NaOMe (14.86 g, 275.22 mmol) and the reaction mixture was allowed to stir at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the title compound **2** (55 g) as a yellow solid. LCMS Calculated for C₈H₅BrFNO: 228.95; Found: 229.5 (M+1).

[1482] Synthesis of methyl 4-cyano-3-fluoro-5-methoxybenzoate (3)

[1483] To a solution of compound **2** (13 g, 56.511 mmol) in methanol (140 mL) in steel bomb was added triethylamine (1.58 mL, 11.303 mmol) and purged with nitrogen for 5 min. Palladium(II) acetate (634 mg, 2.823 mmol) and DPPP (1,3-Bis(diphenylphosphino)propane) (2.33 g, 5.59 mmol) were added and reaction mixture was heated at 80°C in presence of CO gas (110 psi) for 16 h. After completion (monitored by TLC), the mixture was cooled to room temperature and filtered through a celite bed. The filtrate was concentrated *in vacuo* and purified by combi flash chromatography using 14% EtOAc /Hexane to afford methyl 4-cyano-3-fluoro-5-methoxybenzoate **3** (10 g, 47.81%) as a white solid. TLC: 20% EtOAc/Heptane (R_f: 0.5). LCMS Calculated form C₁₀H₈FNO₃: 209.05; Found: 210.0 (M+1).

[1484] Synthesis of 2-fluoro-4-(hydroxymethyl)-6-methoxybenzonitrile (4)

[1485] To a stirred solution of LiBH₄ (2.08 g, 95.611 mmol) in THF (100 mL) at 0 °C was added compound **3** (10 g, 47.80 mmol) in THF (600 mL) dropwise. The reaction mixture was stirred at 80 °C for 4h. After completion (monitored by TLC), the mixture was cooled to RT and quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to

afford the title compound **4** (6 g, 69.27%) as a white solid. TLC: 50% EtOAc/Heptane (R_f : 0.25). LCMS Calculated for $C_9H_8FNO_2$: 181.05; Found: 182.0 ($M+1$).

[1486] Synthesis of 4-(bromomethyl)-2-fluoro-6-methoxybenzonitrile (5)

[1487] To a stirred solution of compound **4** (7 g, 38.637 mmol) in ACN (70 mL) was added and PPh_3 (16.82 g, 64.138 mmol) followed by Br_2 (3.08 mL, 64.137 mmol) at 0°C. The reaction mixture was stirred at 60°C for 2h. After completion (monitored by TLC), the mixture was quenched with sodium thiosulphate (110 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude was purified by combi-flash chromatography (15% EtOAc in Heptane) to afford the title compound **5** (4 g, 16.389 mmol, 42.46%) as a white solid. TLC: 30% EtOAc/Heptane (R_f : 0.6). LCMS Calculated for C_9H_7BrFNO : 242.97; Found: 244.2 ($M+2$).

[1488] Synthesis of *tert*-butyl 2-(4-cyano-3-fluoro-5-methoxybenzyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate and *tert*-butyl 2-(4-cyano-3-fluoro-5-methoxybenzyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (6)

[1489] To a stirred solution of compound **5** (1.0 g, 4.097 mmol) in acetonitrile (5 mL) was added DIPEA (2.146 mL, 12.292 mmol) followed by *tert*-butyl 2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (1.02 g, 4.916 mmol). The reaction mixture was heated at 70 °C for 6 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel (100-200 mesh) column chromatography using a gradient method of 0-50% EtOAc/Heptane to afford the title compound **6** (1.0 g, 48.65%, isolated as inseparable mixture regioisomers) as a yellow solid. TLC: 80% EtOAc/Heptane (R_f : 0.45). LCMS Calculated for $C_{19}H_{21}FN_4O_3$: 372.16; Found: 373.40 ($M+1$).

[1490] Synthesis of *tert*-butyl 1-((3-amino-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate and *tert*-butyl 2-((3-amino-4-methoxybenzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (7)

[1491] To a stirred solution of compound **6** (mixture of regioisomers) (0.50 g, 1.34 mmol) in DMF (7 mL) was added acetohydroxamic acid (0.31 g, 4.02 mmol) followed by K_2CO_3 (0.56 g, 4.02 mmol). The reaction mixture was allowed to stir at 65 °C for 16 h. After completion (monitored by TLC), the mixture was cooled to room temperature and quenched with ice water. The aqueous layer was extracted with ethyl acetate. The organic layer was

washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel (100-200 mesh) column chromatography using a gradient method of 0-50% EtOAc/Heptane to afford the title compound **7** (mixture of isomers) (0.20 g, 38.64%, isolated as inseparable mixture of regioisomers) as an off-white solid. TLC: 70% EtOAc/Heptane (R_f: 0.40). LCMS Calculated for C₁₉H₂₃N₅O₄: 385.42; Found: 386.00 (M+1). ¹H NMR is complicated and indicates a regioisomeric mixture.

[1492] Synthesis of tert-butyl 1-((3-((5-chloro-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-4,6-dihydropyrrolo[3,4-c] pyrazole-5(1H)-carboxylate and tert-butyl 2-((3-((5-chloro-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (8)

[1493] To a stirred solution of compound **7** (0.75 g, 1.945 mmol) in THF (20 mL) was added 1M solution of KOtBu in THF (5.8 mL, 5.838 mmol) at 0 °C. The reaction mixture was stirred for 10 min. at 0 °C followed by the addition of 5-chloro-2-methoxybenzenesulfonyl chloride (0.70 g, 2.919 mmol). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi flash column chromatography by using 50-60% EA in Heptane to afford title compound **8** (mixture of regioisomers) (0.50 g, 43.55%) as an off-white solid. TLC: 50% EtOAc/Heptane (R_f: 0.5). LCMS calculated for C₂₆H₂₈ClN₅O₇S: 589.14; found: 590.20 (M+1).

[1494] Synthesis of 5-chloro-N-(6-((5,6-dihydropyrrolo[3,4-c] pyrazol-1(4H)-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride and 5-chloro-N-(6-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride (9)

[1495] To a stirred solution of compound **8** (0.50 g, 0.8475 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **9** (mixture of regioisomers) (0.42 g, 94.17%) as an off-white solid. TLC: 10% MeOH/DCM (R_f: 0.3). LCMS calculated for C₂₁H₂₀ClN₅O₅S: 489.09; found: 490.10 (M+1).

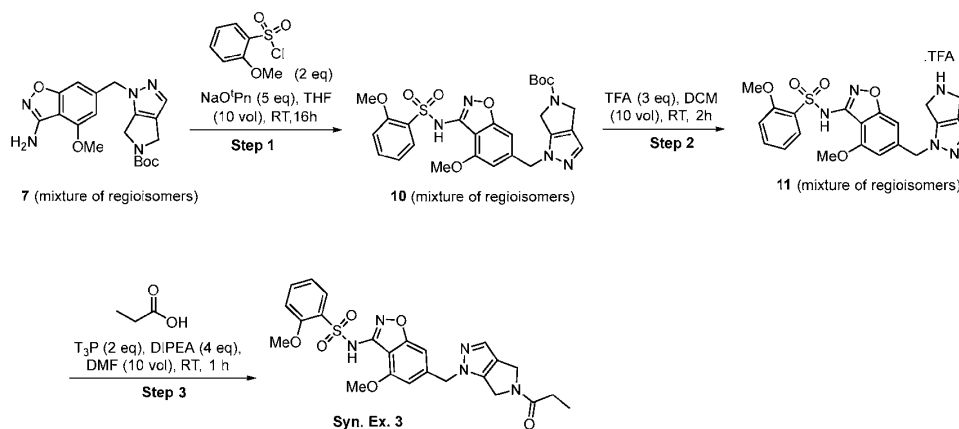
[1496] Synthesis of 5-chloro-2-methoxy-N-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-

yl)benzenesulfonamide (Syn. Ex. 1) and 5-chloro-2-methoxy-*N*-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4*H*)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 2)

[1497] To a stirred solution of compound **9** (0.20 g, 0.379 mmol) in DMF (5 mL) was added propionic acid (0.032 g, 0.455 mmol), DIPEA (0.198 mL, 1.137 mmol) and 50% solution of T₃P in EtOAc (0.36 g, 1.139 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi flash column chromatography by using 5% MeOH in DCM to afford a mixture of regioisomers which was further purified by chiral HPLC to get 5-chloro-2-methoxy-*N*-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4*H*)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 1; 35 mg, 16.15%) as an off white solid and 5-chloro-2-methoxy-*N*-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4*H*)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 2; 15 mg, 7.28%) as an off white solid. TLC: 10% MeOH/DCM (R_f: 0.3), (See Table 1 for analytical data).

EXAMPLE 3

[1498] Scheme 2: Synthesis of 2-methoxy-*N*-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4*H*)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 3)



[1499] Synthesis of tert-butyl 1-((4-methoxy-3-((2-methoxyphenyl) sulfonamido) benzo[d]isoxazol-6-yl) methyl)-4,6-dihydropyrrolo[3,4-c] pyrazole-5(1*H*)-carboxylate

and tert-butyl 2-((4-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (10)

[1500] To a stirred solution of compound **7** (0.3 g, 0.77 mmol) in THF (5 mL) was added 2-methoxybenzenesulfonyl chloride (0.320 g, 1.55 mmol) and NaOPn (0.428 g, 3.89 mmol). The reaction mixture was allowed to stir at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude compound was purified by combi flash using gradient of 70-80% ethyl acetate to afford the title compound **10** (mixture of regioisomers) (310 mg, 71.75 %) as brown solid. TLC: 5% MeOH/DCM (*R_f*: 0.6). LCMS Calculated for C₂₆H₂₉N₅O₇S: 555.18; Found: 556.20 (M+1).

[1501] Synthesis of 2-methoxy-N-(4-methoxy-6-((5-(2,2,2-trifluoroacetyl)-5,6-dihydro-5H-pyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide and 2-methoxy-N-(4-methoxy-6-((5-(2,2,2-trifluoroacetyl)-5,6-dihydro-5H-pyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (11)

[1502] To a stirred solution of compound **10** (mixture of regioisomers) (0.4 g, 0.68 mmol) in DCM (4 mL) was added TFA (0.52 mL, 6.83 mmol) at 0 °C. The reaction was allowed to stir at the room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure, triturated with ether, and dried on vacuum to afford the title compound **11** (mixture of regioisomers) (410 mg, crude) as a brown solid. TLC: 10% MeOH/DCM (*R_f*: 0.5). LCMS Calculated for C₂₁H₂₁N₅O₅S: 455.13; Found: 454.3 (M-1).

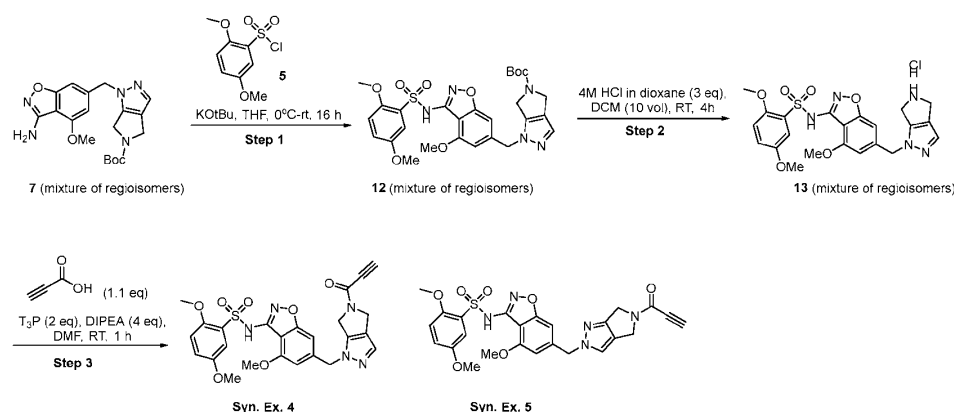
[1503] Synthesis of 2-methoxy-N-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 3)

[1504] To a stirred solution of compound **11** (260 mg, 0.570 mmol) in DMF (3 mL) was added propionic acid (63 mg, 0.856 mmol), DIPEA (0.398 mL, 2.28 mmol) and 50% solution of T₃P in EtOAc (0.867 mL, 1.141 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was triturated with Et₂O and purified by chiral HPLC purification to get 2-methoxy-N-(4-methoxy-6-((5-propionyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 3**; 50 mg, 17.18%) as an off

white solid. The other regioisomer was not isolated in pure form from the mixture TLC: 5% MeOH/DCM (R_f : 0.4). (See Table 1 for analytical data)

EXAMPLES 4-5

[1505] Scheme 3: Synthesis of 2,5-dimethoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 4) and 2,5-dimethoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 5)



[1506] Synthesis of tert-butyl 1-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate and tert-butyl 2-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (12)

[1507] To a stirred solution of compound 7 (mixture of regioisomers) (750 mg, 1.945 mmol) in THF (20 mL) was added at 1M solution of KO^tBu in THF (5.8 mL, 5.837 mmol) 0°C. The reaction mixture was stirred for 10 min followed by addition of 2,5-dimethoxybenzenesulfonyl chloride (0.69 g, 2.917 mmol) at 0°C. The reaction was stirred at room temperature for 16 h. After completion (monitored by TLC), the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi flash column chromatography using 80-90% EA/Heptane to afford title compound **12** (mixture of regioisomers) (450 mg, 39.50%) as an off-white solid. TLC: 50% EA/Heptane (R_f : 0.5). LCMS Calculated for C₂₇H₃₁N₅O₈S: 585.19; Found: 586.2 (M+H).

[1508] **Synthesis of N-(6-((5,6-dihydropyrrolo[3,4-c] pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2,5-dimethoxybenzenesulfonamide hydrochloride and N-(6-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2,5-dimethoxybenzenesulfonamide hydrochloride (13)**

[1509] To a stirred solution of compound **12** (450 mg, 0.768 mmol) in DCM (5mL) was added 4M HCl in 1,4 Dioxane (4 mL) at 0°C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated *in vacuo*. The residue was washed with diethyl ether and dried *in vacuo* to afford the title compound **13** (mixture of regioisomers) (350 mg, 87.28%) as an off-white solid (HCl salt). TLC: 10% MeOH/DCM (*R_f*: 0.2). LCMS Calculated for C₂₂H₂₃N₅O₆S: 485.14; Found: 486.30(M+1).

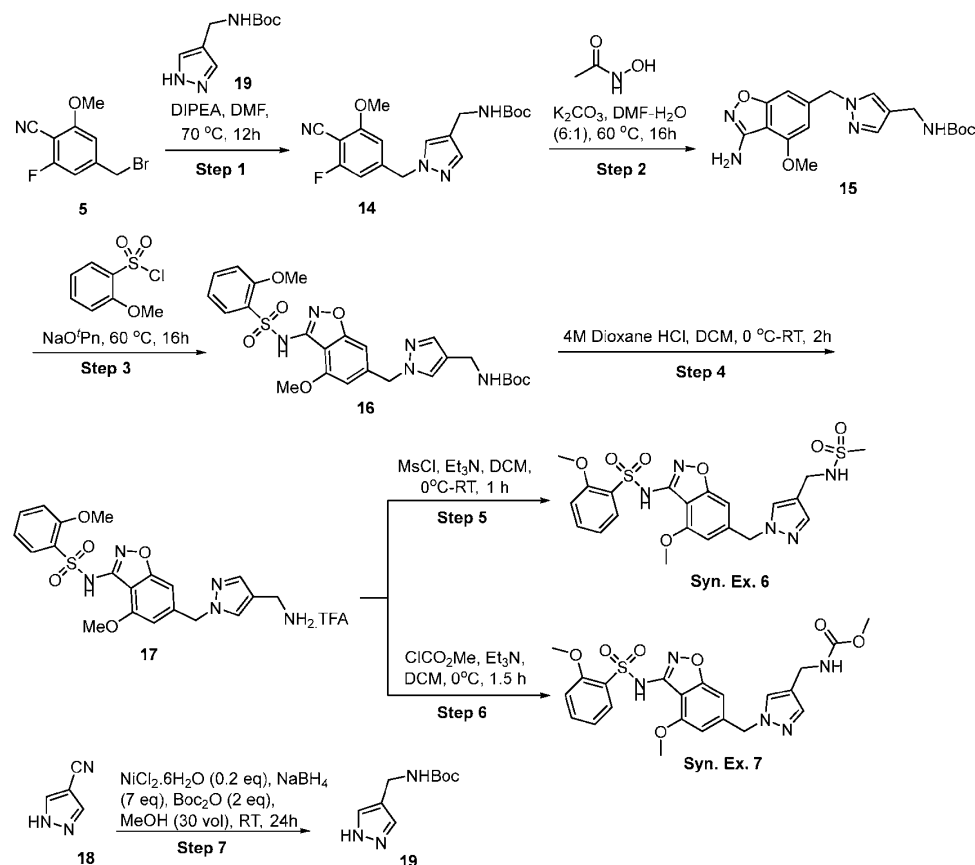
[1510] **Synthesis of 2,5-dimethoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 4) and 2,5-dimethoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 5)**

[1511] To a stirred solution of compound **13** (200 mg, 0.383 mmol) in DMF (5 mL) was added DIPEA (0.2 mL, 1.149 mmol), propiolic acid (32 mg, 0.459 mmol) and 50% solution of T₃P in EtOAc (0.87 mL, 1.149 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was washed with Diethyl ether to afford a mixture of regioisomers which was further purified by chiral HPLC to get 2,5-dimethoxy-N-(4-methoxy-6-((5propioloyl5,6dihydropyrrolo[3,4c]pyrazol1(4H)yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 4**; 35 mg, 15.02%) as off-white and 2,5-dimethoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 5**; 15 mg) as an off-white solid. TLC: 10% MeOH/DCM (*R_f*: 0.4). (See Table 1 for analytical data).

EXAMPLES 6-7

[1512] **Scheme 4: Synthesis of 2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (Syn. Ex. 6) & Synthesis of methyl ((1-((4-methoxy-3-((2-**

methoxyphenyl) sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) carbamate (Syn. Ex. 7)



[1513] Synthesis of tert-butyl ((1H-pyrazol-4-yl) methyl) carbamate (19)

[1514] To a stirred solution of compound 18 (5 g, 53.711 mmol) in methanol (400 mL) was added NiCl₂·6H₂O (5.01 g, 38.671 mmol) followed by addition of sodium borohydride (21.00 g, 549.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h followed by addition of Di-*tert*-butyl dicarbonate (24 mL, 107.422). The mixture was stirred at room temperature for 48h. After completion (monitored by TLC), the mixture was quenched with H₂O (50mL) and evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (5 x 30 mL). The combined organic layer was filtered through a Celite Pad, dried over anhydrous Na₂SO₄ and concentrated in *vacuo* to afford the title compound 19 (2.5 g, 24%) as a blue solid. TLC: 5% MeOH/DCM (R_f: 0.30). LCMS Calculated for C₉H₁₅N₃O₂: 197.12; Found: 198.20 (M+1).

[1515] Synthesis of *tert*-butyl ((1-(4-cyano-3-fluoro-5-methoxybenzyl)-1*H*-pyrazol-4-yl)methyl) carbamate (14)

[1516] To a stirred solution of compound **5** (15 g, 61.460 mmol) in DMF (15 mL) was added DIPEA (21.46 mL, 122.92 mmol) and compound **19** (14.54 g, 73.752 mmol) at the room temperature. The resulting reaction mixture was heated at 70 °C for 12 h. After completion (monitored by TLC), the mixture was cooled to room temperature, quenched with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by Combi-flash chromatography using a gradient method of 40-70% EtOAc/Heptane to afford the title compound **14** (12 g, 33.30%) as a colourless semi solid. TLC: 60% EtOAc/Heptane (*R_f*: 0.45). LCMS Calculated for C₁₈H₂₁FN₄O₃: 360.39; Found: 361.00 (M+1).

[1517] Synthesis of *tert*-butyl ((1-((3-amino-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)carbamate (15)

[1518] To a stirred solution of compound **14** (0.2 g, 0.55 mmol) in a 6:1 mixture of DMF: H₂O (7 mL) was added acetohydroxamic acid (0.112 g, 1.50 mmol) and K₂CO₃ (0.414 g, 3.0 mmol) at room temperature. The reaction mixture was allowed to stir at 60 °C for 16 h. After completion (monitored by TLC), the mixture was cooled to room temperature, quenched with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by Combi flash chromatography using a gradient method of 40-60% EtOAc/Heptane to afford the title compound **15** (0.1 g, 48.25%) as a brown semi-solid. TLC: 80% EtOAc/Heptane (*R_f*: 0.40). LCMS Calculated for C₁₈H₂₃N₅O₄: 373.41; Found: 374.05 (M+1).

[1519] Synthesis *tert*-butyl ((1-((4-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl) carbamate (16)

[1520] To a stirred solution of compound **15** (0.45 g, 1.20 mmol) in THF (5 mL) was added 2-methoxybenzenesulfonyl chloride (0.49 g, 2.41 mmol) followed by NaO^tPn (0.396 g, 3.60 mmol). The resulting reaction mixture was allowed to stir at 60 °C for 16 h. After completion (monitored by TLC), the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude compound was purified by Combi flash chromatography using a gradient method of 60-80% ethyl acetate/Heptane to afford the title

compound **16** (0.130 g, 19.9 %) as a brown gummy solid. TLC: 5% MeOH/DCM (R_f : 0.6). LCMS Calculated for $C_{25}H_{29}N_5O_7S$: 543.60; Found: 542.1 (M-1).

[1521] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride (17)

[1522] To a stirred solution of compound **16** (0.13 g, 0.239 mmol) in DCM (3 mL) was added 4M HCl in 1,4 Dioxane (0.5 mL, 2.39 mmol) at 0 °C. The reaction was allowed to stir at the room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure to afford the title compound **17** (0.1 g, 94.3% HCl salt) as a brown semi solid. TLC: 10% MeOH/DCM (R_f : 0.5). LCMS Calculated for $C_{20}H_{22}ClN_5O_5S$: 479.10; Found: 442.4(M-1).

[1523] Synthesis of 2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (Syn. Ex. 6)

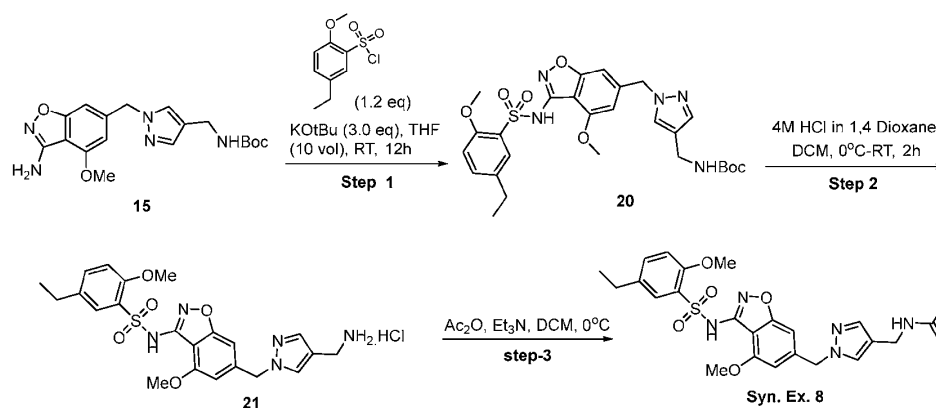
[1524] To a stirred solution of compound **17** (0.13 g, 0.270 mmol) in DCM (5 mL) were added Et_3N (0.11 mL, 0.812 mmol) followed by MsCl (0.037 g, 0.324 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford title compound 2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (**Syn. Ex. 6**, 30 mg, 21.24%) as an off-white solid. TLC: 40% EtOAc/Heptane (R_f : 0.5). (See Table 1 for analytical data).

[1525] Synthesis of methyl ((1-((4-methoxy-3-((2-methoxyphenyl) sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) carbamate (Syn. Ex. 7)

[1526] To a solution of compound **17** (0.12 g, 0.250 mmol) in DCM (10 mL) was added Et_3N (0.1 mL, 0.750 mmol) followed by methyl chloroformate (0.028 g, 0.300 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified using prep HPLC to afford title compound methyl ((1-((4-methoxy-3-((2-methoxyphenyl) sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) carbamate (**Syn. Ex. 7**; 25 mg, 20%) as an off-white solid. TLC: 50% EtOAc/Heptane (R_f : 0.5). (See Table 1 for analytical data).

EXAMPLE 8

[1527] Scheme 5: Synthesis of *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acetamide (Syn. Ex. 8)



[1528] Synthesis of *tert*-butyl ((1-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) carbamate (20)

[1529] To a stirred solution of compound **15** (0.150 g, 0.401 mmol) in THF (3 mL) was added 1M solution of *t*BuOK in THF (1.2 mL, 1.20 mmol) followed by 5-ethyl-2-methoxybenzenesulfonyl chloride (185 mg, 0.898 mmol) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by Combi flash column chromatography using a gradient method of 40-60% EtOAc/Heptane to afford the title compound **20** (130 mg, 56.76%) as an off-white solid. TLC: 80% EtOAc/Heptane (R_f: 0.35). LCMS Calculated for C₂₇H₃₃N₅O₇S: 571.21; Found: 572.03 (M+1).

[1530] Synthesis of *N*-(6-((4-(aminomethyl)-1H-pyrazol-1-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (**21**)

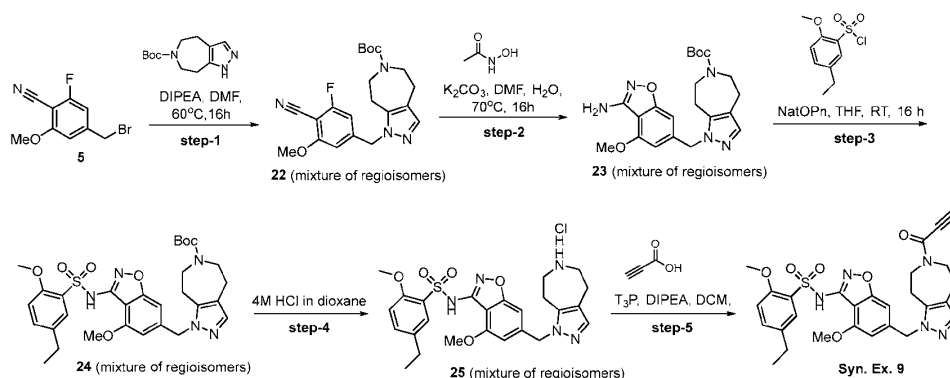
[1531] To a stirred solution of compound **20** (130 mg, 0.227 mmol) in DCM (2 mL) was added 4M HCl in 1,4-dioxane (2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h. After completion (monitored by TLC), the mixture was evaporated under reduced pressure. The crude was triturated with DCM/Heptane to afford the title compound **21** (100 mg, salt) as an off-white solid. TLC: 5% MeOH/DCM (R_f: 0.3). LCMS Calculated for C₂₂H₂₅N₅O₅S: 471.16; Found: 472.30.

[1532] Synthesis of *N*-((1-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) acetamide (Syn. Ex. 8)

[1533] To a stirred solution of compound **21** (100 mg, 0.196 mmol) in DCM (3 mL) was added triethylamine (0.082 mL, 0.590 mmol) at 0 °C. The reaction mixture was stirred for 10 min. followed by addition of Ac₂O (0.022 mL, 0.235 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get crude. The crude was purified using prep. HPLC to afford *N*-((1-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl) acetamide (**Syn. Ex. 8**; 45 mg, 44.55%) as an off-white solid. TLC: 10% MeOH/DCM (*R_f*: 0.5). (See Table 1 for analytical data).

EXAMPLE 9

[1534] Scheme 6: Synthesis of 5-ethyl-2-methoxy-*N*-(4-methoxy-6-((6-propioloyl-5,6,7,8-tetrahydropyrazolo[3,4-d]azepin-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 9)



[1535] Synthesis of tert-butyl 1-(4-cyano-3-fluoro-5-methoxybenzyl)-4,5,7,8-tetrahydropyrazolo[3,4-d] azepine-6(1H)-carboxylate and tert-butyl 2-(4-cyano-3-fluoro-5-methoxybenzyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (22**)**

[1536] To a stirred solution of compound **5** (0.75 g, 3.073 mmol) in DMF (7 mL) was added DIPEA (1.6 mL, 9.219 mmol) followed by tert-butyl 4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(1H)-carboxylate (0.729 g, 3.073 mmol). The reaction mixture was stirred at 60°C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and

extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude compound **22** (1.2 g, crude) as a brown liquid. TLC: 40% EtOAc/Heptane (R_f: 0.4). LCMS Calculated for C₂₁H₂₅N₄O₃: 400.19; Found: 400.30

[1537] Synthesis of tert-butyl 1-((3-amino-4-methoxybenzo[d]isoxazol-6-yl) methyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(1H)-carboxylate and tert-butyl 2-((3-amino-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (23)

[1538] To a solution of compound **22** (1.2 g, 2.996 mmol) in a mixture of DMF: H₂O (48 mL, 6:1 ratios) was added K₂CO₃ (2.48 g, 17.979 mmol) and N-hydroxy acetamide (0.674 g, 8.988 mmol). The reaction mixture was stirred at 70°C for 16h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford the title compound **23** (750 mg, 60.53%) as a yellow solid. TLC: 40% EtOAc/Heptane (R_f: 0.4). LCMS Calculated for C₂₁H₂₇N₅O₄: 413.21; Found: 414.5 (M+1).

[1539] Synthesis of tert-butyl 1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(1H)-carboxylate and tert-butyl 2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,5,7,8-tetrahydropyrazolo[3,4-d]azepine-6(2H)-carboxylate (24)

[1540] To a stirred solution of compound **23** (750 mg, 1.813 mmol) in THF (8 mL) was added NaO^tBu (0.87 g, 9.069 mmol) followed by 5-ethyl-2-methoxybenzenesulfonyl chloride (0.510 g, 2.175 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to offer the title compound **24** (1.1 g, 99.18%) as a brown gummy oil. The crude was carried forward to the next step without further purification. TLC: 40% EtOAc/Heptane (R_f: 0.4). LCMS Calculated for C₃₀H₃₇N₅O₇S: 611.24; Found: 612.5(M+1).

[1541] Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((5,6,7,8-tetrahydropyrazolo[3,4-d]azepin-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide hydrochloride and 5-ethyl-2-methoxy-N-(4-methoxy-6-((5,6,7,8-tetrahydropyrazolo[3,4-d]azepin-2(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide hydrochloride (25)

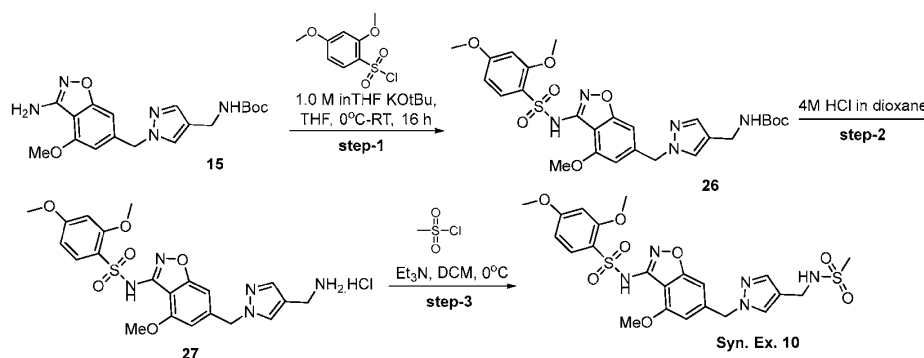
[1542] To a solution of compound **24** (1.0 g, 1.63 mmol) in DCM (10 mL) was added 4M HCl in 1,4 Dioxane (5 mL) at 0°C and the reaction mixture was stirred at room temperature for 4h. After completion (reaction monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed diethyl ether 3 times and dried *in vacuo* to afford the title compound **25** (750 mg, HCl salt) as an off-white solid. The crude has been carried forward in next reaction. It was taken to the next step with no further purification. TLC: 40% EtOAc/Heptane (R_f : 0.4). LCMS Calculated for C₂₅H₂₉N₅O₅S: 511.19; Found: 512.30.

[1543] **Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((6-propioloyl-5,6,7,8-tetrahydropyrazolo[3,4-d]azepin-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 9)**

[1544] To a stirred solution of compound **25** (0.750 g, 1.368 mmol) and prop-2-ynoic acid (0.143 g, 2.052 mmol) in DMF (7.5 mL) were added DIPEA (0.716 mL, 4.104 mmol) and 50% solution of T₃P in EtOAc (5.22 mL, 8.208 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography (5% MeOH in DCM) followed by prep-HPLC to get the desired compound as a mixture of regioisomers. The desired regioisomer (**Syn. Ex. 9**) was obtained by subjecting this mixture to prep-SFC to afford 5-ethyl-2-methoxy-N-(4-methoxy-6-((6-propioloyl-5,6,7,8-tetrahydropyrazolo[3,4-d]azepin-1(4H)-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 9**; 55 mg, 7.13%) as an off-white solid. The other regioisomer was not isolated. TLC: 10% MeOH/DCM (R_f : 0.5). (See analytical data in Table 1).

EXAMPLE 10

[1545] **Scheme 7: Synthesis of 2,4-dimethoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 10)**



[1546] Synthesis of tert-butyl ((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (26**)**

[1547] To a stirred solution of compound **15** (500 mg, 1.339 mmol) in THF (15 mL) was added 1M solution of KO^tBu solution in THF (4 mL, 4.017 mmol) at 0°C. The reaction mixture was stirred for 10 min at 0°C followed by addition of 2,4-dimethoxybenzenesulfonyl chloride (0.475 g, 2.008 mmol) in THF (1 mL). The reaction was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by combi flash chromatography using (neutral alumina) gradient 30-50% EA/Heptane to afford the title compound **26** (140 mg, 18.22%) as a pale-yellow solid. TLC: 10% MeOH/DCM (*R_f*: 0.6). LCMS Calculated for C₂₆H₃₁N₅O₈S: 573.62; Found: 574.06 (M+1).

[1548] Synthesis of N-(6-((4-(amino methyl)-1H-pyrazol-1-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2,4-dimethoxybenzenesulfonamide hydrochloride (27**)**

[1549] To a stirred solution of compound **26** (140 mg, 0.274 mmol) in DCM (3 mL) was added 4M HCl in 1,4 Dioxane (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with diethyl ether to afford the title compound **27** (110 mg, 74.24%) as an off-white solid (HCl salt). TLC: 10% MeOH/DCM (*R_f*: 0.6). LCMS Calculated for C₂₁H₂₃N₅O₆S: 473.14; found: 474.20.

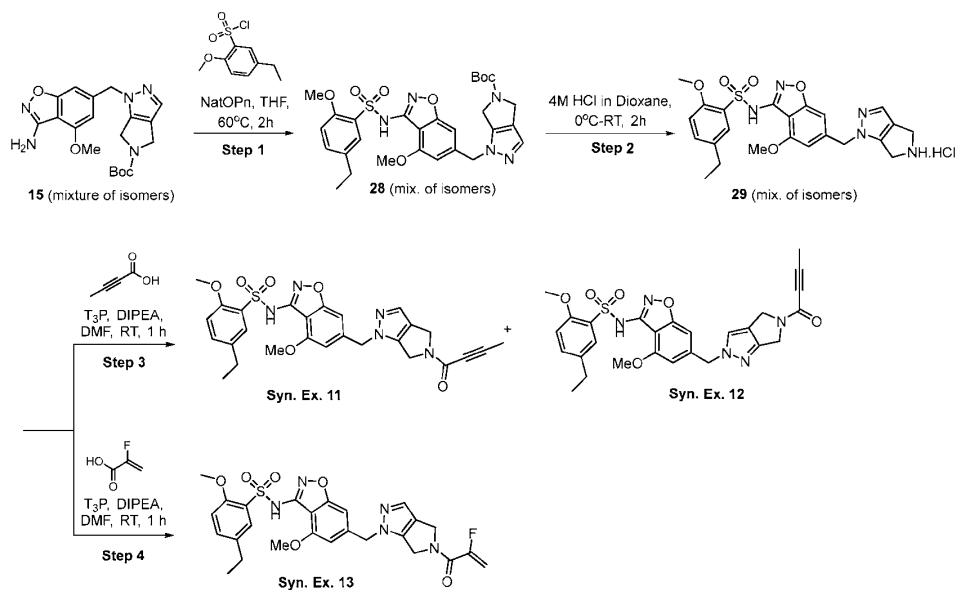
[1550] Synthesis of 2,4-dimethoxy-N-(4-methoxy-6-((4-(methanesulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 10)

[1551] To a stirred solution of compound **27** (110 mg, 0.2157 mmol) in DCM (3 mL) was added triethylamine (0.09 mL, 0.647 mmol) followed by methanesulfonyl chloride (0.029 g, 0.2588 mmol) in DCM (1 mL) at 0°C. The reaction mixture was stirred at room

temperature for 15 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by using prep-HPLC to afford 2,4-dimethoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 10**; 29 mg, 24.57%) as an off-white solid. TLC: 10% MeOH/DCM (R_f: 0.5). (See Table 1 for analytical data).

EXAMPLES 11-13

[1552] **Scheme 8: Synthesis of N-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 11), N-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 12) and 5-ethyl-N-(6-((5-(2-fluoroacryloyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (Syn. Ex. 13)**



[1553] **Synthesis of tert-butyl 1-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate and tert-butyl 2-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (28)**

[1554] To a stirred solution of compound **15** (mixture of isomers) (1.3 g, 3.372 mmol) in THF (20 mL) was added NaO^tPn (2.22 g, 20.237 mmol) followed by 5-ethyl-2-methoxybenzenesulfonyl chloride (1.58 g, 6.744 mmol) at 0 °C. The reaction was allowed to stir at 60 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by Combi flash using a gradient method of 20-60% EtOAc/Heptane to afford the title compound **28** (mixture of isomers) (1.0 g, 51.02%) as a pale-yellow solid. TLC: 100% EtOAc (R_f: 0.5). LCMS Calculated for: C₂₈H₃₃N₅O₇S; 583.21; Found: 584.5 (M+1).

[1555] **Synthesis of N-(6-((5,6-dihydropyrrolo[3,4-c] pyrazol-1(4H)-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride and N-(6-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (29)**

[1556] To a stirred solution of compound **28** (mixture of isomers) (1 g, 1.713 mmol) in DCM (5 mL) was added 4M HCl in 1,4 Dioxane (4.28 mL, 17.133 mmol) at 0°C. The reaction was allowed to stir at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure and triturated with Et₂O to afford the title compound **29** (mixture of isomers) (750 mg, HCl salt) as a gummy off-white solid. TLC: 5% MeOH/DCM (R_f: 0.2). LCMS Calculated for: C₂₃H₂₅N₅O₅S; 483.16; Found: 484.20.

[1557] **Synthesis of N-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 11) and N-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 12)**

[1558] To a stirred solution of compound **29** (mix. of isomers) (350 mg, 0.673 mmol) in DMF (3 mL) was added DIPEA (0.352 mL, 2.019 mmol), but-2-ynoic acid (67 mg, 0.807 mmol) followed by 50% solution of T₃P in EtOAc (1.28 mL, 2.019 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 16h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by Chiral HPLC purification to afford the 2 isomers *N*-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (**Syn. Ex. 11**; 45 mg, 11.31%) as an off white solid and *N*-(6-

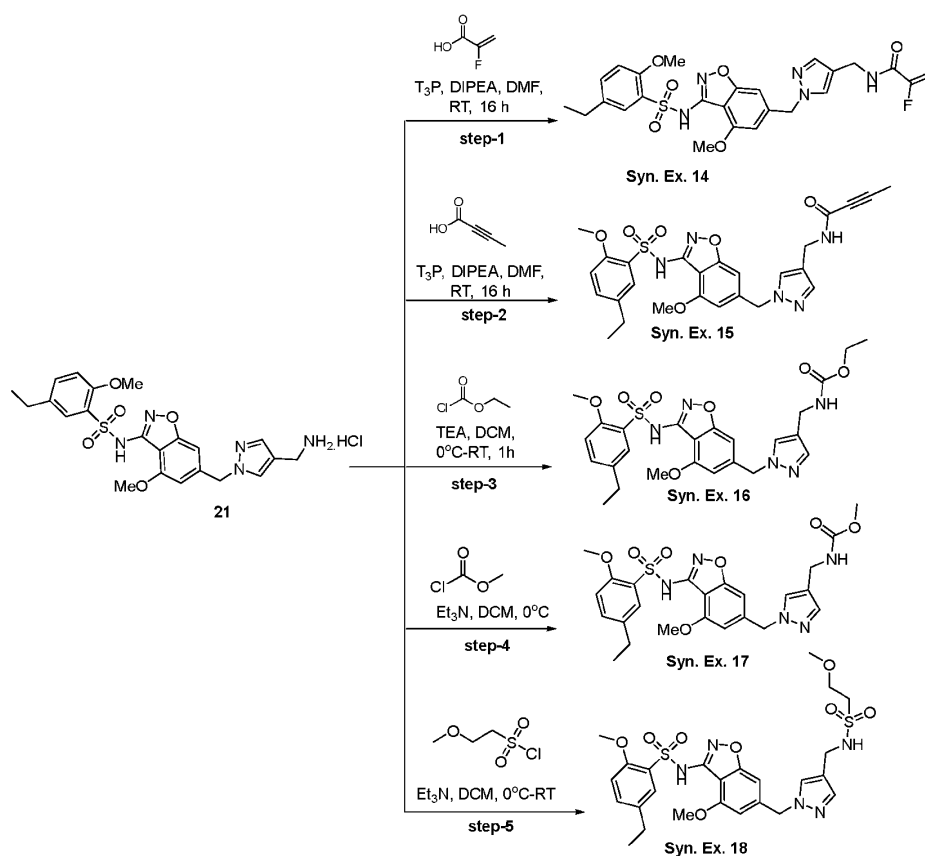
((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (**Syn. Ex. 12**; 14 mg, 5.31% yield) as an off white solid. TLC: 5% MeOH/DCM (R_f : 0.5). (See Table 1 for analytical data).

[1559] Synthesis of 5-ethyl-N-(6-((5-(2-fluoroacryloyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (Syn. Ex. 13**)**

[1560] To a stirred solution of compound **29** (mix. of isomers) (200 mg, 0.384 mmol) in DMF (3 mL) was added DIPEA (0.2 mL, 1.153 mmol), 2-fluoroacrylic acid (41 mg, 0.460 mmol) followed by 50% solution of T₃P in EtOAc (0.733 mL, 1.153 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 1h. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The crude was purified by Chiral HPLC purification to afford the title compound *N*-(6-((5-(but-2-ynoyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (**Syn. Ex. 13**; 15 mg, 6.52% yield) as an off white solid. TLC: 5% MeOH/DCM (R_f : 0.5) (See Table 1 for analytical data). The other isomer was not isolated.

EXAMPLES 14-18

[1561] Scheme 9: N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 14**), N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 15**), ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 16**), methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 17**) and 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-((2-methoxyethyl)sulfonamido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 18**)**



[1562] Synthesis of N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 14)

[1563] To a stirred solution of compound **21** (0.12 g, 0.236 mmol) in DMF (2 mL) was added 2-fluoroacrylic acid (0.042 g, 0.472 mmol) and DIPEA (0.20 mL, 1.181 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by the addition of 50% solution of T₃P in EtOAc (0.375 mL, 0.590 mmol) at 0 °C. The mixture was allowed to stir at room temperature for 3h. After completion (monitored by TLC), the mixture was quenched with ice water (10 mL). The solid precipitate was filtered, washed with heptane, and dried under reduced pressure. The crude was purified by prep HPLC to afford the title compound N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 14**; 3.8 mg, 2.96%) as an off-white solid. (See Table 1 for analytical data).

[1564] Synthesis of N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (Syn. Ex. 15)

[1565] To a stirred solution of compound **21** (0.12 g, 0.236 mmol) in DMF (2 mL) was added but-2-ynoic acid (0.039 g, 0.472 mmol) and DIPEA (0.20, 1.181 mmol) at 0°C. The reaction mixture was stirred for 10 min followed by the addition of 50% solution of T₃P in EtOAc (0.36 mL, 0.590 mmol) at 0°C. The mixture was allowed to stir at room temperature for 3 h. After completion (monitored by TLC), the mixture was quenched with ice cold water (20 mL). The solid precipitate was filtered, washed with heptane, and dried under reduced pressure. The crude was purified by prep HPLC to afford title compound N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 15**; 5.4 mg, 4.28%) as an off-white solid. (See Table 1 for analytical data)

[1566] Synthesis of ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 16)

[1567] To a stirred solution of compound **21** (150 mg, 0.295 mmol) in DCM (2 mL) was added TEA (0.12 mL, 0.885 mmol) followed by ethyl chloroformate (48 mg, 0.442 mmol) in DCM (1 mL) at 0°C. The reaction mixture was allowed to stir at 0°C for 1h. After completion (monitored by TLC and LCMS), the mixture was quenched with ice-water (20mL) and extracted with DCM (30 mL x 3). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude which was purified using prep-HPLC to afford ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 16**; 14 mg, 8.75%) as an off-white solid. (See Table 1 for analytical data).

[1568] Synthesis of methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 17)

[1569] To a stirred solution of compound **21** (120 mg, 0.236 mmol) in DCM (2 mL) was added TEA (0.09 mL, 0.708 mmol) followed by methyl chloroformate (26 mg, 0.283 mmol) in DCM (1 mL) at 0°C. The reaction mixture was allowed to stir at 0°C for 1h. After completion (monitored by TLC and LCMS), the reaction mixture was quenched with ice cold water (30mL) and extracted with ethyl acetate (100 mL x 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude which was purified using prep-HPLC to afford methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-

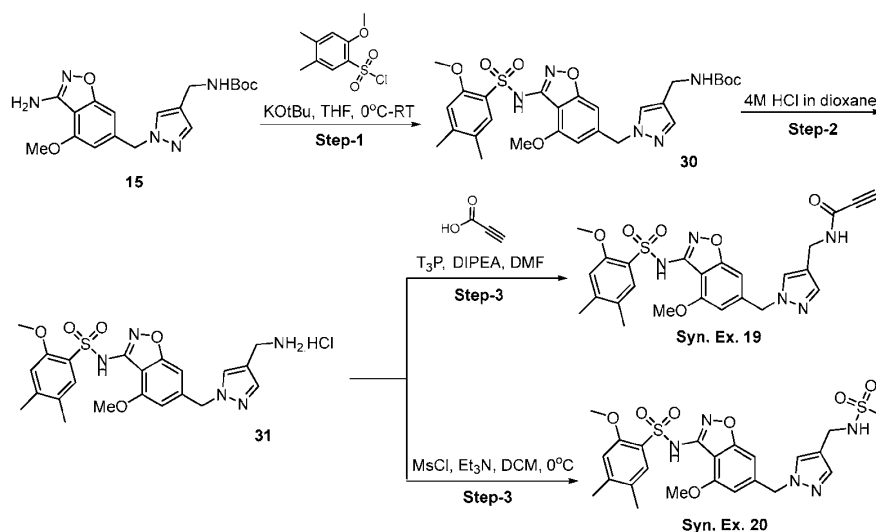
4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 17**; 9 mg, 6.834%) as an off-white solid. (See Table 1 for analytical data).

[1570] Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-(((4-(((2-methoxyethyl)sulfonamido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide) (Syn. Ex. 18**)**

[1571] To a stirred solution of compound **21** (120 mg, 0.236 mmol) in DCM (2 mL) was added TEA (0.09 mL, 0.708 mmol) followed by 2-methoxyethane-1-sulfonyl chloride (44 mg, 0.283 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C to room temperature for 16h. After completion (monitored by TLC and LCMS), the mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep-HPLC purification to afford 5-ethyl-2-methoxy-N-(4-methoxy-6-(((4-(((2-methoxyethyl)sulfonamido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 18**; 4.5 mg, 3.04%) as an off-white solid. (See Table 1 for analytical data).

EXAMPLES 19-20

[1572] Scheme 10: Synthesis of N-(((1-(((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide) (Syn. Ex. 19**) and Synthesis of 2-methoxy-N-(4-methoxy-6-(((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-4,5-dimethylbenzenesulfonamide (**Syn. Ex. 20**)**



[1573] Synthesis of tert-butyl ((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl) carbamate (30)

[1574] To a stirred solution of compound **15** (1.0 g, 2.678 mmol) in THF (10 mL) was added 1.0 M KOtBu in THF (8.0 mL, 8.034 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by the addition of 2-methoxy-4,5-dimethylbenzenesulfonyl chloride (0.628 g, 3.213 mmol). The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water (50 mL) and extracted with 10% MeOH in DCM (3 x 50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash column chromatography (neutral silica gel) using 80-90% EtOAc in Heptane to afford title compound **30** (0.23 g, 15.03%) as an off-white solid. LCMS calculated for C₂₇H₃₃N₅O₇S: 571.21; found: 572.46 (M+1).

[1575] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxy-4,5-dimethylbenzenesulfonamide hydrochloride (31)

[1576] To a solution of compound **30** (0.31 g, 0.542 mmol) in dioxane (3 mL) was added 4M HCl in dioxane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was triturated with Et₂O (3 x 20 mL) and dried under reduced pressure to afford the title compound **31** (0.28 g, HCl salt) as an off-white solid. LCMS calculated for C₂₂H₂₆ClN₅O₅S: 471.16; found: 472.42 (M+1).

[1577] Synthesis of N-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 19)

[1578] To a stirred solution of compound **31** (0.10 g, 0.196 mmol) in DMF (1 mL) was added DIPEA (0.10 mL, 0.590 mmol), propiolic acid (0.027 g, 0.393 mmol) and 50% solution of T₃P in EtOAc (0.373 mL, 0.588 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by prep HPLC to afford the title compound N-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-

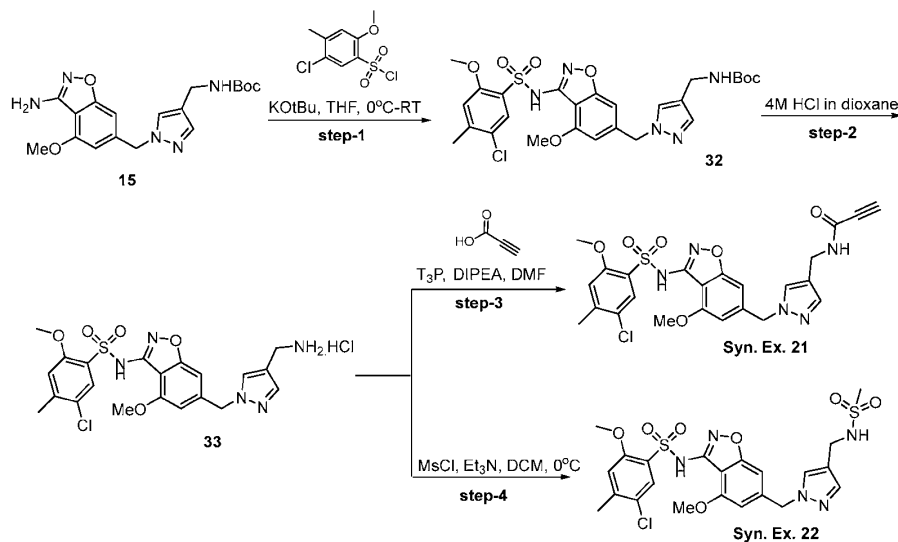
1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 19; 24 mg, 23.30%) as an off-white solid. (See Table 1 for analytical data).

[1579] **Synthesis of 2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl)-4,5-dimethylbenzenesulfonamide (Syn. Ex. 20)**

[1580] To a stirred solution of compound **31** (0.10 g, 0.196 mmol) in DCM (2 mL) was added Et₃N (0.08 mL, 0.588 mmol) and methane sulfonyl chloride (0.020 g, 0.176 mmol) in DCM (1 mL) at 0°C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by prep HPLC to afford the title compound 2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-4,5-dimethylbenzenesulfonamide (Syn. Ex. 20; 25 mg, 23.14% Yield) as an off-white solid. (See Table 1 for analytical data)

EXAMPLES 21-22

[1581] **Scheme 11: N-((1-((3-((5-chloro-2-methoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 21) & 5-chloro-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-4-methylbenzenesulfonamide (Syn. Ex. 22)**



[1582] Synthesis of tert-butyl ((1-((3-((5-chloro-2-methoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (32)

[1583] To a stirred solution of compound **15** (0.50 g, 1.339 mmol) in THF (5 mL) was added 1.0 M solution of KO^tBu in THF (4.45 mL, 4.017 mmol) at 0 °C. The reaction mixture was stirred for 10 min followed by the addition of 5-chloro-2-methoxy-4-methylbenzenesulfonyl chloride (0.512 g, 2.008 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with EtOAc (3 x 80 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford title compound **32** (0.38 g, 47.97%) as a brown solid. LCMS calculated for C₂₆H₃₀ClN₅O₇S: 591.16; found: 592.63 (M+1).

[1584] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-chloro-2-methoxy-4-methylbenzenesulfonamide hydrochloride (33)

[1585] To a stirred solution of compound **32** (0.38 g, 0.641 mmol) in DCM (5 mL) was added 4M HCl in Dioxane (1.6 mL, 6.418 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O (2 x 5 mL) to afford title compound **33** (0.30 g, HCl salt) as a brown semi solid. LCMS calculated for C₂₁H₂₂ClN₅O₅S: 491.10; found: 493.00 (M+2).

[1586] Synthesis of N-((1-((3-((5-chloro-2-methoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 21)

[1587] To a stirred solution of compound **33** (0.10 g, 0.189 mmol) in DMF (3 mL) was added DIPEA (0.13 mL, 0.756 mmol) at 0 °C. The reaction mixture was stirred for 5 min followed by the addition of propiolic acid (0.015 g, 0.226 mmol) and 50% solution of T₃P in EtOAc (0.360 mL, 0.567 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the crude. The crude was purified by combi flash chromatography using with 95-100% EA/Heptane to afford the title compound N-((1-((3-((5-chloro-2-methoxy-4-methylphenyl)sulfonamido)-4-

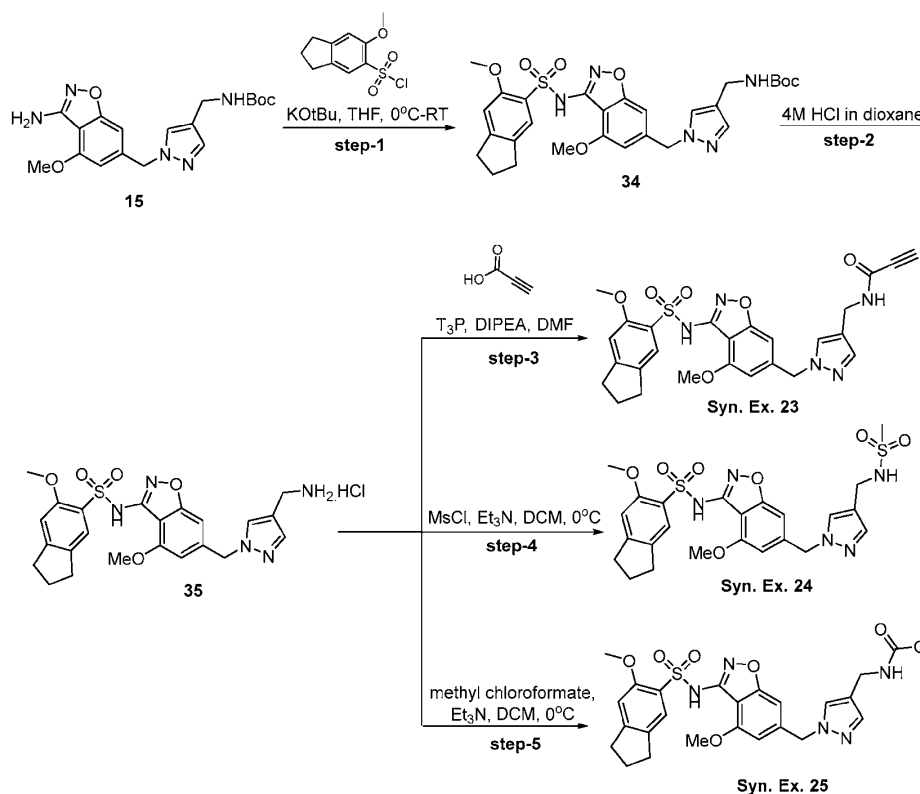
methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 21; 19 mg, 18.46%) as an off-white solid. (See Table 1 for analytical data)

[1588] Synthesis of 5-chloro-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-4-methylbenzenesulfonamide (Syn. Ex. 22)

[1589] To a stirred solution of compound **33** (0.12 g, 0.227 mmol) in DCM (5 mL) were added Et₃N (0.095 mL, 0.681 mmol) and methane sulfonyl chloride (0.031 g, 0.272 mmol) in DCM (0.5 mL) at 0°C. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the crude which was purified by prep. HPLC to afford the title compound 5-chloro-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-4-methylbenzenesulfonamide (Syn. Ex. 22; 73 mg, 56.41%) as an off-white solid. (See Table 1 for analytical data)

EXAMPLES 23-25

[1590] Scheme 12: N-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 23), 6-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-2,3-dihydro-1H-indene-5-sulfonamide (Syn. Ex. 24) and methyl ((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 25)



[1591] **Synthesis of tert-butyl ((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl) carbamate (**34**)**

[1592] To a stirred solution of compound **15** (0.35 g, 0.937 mmol) in THF (40 mL) was added 1M solution of KOtBu in THF (2.81 mL, 2.812 mmol) and 6-methoxy-2,3-dihydro-1H-indene-5-sulfonyl chloride (0.30 g, 1.219 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi flash column chromatography using 70-75% EA:Heptane to afford title compound **34** (0.20 g, 36.55%) as an off-white solid. LCMS calculated for C₂₈H₃₃N₅O₇S: 583.21; found: 584.49 (M+1).

[1593] **Synthesis of N-(6-((4-(amino methyl)-1H-pyrazol-1-yl) methyl)-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide hydrochloride (**35**)**

[1594] To a solution of compound **34** (0.20 g, 0.342 mmol) in DCM (2 mL) was added 4M HCl in 1,4 dioxane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **35** (0.16 g, 89.88%) as an off-white solid. LCMS calculated for C₂₃H₂₅N₅O₅S: 483.16; found: 484.76 (M+1).

[1595] Synthesis of N-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 23)

[1596] To a stirred solution of compound **35** (0.13 g, 0.250 mmol) in DMF (5 mL) was added DIPEA (0.18 mL, 1.075 mmol) at 0 °C. The reaction mixture was stirred for 5 min followed by addition of propiolic acid (0.026 g, 0.375 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (0.23 g, 0.750 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi flash chromatography using 95-100% EA/PE to afford title compound N-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 23**; 30 mg, 22.42%) as an off-white solid. (See Table 1 for analytical data)

[1597] Synthesis of 6-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-2,3-dihydro-1H-indene-5-sulfonamide (Syn. Ex. 24)

[1598] To a stirred solution of compound **35** (100 mg, 0.192 mmol) in DCM (3 mL) was added Et₃N (0.08 mL, 0.576 mmol) followed by methane sulfonyl chloride (0.018 mL, 0.230 mmol) in DCM (1 mL) at 0°C. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM (3 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford the title compound 6-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)-2,3-dihydro-1H-indene-5-sulfonamide (**Syn. Ex. 24**; 21 mg, 19.44%) as an off-white solid. (See Table 1 for analytical data)

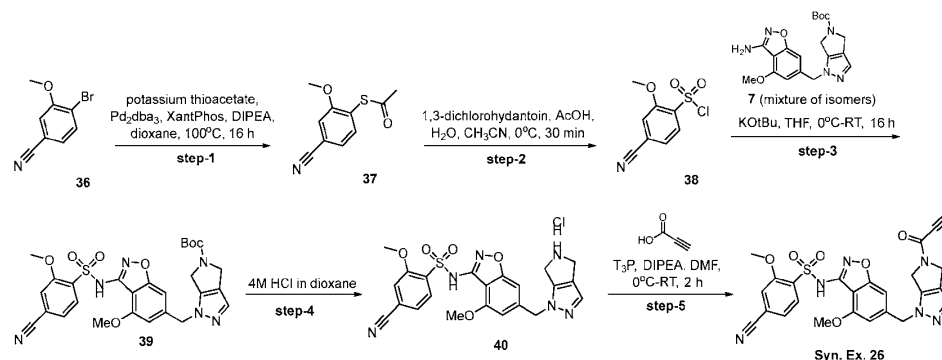
[1599] Synthesis of methyl ((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 25)

Ex. 25)

[1600] To a stirred solution of compound **35** (80 mg, 0.153 mmol) in DCM (3 mL) was added triethylamine (0.064 mL, 0.461 mmol) and methyl chloroformate (0.015 mL, 0.1836 mmol) in DCM (0.5 mL) at 0°C. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in *vacuo* to afford the crude which was purified by prep HPLC purification to get methyl ((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 25; 16 mg, 19.20%) as an off-white solid. (See Table 1 for analytical data)

EXAMPLE 26

[1601] Scheme 13: Synthesis of 4-cyano-2-methoxy-N-[4-methoxy-6-[(5-prop-2-ynoyl-4,6-dihydropyrrolo[3,4-c]pyrazol-1-yl)methyl]-1,2-benzoxazol-3-yl]benzenesulfonamide (Syn. Ex. 26)



[1602] Synthesis of S-(4-cyano-2-methoxyphenyl) ethanethioate (37)

[1603] To a solution of compound **36** (1 g, 4.715 mmol) in 1,4-Dioxane (10 mL) was added KSAc (0.646 g, 5.658 mmol), DIPEA (2.46 mL, 14.145 mmol) and followed by XantPhos (0.554 g, 0.943 mmol) at room temperature. The reaction mixture was purged with nitrogen for 10 min. followed by addition of Pd₂(dba)₃ (0.431 g, 0.47161 mmol). The mixture was stirred in sealed tube at 110°C for 16 h. After completion (monitored by TLC and LCMS), the mixture was cooled to room temperature and filtered through a celite bed. The filtrate was diluted with H₂O (30 mL) and extracted with EtOAc (3 x 20mL). The combined organic

layer dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude was purified by column chromatography (neutral silica gel) using 10% EtOAc in Heptane to afford the title compound **37** (300 mg, 30.70%) as a pale-yellow solid. TLC: 20% EtOAc in Hexane (R_f: 0.5), LCMS Calculated for: C₁₀H₉NO₂S: 207.04; Found: 208.5 (M+1).

[1604] Synthesis of 4-cyano-2-methoxybenzenesulfonyl chloride (38)

[1605] A solution of compound **37** (0.35 g, 1.688 mmol) in ACN (14 mL) was added AcOH (0.6 mL) and water (0.35 mL) followed by 1,3-Dichloro-5,5-dimethylhydantoin (0.665 g, 3.376 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the reaction mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford the title compound **38** (650 mg, crude) as an off-white solid. TLC: 60% EtOAc in Heptane (R_f: 0.4). LCMS Calculated for: C₈H₆ClNO₃S: 230.98; Found: 231.2 (M+1).

[1606] Synthesis of tert-butyl 1-((3-((4-cyano-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-4,6-dihydropyrrolo[3,4-c] pyrazole-5(1H)-carboxylate and tert-butyl 2-((3-((4-cyano-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (39)

[1607] To a solution of compound **7** (mixture of isomers) (0.350 g, 0.908 mmol) in THF (10 mL) was added 1M solution of KOtBu in THF (2.7 mL, 2.724 mmol) at 0 °C. The reaction mixture was stirred for 10 minutes followed by addition of 4-cyano-2-methoxybenzenesulfonyl chloride **38** (0.631 g, 2.724 mmol) in THF (2 mL) at 0°C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC and LCMS), the reaction mixture was poured into ice-cold H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude was triturated with diethyl ether (2 x 10 mL) to get title compound **39** (200 mg, 37.95%) as a pale-yellow solid. TLC: 60% EtOAc in Heptane. LCMS Calculated for: C₂₇H₂₈N₆O₇S: 580.17; Found: 581.2 (M+1).

[1608] Synthesis of 4-cyano-N-(6-((5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride and 4-cyano-N-(6-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride (40)

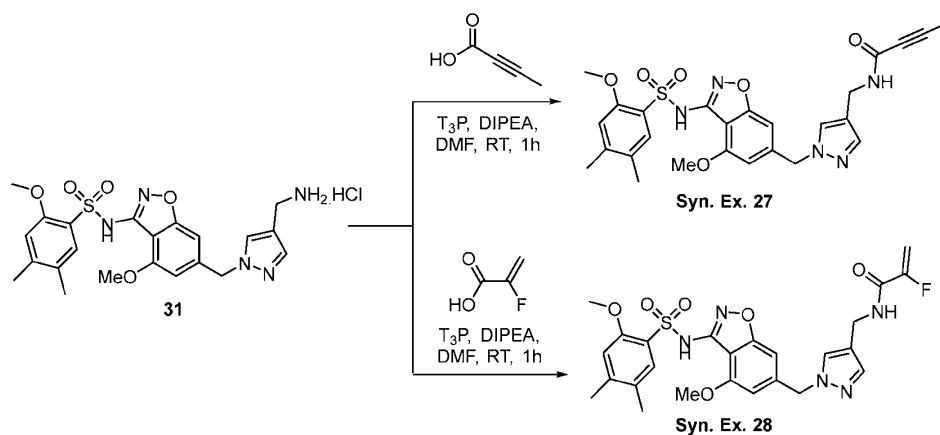
[1609] To a solution of compound **39** (200 mg, 0.3445 mmol) in 1,4-Dioxane (2 mL) was added 4M HCl in 1,4 Dioxane (0.4 mL, 1.722 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was concentrated in *vacuo*. The crude was triturated with Diethyl ether (2 x 10 mL) and dried in *vacuo* to afford the title compound **40** (180 mg, HCl salt) as a pale-yellow solid. TLC: 10% MeOH in DCM (R_f, 0.3), LCMS Calculated for: C₂₂H₂₀N₆O₅S: 480.12 Found: 480.20 (M+1).

[1610] **Synthesis of 4-cyano-2-methoxy-N-(4-methoxy-6-((5-propioloyl-5,6-dihydropyrrolo[3,4-c] pyrazol-1(4H)-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (Syn. Ex. 26)**

[1611] To a stirred solution of compound **40** (180 mg, 0.348 mmol) in DMF (2 mL) was added DIPEA (0.18mL, 1.044 mmol), prop-2-ynoic acid (48 mg, 0.696 mmol) followed by 50% solution of T₃P in EtOAc (0.66 mL, 1.044 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with H₂O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in *vacuo*. The crude was purified by chiral prep-HPLC to afford the title compound 4-cyano-2-methoxy-N-[4-methoxy-6-[(5-prop-2-ynoyl-4,6-dihydropyrrolo[3,4-c]pyrazol-1-yl)methyl]-1,2-benzoxazol-3-yl]benzenesulfonamide (**Syn. Ex. 26**; 26 mg, 13.97%) as an off-white solid. TLC: 10% MeOH in DCM (R_f, 0.5). (See Table 1 for analytical data). The other regioisomer was not isolated.

EXAMPLES 27-28

[1612] **Scheme 14: Synthesis of N-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl) but-2-ynamide (Syn. Ex. 27) and 2-fluoro-N-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 28)**



[1613] Synthesis of *N*-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)but-2-ynamide (Syn. Ex. 27)

[1614] To a stirred solution of compound **31** (0.11 g, 0.216 mmol) in DMF (3 mL) was added DIPEA (0.11 mL, 0.649 mmol), but-2-ynoic acid (0.036 g, 0.432 mmol) and 50% solution of T_3P in EtOAc (0.40 mL, 0.649 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude obtained was purified by combi flash chromatography (neutral silica) with 80% EtOAc in Heptane to afford title compound *N*-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 27**; 45 mg, 38.79%) as an off-white solid. TLC: 10% MeOH in DCM. (See analytical data in Table 1).

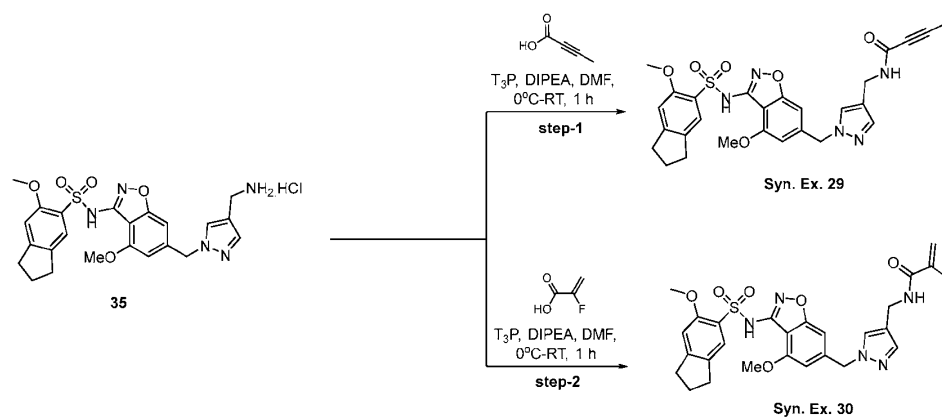
[1615] Synthesis of 2-fluoro-*N*-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 28)

[1616] To a stirred solution of compound **31** (0.1 g, 0.196 mmol) in DMF (3 mL) was added DIPEA (0.1 mL, 0.590 mmol), 2-fluoroprop-2-enoic acid (0.035 g, 0.392 mmol) and 50% solution of T_3P in EtOAc (0.375 mL, 0.590 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude

was purified by combi flash chromatography (neutral silica) using 80% EtOAc in Heptane to afford title compound 2-fluoro-*N*-((1-((4-methoxy-3-((2-methoxy-4,5-dimethylphenyl)sulfonamido) benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 28**; 30 mg, 28.03%) as an off white solid. (See analytical data in Table 1).

EXAMPLES 29-30

[1617] **Scheme 15: Synthesis of *N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 29**) and 2-fluoro-*N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido) benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 30**)**



[1618] **Synthesis of *N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl) but-2-ynamide (**Syn. Ex. 29**)**

[1619] To a stirred solution of compound **35** (0.1 g, 0.192 mmol) in DMF (3 mL) was added DIPEA (0.1 mL, 0.576 mmol), but-2-ynoic acid (0.032, 0.384 mmol) and 50% solution of T₃P in EtOAc (0.366 mL, 0.576 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was diluted with ice-cold water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude was purified by prep HPLC to afford title compound *N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido) benzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl) but-2-ynamide (**Syn.**

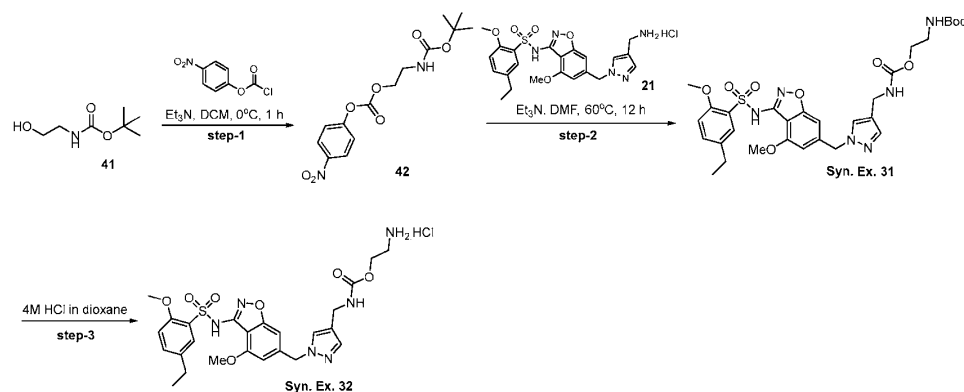
Ex. 29; 23 mg, 21.90%) as an off-white solid. TLC: 10% MeOH in DCM. (See analytical data in Table 1).

[1620] Synthesis of 2-fluoro-*N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido)benzo[*d*]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 30)

[1621] To a stirred solution of compound **35** (0.10 g, 0.192 mmol) in DMF (2 mL) was added DIPEA (0.10 mL, 0.576 mmol), 2-fluoroprop-2-enoic acid (0.034 g, 0.384 mmol) and 50% solution of T₃P in EtOAc (0.366 mL, 0.576 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep HPLC to afford title compound 2-fluoro-*N*-((1-((4-methoxy-3-((6-methoxy-2,3-dihydro-1*H*-indene)-5-sulfonamido)benzo[*d*]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 30**; 40 mg, 37.73%) as an off-white solid. TLC: 10% MeOH in DCM. (See analytical data in Table 1).

EXAMPLES 31-32

[1622] Scheme 16: Synthesis of 2-((tert-butoxycarbonyl amino) ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[*d*]isoxazol-6-yl)methyl)-1*H*pyrazol4yl) methyl) carbamate (Syn. Ex. 31) and 2-aminoethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[*d*]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl) carbamate (Syn. Ex. 32)



[1623] Synthesis of *tert*-butyl (2-(((4-nitrophenoxy) carbonyl) oxy) ethyl) carbamate (42)

[1624] To a stirred solution of compound **41** (2.0 g, 12.406 mmol) in DCM (20 mL) was added Et₃N (3.48 mL, 24.813 mmol) and 4-nitrophenyl carbonochloridate (3.75 g, 18.609 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 24h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by combi flash with 20-25% ethyl acetate in heptane to afford title compound **42** (1.50 g, 28.30%) as a pale-yellow semi-solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.43 - 8.26 (m, 2H), 7.69 - 7.48 (m, 2H), 7.14 - 7.02 (m, 1H), 4.22 (br t, J = 5.4 Hz, 2H), 3.30 - 3.26 (m, 2H), 1.45 - 1.34 (m, 9H).

[1625] **Synthesis of 2-((tert-butoxycarbonyl)amino)ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 31)**

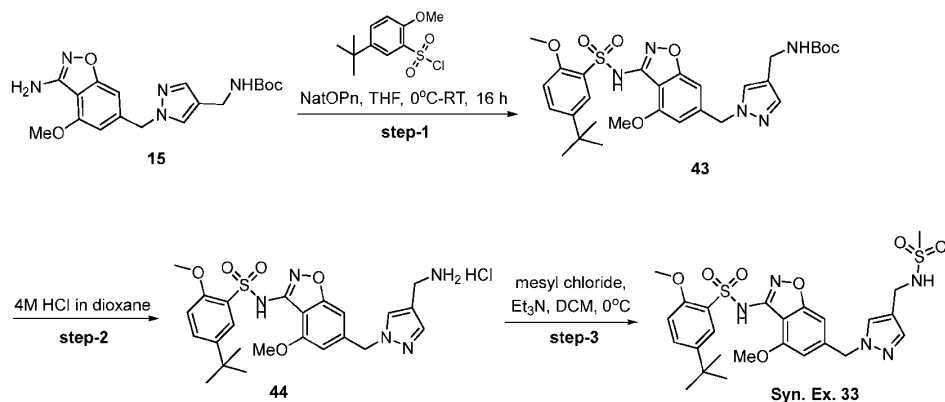
[1626] To a stirred solution of compound **21** (0.25 g, 0.492 mmol) in DMF (3 mL) was added Et₃N (0.2 mL, 1.476 mmol) followed by compound **42** (0.24 g, 0.738 mmol) in DMF (2 mL) drop wise at 0°C. The reaction mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography with 4% MeOH in DCM to afford title compound 2-((tert-butoxycarbonyl)amino)ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 31**; 0.24 g, 74.07%) as an off-white solid. (See analytical data in Table 1).

[1627] **Synthesis of 2-aminoethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 32)**

[1628] To a stirred solution of **Syn. Ex. 31** (0.13 g, 0.197 mmol) in DCM (1.5 mL) was added 4M HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound 2-aminoethyl((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate hydrochloride (**Syn. Ex. 32**; 96 mg, 82.05%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 33

[1629] Scheme 17: 5-(*tert*-butyl)-2-methoxy-*N*-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1*H*-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 33)



[1630] Synthesis of *tert*-butyl ((1-((3-((5-(*tert*-butyl)-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl) carbamate (43)

[1631] To a solution of compound **15** (0.40 g, 1.071 mmol) in THF (15 mL) was added 1M solution of KO^tBu in THF (3.2mL, 3.213 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. followed by the addition of 5-(*tert*-butyl)-2-methoxybenzenesulfonyl chloride (0.36 g, 1.392 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography using 0-72% EA in Heptane to afford title compound **43** (0.22 g, 34.26%) as an off-white solid. LCMS calculated for C₂₉H₃₇N₅O₇S: 599.24; Found: 600.79 (M+1).

[1632] Synthesis of *N*-(6-((4-(aminomethyl)-1*H*-pyrazol-1-yl) methyl)-4-methoxybenzo[d] isoxazol-3-yl)-5-(*tert*-butyl)-2-methoxybenzenesulfonamide hydrochloride (**44**)

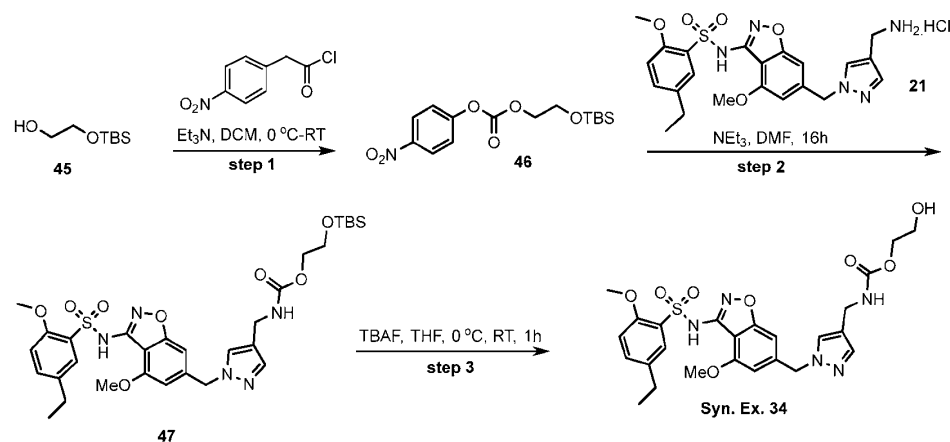
[1633] To a stirred solution of compound **43** (0.22 g, 0.366 mmol) in DCM (3 mL) was added 4M HCl in 1,4-Dioxane (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **44** (0.17 g, 86.73%) as an off-white solid. LCMS calculated for C₂₄H₂₉N₅O₅S: 499.19; Found: 500.78 (M+1).

[1634] **Synthesis of 5-(tert-butyl)-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 33)**

[1635] To a solution of compound **44** (0.15 g, 0.279 mmol) in DCM (1 mL) was added TEA (0.11 g, 0.839 mmol) followed by methane sulfonyl chloride **5** (0.041 g, 0.362 mmol) in DCM (1mL) drop-wise at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep HPLC to afford title compound 5-(tert-butyl)-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 33**; 85 mg, 52.79%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 34

[1636] **Scheme 18: Synthesis of 2-hydroxyethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 34)**



[1637] **Synthesis of 2-((tert-butyldimethylsilyl)oxy)ethyl (4-nitrophenyl) carbonate (46)**

[1638] To a stirred solution of compound **45** (0.50 g, 2.835 mmol) in DCM (5 mL) was added Et₃N (1 mL, 7.087 mmol) and (4-nitrophenyl) carbonochloridate (0.56 g, 2.835 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL), extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄,

filtered, and concentrated under reduced pressure. The crude was purified by combi flash chromatography using 7-12% of EA in Heptane to afford title compound **46** (0.32 g, 33.05%) as a brown oil. LCMS calculated for C₁₅H₂₃NO₆Si: 341.13; Found: the expected product from the reaction was not ionised as evidenced from LCMS.

[1639] Synthesis of 2-((tert-butyldimethylsilyl)oxy)ethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl) carbamate (47)

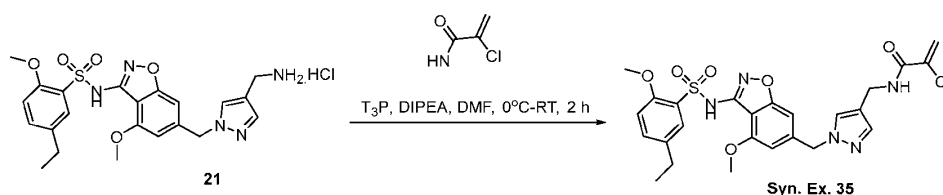
[1640] To a stirred solution of compound **21** (0.25 g, 0.492 mmol) in DMF (3 mL) was added Et₃N (0.2 mL, 1.476 mmol) followed by of compound **46** (0.251 g, 0.738 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (50 mL), extracted with EtOAc (3 x 50 mL) and the combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography with 80-90% EA in Heptane to afford title compound **47** (0.16 g, 48.33%) as a brown solid. LCMS calculated for C₃₁H₄₃N₅O₈SSi: 673.26; Found: 674.80 (M+1).

[1641] Synthesis of 2-hydroxyethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 34)

[1642] To a stirred solution of compound **47** (0.14 g, 0.207 mmol) in THF (2.0 mL) at 0 °C was added 1M TBAF solution in THF (0.4 mL, 0.4155 mmol). The reaction mixture was stirred for 1h at room temperature. After completion (monitored by TLC), the mixture was concentrated under reduced pressure to obtain brown gummy compound which was purified by prep HPLC to afford title compound 2-hydroxyethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 34**; 17 mg, 14.65%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 35

[1643] Scheme 19: Synthesis of 2-chloro-N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 35)

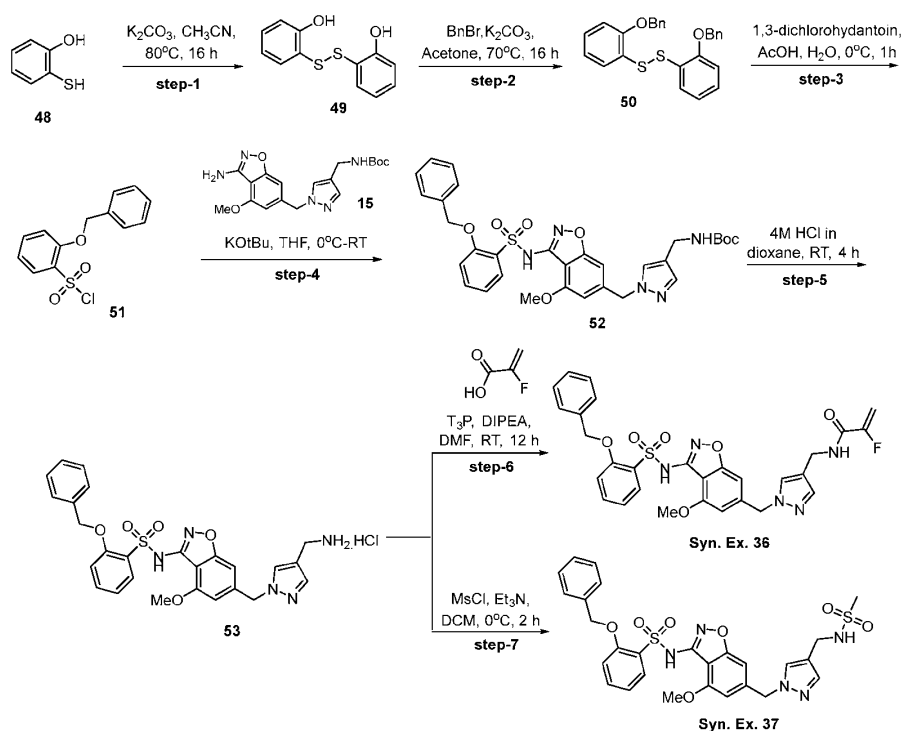


[1644] Synthesis of 2-chloro-N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 35)

[1645] To a stirred solution of compound **21** (0.13 g, 0.255 mmol) in DMF (3 mL) was added DIPEA (0.13 mL, 0.767 mmol) and 2-chloroacrylic acid (0.040 g, 0.382 mmol) followed by 50% solution of T₃P in EtOAc (0.48 g, 0.767 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi flash chromatography (neutral silica) using 80% EtOAc in Heptane to afford title compound 2-chloro-N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 35**; 10 mg, 6.97%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 36-37

[1646] Scheme 20: Synthesis of N-((1-((3-((2-(benzyloxy) phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 36) and 2-(benzyloxy)-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (Syn. Ex. 37)



[1647] Synthesis of 2,2'-disulfanediyldiphenol (49)

[1648] To a solution of 2-mercaptophenol **48** (4.0 g, 31.703 mmol) in ACN (60 mL) was added K_2CO_3 (13.14 g, 95.109 mmol). The reaction mixture was stirred at $80^\circ C$ for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to afford title compound **49** (3.20 g, 40.35%) as a light-yellow liquid. LCMS calculated for $C_{12}H_{10}O_2S_2$: 250.01; Found: 251.13 (M+1).

[1649] Synthesis of 1,2-bis(2-(benzyloxy) phenyl) disulfane (50)

[1650] To a solution of 2,2'-disulfanediyldiphenol **49** (3.20 g, 12.783 mmol) in Acetone (32 mL) at room temperature was added K_2CO_3 (8.83 g, 63.915 mmol) and bromomethyl benzene (5.46 g, 31.957 mmol). The reaction mixture was stirred at $70^\circ C$ for 16 h. After completion (monitored by TLC), the mixture was quenched with water (100 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi flash column chromatography using 5-10% EtOAc in Heptane to afford title compound **50** (3.0 g,

54.54%) as an off-white solid. LCMS calculated for C₂₆H₂₂O₂S₂: 430.11; Found: 431.20 (M+1).

[1651] Synthesis of 2-(benzyloxy)benzenesulfonyl chloride (51)

[1652] To a solution of compound **50** (0.80 g, 1.857 mmol) in ACN (3 mL), AcOH (1.20 mL) and H₂O (0.80 mL) at 0 °C was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (0.732 g, 3.716 mmol) in ACN (1.0 mL) drop wise. The reaction mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched with saturated NaHCO₃ solution (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford title compound **51** (0.45 g, 85.71%) as an off-white solid. LCMS calculated for C₁₃H₁₁ClO₃S: 282.01; Found: 263.22 [(M-1); LCMS shows sulphonic acid mass fragment].

[1653] Synthesis of *tert*-butyl ((1-((3-((2-(benzyloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)carbamate (52)

[1654] To a solution of compound **15** (0.40 g, 1.071 mmol) in THF (10 mL) was added 1M solution of KO^tBu in THF (3.2 mL, 3.213 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. followed by addition of compound **51** (0.36 g, 1.285 mmol). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was dried under reduced pressure. The crude was purified by combi flash chromatography (neutral silica gel) using 35-40% EtOAc in Heptane to afford title compound **52** (0.18 g, 27.14%) as a brown solid. LCMS calculated for C₃₁H₃₃N₅O₇S: 619.21; Found: 620.44 (M+1).

[1655] Synthesis of *N*-(6-((4-(aminomethyl)-1*H*-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-(benzyloxy)benzenesulfonamide hydrochloride (53)

[1656] To a solution of compound **52** (0.18 g, 0.290 mmol) in DCM (2 mL) was added 4M HCl (in Dioxane (0.2 mL, 0.87 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O (3 x 5 mL) followed by EtOAc (5 mL) and dried under reduced pressure to afford title compound **53** (0.18 g, HCl salt) as a light brown solid. LCMS calculated for C₂₆H₂₅N₅O₅S: 519.16; Found: 520.40 (M+1).

[1657] Synthesis of *N*-((1-((3-((2-(benzyloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 36)

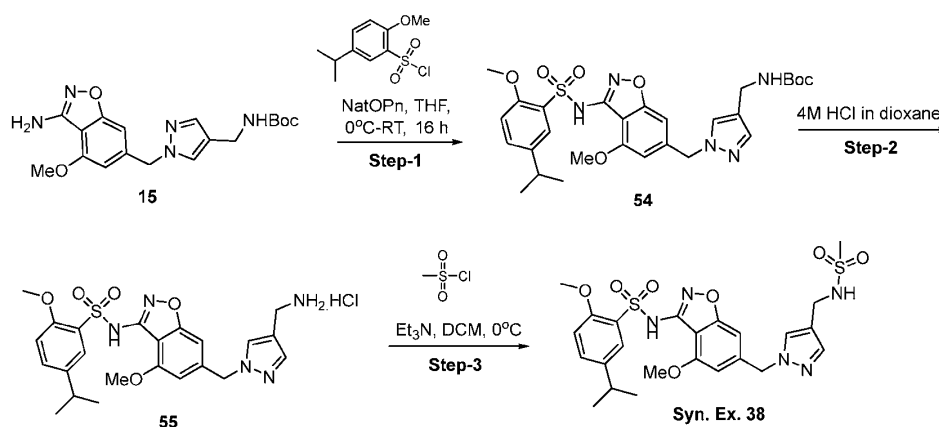
[1658] To a stirred solution of compound **53** (0.08 g, 0.143 mmol) in DMF (1 mL) was added DIPEA (0.075 mL, 0.431 mmol), 2-fluoroacrylic acid (0.025 g, 0.287 mmol) followed by 50% solution of T₃P in EtOAc (0.27 mL, 0.429 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12h. After completion (monitored by TLC), the mixture was quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N*-((1-((3-((2-(benzyloxy) phenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl)-2-fluoroacrylamide (**Syn. Ex. 36**; 22 mg, 25.98%) as a white solid. (See analytical data in Table 1).

[1659] **Synthesis of 2-(benzyloxy)-*N*-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1*H*-pyrazol-1-yl) methyl) benzo[d]isoxazol-3-yl) benzenesulfonamide (Syn. Ex. 37)**

[1660] To a solution of compound **53** (0.10 g, 0.179 mmol) in DCM (2 mL) was added Et₃N (0.075 mL, 0.539 mmol) followed by methane sulfonyl chloride (0.020 g, 0.179 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (10 mL) and extracted with DCM. The organic layer dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound 2-(benzyloxy)-*N*-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1*H*-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 37**; 0.019 g, 17.75%) as a white solid. (See analytical data in Table 1).

EXAMPLE 38

[1661] **Scheme 22: Synthesis of 5-isopropyl-2-methoxy-*N*-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1*H*-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 38)**



[1662] Synthesis of *tert*-butyl((1-((3-((5-isopropyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl)carbamate (54**)**

[1663] To a solution of compound **15** (0.25 g, 0.669 mmol) in THF (10 mL) was added 1M solution of KOtBu in THF (2.0 mL, 2.008 mmol) drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. followed by the addition of 5-isopropyl-2-methoxybenzenesulfonyl chloride (0.21 g, 0.874 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **54** (0.350 g, 89.28%) as an off-white solid. LCMS calculated for C₂₈H₃₅N₅O₇S: 585.22; Found: 584.40 (M-1).

[1664] Synthesis of *N*-(6-((4-(aminomethyl)-1*H*-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-isopropyl-2-methoxybenzenesulfonamide hydrochloride (55**)**

[1665] To a solution of compound **54** (0.25 g, 0.426 mmol) in DCM (3 mL) was added HCl (4 mol/L) in Dioxane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was triturated with DCM (2 x 5 mL), co-distilled with Et₂O and dried under reduced pressure to afford title compound **55** (0.20 g, HCl salt) as an off-white solid. LCMS calculated for C₂₃H₂₇N₅O₅S: 485.17; Found: 484.40 (M-1).

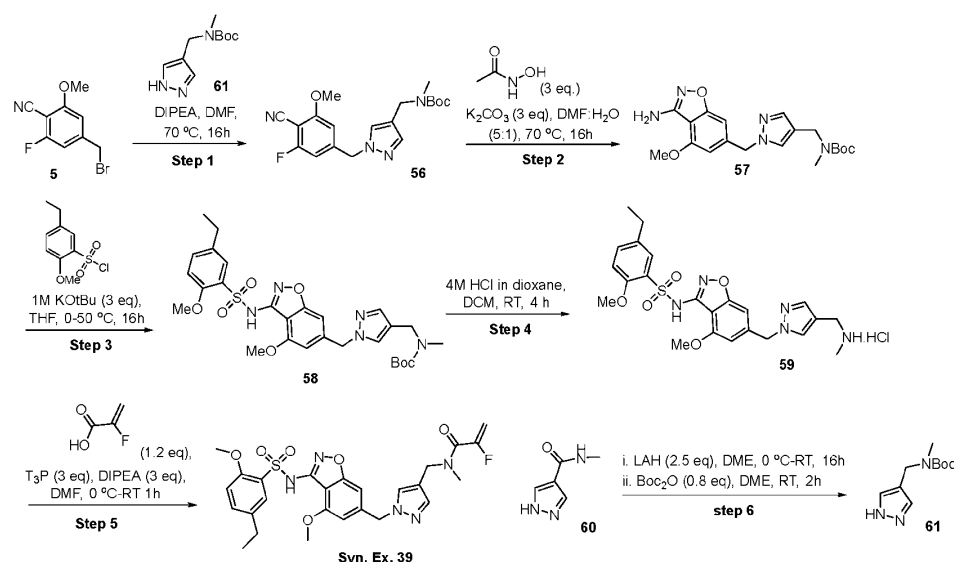
[1666] Synthesis of 5-isopropyl-2-methoxy-*N*-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1*H*-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 38)

[1667] To a solution of compound **55** (0.18 g, 0.344 mmol) in DCM (4 mL) was added Et₃N (0.096 mL, 0.688 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min.

followed by drop wise addition of methane sulfonyl chloride (0.078 g, 0.688 mmol) in DCM (1 mL). The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was evaporated under reduced pressure. The crude was purified by prep HPLC to afford title 5-isopropyl-2-methoxy-N-(4-methoxy-6-((4-(methylsulfonamidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 38**; 55 mg, 28.30%) (See analytical data in Table 1).

EXAMPLE 39

[1668] **Scheme 23: N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoro-N-methylacrylamide (**Syn. Ex. 39**)**



[1669] **Synthesis of *tert*-butyl ((1-(4-cyano-3-fluoro-5-methoxybenzyl)-1H-pyrazol-4-yl)methyl) (methyl)carbamate (**56**)**

[1670] To a solution of compound **61** described below (0.571 g, 2.703 mmol) in DMF (6 mL) was added DIPEA (1.28 mL, 7.374 mmol) followed by compound **5** (0.60 g, 2.458 mmol). The reaction mixture was stirred at 60 °C for 6h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography using 20-25% EA in Heptane to afford title compound **56** (0.55 g, 59.78%) as a pale-yellow semi solid. LCMS calculated for C₁₉H₂₃FN₄O₃: 374.17; Found: 375.59 (M+1).

[1671] **Synthesis of *tert*-butyl ((1-((3-amino-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl)methyl)(methyl)carbamate (57)**

[1672] To a solution of compound **56** (0.70 g, 1.869 mmol) in DMF (7 mL) and water (4 mL) were added K₂CO₃ (0.77 g, 5.608 mmol) and *N*-hydroxy acetamide (0.420 g, 5.608 mmol). The reaction mixture was stirred at 70 °C for 16h. After completion (monitored by TLC), the mixture was diluted with water (10 mL) and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **57** (0.65 g, 89.77%) as a yellow solid. LCMS calculated for C₁₉H₂₅N₅O₄: 387.19; Found: 388.30 (M+1).

[1673] **Synthesis of *tert*-butyl((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)(methyl)carbamate (58)**

[1674] To a solution of compound **57** (0.60 g, 1.548 mmol) in THF (20 mL) was added 1M solution of KO^tBu in THF (4.6 mL, 4.644 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by the addition of 5-ethyl-2-methoxybenzenesulfonyl chloride (0.472 g, 2.013 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash column chromatography using 55-60% EA: Heptane to afford title compound **58** (0.55 g, 60.70%) as an off-white solid. LCMS calculated for C₂₈H₃₅N₅O₇S: 585.22; Found: 586.65 (M+1).

[1675] **Synthesis of 5-ethyl-2-methoxy-*N*-(4-methoxy-6-((4-((methylamino)methyl)-1*H*-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (59)**

[1676] To a solution of compound **58** (0.53 g, 0.904 mmol) in DCM (6 mL) was added 4M HCl in 1,4 Dioxane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **59** (0.40 g, HCl salt) as an off-white solid. LCMS calculated for C₂₃H₂₇N₅O₅S: 485.17; Found: 486.77 (M+1).

[1677] **Synthesis of *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)-2-fluoro-*N*-methylacrylamide (Syn. Ex. 39)**

[1678] To a stirred solution of compound **59** (0.15 g, 0.287 mmol) in DMF (2 mL) was added DIPEA (0.15 mL, 0.862 mmol) and 2-fluoroacrylic acid (0.031 g, 0.344 mmol) and

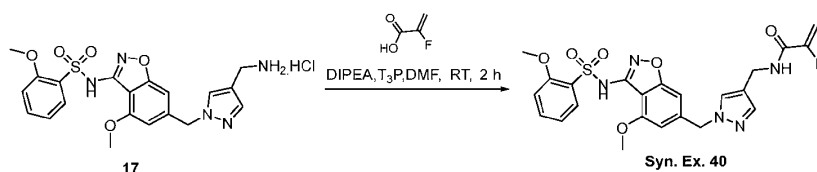
50% T₃P in EtOAc (0.54 mL, 0.861 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)-2-fluoro-*N*-methylacrylamide (**Syn. Ex. 39**; 26 mg, 16.25%) as an off-white solid. TLC: 10% MeOH in DCM. (See analytical data in Table 1).

[1679] Synthesis of tert-butyl ((1*H*-pyrazol-4-yl)methyl)(methyl)carbamate (61)

[1680] To a stirred solution of compound **60** (1.0 g, 7.991 mmol) in 1,2-Dimethoxyethane (20 mL) was added LAH (2.0 mol/L) in THF (9.1 mL, 19.97 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with 20% NaOH in water (80 mL) and extracted with DME. The organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was dissolved in 1,2-dimethoxyethane (50 mL) and added di-*tert*-butyl dicarbonate (1.36 mL, 6.297 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography to afford title compound **61** (0.50 g, 29.76%) as a pale-yellow liquid. LCMS calculated for C₁₀H₁₇N₃O₂: 211.13; Found: 212.30 (M+1).

EXAMPLE 40

[1681] Scheme 24: 2-fluoro-*N*-((1-((4-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 40**)**

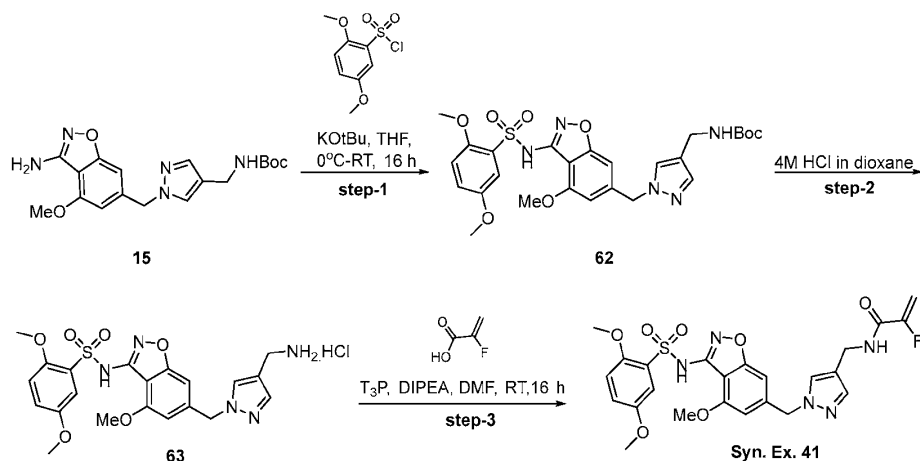


[1682] Synthesis of 2-fluoro-*N*-((1-((4-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 40**)**

[1683] To a stirred solution of compound **17** (0.14 g, 0.291 mmol) in DMF (2 mL) was added 2-fluoroacrylic acid (0.052 g, 0.582 mmol), DIPEA (0.152 mL, 0.873 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. followed by addition of 50% T₃P in EtOAc (0.55 mL, 0.873 mmol). The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), it was quenched with ice-cold water (20 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound 2-fluoro-N-((1-((4-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 40**; 21 mg, 14.00%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 41

[1684] **Scheme 25: Synthesis of N-((1-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 41**)**



[1685] **Synthesis of tert-butyl ((1-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**62**)**

[1686] To a stirred solution of compound **15** (0.40 g, 1.071 mmol) in THF (8 mL) were added 1M KO^tBu in THF (3.2 mL, 3.213 mmol), 2,5-dimethoxybenzenesulfonyl chloride **2** (0.506 g, 2.142 mmol) dissolved in THF (2mL) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi flash

column chromatography using 65% EtOAc/ Hexane to afford title compound *tert*-butyl((1-((3-((2,5-dimethoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl) carbamate **62** (0.30 g, 48.85%) as a white solid. LCMS calculated for C₂₆H₃₁N₅O₈S: 573.19; Found: 574.64 (M+1).

[1687] Synthesis of N-(6-((4-(aminomethyl)-1*H*-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2,5-dimethoxybenzenesulfonamide hydrochloride (63**)**

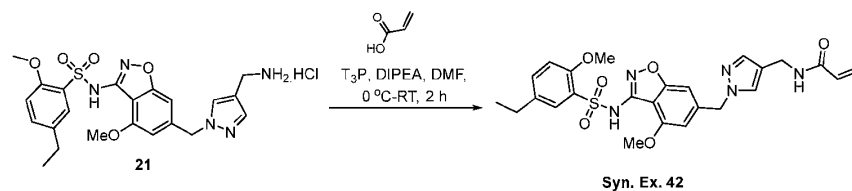
[1688] To a solution of compound **62** (0.30 g, 0.522 mmol) in DCM (5 mL) was added 4M HCl in 1,4 Dioxane (3 mL) at 0 °C. The reaction was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with DCM (2 x 5 mL), co-distilled with ether, dried under reduced pressure to afford title compound **63** (0.20 g, 75.18%, HCl salt) as an off-white solid. LCMS calculated for C₂₁H₂₃N₅O₆S: 473.14; Found: 474.65 (M+1).

[1689] Synthesis of N-((1-((3-((2,5-dimethoxy phenyl)sulfonamido)-4-methoxy benzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl)-2-fluoroacrylamide (Syn. Ex. 41)

[1690] To a solution of compound **63** (0.10 g, 0.196 mmol) in DMF (2 mL) was added DIPEA (0.076 mL, 0.588 mmol), 2-fluoroacrylic acid (0.035 g, 0.392 mmol) and 50% T₃P in EtOAc (0.373 mL, 0.588 mmol) at 0 °C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), it was quenched with ice-cold water (20 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title *N*-((1-((3-((2,5-dimethoxy phenyl)sulfonamido)-4-methoxy benzo[d]isoxazol-6-yl) methyl)-1*H*-pyrazol-4-yl) methyl)-2-fluoroacrylamide (**Syn. Ex. 41**; 7 mg, 6.60%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 42

[1691] Scheme 26: Synthesis of N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 42)

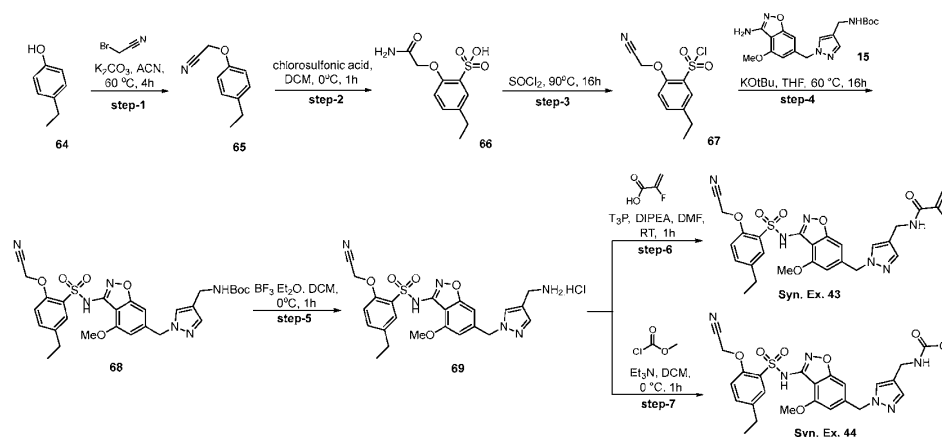


[1692] To a stirred solution of compound **21** (0.10 g, 0.196 mmol) in DMF (2 mL) was added DIPEA (0.076 mL, 0.590 mmol), acrylic acid (0.017 g, 0.235 mmol), 50% T₃P in

EtOAc (0.373 mL, 0.588 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, and extracted with 10% MeOH/ DCM (2 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 42**; 10 mg, 9.70%) as an off-white solid. TLC: 5% MeOH in DCM; (R_f: 0.55), (See analytical data in Table 1).

EXAMPLES 43-44

[1693] **Scheme 27: *N*-((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 43**) and methyl ((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1*H*-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 44**)**



[1694] **Synthesis of 2-(4-ethylphenoxy)acetonitrile (65)**

[1695] To a solution of 4-ethylphenol **64** (5.0 g, 40.926 mmol) in ACN (30 mL) were added K₂CO₃ (16.96 g, 122.77 mmol) and 2-bromoacetonitrile (7.36 g, 61.389 mmol). The mixture was stirred at 60 °C for 4h. After completion (monitored by TLC), the mixture was quenched with water (50 mL), extracted with EtOAc (3 x 30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi flash chromatography (neutral silica) with 10% EtOAc in Heptane to afford title compound **65** (6.40 g, 97.11%) as a pale-yellow liquid. TLC: 30% EtOAc in Heptane. LCMS calculated for C₁₀H₁₁NO: 161.08; Found: 162.14 (M+1).

[1696] **Synthesis of 2-(2-(2-amino-2-oxoethoxy)-5-ethylbenzenesulfonic acid (66)**

[1697] To a solution of compound **65** (6.4 g, 39.70 mmol) in DCM (30 mL) was added chlorosulfonic acid (13.8 g, 119.10 mmol) at 0 °C. The mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold NaHCO₃ solution (20 mL), extracted with DCM, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **66** (4 g, 38.87%) as an off-white solid. TLC: 30% EtOAc in Heptane (R_f: 0.6) LCMS calculated for C₁₀H₁₃NO₅S: 259.05; Found: 258.17 (M-1).

[1698] Synthesis of 2-(cyanomethoxy)-5-ethylbenzenesulfonyl chloride (67)

[1699] To a compound **66** (1.5 g, 5.785 mmol) was added SOCl₂ (10 mL) at 0 °C. The mixture was stirred at 90 °C for 16h. After completion (monitored by TLC), it was concentrated under reduced pressure and co-distilled with toluene (2 x 10 mL). The crude was purified by column chromatography (5-10% EtOAc in Heptane over neutral silica) to afford title compound **67** (1.5 g, 99.86%) as a colorless semi-solid. TLC: 30% EtOAc in Heptane (R_f: 0.5); LCMS calculated for C₁₀H₁₀ClNO₃S: 259.01; Found: 256.99 (M-2).

[1700] Synthesis of tert-butyl ((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (68)

[1701] To a stirred solution of compound **15** (0.74 g, 2.008 mmol) in THF (20 mL) was added 1M KOtBu in THF (6.0 mL, 6.024 mmol) at 0 °C. The mixture was stirred for 10 min. followed by addition of compound **67** (1.04 g, 4.017 mmol) at 0 °C. The mixture was stirred at 60 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography (70-80% EtOAc in heptane) with neutral silica to afford title compound **68** (0.18 g, 15.12%) as a pale-yellow solid. TLC: 80% EtOAc in Heptane. LCMS calculated for C₂₈H₃₂N₆O₇S: 596.21; Found: 597.54 (M+1).

[1702] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-(cyanomethoxy)-5-ethylbenzenesulfonamide (69)

[1703] To a stirred solution of compound **68** (100 mg, 0.167 mmol) in DCM (2 mL) was added 50% Boron trifluoride etherate in diethyl ether (0.056 mL, 0.200 mmol) at 0 °C. The mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O (2 x 10 mL) and concentrated under reduced pressure to afford title compound **69** (90 mg, HCl salt) as a light-yellow solid. TLC: 10% MeOH in DCM (R_f: 0.3). LCMS calculated for C₂₃H₂₄N₆O₅S: 496.15; Found: 497.71 (M+1).

[1704] **Synthesis of *N*-((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 43)**

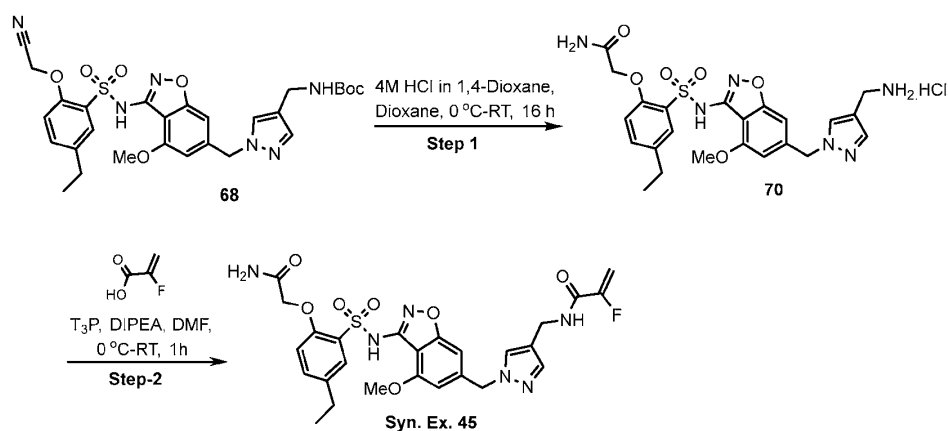
[1705] To a stirred solution of compound **69** (90 mg, 0.168 mmol) in DMF (2 mL) were added DIEPA (0.088 mL, 0.506 mmol), 2-fluoroacrylic acid (30 mg, 0.336 mmol) and 50% T₃P in EtOAc (0.320 mL, 0.504 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N*-((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 43**, 10 mg, 10.41%) as an off-white solid. TLC: 10% MeOH in DCM; (R_f, 0.6), (See analytical data in Table 1).

[1706] **Synthesis of methyl ((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 44)**

[1707] To a stirred solution of compound **69** (0.12 g, 0.225 mmol) in DCM (2 mL) were added Et₃N (0.094 mL, 0.675 mmol) followed by methyl chloroformate (25 mg, 0.270 mmol) in DCM (0.5 mL) portion-wise while maintaining the pH ~7-8. The mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with DCM (3 x 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl ((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 44**; 110 mg, 14.51%) as an off-white solid. TLC: 10% MeOH in DCM, (R_f, 0.55). (See analytical data in Table 1).

EXAMPLE 45

[1708] **Scheme 28: Synthesis of *N*-((1-((3-((2-(2-amino-2-oxoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 45)**



[1709] Synthesis of 2-(2-(N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)acetamide hydrochloride (70)

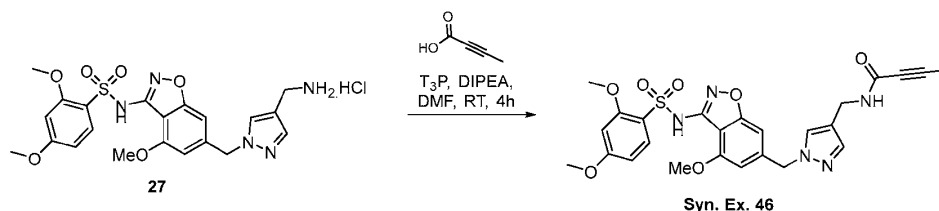
[1710] To a stirred solution of compound **68** (60 mg, 0.100 mmol) in 1,4-Dioxane (1 mL) was added 4M HCl in 1,4-dioxane (0.12 mL, 0.502 mmol) at 0 °C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O (2 x 10 mL) and dried under reduced pressure to afford title compound **70** (60 mg, HCl salt) as a pale-yellow solid. TLC: 10% MeOH in DCM-(R_f: 0.0). LCMS calculated for C₂₃H₂₆N₆O₆S: 514.16; Found: 515.39 (M+1)

[1711] Synthesis of N-((1-((3-((2-(2-amino-2-oxoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide

[1712] To a stirred solution of compound **70** (60 mg, 0.108 mmol) in DMF (1 mL) were added DIPEA (0.057 mL, 0.326 mmol), 2-fluoroacrylic acid (19 mg, 0.216 mmol) and 50% T₃P in ethyl acetate (0.2 mL, 0.324 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N-((1-((3-((2-(2-amino-2-oxoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide* (**Syn. Ex. 45**; 10 mg, 15.87%) as an off-white solid. TLC: 5% MeOH in DCM-(R_f: 0.55). (See analytical data in Table 1).

EXAMPLE 46

[1713] **Scheme 29: Synthesis of *N*-((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (Syn. Ex. 46)**

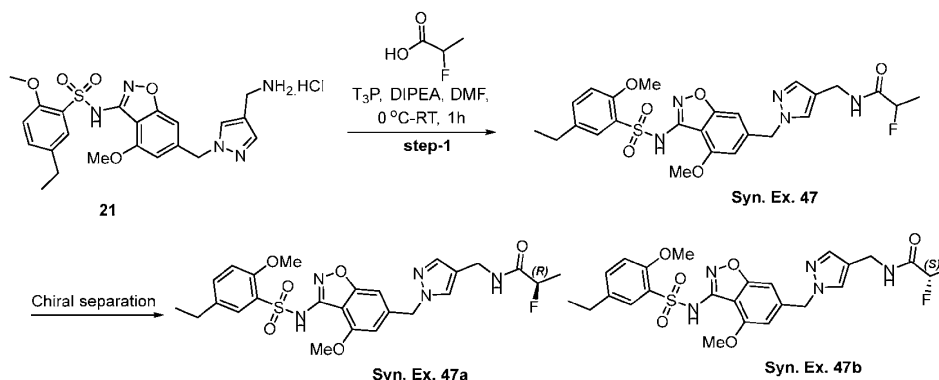


[1714] **Synthesis of *N*-((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide**

[1715] To a stirred solution of compound **27** (0.14 g, 0.274 mmol) in DMF (2 mL) was added DIPEA (0.14 mL, 0.823 mmol), but-2-ynoic acid (46 mg, 0.548 mmol) and 50% T₃P in ethyl acetate (0.522 mL, 0.822 mmol) at 0 °C. The mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with water (50 mL), extracted with 10% MeOH in DCM (3 x 50 mL), dried over anhydrous Na₂SO₄. The crude was purified by prep. HPLC to afford title compound *N*-((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 46**; 15 mg, 10.13%) as an off-white solid. TLC: 10% MeOH in DCM, (R_f: 0.35). (See analytical data in Table 1).

EXAMPLE 47

[1716] **Scheme 30: Synthesis of *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoropropanamide (Syn. Ex. 47)**



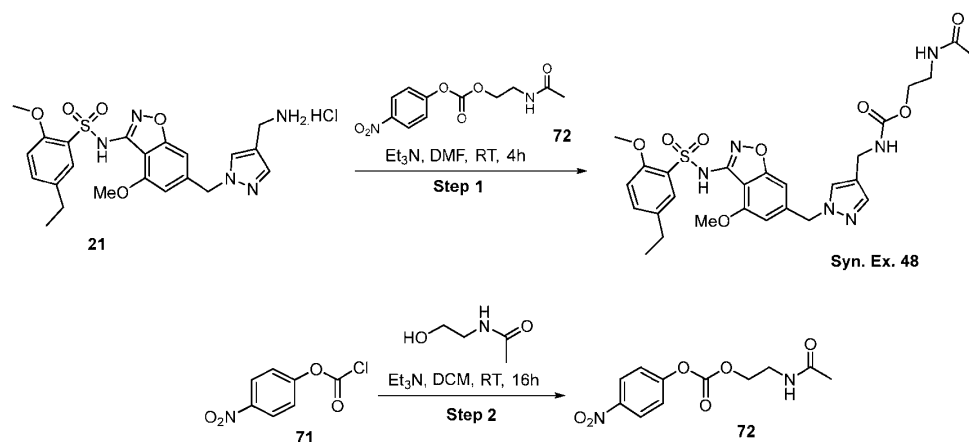
[1717] To a stirred solution of compound **21** (0.1 g, 0.196 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.590 mmol), 2-fluoropropanoic acid (36 mg, 0.392 mmol) and 50% T₃P in ethyl acetate (0.373 mL, 0.588 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoropropanamide (**Syn. Ex. 47**; 57.5 mg, 53.73%) as an off-white solid. TLC: 10% MeOH in DCM-(R_f: 0.58). (See analytical data in Table 1). **Syn. Ex. 47** (64mg) was purified by chiral HPLC to afford (*R*)-*N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoropropanamide (**Syn. Ex. 47a**; 10 mg) as an off-white solid. TLC: 10% MeOH in DCM-(R_f: 0.58). (See analytical data in Table 1) and (*S*)-*N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoropropanamide (**Syn. Ex. 47b**; 6 mg) as an off-white solid; The stereochemistry was randomly assigned and not definitively confirmed (See analytical data in Table 1)

[1718] **Chiral Method:**

[1719] Column: CHIRALPAK-IG (250 x 4.6mm, 5μm), Mobile Phase A: EtOH/MeOH, A/B:100%, Flow: 1.0 mL/min, PDA: IG_010 IS

EXAMPLE 48

[1720] **Scheme 31: Synthesis of 2-acetamidoethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 48**)**



[1721] Synthesis of 2-acetamidoethyl (4-nitrophenyl) carbonate (72)

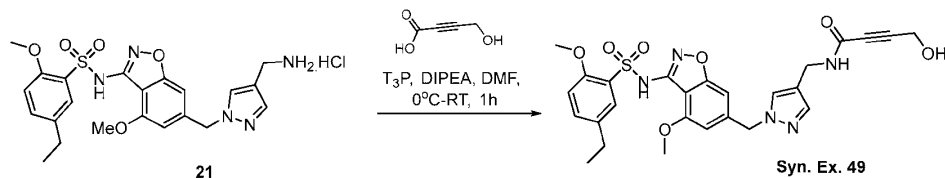
[1722] To a stirred solution of N-(2-hydroxyethyl)acetamide (0.51 g, 4.94 mmol) in DCM (10 mL) were added Et₃N (2.10 mL, 14.82 mmol) followed by 4-nitrophenyl carbonochloride **71** (0.995 g, 4.94 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **72** (0.60 g, 45.45%) as a yellow oil. LCMS calculated for C₁₁H₁₂N₂O₆: 268.07; Found: 269.13 (M+1).

[1723] Synthesis of 2-acetamidoethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 48)

[1724] To a stirred solution of compound **21** (0.14 g, 0.275 mmol) in DMF (3 mL) was added Et₃N (0.115 mL, 0.826 mmol) and compound **72** (0.088 g, 0.330 mmol) at 0 °C. The mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified prep. HPLC to afford title compound 2-acetamidoethyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 48**; 55 mg, 33.33%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 49

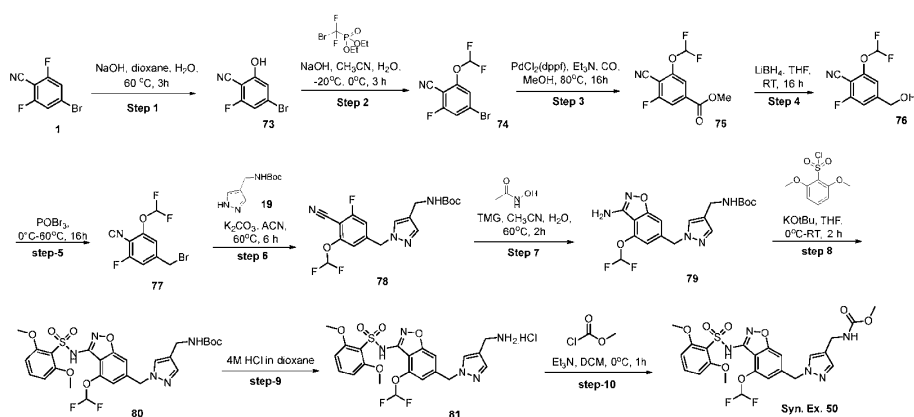
[1725] Scheme 32: Synthesis of *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-4-hydroxybut-2-ynamide (Syn. Ex. 49)



[1726] To a stirred solution of compound **21** (0.10 g, 0.196 mmol) in DMF (2 mL) were added DIPEA (0.10 mL, 0.588 mmol), 4-hydroxybut-2-ynoic acid (39 mg, 0.392 mmol) followed by 50% T₃P in ethyl acetate (0.37 mL, 0.588 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N*-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-4-hydroxybut-2-ynamide (Syn. Ex. 49; 20 mg, 18.51%) as an off-white solid. TLC: 5% MeOH in DCM; (R_f 0.6). (See analytical data in Table 1).

EXAMPLE 50

[1727] Scheme 32: Synthesis of methyl ((1-((4-(difluoromethoxy)-3-((2,6-dimethoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 50)



[1728] Synthesis of 4-bromo-2-fluoro-6-hydroxybenzonitrile (73)

[1729] To a stirred solution of compound **1** (20 g, 91.743 mmol) in 1,4-Dioxane: water (400 mL, 1:1) was added NaOH (21.79 g, 544.954 mmol) portion-wise at 0 °C. The mixture was stirred at 60 °C for 3h. After completion (monitored by TLC), the mixture was diluted with water (50 mL). The aqueous layer was acidified with 1N HCl to adjust the pH ~ 6 and extracted with ethyl acetate (3 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and crude was purified by combi-flash chromatography (neutral silica) with 20% EtOAc in Heptane to afford title compound **73** (15 g, 75.71%) as an off-white solid. LCMS calculated for C₇H₃BrFNO: 214.94; Found: NA. ¹H NMR (400 MHz, DMSO-d₆) δ 12.18 (br s, 1H), 7.55 (br d, J = 6.8 Hz, 1H), 7.25 (br d, J = 8.8 Hz, 1H).

[1730] **Synthesis of 4-bromo-2-(difluoromethoxy)-6-fluorobenzonitrile (74)**

[1731] To a stirred solution compound **73** (15 g, 69.441 mmol) in ACN: Water (300 mL, 1:1) was added NaOH (10.8 g, 270.819 mmol) at -20 °C. The mixture was stirred at -20 °C for 10 min. followed by addition of diethyl (bromodifluoromethyl)phosphonate (37.08 g, 138.882 mmol). The mixture was stirred at 0 °C and for 3h. After completion (monitored by TLC), the reaction was diluted with ice-cold water and extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography (neutral silica) with 20% EtOAc/Heptane to afford title compound **74** (11 g, 59.55%) as a colorless liquid. LCMS calculated for C₈H₃BrF₃NO: 264.94; Found: 266.2 (M+2).

[1732] **Synthesis of methyl 4-cyano-3-(difluoromethoxy)-5-fluorobenzoate (75)**

[1733] A stirred solution of compound **74** (4 g, 15.036 mmol) in MeOH (80 mL) in a steel bomb was purged with N₂ atmosphere for 10 min. followed by addition of Et₃N (4.2 mL, 30.072 mmol) and PdCl₂(dppf) (1.8 g, 2.596 mmol). The mixture was stirred at 80 °C for 16h under CO gas at 110 psi pressure. After completion (monitored by TLC), the mixture was filtered through a celite pad and washed with MeOH. The filtrate was concentrated under reduced pressure and crude was purified by combi-flash chromatography with 20% EtOAc/Hexane to afford title compound **75** (1.6 g, 43.47%) LCMS calculated for C₁₀H₆F₃NO₃: 245.03; Found: 246.5 (M+1).

[1734] **Synthesis of 2-(difluoromethoxy)-6-fluoro-4-(hydroxymethyl)benzonitrile (76)**

[1735] To a stirred solution of THF (30 mL) was added 2M LiBH₄ in THF (8.97 mL, 17.947 mmol) followed by methyl 4-cyano-3-(difluoromethoxy)-5-fluorobenzoate **75** (2.20 g,

8.973 mmol) in THF (10 mL) at 0°C. The mixture was stirred at RT for 16h. After completion (monitored by TLC), the mixture was quenched with cold water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **76** (1.7 g, 87.62%) as a white solid. LCMS calculated for C₉H₆F₃NO₂: 217.04; Found: NA; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.36 - 7.22 (m, 2H), 5.69 (br t, J = 5.1 Hz, 1H), 4.59 (br d, J = 4.9 Hz, 2H).

[1736] Synthesis of 4-(bromomethyl)-2-(difluoromethoxy)-6-fluorobenzonitrile (77)

[1737] To a stirred solution of compound **76** (1 g, 4.605 mmol) in 1,2-Dichloroethane (10 mL) was added POBr₃ (2.5 g, 9.210 mmol) at 0 °C. The mixture was stirred at 60 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM (3 x 100 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography with 12-18% EtOAc in heptane to afford title compound **77** (0.90 g, 70.31%) as a brown gummy solid. LCMS calculated for C₉H₅BrF₃NO: 278.95; Found: NA. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 - 7.25 (m, 3H), 4.76 (s, 2H).

[1738] Synthesis of tert-butyl ((1-(4-cyano-3-(difluoromethoxy)-5-fluorobenzyl)-1H-pyrazol-4-yl)methyl)carbamate (78)

[1739] To a stirred solution of compound **77** (0.40 g, 1.428 mmol) in ACN (10 mL) were added compound **19** (0.84 g, 4.284 mmol) followed by K₂CO₃ (0.39 g, 2.856 mmol) at room temperature. The mixture was stirred at 60 °C for 6h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, quenched with ice-cold water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and crude was purified by combi-flash chromatography (neutral silica) with 40% EtOAc in heptane to afford title compound **78** (0.20 g, 35.97%) as a colourless liquid. LCMS calculated for C₁₈H₁₉F₃N₄O₃: 396.14; Found: 397.10 (M+1).

[1740] Synthesis of tert-butyl ((1-((3-amino-4-(difluoromethoxy) benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (79)

[1741] To a stirred solution of compound **78** (0.40 g, 1.009 mmol) in acetonitrile (5 mL) and water (1 mL) was added acetohydroxamic acid (0.11g, 1.513 mmol) and 1,1,3,3-tetramethylguanidine (1.47 g, 12.765 mmol) at room temperature. The mixture was stirred at 60 °C for 2h. After completion (monitored by TLC), the reaction was quenched with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The organic layer was dried over

anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography with 40% EtOAc/Heptane to afford title compound **79** (0.30 g, 72.63%) as a colourless liquid. LCMS calculated for C₁₈H₂₁F₂N₅O₄: 409.16; Found: 410.2 (M+1).

[1742] Synthesis of tert-butyl ((1-((4-(difluoromethoxy)-3-((2,6-dimethoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (80)

[1743] To a stirred solution compound **79** (180 mg, 0.4397 mmol) in dry THF (10 mL) was added 1M KO^tBu in THF (1.31 mL, 1.319 mmol) at 0°C. The reaction was stirred for 10 min followed by addition of 2,6-dimethoxybenzenesulfonyl chloride (0.156 g, 0.6595 mmol) at 0°C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), mixture was quenched with ice cold water and acidified with 1N HCl to pH ~ 6.0. The aqueous layer was extracted with ethyl acetate (3x100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get title compound **80** (100 mg crude) as a brown solid. LCMS calculated for C₂₆H₂₉F₂N₅O₈S: 609.17; Found: 610.39 (M+1).

[1744] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl) methyl)-4-(difluoromethoxy) benzo[d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (81)

[1745] To a stirred solution of compound **80** (100 mg, 0.1640 mmol) in 1,4-Dioxane (4 mL) was added 4M HCl in 1,4 Dioxane (0.2 mL, 0.8202 mmol) at 0°C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), mixture was concentrated under reduced pressure. The residue was triturated with DCM (2 x 5 mL) was co-distilled with ether to afford title compound **81** (80 mg, HCl salt) as an off-white solid. LCMS calculated for C₂₁H₂₁F₂N₅O₆S: 509.12; Found: 510.2 (M+1).

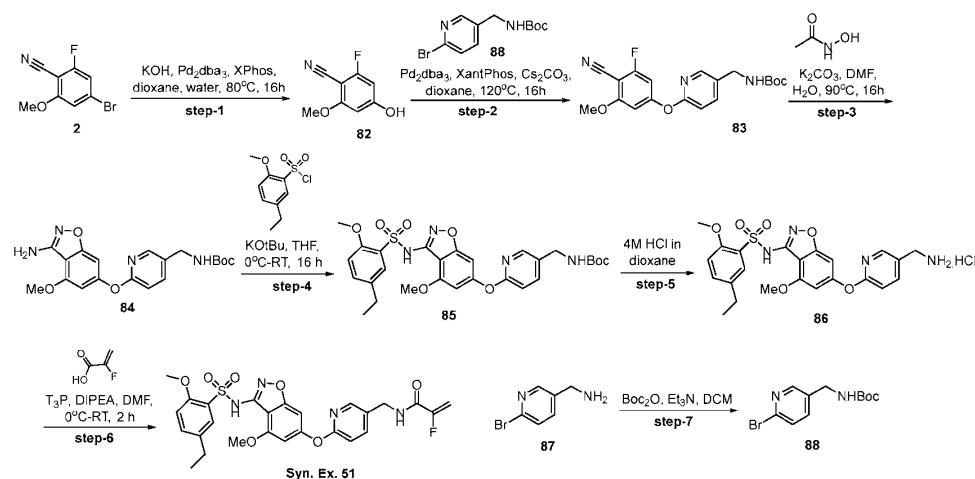
[1746] Synthesis of methyl ((1-((4-(difluoromethoxy)-3-((2,6-dimethoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 50)

[1747] To a stirred solution of compound **81** (70 mg, 0.128 mmol) in DCM (10 mL) was added Et₃N (0.09 mL, 0.641 mmol) and methyl chloroformate (12 mg, 0.128 mmol) in DCM (1 mL) at 0°C. The mixture was stirred at 0°C for 30 min. After completion (monitored by TLC), mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and crude was purified by prep. HPLC to afford title compound methyl ((1-((4-(difluoromethoxy)-3-((2,6-dimethoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-

yl)methyl)carbamate (**Syn. Ex. 50**; 4 mg, 5.55%) as an off-white solid. (See analytical Data in Table-1).

EXAMPLE 51

[1748] **Scheme 33: Synthesis of N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 51**)**



[1749] **Synthesis of 2-fluoro-4-hydroxy-6-methoxybenzonitrile (82)**

[1750] To a stirred solution of compound **2** (2.80 g, 12.171 mmol) in 1,4-Dioxane (30 mL) and water (3 mL) at room temperature was added KOH (2.04 g, 36.515 mmol). The mixture was purged with nitrogen gas for 10 min followed by addition of Pd₂(dba)₃ (0.55 g, 0.608 mmol) and XPhos (0.58 g, 1.217 mmol). The mixture was stirred at 80 °C for 16h. After completion (monitored by TLC), the mixture was filtered through a celite pad, washed with EtOAc (2 x 100 mL) and 10% MeOH in DCM. The filtrate was concentrated under reduced pressure and crude was triturated with Et₂O (100 mL), solid was dried under reduced pressure to afford title compound 2-fluoro-4-hydroxy-6-methoxybenzonitrile **82** (2.0 g, 98.52%) as a yellow solid. LCMS calculated for C₈H₆FN₂O₂: 167.04; Found: 168.01 (M+1).

[1751] **Synthesis of tert-butyl ((6-(4-cyano-3-fluoro-5-methoxyphenoxy)pyridin-3-yl)methyl)carbamate (83)**

[1752] To a stirred solution of compound **82** (1.0 g, 5.983 mmol) in 1,4-Dioxane (10 mL) was added compound **88** (1.88 g, 6.581 mmol), Cs₂CO₃ (4.87 g, 14.957 mmol) at room temperature. The mixture was degassed under N₂ atmosphere for 10 min followed by addition of Pd₂(dba)₃ (0.54 g, 0.598 mmol) and XantPhos (0.71 g, 1.196 mmol). The reaction was

stirred at 120 °C for 16h. After completion (monitored by TLC), the mixture was filtered through a celite pad and washed with EtOAc (2 x 200 mL). The filtrate was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and crude was purified by combi-flash chromatography using 30-40% EtOAc in Heptane to afford title compound **83** (0.55 g, 24.66%) as a brown liquid. LCMS calculated for C₁₉H₂₀FN₃O₄: 373.14; Found: 374.31 (M+1).

[1753] Synthesis of tert-butyl ((6-(4-cyano-3-fluoro-5-methoxyphenoxy)pyridin-3-yl)methyl)carbamate (84)

[1754] To a stirred solution of tert-butyl ((6-(4-cyano-3-fluoro-5-methoxyphenoxy)pyridin-3-yl)methyl)carbamate **83** (0.50 g, 1.339 mmol) in DMF (16 mL) and water (3 mL) at room temperature was added K₂CO₃ (0.92, 6.695 mmol). The mixture was stirred at room temperature for 5 min followed by addition of N-hydroxyacetamide (0.30 g, 4.017 mmol). The mixture was stirred at 90 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (50 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified combi-flash chromatography using 50-60% ethyl acetate in Heptane with neutral silica to afford title compound tert-butyl ((6-(4-cyano-3-fluoro-5-methoxyphenoxy)pyridin-3-yl)methyl)carbamate **84** (0.20 g, 38.68%) as a colourless gummy syrup. LCMS calculated for C₁₉H₂₂N₄O₅: 386.16; Found: 387.77 (M+1).

[1755] Synthesis of tert-butyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)carbamate (85)

[1756] To a stirred solution of tert-butyl ((6-(4-cyano-3-fluoro-5-methoxyphenoxy)pyridin-3-yl)methyl)carbamate **84** (0.15 g, 0.388 mmol) in THF (2 mL) at 0 °C was added 1M KOtBu in THF (1.16 mL, 1.164 mmol). The mixture was stirred at 0 °C under N₂ atmosphere for 10 min followed by addition of 5-ethyl-2-methoxybenzenesulfonyl chloride (0.11 g, 0.504 mmol). The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with ethyl acetate (2 x 60 mL). The organic layer was dried over anhydrous Na₂SO₄, was concentrated under reduced pressure and crude was purified by combi-flash column chromatography (60-70% of EtOAc in Heptane) over neutral silica to afford title compound **85** (0.17 g, 75.22%) as an off-white semi-solid. LCMS calculated for C₂₈H₃₂N₄O₈S: 584.19; Found: 585.30 (M+1).

[1757] Synthesis of tert-butyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)carbamate (86)

[1758] To a stirred solution of compound **85** (150 mg, 0.2565 mmol) in DCM (2 mL) was added 4M HCl in 1,4 Dioxane (0.64 mL, 2.566 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was triturated with ether and dried under reduced pressure to get title compound **86** (155 mg, 0.2143 mmol, HCl salt) as an off-white gummy solid.

[1759] **Synthesis of *tert*-Butyl ((6-bromopyridin-3-yl)methyl)carbamate (88)**

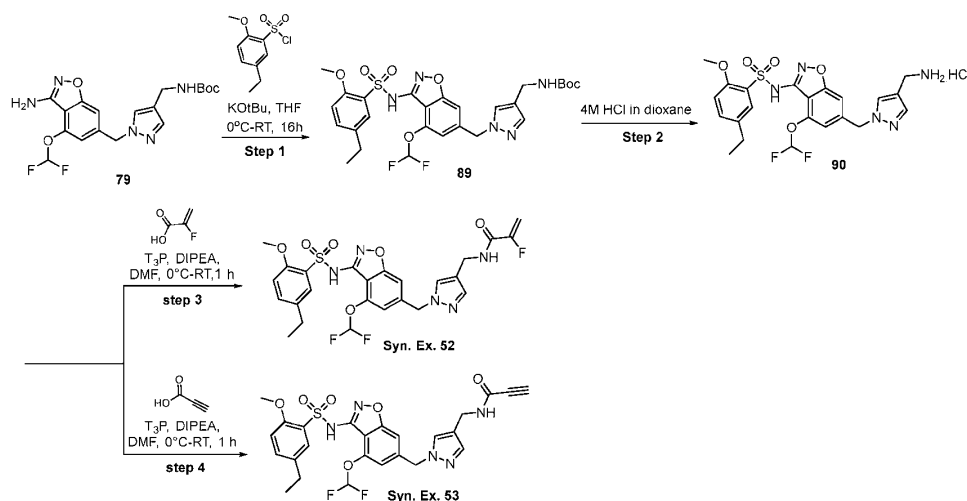
[1760] To a stirred solution of compound **87** (4 g, 21.385 mmol) in DCM (160 mL) was added Triethylamine (5.99 mL, 42.771 mmol) and (Boc)₂O (4.6 g, 21.385 mmol) drop wise. The reaction mixture was stirred at room temperature for 5 h. After completion, mixture was diluted with DCM, washed with ice-cold water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get title compound **88** (6 g, 97.33%) as an off-white solid. LCMS calculated for C₁₁H₁₅BrN₂O₂: 286.03; Found: 287.13 (M+1).

[1761] **Synthesis of N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 51)**

[1762] To a stirred solution of compound **86** (0.15 g, 0.287 mmol) in DMF (2 mL) were added 2-fluoroacrylic acid (0.038 g, 0.431 mmol) followed by DIPEA (0.15 mL, 0.861 mmol) and T₃P 50% in EtOAc (0.365 mL, 0.574 mmol). The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep-HPLC purification to afford title compound N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 51**; 6 mg, 3.75%) as an off-white solid.

EXAMPLES 52-53

[1763] **Scheme 34: Synthesis of N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 52) and N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 53)**



[1764] Synthesis of *tert*-Butyl ((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (89**)**

[1765] To a stirred solution of compound **79** (0.30 g, 0.732 mmol) in THF (20 mL) was added 1M KO^tBu in THF (2.19 mL, 2.198 mmol) at 0 °C and stirred for 10 min. followed by addition of 5-ethyl-2-methoxybenzenesulfonyl chloride (0.257 g, 1.098 mmol). The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to pH ~6 and extracted with EtOAc (3 x 100 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **89** (0.30 g, 67.41%) as a brown solid. LCMS calculated for C₂₇H₃₁F₂N₅O₇S: 607.19; Found: 608.30 (M+1).

[1766] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-(difluoromethoxy)benzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (90**)**

[1767] To a stirred solution of compound **89** (0.30 g, 0.493 mmol) in 1,4-Dioxane (10 mL) was added 4M HCl in 1,4-Dioxane (0.085 mL, 2.465 mmol) at 0 °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The solid precipitate was washed with DCM (2 x 5 mL), co-distilled with Et₂O and dried under reduced pressure to afford title compound **90** (0.25 g, 93.28%) as an off-white solid. LCMS calculated for C₂₂H₂₃F₂N₅O₅S: 507.14; Found: 506.2 (M-1).

[1768] **Synthesis of N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 52)**

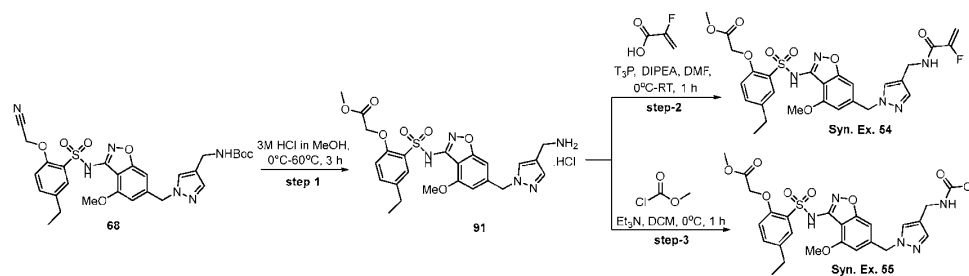
[1769] To a stirred solution of compound **90** (0.13 g, 0.238 mmol) in DMF (5 mL) was added DIPEA (0.125 mL, 0.716 mmol), 2-fluoroacrylic acid **4** (42 mg, 0.477 mmol) dissolved in DMF (1 mL) and 50% T₃P in EtOAc (0.45 mL, 0.716 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 52**; 5.0 mg, 3.62%) as an off-white solid. (See analytical data in Table 1).

[1770] **Synthesis of N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 53)**

[1771] To a stirred solution of compound **90** (0.13 g, 0.238 mmol) in DMF (5 mL) was added DIPEA (0.125 mL, 0.716 mmol), propiolic acid **5** (0.033 g, 0.477 mmol) dissolved in DMF (2 mL) and 50% T₃P in EtOAc (0.45 mL, 0.716 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound N-((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 53**; 14 mg, 10.52%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 54-55

[1772] **Scheme 35: methyl 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (Syn. Ex. 54) and and methyl 2-(4-ethyl-2-(N-(4-methoxy-6-((4-(((methoxycarbonyl)amino)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (Syn. Ex. 55)**



[1773] Synthesis of methyl 2-(2-(N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)acetate hydrochloride (91)

[1774] To a stirred solution of compound **68** (0.22 g, 0.368 mmol) in MeOH (2.5 mL) was added 3M HCl in MeOH (2.45 mL, 7.360 mmol) at 0 °C. The mixture was stirred at 60 °C for 3h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure and co-distilled with toluene (2 x 10 mL). The solid precipitate was washed with Et₂O (2 x 10 mL) and dried under reduced pressure to afford title compound **91** (0.20 g, HCl salt) as a light-yellow solid. LCMS calculated for C₂₄H₂₇N₅O₇S:529.16; Found: 530.93 (M+1).

[1775] Synthesis of methyl 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (Syn. Ex. 54)

[1776] To a stirred solution of compound **91** (0.10 g, 0.176 mmol) in DMF (2 mL) at 0 °C were added DIPEA (0.092 mL, 0.528 mmol), 2-fluoroacrylic acid **2** (31 mg, 0.352 mmol) followed by 50% T₃P in EtOAc (0.335 mL, 0.528 mmol) the mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (**Syn. Ex. 54**: 8.0 mg, 7.54%) as an off-white solid. (See analytical data in Table 1).

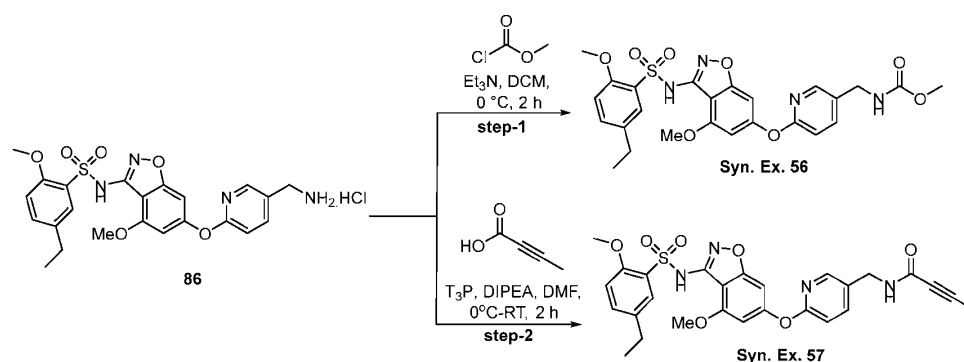
[1777] Synthesis of methyl 2-(4-ethyl-2-(N-(4-methoxy-6-((4-(((methoxycarbonyl)amino)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (Syn. Ex. 55)

[1778] To a stirred solution of compound **91** (0.10 g, 0.176 mmol) in DCM (2 mL) was added Et₃N (0.073 mL, 0.528 mmol) and methyl chloroformate (0.02 g, 0.212 mmol) in

DCM (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl 2-(4-ethyl-2-(N-(4-methoxy-6-((4-(((methoxycarbonyl)amino)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetate (**Syn. Ex. 55**; 11 mg, 10.67%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 56-57

[1779] **Scheme 36: methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)carbamate (**Syn. Ex. 56**) and N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)but-2-ynamide (**Syn. Ex. 57**)**



[1780] **Synthesis of methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)carbamate (**Syn. Ex. 56**)**

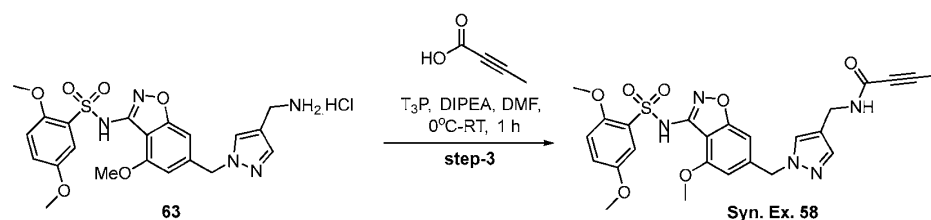
[1781] To a stirred solution of compound **86** (0.10 g, 0.191 mmol) in DCM (1 mL) was added Et₃N (0.053 mL, 0.382 mmol) at 0 °C. The mixture was stirred for 10 min. followed by drop-wise addition of methyl chloroformate (0.018 g, 0.191 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)carbamate (**Syn. Ex. 56**; 4 mg, 3.84%) as an off-white solid. (See analytical data in Table 1).

[1782] **Synthesis of N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)but-2-ynamide (Syn. Ex. 57)**

[1783] To a stirred solution of compound **86** (0.09 g, 0.172 mmol) in DMF (1 mL) was added DIPEA (0.09 mL, 0.516 mmol), but-2-ynoic acid (21 mg, 0.258 mmol) and 50% T₃P in EtOAc (0.21 g, 0.344 mmol) at 0 °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)but-2-ynamide (**Syn. Ex. 57**; 8 mg, 8.42%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 58

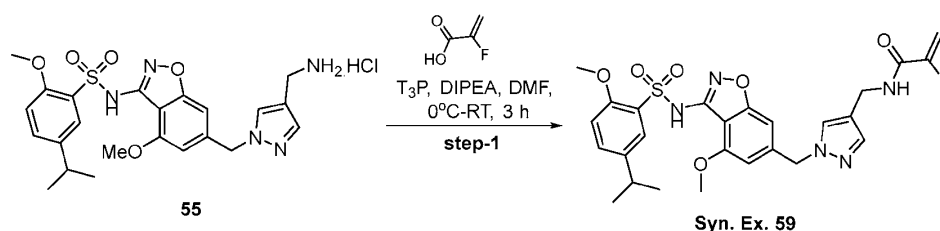
[1784] **Scheme 37: Synthesis of N-((1-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (Syn. Ex. 58)**



[1785] To a stirred solution of compound **63** (0.10 g, 0.196 mmol) in DMF (2 mL) was added DIPEA (0.0066 mL, 0.038 mmol), but-2-ynoic acid **5** (32 mg, 0.392 mmol) and 50% T₃P in EtOAc (0.18 mL, 0.294 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound N-((1-((3-((2,5-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)but-2-ynamide (**Syn. Ex. 58**; 16 mg, 15.23%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 59

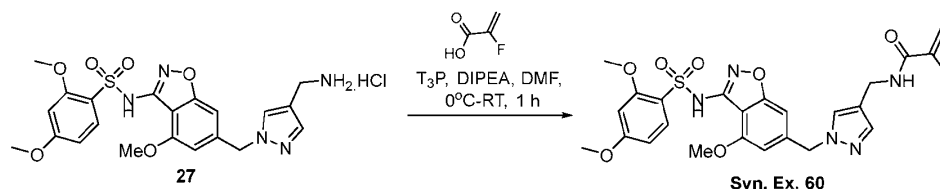
[1786] **Scheme 38: Synthesis of 2-fluoro-N-((1-((3-((5-isopropyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 59)**



[1787] To a stirred solution of compound **55** (0.09 g, 0.172 mmol) in DMF (2 mL) was added DIPEA (0.09 mL, 0.516 mmol), 2-fluoroacrylic acid (30 mg, 0.344 mmol) and 50% T₃P in EtOAc (0.328 mL, 0.516 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (30 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound 2-fluoro-*N*-((1-((3-((5-isopropyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 59**; 23 mg, 23.93%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 60

[1788] **Scheme 39: Synthesis of *N*-((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 60**)**

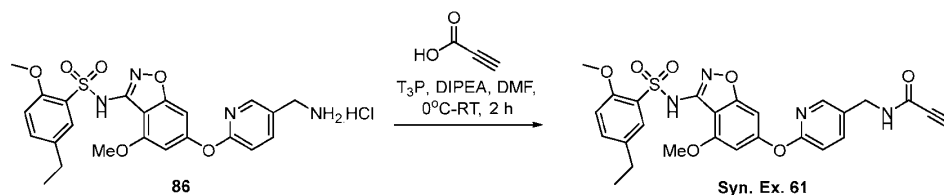


[1789] To a stirred solution of compound **60** (0.15 g, 0.294 mmol) in DMF (5 mL) were added DIPEA (0.15 mL, 0.882 mmol), 2-fluoroacrylic acid **2** (52 mg, 0.588 mmol) and 50% T₃P in EtOAc (0.560 mL, 0.882 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography (80% EtOAc in Hexane) to afford title compound *N*-((1-((3-((2,4-dimethoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-

yl)methyl)-1H-pyrazol-4-yl) methyl)-2-fluoroacrylamide (**Syn. Ex. 60**; 20 mg, 12.5%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 61

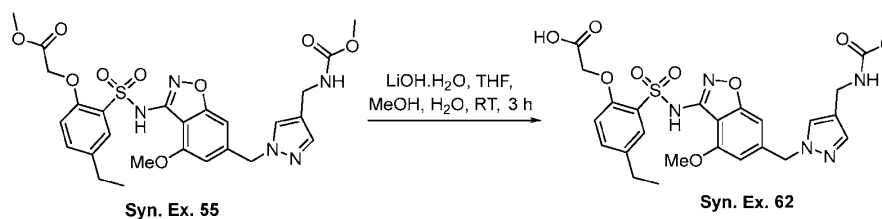
[1790] **Scheme 40: Synthesis of N-((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)propiolamide (**Syn. Ex. 61**)**



[1791] To a stirred solution of compound **86** (0.12 g, 0.230 mmol) in DMF (1 mL) were added propiolic acid (24 mg, 0.345 mmol), DIPEA (0.12 mL, 0.69 mmol) and 50% T₃P in EtOAc (0.292 mL, 0.460 mmol) at 0 °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound *N*-((6-((3-((5-ethyl-2-methoxyphenyl) sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)methyl)propiolamide (**Syn. Ex. 61**; 7 mg, 5.83%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 62

[1792] **Scheme 41: Synthesis of 2-(4-ethyl-2-(N-(4-methoxy-6-(((methoxycarbonyl) amino) methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetic acid (**Syn. Ex. 62**)**

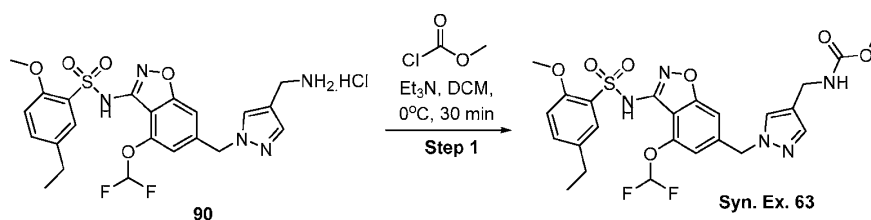


[1793] To a stirred solution of **Syn. Ex. 55** (5 mg, 0.008 mmol) in mixture of THF (0.5 mL), H₂O (0.5 mL) and MeOH (0.5 mL) was added LiOH·H₂O (0.714 mg, 0.016 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, residue was dissolved in water, acidified with citric acid to pH 4-5 and extracted with 10% MeOH in DCM (3 x 5 mL). The

mixture was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was triturated with n-pentane (10 mL) to afford title compound 2-(4-ethyl-2-(N-(4-methoxy-6-((4-(((methoxycarbonyl)amino)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl) sulfamoyl)phenoxy)acetic acid (**Syn. Ex. 62**; 4.5 mg, 93.75% yield) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 63

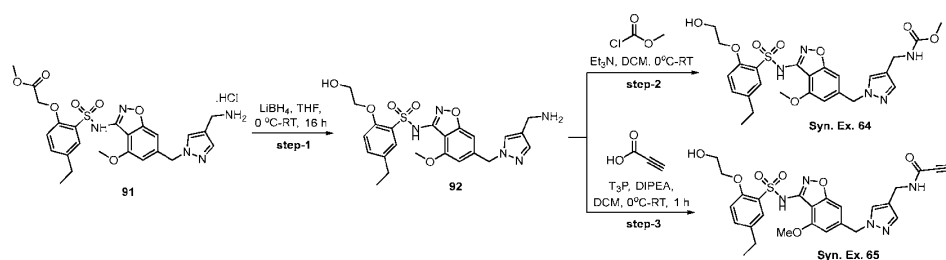
[1794] **Scheme 42: Synthesis of methyl ((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl) sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 63**)**



[1795] To a stirred solution of compound **90** (0.13 g, 0.238 mmol) in DCM (10 mL) were added Et₃N (0.066 mL, 0.476 mmol) and methyl carbonochloridate (22 mg, 0.238 mmol) in DCM (1 mL) drop-wise at 0 °C. The mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford title compound methyl ((1-((4-(difluoromethoxy)-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 63**; 3 mg, 2.22%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 64-65

[1796] **Scheme 43: Synthesis of methyl ((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 64**) and N-((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 65**)**



[1797] Synthesis of N-((4-((aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-(2-hydroxyethoxy)benzenesulfonamide hydrochloride (92)

[1798] To a stirred solution of compound **91** (0.15 g, 0.265 mmol) in THF (5 mL) was added 2M LiBH_4 solution in THF (0.39 mL, 0.795 mmol) at 0°C . The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with aqueous NH_4Cl and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to afford title compound **92** (6 mg, 24.83%) as a light-yellow solid. LCMS calculated for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_6\text{S}$: 501.17; Found: 502.26 ($\text{M}+1$).

[1799] Synthesis of methyl ((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 64)

[1800] To a stirred solution of compound **92** (0.10 g, 0.185 mmol) in DCM (5 mL) was added Et_3N (0.077 mL, 0.557 mmol) and methyl chloroformate (0.03 g, 0.371 mmol) in DCM (0.50 mL) at 0°C for 1h while maintaining the pH 7-8. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 64**, 8 mg, 3.04%) as an off-white solid. (See analytical data in Table 1).

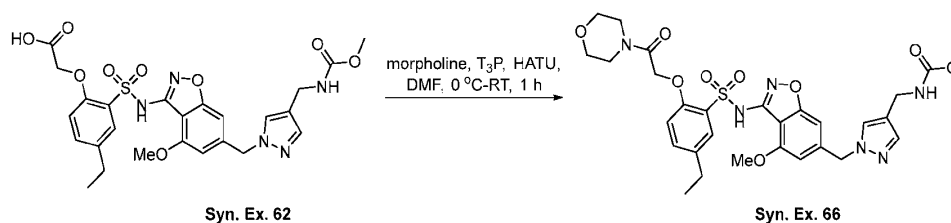
[1801] Synthesis of N-((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 65)

[1802] To a stirred solution of compound **92** (0.10 g, 0.199 mmol) in DMF (5 mL) were added DIPEA (0.10 mL, 0.598 mmol), propiolic acid (0.02 g, 0.398 mmol) and 50% T_3P in

EtOAc (0.38 mL, 0.598 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 65**; 5 mg, 4.44%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 66

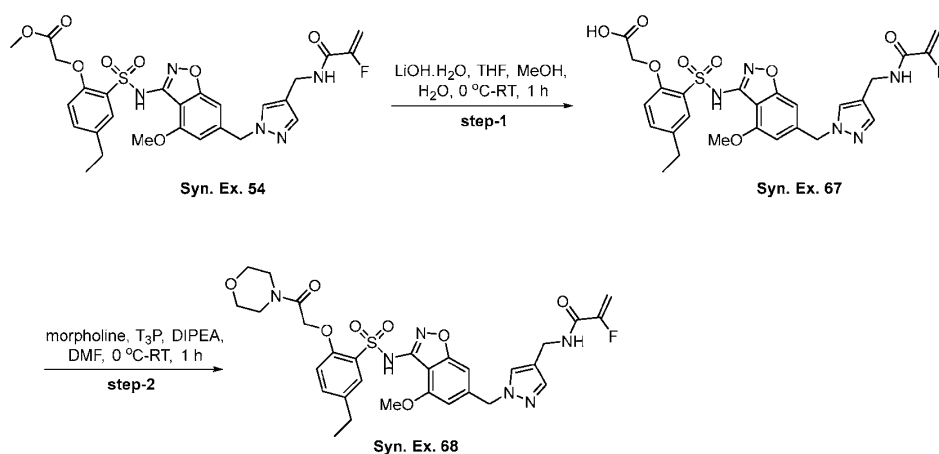
[1803] **Scheme 44: Synthesis of methyl ((1-((3-((5-ethyl-2-(2-morpholino-2-oxoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 66**)**



[1804] To a stirred solution of **Syn. Ex. 62** (0.10 g, 0.174 mmol) in DMF (5 mL) were added DIPEA (0.091 mL, 0.523 mmol), morpholine (0.03 g, 0.348 mmol) followed by 50% T₃P in EtOAc (0.33 mL, 0.523 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(2-morpholino-2-oxoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 66**; 18 mg, 15.83%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 67-68

[1805] **Scheme 45: Synthesis of 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetic acid (**Syn. Ex. 67**) and N-((1-((3-((5-ethyl-2-(2-morpholino-2-oxoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 68**)**



[1806] Synthesis of 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetic acid (Syn. Ex. 67)

[1807] To a stirred solution of **Syn. Ex. 54** (0.20 g, 0.332 mmol) in mixture of THF: MeOH: H₂O (2:2:2; 6 mL) was added LiOH·H₂O (0.069 g, 1.662 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, diluted with ice-cold water and acidified with citric acid to pH 4-5. The aqueous layer was extracted with 10% MeOH in DCM, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford crude (0.15 g). The crude (30 mg) was purified by prep. HPLC to afford 2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)acetic acid (**Syn. Ex. 67**; 5.00 mg) as an off-white solid. (See analytical data in Table 1).

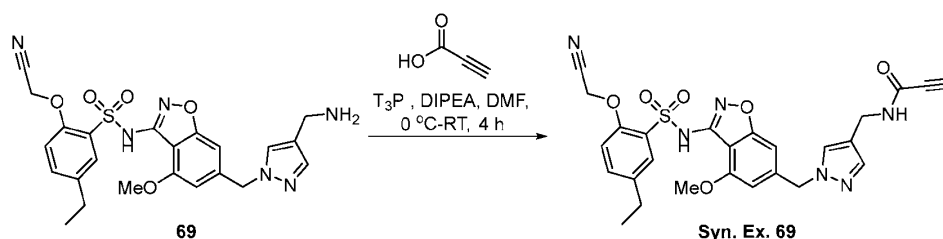
[1808] Synthesis of N-((1-(3-((5-ethyl-2-(2-morpholino-2-oxoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 68)

[1809] To a stirred solution of compound **Syn. Ex. 67** (0.10 g, 0.170 mmol) in DMF (5 mL) were added DIPEA (0.089 mL, 0.510 mmol), morpholine (0.029 g, 0.340 mmol) and 50% T₃P in EtOAc (0.32 mL, 0.510 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-(3-((5-ethyl-2-(2-morpholino-2-oxoethoxy)phenyl)sulfonamido)-4-

methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 68; 6 mg, 5.30%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 69

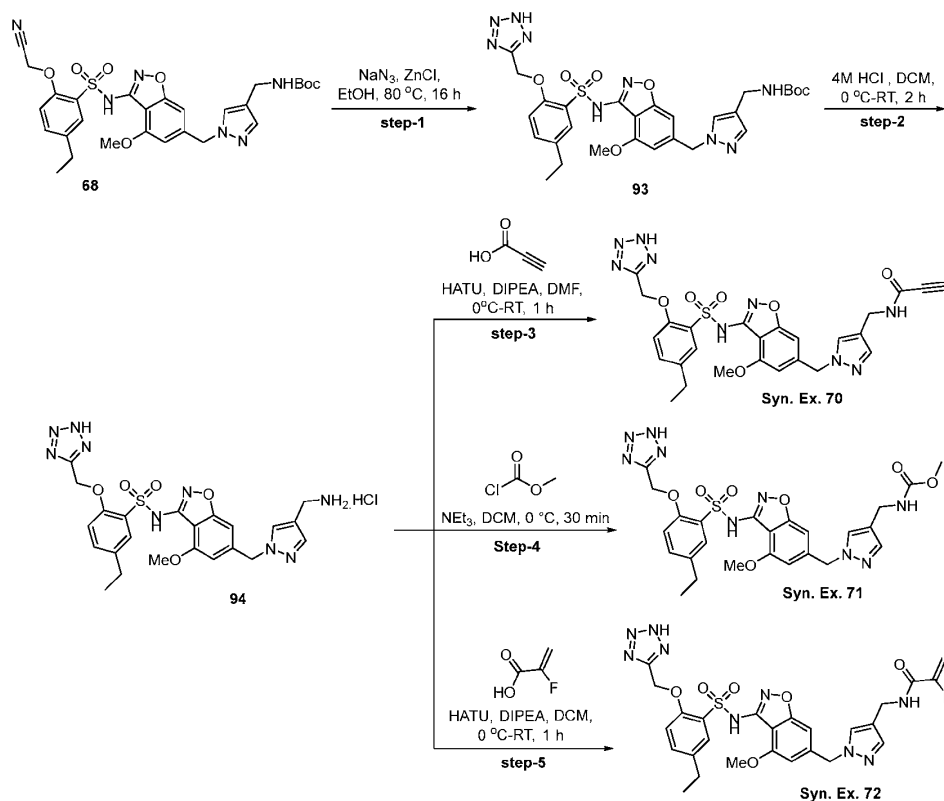
[1810] Scheme 46: Synthesis of N-((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 69)



[1811] To a stirred solution of compound **69** (0.10 g, 0.187 mmol) in DMF (2 mL) were added DIPEA (0.098 mL, 0.562 mmol), propiolic acid (0.026 g, 0.375 mmol) and 50% T₃P in EtOAc (0.35 mL, 0.562 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-(cyanomethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 69; 5 mg, 4.81%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 70-72

[1812] Scheme 47: Synthesis of N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 70), Synthesis of methyl ((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 71) and N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 72)



[1813] Synthesis of *tert*-Butyl ((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (93)

[1814] To a stirred solution of compound **68** (20 mg, 0.033 mmol) in EtOH (1 mL) was added ZnCl_2 (6.8 mg, 0.050 mmol) and NaN_3 (3.2 mg, 0.050 mmol) at room temperature. The reaction mixture was stirred at 80°C for 16h. After completion (monitored by TLC), the mixture was filtered through a celite pad. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **93** (15 mg, 45.12%) as a yellow solid. LCMS calculated for $\text{C}_{28}\text{H}_{33}\text{N}_9\text{O}_7\text{S}$: 639.22; Found: 640.20 ($\text{M}+1$).

[1815] Synthesis of 2-((2H-tetrazol-5-yl)methoxy)-N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethylbenzenesulfonamide hydrochloride (94)

[1816] To a stirred solution of compound **93** (0.15 g, 0.234 mmol) in DCM (5 mL) was added 4M HCl in 1,4-Dioxane (0.29 mL, 1.172 mmol) at 0°C . The reaction mixture was

stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with DCM, co-distilled with Et₂O and concentrated under reduced pressure to title compound **94** (0.14 g, 73.10%) as an off-white solid. LCMS calculated for C₂₃H₂₆N₉O₅S: 539.17; Found: 538.20 (M-1).

[1817] Synthesis of N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 70)

[1818] To a stirred solution of compound **94** (70 mg, 0.121 mmol) in DMF (4 mL) were added DIPEA (0.063 mL, 0.364 mmol), propiolic acid (0.01 g, 0.145 mmol) and HATU (0.072 g, 0.182 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 70**; 7 mg, 9.53%) as an off-white solid. (See analytical data in Table 1).

[1819] Synthesis of methyl ((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 71)

[1820] To a stirred solution of compound **94** (60 mg, 0.104 mmol) in DCM (4 mL) was added NEt₃ (0.029 mL, 0.208 mmol) and methyl chloroformate (12 mg, 0.125 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified prep. HPLC to afford methyl ((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 71**; 5 mg, 7.98%) as an off-white solid. (See analytical data in Table 1).

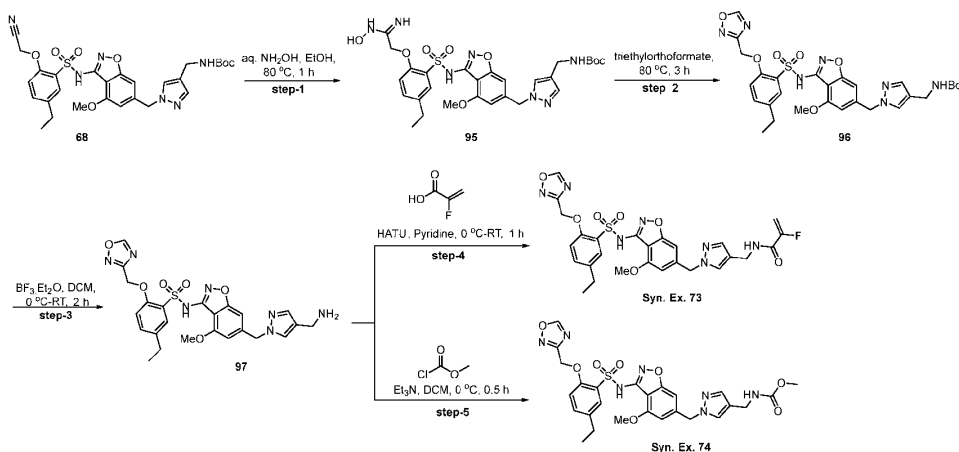
[1821] Synthesis of N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 72)

[1822] To a stirred solution of compound **94** (0.12 g, 0.208 mmol) in DCM (6 mL) were added 2-fluoroacrylic acid (0.02 g, 0.328 mmol), DIPEA (0.14 mL, 0.850 mmol) and HATU

(0.16 g, 0.429 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((2H-tetrazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 72**; 14.6 mg, 11.23%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 73-74

[1823] **Scheme 48: Synthesis of N-((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 73**) and methyl ((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 74**)**



[1824] **Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**95**)**

[1825] To a stirred solution of compound **68** (0.30 g, 0.502 mmol) in EtOH (10 mL) was added 50% aqueous NH₂OH (0.49 mL, 16.361 mmol). The reaction mixture was stirred at 80 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **95**

(0.30 g, 94.75%) as an off-white solid. LCMS calculated for C₂₈H₃₅N₇O₈S: 629.23; Found: 630.30 (M+1).

[1826] Synthesis of *tert*-Butyl ((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (96)

[1827] A solution of compound **95** (0.30 g, 0.476 mmol) in triethylorthoformate (10 mL) was stirred at 80 °C for 3 h. After completion (monitored by TLC), the mixture was cooled at room temperature and concentrated under reduced pressure to afford title compound **96** (0.30 g, 98.45%) as an off-white solid. LCMS calculated for C₂₉H₃₃N₇O₈S: 639.21; Found: 638.30 (M-1).

[1828] Synthesis of 2-((1,2,4-oxadiazol-3-yl)methoxy)-N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethylbenzenesulfonamide (97)

[1829] To a stirred solution of compound **96** (0.28 g, 0.437 mmol) in DCM (50 mL) was added BF₃·Et₂O (0.50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, triturated with Et₂O to afford title compound **97** (0.28 g, 67.58%) as an off-white solid. LCMS calculated for C₂₄H₂₅N₇O₆S: 539.16; Found: 540.30 (M+1).

[1830] Synthesis of N-((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 73)

[1831] To a stirred solution of 2-fluoroacrylic acid (0.02 g, 0.222 mmol) in pyridine (5 mL) were added HATU (0.14 g, 0.370 mmol) and compound **97** (0.10 g, 0.185 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 73**; 48 mg, 41.95%) as an off-white solid. (See analytical data in Table 1).

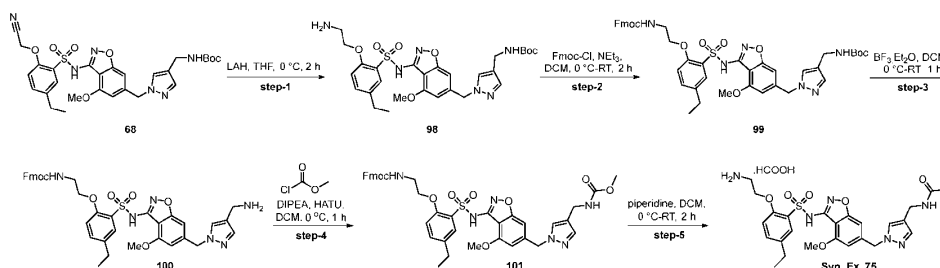
[1832] Synthesis of methyl ((1-((3-((2-((1,2,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 74)

[1833] To a stirred solution of compound **97** (0.10 g, 0.185 mmol) in DCM (5 mL) were added NEt₃ (0.05 mL, 0.370 mmol) and methyl chloroformate (0.01 g, 0.185 mmol) at 0 °C.

The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-((1,4-oxadiazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 74**; 4.00 mg, 3.50%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 75

[1834] **Scheme 49: Synthesis of methyl ((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 75**)**



[1835] **Synthesis of *tert*-Butyl ((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**98**)**

[1836] To a stirred solution of compound **68** (1 g, 1.675 mmol) in THF (10 mL) were added 2M LAH in THF (0.83 mL, 1.675 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold NH₄Cl and extracted with 10% MeOH in DCM. The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and purified by combi-flash chromatography using 5-10% MeOH/DCM to afford title compound **98** (0.36 g, 27.72%) as an off-white solid. LCMS calculated for C₂₈H₃₆N₆O₇S: 600.24; Found: 601.30 (M+1).

[1837] **Synthesis of (9H-fluoren-9-yl)methyl (2-(2-(N-(6-(((4-(((*tert*-butoxycarbonyl)amino)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)ethyl)carbamate (**99**)**

[1838] To a stirred solution of compound **98** (0.23 g, 0.382 mmol) in DCM (10 mL) were added NEt₃ (0.16 mL, 1.148 mmol) and Fmoc-Cl (0.12 g, 0.459 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with DCM, dried over anhydrous

Na₂SO₄ and concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **99** (0.31 g, 65.92%) as a pale-yellow solid. LCMS calculated for C₄₃H₄₆N₆O₉S: 822.30; Found: 723.30 [(M-Boc)+1].

[1839] Synthesis of (9H-fluoren-9-yl)methyl (2-(2-(N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)ethyl)carbamate (100)

[1840] To a stirred solution of compound **99** (0.31 g, 0.376 mmol) in DCM (5 mL) was added BF₃·Et₂O (0.16 g, 0.565 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried under reduced pressure to afford title compound **100** (0.29 g, 31.95%) as a pale-yellow solid. LCMS calculated for C₃₈H₃₈N₆O₇S: 722.25; Found: 723.30 (M+1).

[1841] Synthesis of methyl ((1-((3-((2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (101)

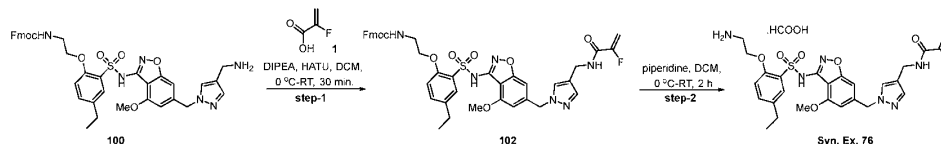
[1842] To a stirred solution of compound **100** (0.14 g, 0.193 mmol) in DCM (5 mL) were added NEt₃ (0.08 mL, 0.581 mmol) and methyl chloroformate (0.03 g, 0.387 mmol) in DCM (0.50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **101** (0.17 g, 49.34 %) as an off-white gummy solid. LCMS calculated for C₄₀H₄₀N₆O₉S: 780.26; Found: 781.30 (M+1).

[1843] Synthesis of methyl ((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 75)

[1844] To a stirred solution of compound **101** (0.14 g, 0.179 mmol) in DCM (5 mL) was added piperidine (0.03 g, 0.358 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 75**; 6 mg, 5.89%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 76

[1845] Scheme 50: Synthesis of N-((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 76)



[1846] Synthesis of (9H-fluoren-9-yl)methyl (2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)ethyl)carbamate (102)

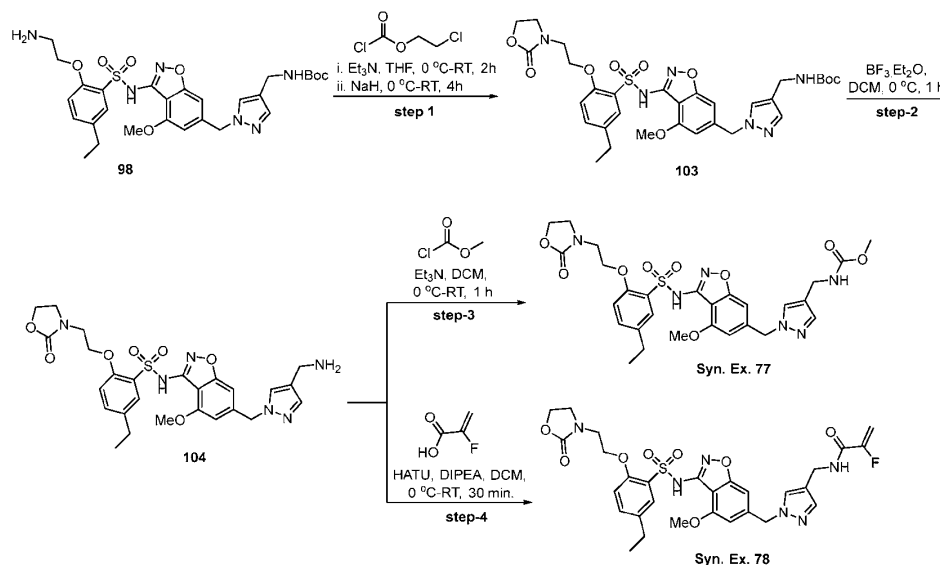
[1847] To a stirred solution of 2-fluoroacrylic acid (0.03 g, 0.415 mmol) in DCM (5 mL) were added DIPEA (0.18 mL, 1.037 mmol) and HATU (0.11 g, 0.311 mmol) followed by the addition of compound **100** (0.15 g, 0.207 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **102** (0.20 g, 36.37%) as a brown gummy solid. LCMS calculated for C₄₁H₃₉FN₆O₈S: 794.25; Found: 795.40 (M+1).

[1848] Synthesis of N-((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 76)

[1849] To a stirred solution of compound **102** (0.15 g, 0.188 mmol) in DCM (5 mL) was added piperidine (0.03 g, 0.377 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-(2-aminoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 76; 12 mg, 11.07%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 77-78

[1850] Scheme 51: Synthesis of methyl ((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 77) and N-((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 78)



[1851] Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**103**)

[1852] To a stirred solution of compound **98** (0.30 g, 0.499 mmol) in THF (20 mL) were added NEt₃ (0.27 mL, 1.997 mmol) and 2-chloroethyl chloroformate (0.10 g, 0.749 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h followed by addition of 60% NaH in oil (0.19 g, 4.994 mmol) was at 0 °C. The reaction mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 5-10% MeOH/DCM to afford title compound **103** (0.19 g, 39.70%) as a pale-yellow solid. LCMS calculated for C₃₁H₃₈N₆O₉S: 670.24; Found: 669.40 (M-1).

[1853] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)benzenesulfonamide (104)

[1854] To a stirred solution of compound **103** (0.18 g, 0.268 mmol) in DCM (5 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.15 g, 0.536 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et_2O and dried under reduced pressure to afford title compound **104** (0.20 g) as a light-yellow solid. LCMS calculated for $\text{C}_{26}\text{H}_{30}\text{N}_6\text{O}_7\text{S}$: 570.19; Found: 571.40 (M+1).

[1855] Synthesis of methyl ((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 77)

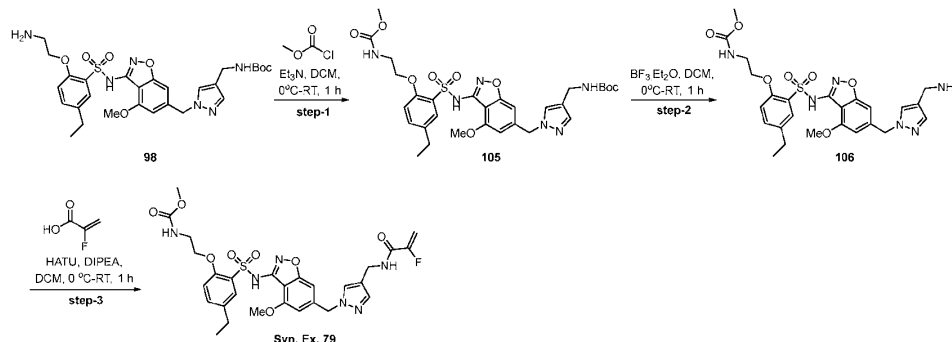
[1856] To a stirred solution of compound **104** (0.10 g, 0.175 mmol) in DCM (5 mL) were added NEt_3 (0.07 mL, 0.525 mmol) and methyl chloroformate (0.033 mL, 0.350 mmol) in DCM (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 77**; 24 mg, 22.94%) as an off-white solid. (See analytical data in Table 1).

[1857] Synthesis of N-((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 78)

[1858] To a stirred solution of 2-fluoroacrylic acid (0.028 g, 0.315 mmol) in DCM (1 mL) were added DIPEA (0.13 mL, 0.788 mmol) and HATU (0.09 g, 0.236 mmol) and **104** (0.09 g, 0.157 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((5-ethyl-2-(2-(2-oxooxazolidin-3-yl)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 78**; 15.5 mg, 15.22%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 79

[1859] **Scheme 52: Synthesis of methyl (2-(4-ethyl-2-(N-(6-((4-(2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)ethyl)carbamate (Syn. Ex. 79)**



[1860] **Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-(2-(methoxycarbonyl)amino)ethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (105)**

[1861] To a stirred solution of compound **98** (0.20 g, 0.332 mmol) in DCM (5 mL) were added Et₃N (0.13 mL, 0.998 mmol) and methyl chloroformate (0.06 g, 0.665 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **105** (0.20 g, 75.30%) as a pale-yellow solid. LCMS calculated for C₃₀H₃₈N₆O₉S: 658.24; Found: 657.30 (M-1).

[1862] **Synthesis of methyl (2-(2-(N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)ethyl)carbamate (106)**

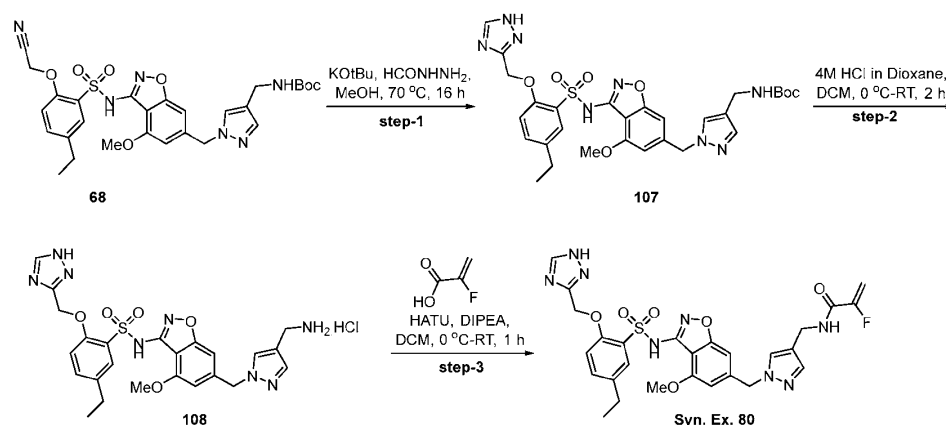
[1863] To a stirred solution of compound **105** (0.19 g, 0.288 mmol) in DCM (5 mL) was added BF₃·Et₂O (0.12 g, 0.432 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated Et₂O and dried under reduced pressure to afford title compound **106** (0.15 g, 80.81%) as an off-white gummy solid. LCMS calculated for C₂₅H₃₀N₆O₇S: 558.19; Found: 559.30 (M+1).

[1864] **Synthesis of methyl (2-(4-ethyl-2-(N-(6-((4-(2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)ethyl)carbamate (Syn. Ex. 79)**

[1865] To a stirred solution of 2-fluoroacrylic acid (0.04 g, 0.465 mmol) in DCM (5 mL) were added DIPEA (0.20 mL, 1.163 mmol) and HATU (0.13 g, 0.349 mmol) and compound **106** (0.13 g, 0.232 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl (2-(4-ethyl-2-(N-(6-((4-((2-fluoroacrylamido)methyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)phenoxy)ethyl)carbamate (**Syn. Ex. 79**; 8 mg, 5.38%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 80

[1866] **Scheme 53: Synthesis of N-((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 80**)**



[1867] **Synthesis of *tert*-Butyl ((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**106**)**

[1868] To a stirred solution of compound **68** (0.20 g, 0.335 mmol) in MeOH (5 mL) was added KOtBu (0.04 g, 0.402 mmol). The reaction mixture was stirred at 70 °C for 2 h and cooled at room temperature followed by addition of HCONHNH₂ (0.10 g, 1.675 mmol). The reaction mixture was stirred at 70 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 7-11% MeOH/ DCM to afford title

compound **107** (0.135 g, 59.26%) as a brown semi-solid. LCMS calculated for C₂₉H₃₄N₈O₇S: 638.23; Found: 639.20 (M+1).

[1869] Synthesis of 2-((1H-1,2,4-triazol-3-yl)methoxy)-N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethylbenzenesulfonamide hydrochloride (108)

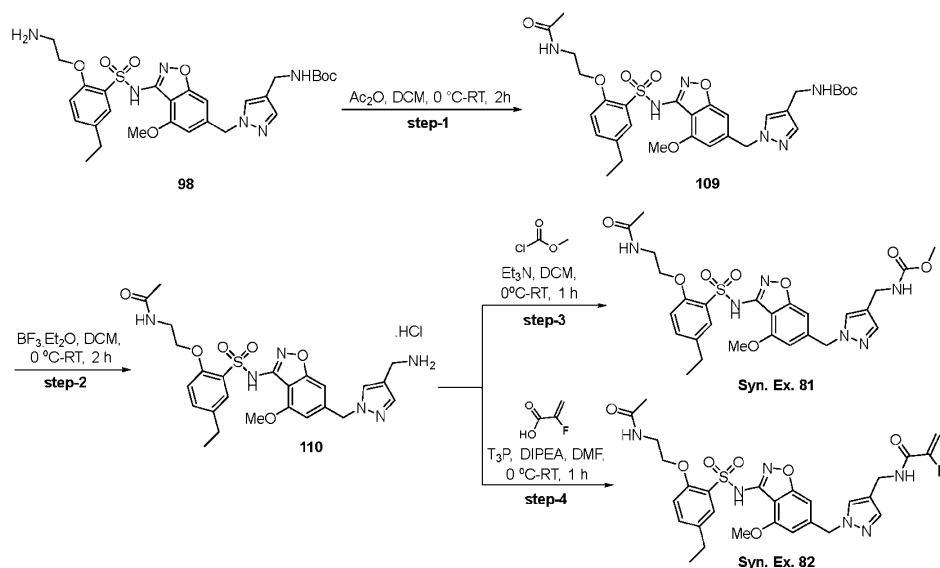
[1870] To a stirred solution of compound **107** (0.13 g, 0.203 mmol) in DCM (3 mL) was added 4M HCl in Dioxane (0.50 mL, 2.035 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **108** (0.11 g, 93.06%) as a brown solid. LCMS calculated for C₂₄H₂₆N₈O₅S: 538.17; Found: 539.20 (M+1).

[1871] Synthesis of N-((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 80)

[1872] To a stirred solution of compound **108** (0.10 g, 0.1739 mmol) in DCM (3 mL) were added DIPEA (0.09 mL, 0.521 mmol) and HATU (0.10 g, 0.260 mmol) and 2-fluoroacrylic acid (0.01 g, 0.208 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 80**; 26 mg, 23.89%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 81-82

[1873] Scheme 54: Synthesis of methyl ((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 81) and N-((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 82)



[1874] Synthesis of *tert*-Butyl ((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (109**)**

[1875] To a stirred solution of compound **98** (0.22 g, 0.366 mmol) in DCM (5 mL) was added triethylamine (0.14 mL, 1.098 mmol) and Ac_2O (0.07 mL, 0.732 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH/ DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was triturated with Et_2O to afford title compound **109** (0.18 g, 70.94%) as a pale-yellow solid. LCMS calculated for $\text{C}_{30}\text{H}_{38}\text{N}_6\text{O}_8\text{S}$: 642.25; Found: 643.40 ($\text{M}+1$).

[1876] Synthesis of N-(2-(2-(N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)sulfamoyl)-4-ethylphenoxy)ethyl)acetamide (110**)**

[1877] To a stirred solution of compound **109** (0.18 g, 0.280 mmol) in DCM (2 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.11 g, 0.420 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et_2O and dried under reduced pressure to afford title compound **110** (0.17 g, 99.58%) as a light-yellow solid. LCMS calculated for $\text{C}_{25}\text{H}_{30}\text{N}_6\text{O}_6\text{S}$: 542.19; Found: 543.30 ($\text{M}+1$).

[1878] Synthesis of methyl ((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 81)

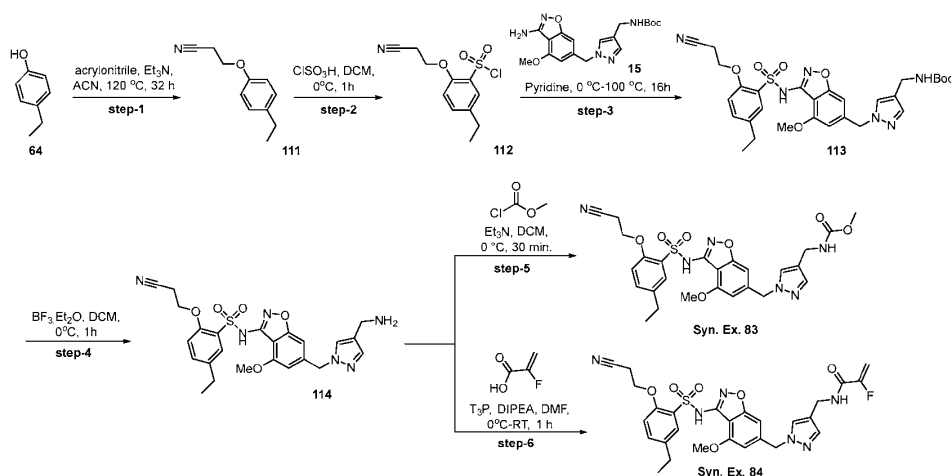
[1879] To a stirred solution of compound **110** (0.08 g, 0.138 mmol) in DCM (5 mL) was added NEt₃ (0.057 mL, 0.414 mmol) and methyl chloroformate (0.026 g, 0.276 mmol) in DCM (0.50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 81**; 18 mg, 21.60%) as an off-white solid. (See analytical data in Table 1).

[1880] Synthesis of N-((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 82)

[1881] To a stirred solution of compound **110** (0.10 g, 0.172 mmol) in DMF (2 mL) were added DIPEA (0.09 mL, 0.518 mmol), 2-fluoroacrylic acid **2** (0.03 g, 0.345 mmol) and 50% T₃P in EtOAc (0.32 mL, 0.518 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-(2-acetamidoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 82**; 18 mg, 16.85%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 83-84

[1882] Scheme 55: Synthesis of methyl ((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 83) and N-((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 84)



[1883] Synthesis of 3-(4-ethylphenoxy)propanenitrile (111)

[1884] To a stirred solution of compound **64** (2 g, 16.370 mmol) in ACN (10 mL) was added Et₃N (27.40 mL, 196.447 mmol) at room temperature. The reaction mixture was stirred for 5 min, followed by the addition of acrylonitrile (10 mL). The reaction mixture was stirred at 120 °C for 32h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was diluted with EtOAc and washed with 1M NaOH. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **111** (1.54 g, 21.49%) as a brown liquid. LCMS calculated for C₁₁H₁₃NO: 175.10; Found: 176.20 (M+1).

[1885] Synthesis of 2-(2-(2-cyanoethoxy)-5-ethylphenyl)sulfonyl chloride (112)

[1886] To a stirred solution of compound **111** (1.30 g, 7.418 mmol) in DCM (10 mL) was added ClSO₃H (1.49 mL, 22.256 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was quenched ice-cold water and extracted with DCM. The combined organic layer was concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 20-25% EtOAc/Heptane to afford title compound **112** (0.80 g) as a pale-yellow liquid.

[1887] Synthesis of *tert*-Butyl ((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (113)

[1888] To a stirred solution of compound **15** (0.50 g, 1.339 mmol) in pyridine (5 mL) was added compound **112** (0.54 mL, 2.008 mmol) at 0 °C. The reaction mixture was stirred at 100 °C for 16h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, co-distilled with toluene and dried under reduced pressure. The crude was

purified by combi-flash chromatography using 80-90% EtOAc/Heptane to afford title compound **113** (0.35 g, 38.91%) as an off-white solid. LCMS calculated for C₂₉H₃₄N₆O₇S: 610.22; Found: 611.30 (M+1).

[1889] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-(2-cyanoethoxy)-5-ethylbenzenesulfonamide (114)

[1890] To a stirred solution of compound **113** (0.20 g, 0.327 mmol) in DCM (10 mL) was added BF₃·Et₂O (0.069 g, 0.491 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried under reduced pressure to afford title compound **114** (0.15 g, 69.28%) as an off-white solid. LCMS calculated for C₂₄H₂₆N₆O₅S: 510.17; Found: 511.30 (M+1).

[1891] Synthesis of methyl ((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 83)

[1892] To a stirred solution of compound **114** (0.15 g, 0.293 mmol) in DCM (10 mL) were added Et₃N (0.12 mL, 0.881 mmol) and methyl chloroformate (0.033 g, 0.352 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 83**; 70 mg, 41.24%) as an off-white solid. (See analytical data in Table 1).

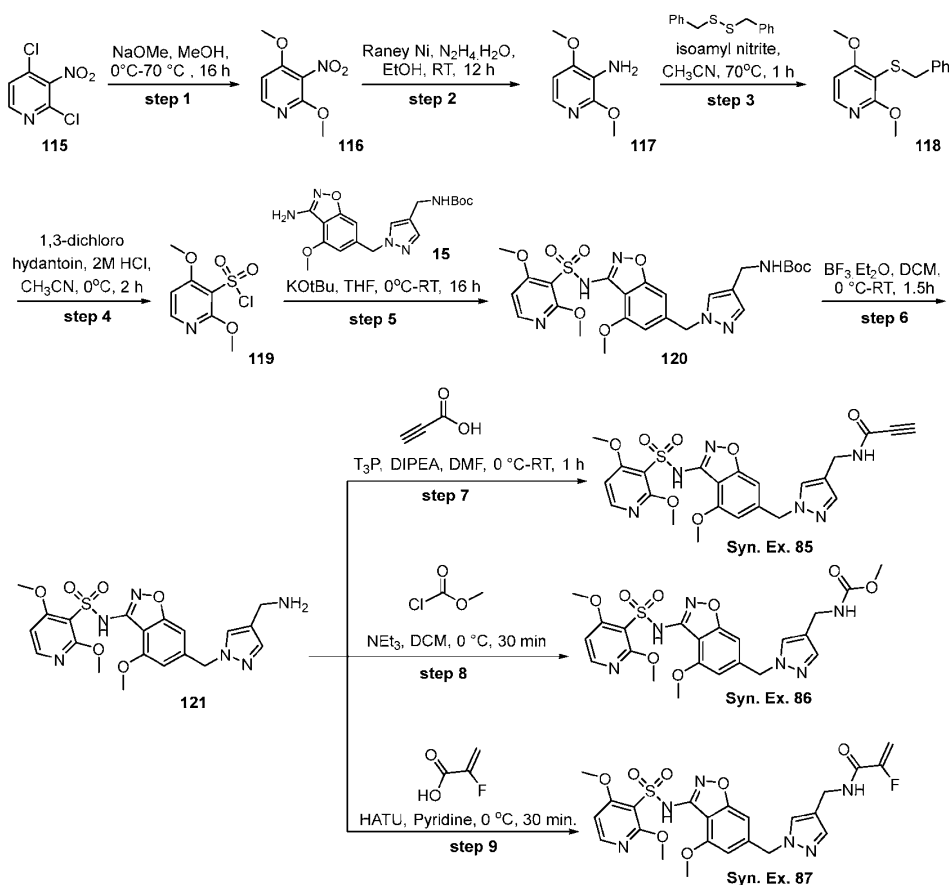
[1893] Synthesis of N-((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 84)

[1894] To a stirred solution of compound **114** (0.08 g, 0.156 mmol) in DMF (4 mL) were added DIPEA (0.08 g, 0.470 mmol), 2-fluoroacrylic acid (0.029 g, 0.313 mmol) and T₃P 50% in EtOAc (0.29 g, 0.470 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-(2-cyanoethoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-

yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 84**; 70 mg, 69.86%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 85-87

[1895] **Scheme 56: Synthesis of N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 85**), Synthesis of methyl ((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 86**) and N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 87**)**



[1896] **Synthesis of 2,4-dimethoxy-3-nitropyridine (116)**

[1897] To a stirred solution of compound **115** (5 g, 25.909 mmol) in MeOH (50 mL) was added NaOMe (7.14 g, 129.547 mmol) at 0 °C. The reaction mixture was stirred at 70 °C for 16h. After completion (monitored by TLC), the mixture was concentrated under reduced

pressure, quenched with ice cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford title compound **116** (4.70 g, 64.03%) as an off-white solid. LCMS calculated for C₇H₈N₂O₄: 184.05; Found: 185.10 (M+1).

[1898] Synthesis of 2,4-dimethoxypyridin-3-amine (117)

[1899] To a stirred solution of compound **116** (4.80 g, 26.065 mmol) in EtOH (40 mL) was added Raney Nickel (0.78 g, 9.122 mmol) and 1M hydrazine solution in THF (5.99 mL, 5.99 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12h. After completion (monitored by TLC), the mixture was filtered through a celite pad and filtrate was concentrated under reduced pressure to afford title compound **117** (3.90 g, 96.08%) as an off-white solid. LCMS calculated for C₇H₁₀N₂O₂: 154.07; Found: 155.10 (M+1).

[1900] Synthesis of 3-(benzylthio)-2,4-dimethoxypyridine (118)

[1901] To a stirred solution of compound **117** (3 g, 19.459 mmol) in ACN (30 mL) was added 1,2-dibenzyldisulfane (5.60 g, 22.76 mmol) followed by the addition of isoamyl nitrite (6.30 mL). The resulting mixture was stirred at 70 °C for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 30% EtOAc/Heptane to afford title compound **118** (1.40 g, 26.70%) as a light brown liquid. LCMS calculated for C₁₄H₁₅NO₂S: 261.08; Found: 262.10 (M+1).

[1902] Synthesis of 2,4-dimethoxypyridine-3-sulfonyl chloride (119)

[1903] To a stirred solution of compound **118** (1.30 g, 4.974 mmol) in ACN (52 mL), H₂O (1.30 mL) and AcOH (2.60 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (2 g, 9.948 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **119** (1 g, 84.59%) as a brown solid. LCMS calculated for C₇H₈ClNO₄S: 236.99; Found: 238.0 (M+1).

[1904] Synthesis of *tert*-Butyl ((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (120)

[1905] To a stirred solution of compound **15** (0.40 g, 1.071 mmol) in Dry THF (10 mL) was added 1M KOtBu in THF (3.21 g, 3.213 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. followed by the addition of compound **119** (0.38 g, 1.606 mmol).

The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice cold water, extracted with EtOAc. The aqueous layer was acidified with 1N HCl to adjust the pH ~ 6 and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **120** (0.30 g, 46.30%) as a brown solid. LCMS calculated for C₂₅H₃₀N₆O₈S: 574.18, Found: 519.10 [(M-tBu)+1].

[1906] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2,4-dimethoxypyridine-3-sulfonamide (121)

[1907] To a stirred solution of compound **120** (0.25 g, 0.435 mmol) in DCM (10 mL) was added BF₃.Et₂O (0.24 g, 0.870 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated Et₂O and dried under reduced pressure to afford title compound **121** (0.20 g, 93.02%) as an off-white solid. LCMS calculated for C₂₀H₂₂N₆O₆S: 474.13, Found: 473.20 (M-1).

[1908] Synthesis of N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (Syn. Ex. 85)

[1909] To a stirred solution of compound **121** (0.10 g, 0.210 mmol) in DMF (3 mL) was added DIPEA (0.11 mL, 0.632 mmol), propiolic acid (0.029 g, 0.421 mmol) and 50% T₃P in EtOAc (0.40 mL, 0.632 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)propiolamide (**Syn. Ex. 85**; 4.00 mg, 3.46%) as an off-white solid. (See analytical data in Table 1).

[1910] Synthesis of methyl ((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 86)

[1911] To a stirred solution of compound **121** (0.10 g, 0.210 mmol) in DCM (10 mL) was added methyl chloroformate (0.019 g, 0.210 mmol) and NEt₃ (0.058 mL, 0.421 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced

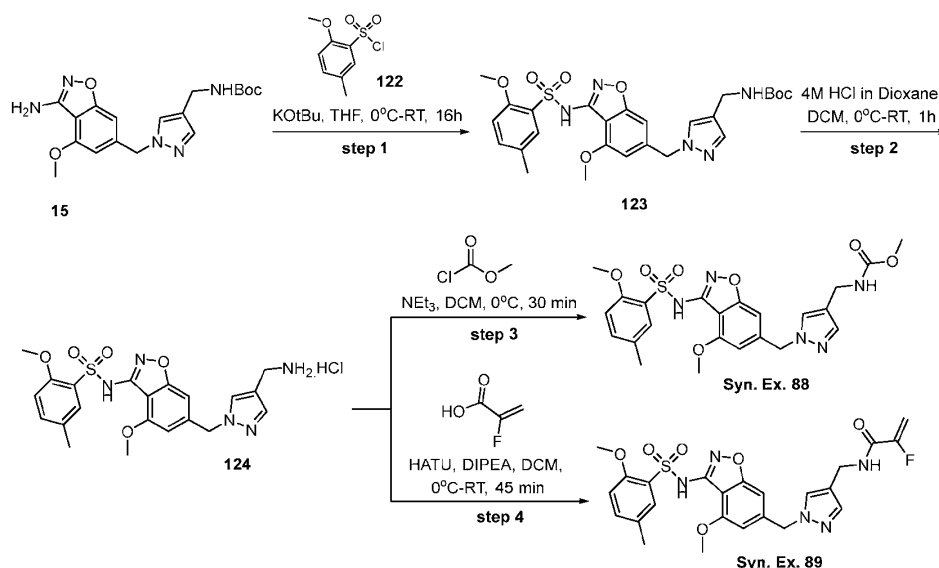
pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 86**; 18 mg, 16.04%) as an off-white solid. (See analytical data in Table 1).

[1912] Synthesis of N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 87**)**

[1913] To a stirred solution of compound **121** (0.10 g, 0.210 mmol) in pyridine (5 mL) were added 2-fluoroacrylic acid (0.02 g, 0.252 mmol) and HATU (0.16 g, 0.421 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified prep. HPLC to afford N-((1-((3-((2,4-dimethoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 87**; 9 mg, 7.78%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 88-89

[1914] Scheme 57: Synthesis of methyl ((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 88**) and 2-fluoro-N-((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 89**)**



[1915] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (123**)**

To a stirred solution of compound **15** (0.50 g, 1.339 mmol) in THF (15 mL) was added 1M KOtBu in THF (1 mL, 4.017 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by the addition of compound **122** (0.44 g, 2.008 mmol). The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 90-92% EtOAc/Heptane to afford title compound **123** (0.30 g, 34.55%) as an off-white solid. LCMS calculated for C₂₆H₃₁N₅O₇S: 557.19; Found: 556.30 (M-1).

[1916] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride (124**)**

[1917] To a stirred solution of compound **123** (0.30 g, 0.538 mmol) in DCM (3 mL) was added 4M HCl in Dioxane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried under reduced pressure to afford title compound **124** (0.25 g, 69.61%) as an off-white solid. LCMS calculated for C₂₁H₂₃N₅O₅S: 457.14; Found: 456.10 (M-1).

[1918] **Synthesis of methyl ((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 88)**

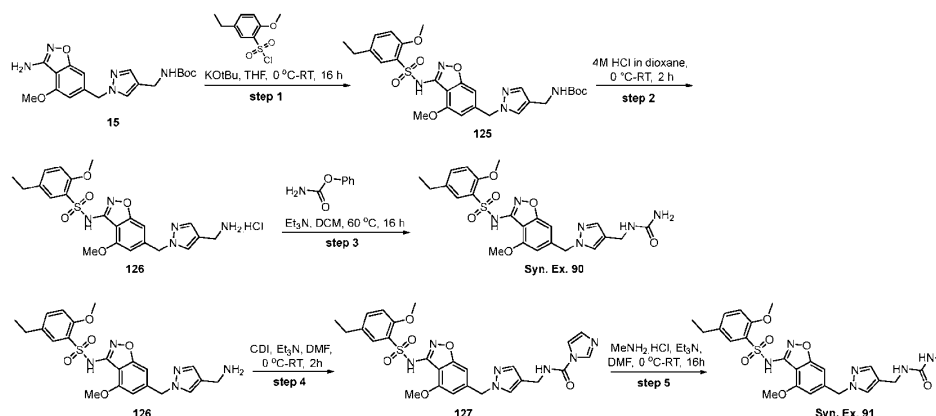
[1919] To a stirred solution of compound **124** (0.12 g, 0.243 mmol) in DCM (5 mL) were added NEt₃ (0.16 mL, 1.216 mmol) and methyl chloroformate (0.027 g, 0.292 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 88**; 24 mg, 18.79 %) as an off-white solid. (See analytical data in Table 1).

[1920] **Synthesis of 2-fluoro-N-((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 89)**

[1921] To a stirred solution of compound **124** (0.10 g, 0.202 mmol) in DCM (2 mL) were added DIPEA (0.17 mL, 1.012 mmol), 2-fluoroacrylic acid (0.036 g, 0.404 mmol) and HATU (0.12 g, 0.303 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 45 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 2-fluoro-N-((1-((4-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (**Syn. Ex. 89**; 33 mg, 30.49%) as a yellow solid. (See analytical data in Table 1).

EXAMPLES 90-91

[1922] **Scheme 58: Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-(ureidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 90) and 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-((3-methylureido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 91)**



[1923] Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (125**)**

[1924] To a stirred solution of compound **15** (2 g, 5.356 mmol) in THF (40 mL) was added 1M KOtBu in THF (16.06 mL, 16.068 mmol) at 0 °C. The reaction was stirred for 10 min followed by addition of 5-ethyl-2-methoxybenzenesulfonyl chloride (1.88 g, 8.034 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 70-72% EtOAc/Heptane to afford title compound **125** (1.20 g, 31.35%) as an off-white solid. LCMS calculated for C₂₇H₃₃N₅O₇S: 571.21; Found: 572.68 (M+1).

[1925] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (126**)**

[1926] To a stirred solution of compound **125** (0.35 g, 0.528 mmol) in DCM (6 mL) was added 4M HCl in 1,4-Dioxane (1.53 mL, 6.122 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried under reduced pressure to afford title compound **126** (0.29 g, 82.99%) as an off-white solid. LCMS calculated for C₂₂H₂₅N₅O₅S: 471.16; Found: 470.20 (M-1).

[1927] Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-(ureidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 90)

[1928] To a stirred solution of compound **126** (0.10 g, 0.196 mmol) in THF (3 mL) was added phenyl carbamate (32 mg, 0.236 mmol) and NEt₃ (0.08 mL, 0.590 mmol) at room

temperature. The reaction mixture was stirred at 60 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-(ureidomethyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 90**; 21 mg, 19.92%) as an off-white solid. (See analytical data in Table 1).

[1929] Synthesis of N-((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-1H-imidazole-1-carboxamide (127)

[1930] To a stirred solution of compound **126** (0.13 g, 0.255 mmol) in DMF (2 mL) was added Et₃N (0.07 mL, 0.511 mmol) and CDI (0.06 g, 0.383 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 7-12% of MeOH/DCM to afford title compound **127** (0.11 g, 69.84%) as a brown gummy solid. LCMS calculated for C₂₆H₂₇N₇O₆S: 565.17; Found: 566.30 (M+1).

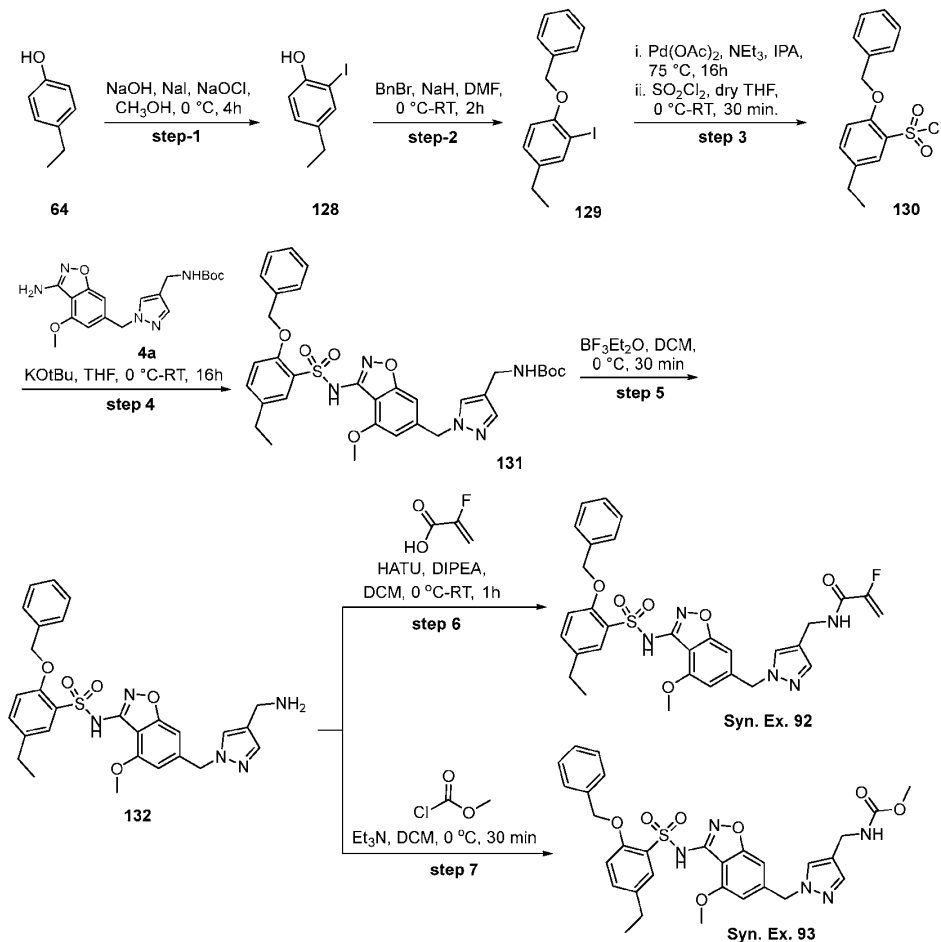
[1931] Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-((3-methylureido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (Syn. Ex. 91)

[1932] To a stirred solution of compound **127** (0.10 g, 0.176 mmol) in DMF (2 mL) were added Et₃N (0.07 mL, 0.530 mmol) followed by the addition of MeNH₂HCl (0.01 g, 0.212 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 5-ethyl-2-methoxy-N-(4-methoxy-6-((4-((3-methylureido)methyl)-1H-pyrazol-1-yl)methyl)benzo[d]isoxazol-3-yl)benzenesulfonamide (**Syn. Ex. 91**; 5.00 mg, 5.29%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 92-93

[1933] Scheme 59: Synthesis of N-((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide

(Syn. Ex. 92) and methyl ((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 93)



[1934] Synthesis of 4-ethyl-2-iodophenol (128)

[1935] To a solution of compound **64** (5 g, 40.926 mmol) in MeOH (50 mL) were added NaI (18.58 g, 122.779 mmol) and NaOH (3.91 g, 94.949 mmol) followed by NaOCl (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4h. After completion (monitored by TLC), the mixture was quenched with 10% Na₂S₂O₃, acidified with 2N HCl to pH ~ 6-5 and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 0-5% EtOAc/Heptane to afford title compound **128** (8.90 g, 71%) as a pale-yellow liquid. LCMS calculated for C₈H₉IO: 247.97; Found: 247 (M-1).

[1936] Synthesis of 1-(benzyloxy)-4-ethyl-2-iodobenzene (129)

[1937] To a stirred solution of compound **128** (4 g, 16.125 mmol) in DMF (35 mL) were added 60% NaH in oil (1.28 g, 32.250 mmol) and benzyl bromide (3.30 g, 19.350 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 4% EtOAc/ Heptane to afford title compound **129** (3.0 g, 37.40%) as a brown oil. LCMS calculated for C₁₅H₁₅IO: 338.02; Found: 339.30 (M+1).

[1938] **Synthesis of 2-(benzyloxy)-5-ethylbenzenesulfonyl chloride (130)**

[1939] To a stirred solution of 1-(benzyloxy)-4-ethyl-2-iodobenzene **129** (0.32 g, 0.946 mmol) in IPA (6 mL) were added NEt₃ (0.39 mL, 2.838 mmol), di(1-adamantyl)-n-butylphosphine (0.02 g, 0.075 mmol) and 1,4-diazabicyclo[2.2.2]octane-1,4-diium-1,4-disulfinate (0.13 g, 0.567 mmol) under Argon atmosphere. The reaction mixture was degassed for 5 min followed by addition of Pd(OAc)₂ (0.01 g, 0.047 mmol). The reaction mixture was stirred at 75 °C for 16h. After completion (monitored by TLC), the mixture was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated under reduced pressure and crude was dissolved in dry THF (6 mL) and SO₂Cl₂ (0.23 mL, 2.839 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was quenched with NH₄Cl, extracted with DCM and concentrated under reduced pressure to afford 2-(benzyloxy)-5-ethylbenzenesulfonyl chloride **130** (0.28 g, 95.23%). The crude was carried forward to the next reaction.

[1940] **Synthesis of *tert*-Butyl ((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (131)**

[1941] To a stirred solution of compound **15** (0.45 g, 1.205 mmol) in THF (6 mL) was added 1M KOtBu in THF (3.61 mL, 3.615 mmol) at 0 °C. The reaction was stirred for 10 min followed by addition of compound **130** (0.44 g, 1.446 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 68-78% EtOAc/Heptane to afford title compound **131** (0.40 g, 48.88%) as a brown solid. LCMS calculated for C₃₃H₃₇N₅O₇S: 647.24; Found: 646.30 (M-1).

[1942] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-(benzyloxy)-5-ethylbenzenesulfonamide (132)

[1943] To a stirred solution of compound **131** (0.30 g, 0.463 mmol) in DCM (6 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.17 mL, 0.694 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et_2O and concentrated under reduced pressure to afford title compound **132** (0.22 g, 79.10%) as a brown solid. LCMS calculated for $\text{C}_{28}\text{H}_{29}\text{N}_5\text{O}_5\text{S}$: 547.19; Found: 546.30 (M-1).

[1944] Synthesis of N-((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 92)

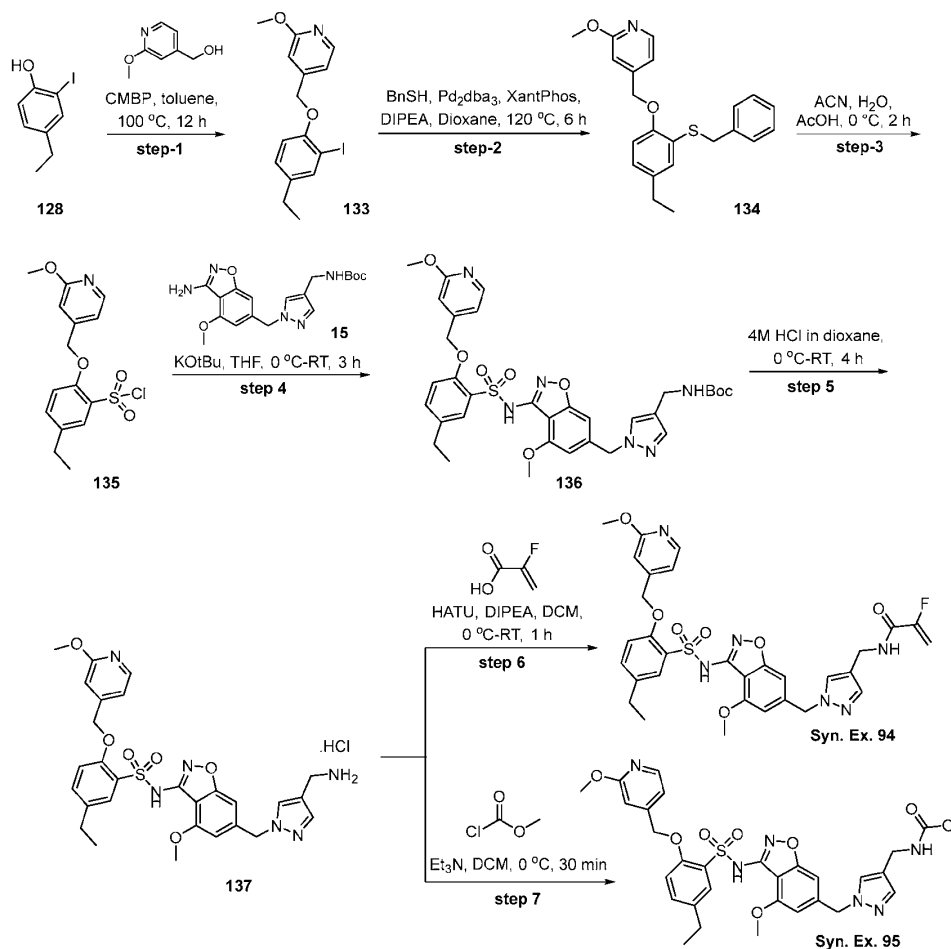
[1945] To a stirred solution of compound **132** (0.11 g, 0.20 mmol) in DCM (4 mL) were added 2-fluoroacrylic acid (0.02 g, 0.241 mmol), DIPEA (0.10 mL, 0.602 mmol) and HATU (0.11 g, 0.301 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 92**; 16 mg, 12.81%) as an off-white solid. (See analytical data in Table 1).

[1946] Synthesis of methyl ((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 93)

[1947] To a stirred solution of compound **132** (0.10 g, 0.182 mmol) in DCM (3 mL) were added NEt_3 (0.07 mL, 0.547 mmol) and methyl chloroformate (0.02 g, 0.219 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-(benzyloxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 93**; 48 mg, 42.32%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 94-95

[1948] Scheme 60: Synthesis of N-((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 94) and methyl ((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 95)



[1949] Synthesis of 4-((4-ethyl-2-iodophenoxy)methyl)-2-methoxypyridine (133)

[1950] To a stirred solution of compound **128** (10 g, 40.312 mmol) in toluene (100 mL) were added (2-methoxypyridin-4-yl)methanol (6.73 g, 48.375 mmol) and (cyanomethylene)tributylphosphorane (12.03 g, 48.375 mmol) at room temperature. The mixture was stirred at 100 °C for 12 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with DCM and concentrated under reduced

pressure. The crude was purified by combi-flash chromatography using 10-15% EtOAc/Heptane to afford title compound **133** (4.50 g, 27.48%) as a pale-yellow liquid. LCMS calculated for C₁₅H₁₆INO₂: 369.02; Found: 370 (M+1).

[1951] Synthesis of 4-((2-(benzylthio)-4-ethylphenoxy)methyl)-2-methoxypyridine (134)

[1952] To a stirred solution of compound **133** (4.50 g, 12.18 mmol) in 1,4-Dioxane (40 mL) were added DIPEA (4.76 mL, 26.81 mmol), benzyl mercaptan (1.51 g, 12.18 mmol) and XantPhos (0.56 g, 0.97 mmol). The reaction mixture was degassed with Argon for 10 min, followed by addition of Pd₂(dba)₃ (0.57 g, 0.609 mmol). The reaction mixture was stirred at 120 °C for 6 h. After completion (monitored by TLC), the mixture was filtered through celite bed and washed with EtOAc. The filtrate was quenched with ice-cold water, extracted with EtOAc and organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 10-15% of EtOAc/Heptane to afford title compound **134** (4.0 g, 80.63%) as a pale-yellow oil. LCMS calculated for C₂₂H₂₃NO₂S: 365.14; Found: 366.20 (M+1).

[1953] Synthesis of 5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)benzenesulfonyl chloride (135)

[1954] To a stirred solution of compound **134** (1.0 g, 2.73 mmol) in ACN (10 mL), AcOH (0.50 mL) and H₂O (0.30 mL) were added 1,3-dichloro-5,5-dimethylhydantoin (1.08 g, 5.52 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **135** (0.60 g, 19.43%) as a brown solid which was directly used in the next step without purification. LCMS calculated for C₁₅H₁₆ClNO₄S: 341.05; Found: 342 (M+1).

[1955] Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (136)

[1956] To a stirred solution of compound **15** (0.06 g, 0.175 mmol) in THF (10 mL) was added 1M KOtBu in THF (0.17 mL, 1.170 mmol) at 0 °C. The reaction was stirred for 10 min followed by addition of compound **135** (0.20 g, 0.585 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed

with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **136** (0.15 g, 20.05%) as a brown solid. LCMS calculated for C₃₃H₃₈N₆O₈S: 678.25; Found: 679.30 (M+1).

[1957] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)benzenesulfonamide hydrochloride (137)

[1958] To a stirred solution of compound **136** (0.15 g, 0.220 mmol) in DCM (3 mL) was added 4M HCl in Dioxane (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried to afford title compound **137** (0.12 g, 56.52%) as a brown solid. LCMS calculated for C₂₈H₃₀N₆O₆S: 578.19; Found: 577.30 (M-1)

[1959] Synthesis of N-((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 94)

[1960] To a stirred solution of compound **137** (0.10 g, 0.162 mmol) in DCM (4 mL) were added 2-fluoroacrylic acid (0.02 g, 0.256 mmol), DIPEA (0.11 mL, 0.663 mmol) and HATU (0.12 g, 0.335 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 94**; 31.30 mg, 29.33%) as an off-white solid. (See analytical data in Table 1).

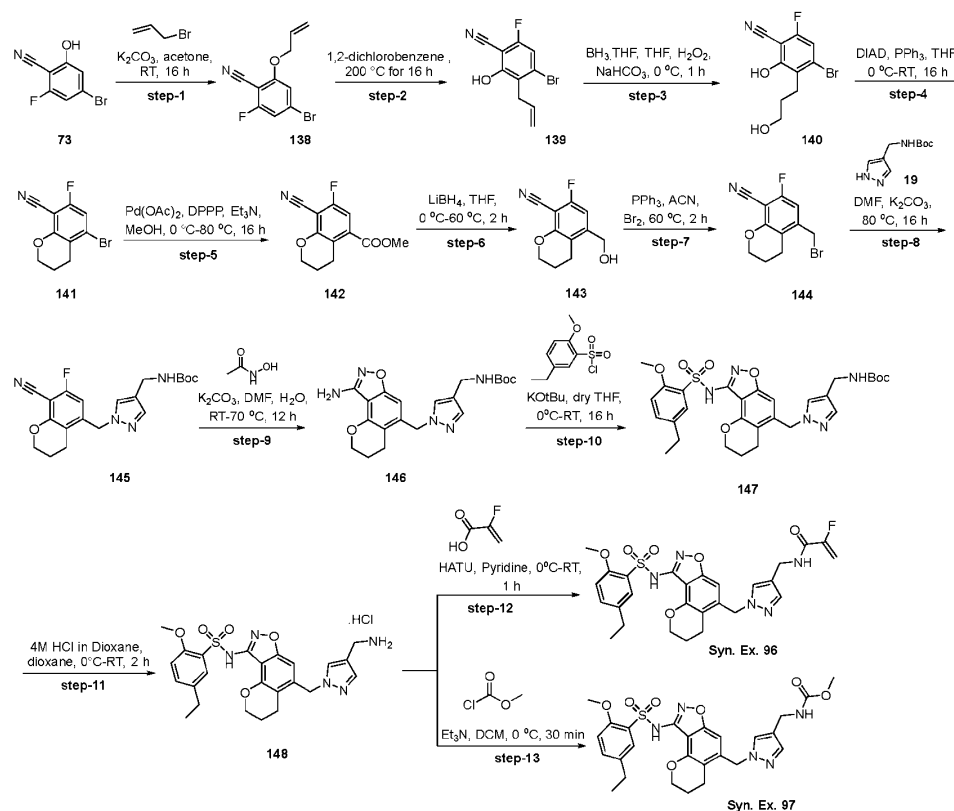
[1961] Synthesis of methyl ((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 95)

[1962] To a stirred solution of compound **137** (0.20 g, 0.325 mmol) in DCM (10 mL) were added NEt₃ (0.13 mL, 0.975 mmol) and methyl chloroformate (0.03 g, 0.390 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was diluted with water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl((1-((3-((5-ethyl-2-((2-methoxypyridin-4-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-

yl)methyl)carbamate (Syn. Ex. 95; 0.015 g, 7.06%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 96-97

[1963] Scheme 61: Synthesis of N-((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 96) and methyl ((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 97)



[1964] Synthesis of 2-(allyloxy)-4-bromo-6-fluorobenzonitrile (138)

[1965] To a stirred solution of compound 73 (27 g, 124.994 mmol) in acetone (400 mL) were added K_2CO_3 (34.54 g, 249.988 mmol) and 3-bromoprop-1-ene (18 mL). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to

afford title compound **138** (25 g, 78.10%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.48 (br d, J = 8.7 Hz, 1H), 7.41 (s, 1H), 6.10 - 5.99 (m, 1H), 5.45 (br d, J = 17.4 Hz, 1H), 5.34 (br d, J = 10.4 Hz, 1H), 4.82 (br d, J = 5.0 Hz, 2H).

[1966] Synthesis of 3-allyl-4-bromo-6-fluoro-2-hydroxybenzonitrile (139)

[1967] A solution of compound **138** (25 g, 97.629 mmol) in 1,2-dichlorobenzene (200 mL) was stirred at 200 °C for 16 h. After completion (monitored by TLC), the reaction mixture was quenched with ice-cold water, extracted with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 25% EtOAc/Heptane to afford title compound **139** (22 g, 66%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 11.44 (br s, 1H), 7.37 (d, J = 9.1 Hz, 1H), 5.93 - 5.71 (m, 1H), 5.03 (br d, J = 10.4 Hz, 1H), 4.90 (br d, J = 17.0 Hz, 1H), 3.52 (br d, J = 5.4 Hz, 2H).

[1968] Synthesis of 4-bromo-6-fluoro-2-hydroxy-3-(3-hydroxypropyl)benzonitrile (140)

[1969] To a stirred solution of compound **139** (20 g, 78.103 mmol) in THF (200 mL) was added $\text{BH}_3\cdot\text{THF}$ complex (78 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h followed by the addition of H_2O_2 (6.25 g, 156.207 mmol) and NaHCO_3 (14.58 g, 156.207 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with 1N HCl and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford title compound **140** (15 g, 31.53%) as a colorless liquid. LCMS calculated for $\text{C}_{10}\text{H}_9\text{BrFNO}_2$: 272.98; Found: 274.10 (M+1).

[1970] Synthesis of 5-bromo-7-fluorochromane-8-carbonitrile (141)

[1971] To a stirred solution of compound **140** (7.50 g, 27.363 mmol) in THF (80 mL) was added PPh_3 (10.76 g, 41.044 mmol) and DIAD (8.29 g, 41.044 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with water, extracted with EtOAc and organic layer was concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 20% EtOAc/Heptane to afford title compound **141** (4.50 g, 63.58%) as an off-white solid. ^1H NMR (400 MHz, CHLOROFORM- d) δ 6.99 (d, J = 7.9 Hz, 1H), 4.31 - 4.27 (m, 2H), 2.72 (br t, J = 6.4 Hz, 2H), 2.13 - 2.01 (m, 2H).

[1972] Synthesis of methyl 8-cyano-7-fluorochromane-5-carboxylate (142)

[1973] To a stirred solution of compound **141** (4.50 g, 17.573 mmol) in MeOH (100 mL) were added NEt_3 (5 mL, 35.673 mmol), DPPP (1.41 g, 3.338 mmol) followed by the addition

of Pd(OAc)₂ (0.39 g, 1.664 mmol). The reaction mixture was stirred at 80 °C for 16 h under CO atmosphere (110 psi). After completion (monitored by TLC), the mixture was cooled at room temperature, filtered and concentrated under reduced pressure to afford title compound **142** (3 g, 71.85%) as a white solid. ¹H NMR (400 MHz, CHCl₃-*d*) δ 7.24 (s, 1H), 4.39 - 4.30 (m, 2H), 3.91 (s, 3H), 3.06 (t, *J* = 6.4 Hz, 2H), 2.08 - 1.98 (m, 2H).

[1974] Synthesis of 7-fluoro-5-(hydroxymethyl)chromane-8-carbonitrile (143)

[1975] To a stirred solution of compound **142** (3.30 g, 14.030 mmol) in THF (40 mL) was added LiBH₄ (0.61 g, 28.060 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with EtOAc and concentrated under reduced pressure to afford title compound **143** (2.80 g, 95.35%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.98 (br d, *J* = 10.4 Hz, 1H), 5.50 (br t, *J* = 5.2 Hz, 1H), 4.49 (br d, *J* = 5.0 Hz, 2H), 4.28 (br t, *J* = 5.0 Hz, 2H), 2.56 (br t, *J* = 6.0 Hz, 2H), 2.00 - 1.91 (m, 2H).

[1976] Synthesis of 5-(bromomethyl)-7-fluorochromane-8-carbonitrile (144)

[1977] To a stirred solution of compound **143** (2.80 g, 13.513 mmol) in ACN (30 mL) were added PPh₃ (5.42 g, 20.683 mmol) and Br₂ (1.04 mL, 20.372 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with sodium thiosulfate, extracted with EtOAc, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 15% EtOAc/Heptane to afford title compound **144** (1.30 g, 35.26%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.15 (d, *J* = 10.1 Hz, 1H), 4.68 (s, 2H), 4.33 (t, *J* = 5.0 Hz, 2H), 2.77 (br t, *J* = 6.4 Hz, 2H), 2.00 (quin, *J* = 5.7 Hz, 2H).

[1978] Synthesis of *tert*-Butyl ((1-((8-cyano-7-fluorochroman-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (145)

[1979] To a stirred solution of compound **19** (0.90 g, 4.564 mmol) in DMF (30 mL) were added K₂CO₃ (1.39 g, 10.129 mmol) and compound **144** (0.90 g, 3.332 mmol). The reaction mixture was stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was cooled at room temperature, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 20% EtOAc/Hexane to afford title compound **145** (0.70 g, 53.82%) as an off-white solid. LCMS calculated for C₂₀H₂₃FN₄O₃: 386.18; Found: 387.20 (M+1).

[1980] Synthesis of *tert*-Butyl ((1-((9-amino-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (146)

[1981] To a stirred solution of compound **145** (0.60 g, 1.552 mmol) in DMF (8 mL) and water (2 mL) was added K₂CO₃ (1.28 g, 9.316 mmol) and acetohydroxamic acid (0.71 g, 9.316 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 12 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **146** (0.25 g, 33.45%) as a colorless liquid. LCMS calculated for C₂₀H₂₅N₅O₄: 399.19; Found: 400.30 (M+1).

[1982] **Synthesis of *tert*-Butyl ((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (147)**

[1983] To a stirred solution of compound **146** (0.15 g, 0.375 mmol) in dry THF (10 mL) were added 1M KOtBu in THF (1.12 mL, 1.126 mmol) and 5-ethyl-2-methoxybenzenesulfonyl chloride (0.17 g, 0.751 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to adjust the pH ~ 6 and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **147** (0.20 g, 80.19%) as a brown solid. LCMS calculated for C₂₉H₃₅N₅O₇S: 597.23; Found: 596.30 (M-1).

[1984] **Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-9-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (148)**

[1985] To a stirred solution of compound **147** (0.20 g, 0.334 mmol) in 1,4-Dioxane (5 mL) was added 4M HCl in Dioxane (0.41 mL, 1.673 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **148** (0.12 g, 51.72%) as an off-white solid. LCMS calculated for C₂₄H₂₇N₅O₅S: 497.17; Found: 498.30 (M+1).

[1986] **Synthesis of N-((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 96)**

[1987] To a stirred solution of 2-fluoroacrylic acid (0.02 g, 0.280 mmol) in pyridine (8 mL) were added HATU (0.14 g, 0.394 mmol) and compound **148** (0.10 g, 0.187 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by

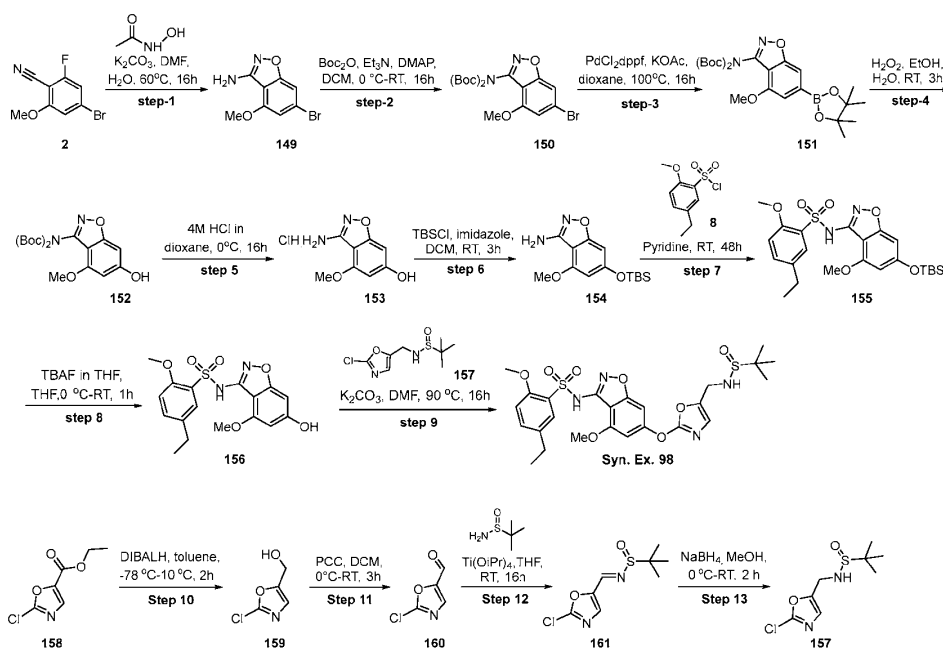
TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 96**; 47 mg, 44.09%) as an off-white solid. (See analytical data in Table 1).

[1988] Synthesis of methyl ((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 97**)**

[1989] To a stirred solution of compound **148** (0.08 g, 0.149 mmol) in DCM (5 mL) were added Et₃N (0.04 mL, 0.299 mmol) and methyl chloroformate (0.01 g, 0.149 mmol) in DCM at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((9-((5-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 97**; 12 mg, 13.84%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 98

[1990] Scheme 62: Synthesis of N-(6-((5-(((*tert*-Butylsulfinyl)amino)methyl)oxazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 98**)**



[1991] Synthesis of 6-bromo-4-methoxybenzo[d]isoxazol-3-amine (149)

[1992] To a stirred solution of compound **2** (25 g, 108.676 mmol) in DMF (550 mL) was added acetohydroxamic acid (24.97 g, 326.030 mmol) and K_2CO_3 (45.01 g, 326.030 mmol) in water (80 mL) at room temperature. The reaction mixture was stirred at $60^\circ C$ for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **149** (16 g, 38.22%) as an off-white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.35 (s, 1 H), 7.13 (br s, 1 H), 5.92 (s, 2 H), 3.86 (s, 3 H).

[1993] Synthesis of *tert*-Butyl (6-bromo-4-methoxybenzo[d]isoxazol-3-yl)(*tert*-butoxycarbonyl)carbamate (150)

[1994] To a stirred solution of compound **149** (8 g, 32.913 mmol) in DCM (120 mL) were added Et_3N (13.77 mL, 98.741 mmol), 4-dimethylaminopyridine (0.80 g, 6.582 mmol) and di-*tert*-butyl dicarbonate (21.76 g, 98.741 mmol) at $0^\circ C$. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **150** (5 g, 33.58%) as an off-white solid. LCMS calculated for $C_{18}H_{23}BrN_2O_6$: 442.07; Found: 286.90 [$M-(Boc+tBu)+1$].

[1995] Synthesis of *tert*-Butyl (*tert*-butoxycarbonyl)(4-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)carbamate (151)

[1996] To a stirred solution of compound **150** (10 g, 22.55 mmol) in 1,4-Dioxane (100 mL) was added bis(pinacolato)diboron (11.81 g, 45.11 mmol) and KOAc (4.47 g, 45.11 mmol). The reaction was degassed with N₂ purging for 10 min followed by addition of PdCl₂(dppf) (0.86 g, 1.187 mmol). The mixture was stirred at 100 °C for 16h. After completion (monitored by TLC), the mixture was filtered through a celite bed and washed with EtOAc. The filtrate was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 15-18% EtOAc/Heptane to afford title compound **151** (6.0 g, 33.52%) as an off-white solid. LCMS calculated for C₂₄H₃₅BN₂O₈: 490.25; Found: 335.20 [M-(Boc+tBu+1)].

[1997] Synthesis of *tert*-Butyl (*tert*-butoxycarbonyl)(6-hydroxy-4-methoxybenzo [d] isoxazol-3-yl)carbamate (152)

[1998] To a stirred solution of compound **151** (6.0 g, 14.698 mmol) in EtOH (66 mL) and H₂O (30 mL) was added 30% H₂O₂ (40.53 mL, 396.85 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was quenched with Na₂CO₃ and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 40% EtOAc/Heptane to afford title compound **152** (4.0 g, 70.82%) as a brown solid. LCMS calculated for C₁₈H₂₄N₂O₇: 380.16; Found: 379.0 (M-1).

[1999] Synthesis of 3-amino-4-methoxybenzo[d]isoxazol-6-ol hydrochloride (153)

[2000] To a stirred solution of compound **152** (0.50 g, 1.31 mmol) in DCM (5 mL) was added 4M HCl in dioxane (1.64 mL, 6.57 mmol) at 0 °C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **153** (0.22 g, 76.42%) as a brown solid. LCMS calculated for C₈H₈N₂O₃: 180.05; Found: 181.0 (M+1).

[2001] Synthesis of 6-((*tert*-Butyldimethylsilyl)oxy)-4-methoxybenzo[d]isoxazol-3-amine (154)

[2002] To a stirred solution of compound **153** (0.22 g, 1.01 mmol) in THF (5 mL) were added imidazole (0.20 g, 3.04 mmol) and *tert*-butyldimethylchlorosilane (0.18 g, 1.21 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by

TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 22-27% EtOAc/Heptane to afford title compound **154** (0.32 g) as a white solid. LCMS calculated for C₁₄H₂₂N₂O₃Si: 294.14; Found: 295.20 (M+1).

[2003] Synthesis of N-(6-((*tert*-Butyldimethylsilyl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (155)

[2004] To a stirred solution of compound **154** (0.15 g, 0.509 mmol) in pyridine (3 mL) was added 5-ethyl-2-methoxybenzenesulfonyl chloride (0.17 g, 0.764 mmol). The mixture was stirred at room temperature for 48h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 28-32% EtOAc/Heptane to afford title compound **155** (0.14 g, 55.77%) as a brown solid. LCMS calculated for C₂₃H₃₂N₂O₆SSi: 492.18; Found: 493.20 (M+1).

[2005] Synthesis of 5-ethyl-N-(6-hydroxy-4-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (156)

[2006] To a stirred solution of compound **155** (0.50 g, 1.014 mmol) in THF (6 mL) was added 1M TBAF in THF (1.11 mL, 1.116 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **156** (0.38 g, 91.14%) as a brown solid. LCMS calculated for C₁₇H₁₈N₂O₆S: 378.09; Found: 379.10 (M+1).

[2007] Synthesis of (2-chlorooxazol-5-yl)methanol (158)

[2008] To a stirred solution of compound **158** (5 g, 28.47 mmol) in THF (60 mL) was added 1M DIBAL-H in Toluene (56.95 mL, 56.95 mmol) at -78 °C. The mixture was cooled to -10 °C and stirred for 2h. After completion (monitored by TLC), the mixture was quenched with saturated aqueous NH₄Cl, diluted with EtOAc, filtered through a celite bed and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **159** (2.45 g, 60.31%) as a brown oil. LCMS calculated for C₄H₄ClNO₂: 132.99; Found: 134.0 (M+1)..

[2009] Synthesis of 2-chlorooxazole-5-carbaldehyde (160)

[2010] To a stirred solution of compound **159** (2.50 g, 18.72 mmol) in DCM (30 mL) was added PCC (6.17 g, 28.083 mmol) at 0 °C. The mixture was stirred at room temperature for 3h. After completion (monitored by TLC), the mixture was filtered through a celite pad and washed with DCM. The filtrate was washed with water, organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **160** (1.20 g, 40.93%) as a brown solid. LCMS calculated for C₄H₂ClNO₂: 130.98; Found: 129.20 (M-2).

[2011] Synthesis of (E)-N-((2-chlorooxazol-5-yl)methylene)-2-methylpropane-2-sulfinamide (161)

[2012] To a stirred solution of compound **160** (1.20 g, 9.12 mmol) in THF (15 mL) were added 2-methylpropane-2-sulfinamide (2.21 g, 18.24 mmol) and Ti(OiPr)₄ (5.34 g, 18.24 mmol) at 0 °C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with saturated NH₄Cl, diluted with EtOAc, filtered through a celite bed and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 13-16% EtOAc/Heptane to afford title compound **161** (1.20 g, 55.28%) as a white solid. LCMS calculated for C₈H₁₁ClN₂O₂S: 234.02; Found: 235.0 (M+1)

[2013] Synthesis of N-((2-chlorooxazol-5-yl)methyl)-2-methylpropane-2-sulfinamide (157)

[2014] To a stirred solution of compound **161** (1.20 g, 5.112 mmol) in MeOH (15 mL) was added NaBH₄ (0.38 g, 10.225 mmol) at 0 °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with saturated NH₄Cl, concentrated under reduced pressure and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **157** (1.10 g, 90.16%) as a brown oil. LCMS calculated for C₈H₁₃ClN₂O₂S: 236.04; Found: 237.10 (M+1).

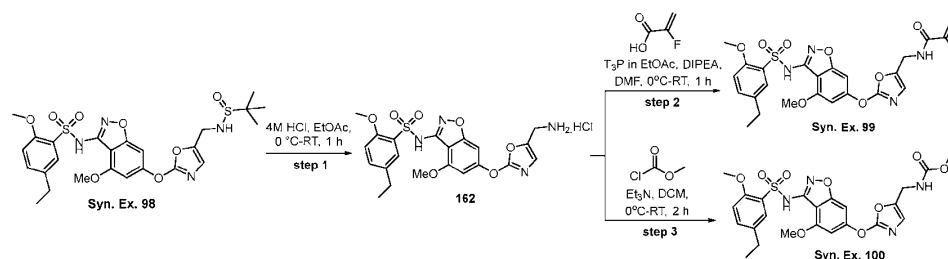
[2015] Synthesis of N-(6-(((5-((tert-Butylsulfinyl)amino)methyl)oxazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 98)

[2016] To a stirred solution of compound **156** (0.20 g, 0.528 mmol) in DMF (2 mL) were added K₂CO₃ (0.21 g, 1.585 mmol) and compound **157** (0.18 g, 0.792 mmol) at room temperature. The mixture was stirred at 90 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl to pH ~ 5 and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous

Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 26-30% EtOAc/Heptane to afford 0.17 g of desired product as a brown solid which was further purified by prep. HPLC to afford N-(6-((5-(((*tert*-Butylsulfinyl)amino)methyl)oxazol-2-yl)oxy)-4-methoxy benzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (**Syn. Ex. 98**; 5.50 mg, 18.15%) as a brown solid. (See analytical data in Table 1).

EXAMPLES 99-100

[2017] **Scheme 63: Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 99) and methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)carbamate (Syn. Ex. 100)**



[2018] **Synthesis of N-(6-((5-(aminomethyl)oxazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (162)**

[2019] To a stirred solution of **Syn. Ex. 98** (0.10 g, 0.172 mmol) in EtOAc (3 mL) was added 4M HCl in 1,4-Dioxane (0.043 mL, 0.172 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, triturated with EtOAc, filtered and dried to afford title compound **162** (50 mg, 49.30%) as a brown solid. LCMS calculated for C₂₁H₂₂N₄O₇S: 474.12; Found: 473.20 (M-1).

[2020] **Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 99)**

[2021] To a stirred solution of compound **162** (0.025 g, 0.052 mmol) in DMF (1 mL) were added DIPEA (0.027 mL, 0.158 mmol), 2-fluoroacrylic acid **2** (0.0056 g, 0.063 mmol) and 50% T₃P in EtOAc (0.10 g, 0.158 mmol) at 0 °C. The mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over

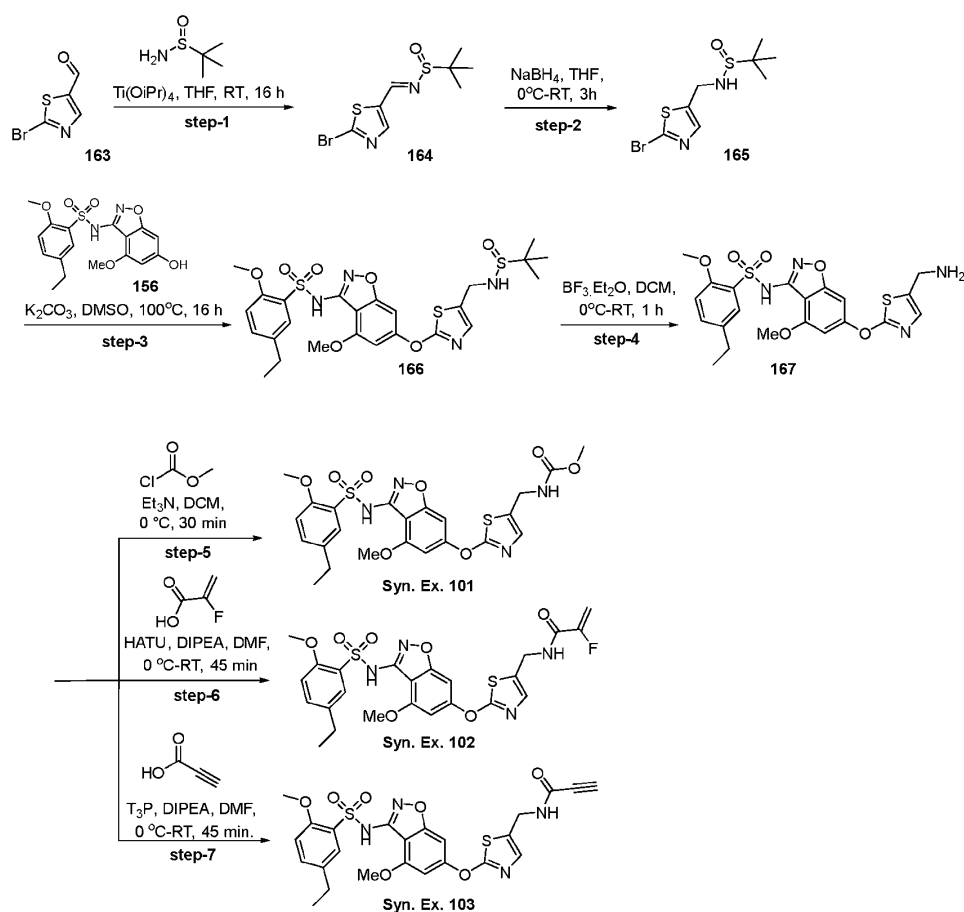
anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was submitted for prep. HPLC to afford N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 99**; 3 mg, 10.12%) as an off-white solid. (See analytical data in Table 1).

[2022] Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)carbamate (Syn. Ex. 100**)**

[2023] To a stirred solution of compound **162** (0.05 g, 0.097 mmol) in DCM (3 mL) was added NEt₃ (0.04 mL, 0.293 mmol) and methyl chloroformate (0.01 g, 0.107 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)oxazol-5-yl)methyl)carbamate (**Syn. Ex. 100**; 6 mg, 11.45%) as a light-brown solid. (See analytical data in Table 1).

EXAMPLES 101-103

[2024] Scheme 64: Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)carbamate (Syn. Ex. 101**), N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 102**) and N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)propiolamide (**Syn. Ex. 103**)**



[2025] Synthesis of (E)-N-((2-bromothiazol-5-yl)methylene)-2-methylpropane-2-sulfonamide (164)

[2026] To a stirred solution of compound **163** (5 g, 26.037 mmol) in THF (50 mL) was added 2-methylpropane-2-sulfonamide (6.31 g, 52.075 mmol) and $\text{Ti}(\text{OiPr})_4$ (15.25 g, 52.075 mmol) at 0 °C. The mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, filtered and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 35-45% EtOAc/Heptane to afford title compound **164** (6.50 g, 83.71%) as a white solid. LCMS calculated for $\text{C}_8\text{H}_{11}\text{BrN}_2\text{OS}_2$: 293.95; Found: 294.90 (M+1)

[2027] Synthesis of N-((2-bromothiazol-5-yl)methyl)-2-methylpropane-2-sulfonamide (165) To a stirred solution of compound **164** (6 g, 20.324 mmol) in THF (60 mL) was added NaBH_4 (1.60 g, 40.649 mmol) at 0 °C. The mixture was stirred at room temperature for 3h.

After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **165** (4 g, 60.25%) as a white solid. LCMS calculated for C₈H₁₃BrN₂O₅S₂: 295.97; Found: 298.90 (M+3).

[2028] Synthesis of N-(6-((5-(((*tert*-Butylsulfinyl)amino)methyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (166)

[2029] To a stirred solution of compound **156** (0.15 g, 0.396 mmol) in DMSO (2 mL) was added compound **165** (0.16 g, 0.554 mmol) and K₂CO₃ (0.16 g, 1.189 mmol). The reaction mixture was stirred at 100 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 10-15% MeOH/DCM to afford title compound **166** (0.17 g, 34.61%) as a brown semi-solid. LCMS calculated for C₂₅H₃₀N₄O₇S₃: 594.13; Found: 595.10 (M+1).

[2030] Synthesis of N-(6-((5-(aminomethyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (167)

[2031] To a stirred solution of compound **166** (0.02 g, 0.033 mmol) in DCM (1 mL) was added BF₃·Et₂O (0.014 g, 0.050 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **167** (0.01 g, 43.04%) as a brown semi-solid. LCMS calculated for C₂₁H₂₂N₄O₆S₂: 490.10; Found: 489.10 (M-1).

[2032] Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)carbamate (Syn. Ex. 101)

[2033] To a stirred solution of compound **167** (0.13 g, 0.265 mmol) in DCM (3 mL) were added Et₃N (1.09 mL, 0.795 mmol) and methyl chloroformate (0.03 g, 0.318 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)carbamate (**Syn. Ex. 101**; 5 mg, 3.33%) as an off-white solid.

[2034] Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 102)

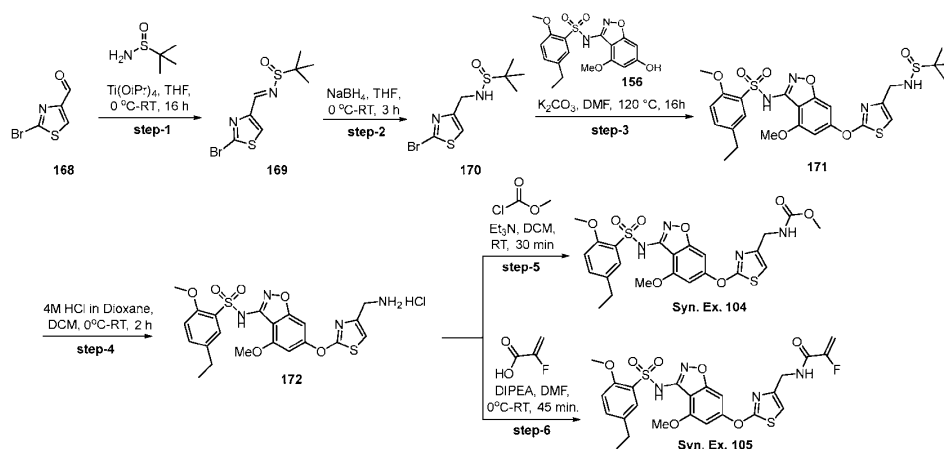
[2035] To a stirred solution of N-(6-((5-(aminomethyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide **167** (0.13 g, 0.265 mmol) in DMF (3 mL) were added DIPEA (0.13 mL, 0.795 mmol), 2-fluoroacrylic acid (0.047 g, 0.530 mmol) and HATU (0.15 g, 0.397 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 45 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 102**; 7 mg, 4.60%) as an off-white solid.

[2036] Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)propiolamide (Syn. Ex. 103)

[2037] To a stirred solution of compound **167** (0.13 g, 0.265 mmol) in DMF (1 mL) were added DIPEA (0.13 mL, 0.795 mmol), propiolic acid (0.037 g, 0.530 mmol) followed by the addition of and 50% T₃P in EtOAc (0.84 mL, 1.325 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 45 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)propiolamide (**Syn. Ex. 103**; 6 mg, 4.17%) as an off-white solid. (See analytical data in Table 1).

EXAMPLES 104-105

[2038] Scheme 65: Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)carbamate (Syn. Ex. 104) and N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 105)



[2039] Synthesis of (Z)-N-((2-bromothiazol-4-yl)methylene)-2-methylpropane-2-sulfonamide (169)

[2040] To a stirred solution of compound **168** (5 g, 26.037 mmol) in THF (50 mL) were added 2-methylpropane-2-sulfonamide (6.31 g, 52.075 mmol) and $\text{Ti}(\text{OiPr})_4$ (15.25 g, 52.075 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 35-45% EtOAc/ Heptane to afford title compound **169** (6.50 g, 83.71%) as a white solid. LCMS calculated for $\text{C}_8\text{H}_{11}\text{BrN}_2\text{OS}_2$: 293.95; Found: 294.90 ($\text{M}+1$)

[2041] Synthesis of N-((2-bromothiazol-4-yl)methyl)-2-methylpropane-2-sulfonamide (170)

[2042] To a stirred solution of compound **169** (6 g, 20.324 mmol) in THF (60 mL) was added NaBH_4 (1.60 g, 40.649 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **170** (4 g, 60.26%) as a white solid. LCMS calculated for $\text{C}_8\text{H}_{13}\text{BrN}_2\text{OS}_2$: 295.97; Found: 298.90 ($\text{M}+3$).

[2043] Synthesis of N-(6-(((4-((tert-Butylsulfinyl)amino)methyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (171)

[2044] To a stirred solution of compound **156** (0.15 g, 0.396 mmol) in DMF (2 mL) was added compound **170** (0.21 g, 0.713 mmol) followed by the addition of K_2CO_3 (0.16 g, 1.189 mmol). The mixture was stirred at 120 °C for 16h. After completion (monitored by TLC), the

mixture was purified by combi-flash chromatography using 90% EtOAc/Heptane to afford title compound **171** (0.10 g, 27.57%) as a yellow solid. LCMS calculated for C₂₅H₃₀N₄O₇S₃: 594.13; Found: 595.20 (M+1)

[2045] Synthesis of N-(6-((4-(aminomethyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (172)

[2046] To a stirred solution of compound **171** (0.10 g, 0.168 mmol) in DCM (1 mL) was added 4M HCl in Dioxane (1 mL, 4 mmol) at 0 °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **172** (0.08 g, 63.64%) as an off-white solid. LCMS calculated for C₂₁H₂₂N₄O₆S₂: 490.10; Found: 491.10 (M+1)

[2047] Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)carbamate (Syn. Ex. 104)

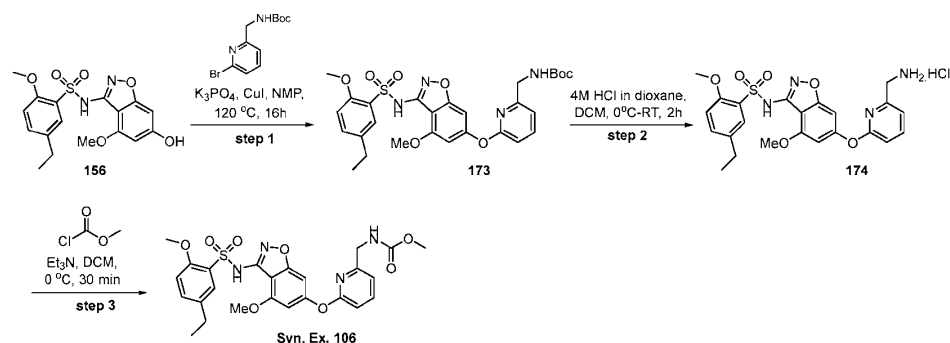
[2048] To a stirred solution of compound **172** (0.17 g, 0.322 mmol) in DCM (1.80 mL) was added NEt₃ (0.0089 mL, 0.064 mmol) followed by the addition of methyl chloroformate (0.016 g, 0.161 mmol) in DCM at 0 °C. The mixture was stirred at room temperature for 30 min. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)carbamate (**Syn. Ex. 104**; 9 mg, 5.07%) as a white solid.

[2049] Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 105)

[2050] To a stirred solution of compound **172** (0.15 g, 0.284 mmol) in DMF (5 mL) were added 2-fluoroacrylic acid (0.03 g, 0.341 mmol), DIPEA (0.10 mL, 0.569 mmol) and HATU (0.22 g, 0.569 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 45 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water (3 mL) and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 105**; 40 mg, 24.98%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 106

[2051] **Scheme 66: Synthesis of methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-2-yl)methyl)carbamate (Syn. Ex. 106)**



[2052] **Synthesis of *tert*-Butyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-2-yl)methyl)carbamate (173)**

[2053] To a stirred solution of compound **156** (0.20 g, 0.528 mmol) in NMP (4 mL) were added *tert*-Butyl ((6-bromopyridin-2-yl)methyl)carbamate (0.22 g, 0.792 mmol) and potassium K_3PO_4 (0.35 g, 1.585 mmol). The mixture was degassed for 10 min with Argon followed by addition of picolinic acid (0.013 g, 0.105 mmol) and CuI (0.003 g, 0.015 mmol). The reaction mixture was stirred at 120 °C for 16h. After completion (monitored by TLC), the mixture was quenched with saturated ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 54-65% EtOAc/Heptane to afford title compound **173** (0.11 g, 17.94%) as a brown solid. LCMS calculated for $C_{28}H_{32}N_4O_8S$: 584.19; Found: 583.20 (M-1)

[2054] **Synthesis of N-(6-((3-((5-ethyl-2-methoxybenzenesulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-2-yl)methyl)carbamate hydrochloride (174)**

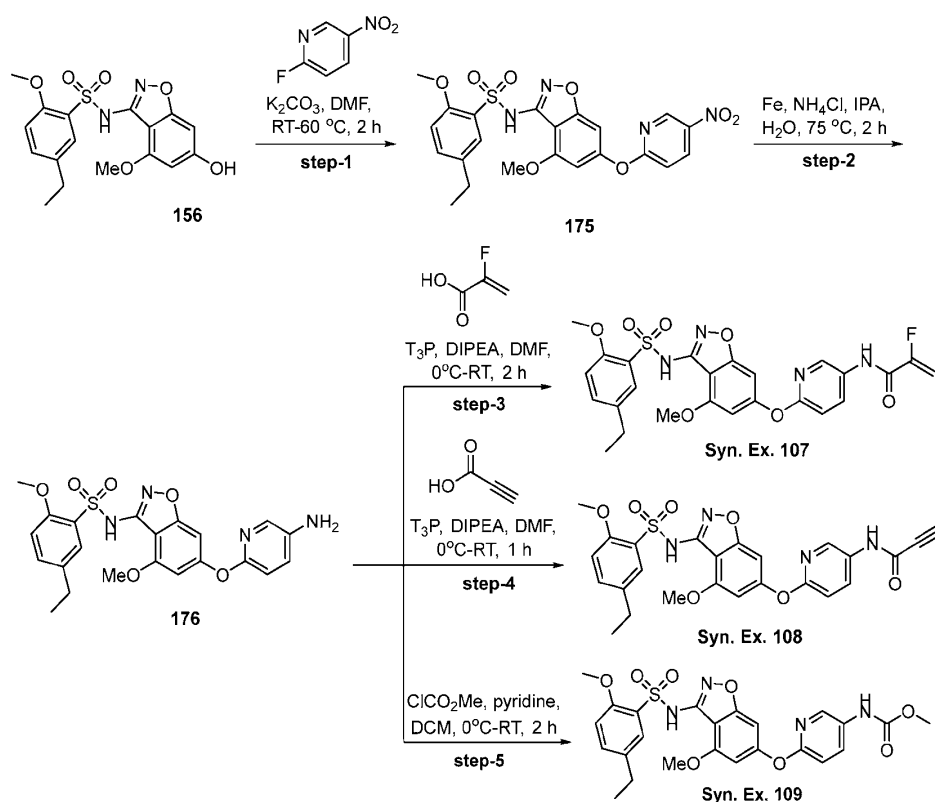
[2055] To a stirred solution of compound **173** (0.11 g, 0.188 mmol) in DCM (4 mL) was added 4M HCl in dioxane (0.47 mL, 1.881 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et_2O and dried under reduced pressure to afford title compound **174** (0.08 g, 69.74%) as a brown solid. LCMS calculated for $C_{23}H_{24}N_4O_6S$: 484.14; Found: 485.0 (M+1).

[2056] **Synthesis of methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-2-yl)methyl)carbamate (Syn. Ex. 106)**

[2057] To a stirred solution of compound **174** (0.08 g, 0.153 mmol) in DCM (4 mL) was added NEt₃ (0.064 mL, 0.460 mmol) and methyl chloroformate (0.017 g, 0.184 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-2-yl)methyl)carbamate (**Syn. Ex.106**; 20 mg, 23.98%) as a gummy solid. (See analytical data in Table 1).

EXAMPLES 107-109

[2058] Scheme 67: Synthesis of N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)-2-fluoroacrylamide (**Syn. Ex. 107**), Synthesis of N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)propiolamide (**Syn. Ex. 108**) and Synthesis of N-(6-((5-aminopyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (**Syn. Ex. 109**)



[2059] Synthesis of 5-ethyl-2-methoxy-N-(4-methoxy-6-((5-nitropyridin-2-yl)oxy)benzo[d]isoxazol-3-yl)benzenesulfonamide (175)

[2060] To a stirred solution of compound **156** (0.20 g, 0.528 mmol) in DMF (3 mL) was added K_2CO_3 (0.14 g, 1.057 mmol) and 2-fluoro-5-nitropyridine (0.09 g, 0.634 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl to adjust the pH 6-7 and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was triturated with Et_2O to afford compound **175** (0.20 g, 67.29%) as a pale-yellow solid. LCMS calculated for $C_{22}H_{20}N_4O_8S$: 500.10; Found: 501.10 (M+1)

[2061] Synthesis of N-(6-((5-aminopyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (176)

[2062] To a stirred solution of compound **175** (0.15 g, 0.299 mmol) in IPA (6 mL) and H_2O (3 mL) were added Fe (0.098 g, 1.498 mmol) and NH_4Cl (0.089 g, 1.498 mmol) at room temperature. The resulting mixture was stirred at 75 °C for 2h. After completion (monitored

by TLC), the mixture was filtered through a celite bed and filtrate was diluted with ice-cold water. The aqueous layer was extracted with EtOAc, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **176** (0.12 g, 62.40%) as a brown-gummy solid. LCMS calculated for C₂₂H₂₂N₄O₆S: 470.13; Found: 471.10 (M+1).

[2063] Synthesis of N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)-2-fluoroacrylamide (Syn. Ex. 107)

[2064] To a stirred solution of compound **176** (0.08 g, 0.170 mmol) in DMF (8 mL) were added DIPEA (0.093 mL, 0.510 mmol) and 50% T₃P in EtOAc (0.32 g, 0.510 mmol). The mixture was stirred at 0 °C for 5 min followed by addition of 2-fluoroacrylic acid (0.018 g, 0.204 mmol). The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)-2-fluoroacrylamide (**Syn. Ex. 107**; 7.7 mg, 8.31%) as an off-white solid. (See analytical data in Table 1).

[2065] Synthesis of N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)propiolamide (Syn. Ex. 108)

[2066] To a stirred solution of compound **176** (0.08 g, 0.170 mmol) in DMF (3 mL) was added DIPEA (0.088 mL, 0.510 mmol), propiolic acid (0.01 g, 0.204 mmol) and 50% T₃P in EtOAc (0.32 mL, 0.510 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-(6-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)propiolamide (**Syn. Ex. 108**; 3 mg, 3.34%) as an off-white solid. (See analytical data in Table 1).

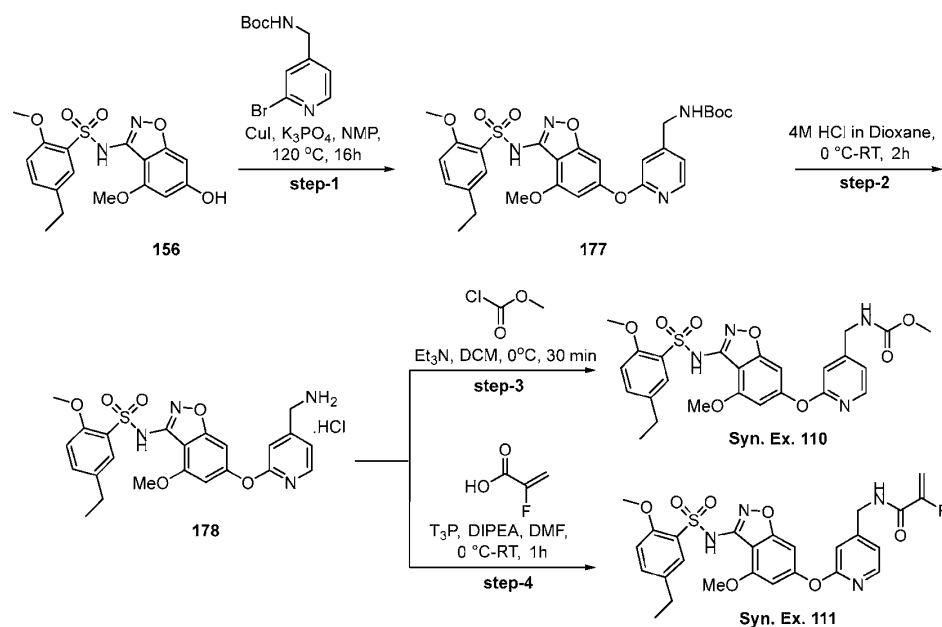
[2067] Synthesis of N-(6-((5-aminopyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 109)

[2068] To a stirred solution of compound **176** (0.07 g, 0.148 mmol) in DCM (3 mL) was added pyridine (0.035 g, 0.446 mmol) and methyl chloroformate (0.017 g, 0.178 mmol) at °C. The mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was quenched with ice cold water, acidified with 1N HCl (5mL) and

extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-(6-((5-aminopyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide (Syn. Ex. 109; 8 mg, 10.07%). (See analytical data in Table 1).

EXAMPLES 110-111

[2069] **Scheme 68: Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)carbamate (Syn. Ex. 110) and Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 111)**



[2070] **Synthesis of *tert*-Butyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)carbamate (177)**

[2071] To a stirred solution of compound 156 (0.20 g, 0.528 mmol) in NMP (3 mL) were added *tert*-Butyl ((2-bromopyridin-4-yl)methyl)carbamate (0.18 g, 0.634 mmol) and K₃PO₄ (0.35 g, 1.585 mmol). The reaction mixture was degassed with Argon for 10 min followed by addition of picolinic acid (0.013 g, 0.105 mmol) and CuI (0.003 g, 0.015 mmol). The reaction mixture was stirred at 120 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl and extracted with EtOAc. The

combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 54-65% EtOAc/Heptane to afford title compound **177** (0.21 g, 65.37%) as a brown solid. LCMS calculated for C₂₈H₃₂N₄O₈S: 584.19; Found: 585.30 (M+1)

[2072] Synthesis of N-(6-((4-(aminomethyl)pyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (178)

[2073] To a stirred solution of compound **177** (0.21 g, 0.359 mmol) in DCM (5 mL) was added 4M HCl in Dioxane (0.89 mL, 3.591 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **178** (0.16 g, 79.44%) as a brown solid. LCMS calculated for C₂₃H₂₄N₄O₆S: 484.14; Found: 485.20 (M+1)

[2074] Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)carbamate (Syn. Ex. 110)

[2075] To a stirred solution of compound **178** (0.08 g, 0.153 mmol) in DCM (3 mL) were added NEt₃ (0.067 mL, 0.484 mmol) and methyl chloroformate (0.017 g, 0.184 mmol) at 0 °C, while maintaining the pH 7-8. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)carbamate (**Syn. Ex. 110**; 24 mg, 28.53%) as a gummy solid. (See analytical data in Table 1).

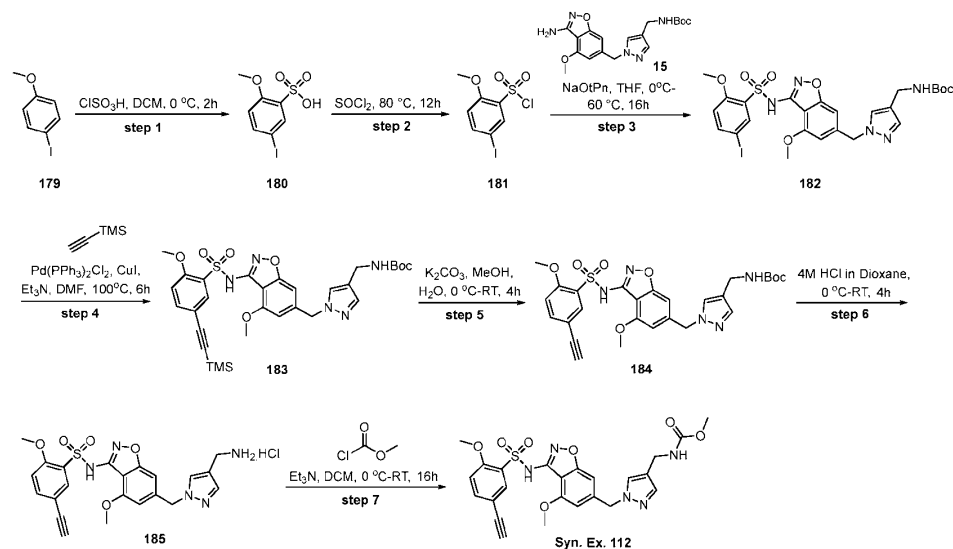
[2076] Synthesis of N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 111)

[2077] To a stirred solution of compound **178** (0.07 g, 0.134 mmol) in DMF (3 mL) was added DIPEA (0.07 mL, 0.411 mmol), 2-fluoroacrylic acid (0.014 g, 0.161 mmol) and 50% T₃P in EtOAc (0.25 mL, 0.403 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep.

HPLC to afford N-((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)oxy)pyridin-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 111**; 18 mg, 23.72%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 112

[2078] Scheme 69: Synthesis of methyl ((1-((3-((5-ethynyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 112**)**



[2079] Synthesis of 5-iodo-2-methoxybenzenesulfonic acid (180)

[2080] To a stirred solution of compound **179** (20 g, 85.455 mmol) in DCM (200 mL) was added ClSO₃H (18.26 mL, 256.366 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2h. After completion (monitored by TLC), the mixture was quenched with saturated NaHCO₃ and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **180** (5.80 g, 9.29%) as a brown solid. LCMS calculated for C₇H₇IO₄S: 313.91; Found: 312.90 (M-1).

[2081] Synthesis of 5-iodo-2-methoxybenzenesulfonyl chloride (181)

[2082] To a stirred solution of compound **180** (4.10 g, 13.053 mmol) was added SOCl₂ (2.86 mL, 39.160 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 12h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 15-17% EtOAc/Heptane to afford title compound **181**. The crude was carried forward to the next reaction.

[2083] Synthesis of *tert*-Butyl ((1-((3-((5-iodo-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (182)

[2084] To a stirred solution of compound **15** (0.50 g, 1.353 mmol) in THF (15 mL) was added compound **181** (1.50 g, 4.510 mmol) followed by sodium *tert*-pentoxide (1.56 g, 13.532 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **182** (0.60 g, 10.72%) as a brown solid. LCMS calculated for C₂₅H₂₈N₅O₇S: 669.08; Found: 670.10 (M+1)

[2085] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((2-methoxy-5-((trimethylsilyl)ethynyl)phenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (183)

[2086] To a stirred solution of compound **182** (1 g, 1.493 mmol) in THF (20 mL) was added DIPEA (0.82 mL, 4.481 mmol). The reaction was degassed with argon purging for 10 min. followed by addition of CuI (0.023 g, 0.119 mmol), ethynyltrimethylsilane (0.44 g, 4.481 mmol) and Pd(PPh₃)₂Cl₂ (0.055 g, 0.074 mmol). The reaction mixture was stirred at 100 °C for 6h. After completion (monitored by TLC), the mixture was cooled at room temperature, filtered through a celite pad, washed with EtOAc and concentrated under reduced pressure. The crude was purified by reverse phase column chromatography using 20-30% ACN/H₂O to afford title compound **183** (0.20 g, 8.18%) as a brown solid. LCMS calculated for C₃₀H₃₇N₅O₇SSi: 639.22; Found: 638.30 (M-1)

[2087] Synthesis of *tert*-Butyl ((1-((3-((5-ethynyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (184)

[2088] To a stirred solution of compound **183** (0.03 g, 0.046 mmol) in MeOH (10 mL) was added K₂CO₃ (0.013 g, 0.056 mmol) followed by the addition of H₂O (2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was quenched with water, extracted with DCM and dried over Na₂SO₄. The DCM layer was dried under reduced pressure to afford title compound **184** (0.01 g, 31.74%) as an off-white solid. LCMS calculated for C₂₇H₂₉N₅O₇S: 567.18; Found: 568.20 (M+1).

[2089] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethynyl-2-methoxybenzenesulfonamide hydrochloride (185)

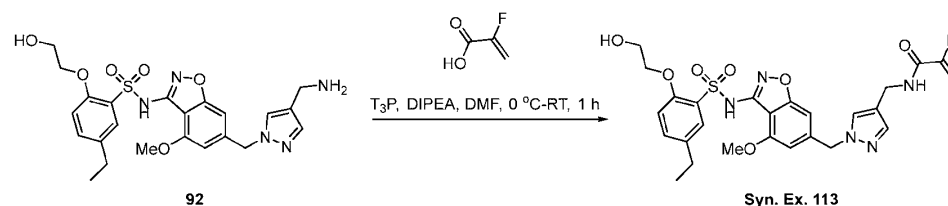
[2090] To a stirred solution of compound **184** (10 mg, 0.017 mmol) in DCM (3 mL) was added 4M HCl in Dioxane (1 mL) at 0 °C. The reaction mixture was at room temperature for 4h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and dried under reduced pressure to afford title compound **185** (6 mg, 28.73%) as a brown solid. LCMS calculated for C₂₂H₂₁N₅O₅S: 467.13; Found: 468.30 (M+1)

[2091] **Synthesis of methyl ((1-((3-((5-ethynyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 112)**

[2092] To a stirred solution of compound **185** (6 mg, 0.011 mmol) in DCM (5 mL) were added Et₃N (0.0052 mL, 0.035 mmol) and methyl chloroformate (1.3 mg, 0.014 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl((1-((3-((5-ethynyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 112**; 2 mg, 31.25%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 113

[2093] **Scheme 70: Synthesis of *N*-((1-((3-((5-ethyl-2-(2-hydroxyethoxy) phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl) methyl)-1H-pyrazol-4-yl) methyl)-2-fluoroacrylamide (Syn. Ex. 113)**

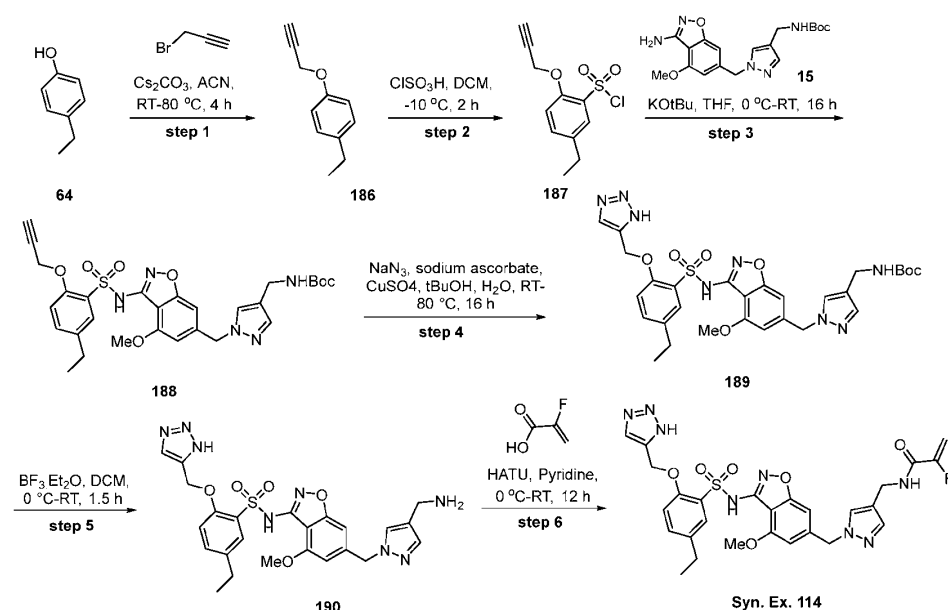


[2094] To a stirred solution of compound **92** (80 mg, 0.159 mmol) in DMF (2 mL) was added DIPEA (0.083 mL, 0.477 mmol), 2-fluoroprop-2-enoic acid (28 mg, 0.318 mmol) and T₃P (50 %) in EtOAc (0.30 mL, 0.477 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep.

HPLC to afford *N*-((1-((3-((5-ethyl-2-(2-hydroxyethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 113**; 10 mg, 10.98%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 114

[2095] **Scheme 71: Synthesis of *N*-((1-((3-((2-((1H-1,2,3-triazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 114**)**



[2096] **Synthesis of 1-ethyl-4-(prop-2-yn-1-yloxy)benzene (186)**

[2097] To a stirred solution of 4-ethylphenol **64** (6 g, 49.111 mmol) in ACN (80 mL) were added Cs_2CO_3 (32 g, 98.213 mmol) and 3-bromoprop-1-yne (5.54 g, 73.667 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 4 h. After completion (monitored by TLC), the mixture was filtered through a celite bed and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 25% EtOAc/Heptane to afford title compound **186** (8 g, 86.41%) as a pale-yellow liquid. LCMS calculated for $\text{C}_{11}\text{H}_{12}\text{O}$: 160.09; Found: 161.20 ($\text{M}+1$)

[2098] **Synthesis of 5-ethyl-2-(prop-2-yn-1-yloxy)benzenesulfonyl chloride (187)**

[2099] To a solution of 1-ethyl-4-(prop-2-yn-1-yloxy)benzene **186** (6 g, 37.448 mmol) in DCM (60 mL) was added ClSO_3H (5.03 mL, 75.653 mmol) at -10 °C. The reaction mixture was stirred at -10 °C for 2 h. After completion (monitored by TLC), the mixture was

quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 5-10% EtOAc/Heptane to afford title compound **187** (0.80 g, 4.95%) as a pale-yellow sticky solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.55 (br s, 1 H), 7.13 (br d, J=8.29 Hz, 1 H), 6.96 (br d, J=7.46 Hz, 1 H), 4.74 (br s, 2 H), 2.44 - 2.58 (m, 3 H), 1.14 (br t, J=7.05 Hz, 3 H).

[2100] Synthesis of tert-Butyl ((1-((3-((5-ethyl-2-(prop-2-yn-1-yloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (188)

[2101] To a stirred solution of compound **15** (0.40 g, 1.071 mmol) in THF (20 mL) were added KOtBu 1M in THF (1.60 mL, 1.606 mmol) and compound **187** (0.41 g, 1.606 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 90% EtOAc/Heptane to afford title compound **188** (0.30 g, 21.62%) as an off-white solid. LCMS calculated for C₂₉H₃₃N₅O₇S: 595.21; Found: 594.30 (M-1)

[2102] Synthesis of tert-Butyl ((1-((3-((2-((1H-1,2,3-triazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (189)

[2103] To a stirred solution of compound **188** (0.30 g, 0.503 mmol) in tBuOH (10 mL) and water (5 mL) were added NaN₃ (0.032 g, 0.503 mmol) and (+) sodium L-ascorbate (0.0099 g, 0.050 mmol) in water (1 mL) followed by the addition of CuSO₄ (0.7 mg, 0.005 mmol) in water (1 mL) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was filtered through celite bed, washed with 10% MeOH in DCM and dried under reduced pressure to afford title compound **189** (0.25 g, 55.65%) as a yellow solid. LCMS calculated for C₂₉H₃₄N₈O₇S: 638.23; Found: 639.20 (M+1)

[2104] Synthesis of 2-((1H-1,2,3-triazol-5-yl)methoxy)-N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethylbenzenesulfonamide (190)

[2105] To a stirred solution of compound **189** (0.20 g, 0.313 mmol) in DCM (10 mL) was added BF₃.Et₂O (0.50 mL, 1.982 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O (10 mL) and dried under reduced

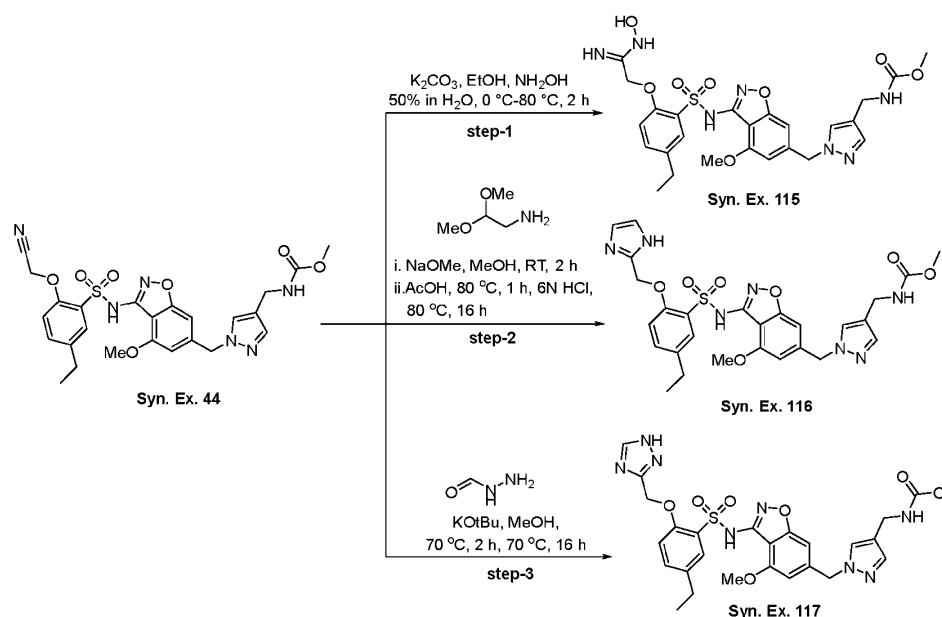
pressure to afford title compound **190** (0.18 g, 90.09 %) as a pale-yellow solid. LCMS calculated for C₂₄H₂₆N₈O₅S: 538.17; Found: 539.20 (M+1)

[2106] Synthesis of N-((1-((3-((2-((1H-1,2,3-triazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 114)

[2107] To a stirred solution of compound **190** (0.15 g, 0.278 mmol) in pyridine (5 mL) were added 2-fluoroacrylic acid (0.03 g, 0.417 mmol) and HATU (0.31 g, 0.835 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion (monitored by TLC), the mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((1H-1,2,3-triazol-5-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 114**; 6 mg, 3.43%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 115-117

[2108] Scheme 72: Synthesis of methyl ((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 115), Synthesis of methyl ((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 116) and methyl ((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 117)



[2109] Synthesis of methyl ((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 115)

[2110] To a stirred solution of **Syn. Ex. 44** (0.12 g, 0.216 mmol) in EtOH (5 mL) were added K_2CO_3 (0.04 g, 0.324 mmol) and 50% NH_2OH in H_2O (0.02 mL, 0.432 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 115**; 15 mg, 11.44 %) as an off-white solid. (See analytical data in Table 1).

[2111] Synthesis of methyl ((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 116)

[2112] To a stirred solution of **Syn. Ex. 44** (0.16 g, 0.288 mmol) in MeOH (5 mL) was added NaOMe (0.04 g, 0.865 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 2 h followed by addition of 2,2-diethoxyethan-1-amine (0.04 g, 0.346 mmol) and AcOH (0.03 mL, 0.577 mmol). The reaction mixture was stirred at 80 °C for 1 h, cooled to room temperature followed by addition of 6N HCl (0.10 mL) and stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure.

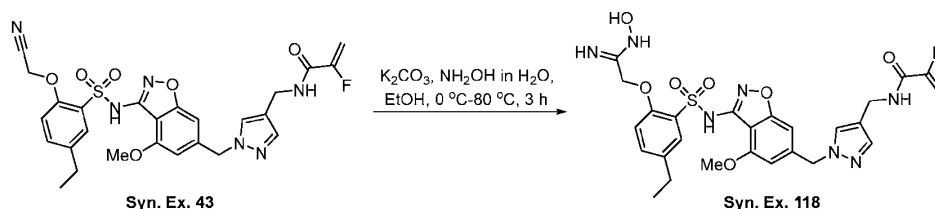
The residue was dissolved in ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 116**; 22.5 mg, 12.84%) as an off-white solid. (See analytical data in Table 1).

[2113] Synthesis of methyl ((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 117**)**

[2114] To a stirred solution of **Syn. Ex. 44** (0.06 g, 0.108 mmol) in MeOH (2 mL) was added KOtBu (0.01 g, 0.129 mmol). The reaction mixture was stirred at 70 °C for 2 h, then cooled to room temperature followed by addition of formyl hydrazide (0.03 g, 0.540 mmol). The reaction mixture was stirred at 70 °C for 16 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-((1H-1,2,4-triazol-3-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 117**; 13 mg, 19.51%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 118

[2115] Scheme 73: Synthesis of N-((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 118**)**

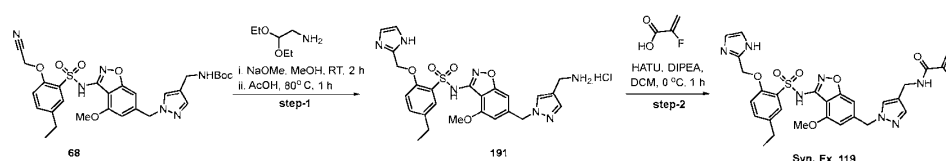


[2116] To a stirred solution of **Syn. Ex. 43** (0.16 g, 0.281 mmol) in EtOH (5 mL) were added K₂CO₃ (0.05 g, 0.421 mmol) and 50% NH₂OH in H₂O (0.03 g, 0.562 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((5-ethyl-2-(2-(hydroxyamino)-2-iminoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 118**; 13 mg, 19.51%) as an off-white solid. (See analytical data in Table 1).

methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 118; 11 mg, 6.34%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 119

[2117] **Scheme 74: Synthesis of N-((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 119)**



[2118] **Synthesis of 2-((1H-imidazol-2-yl)methoxy)-N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethylbenzenesulfonamide hydrochloride (191)**

[2119] To a stirred solution of compound **68** (0.25 g, 0.418 mmol) in MeOH (5 mL) was added NaOMe (0.08 mL, 1.257 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h, followed by addition of 2,2-diethoxyethan-1-amine (0.09 mL, 0.628 mmol) and AcOH (0.04 mL, 0.838 mmol). The reaction mixture was stirred at 80° C for 1 h, cooled to room temperature followed by addition of 6N HCl. The reaction mixture was stirred at 80° C for 16 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, washed with Et₂O and dried under reduced pressure to afford title compound **191** (0.22 g, 76.57%) as a pale-yellow solid. LCMS calculated for C₂₅H₂₇N₇O₅S: 537.18; Found: 536.20 (M-1).

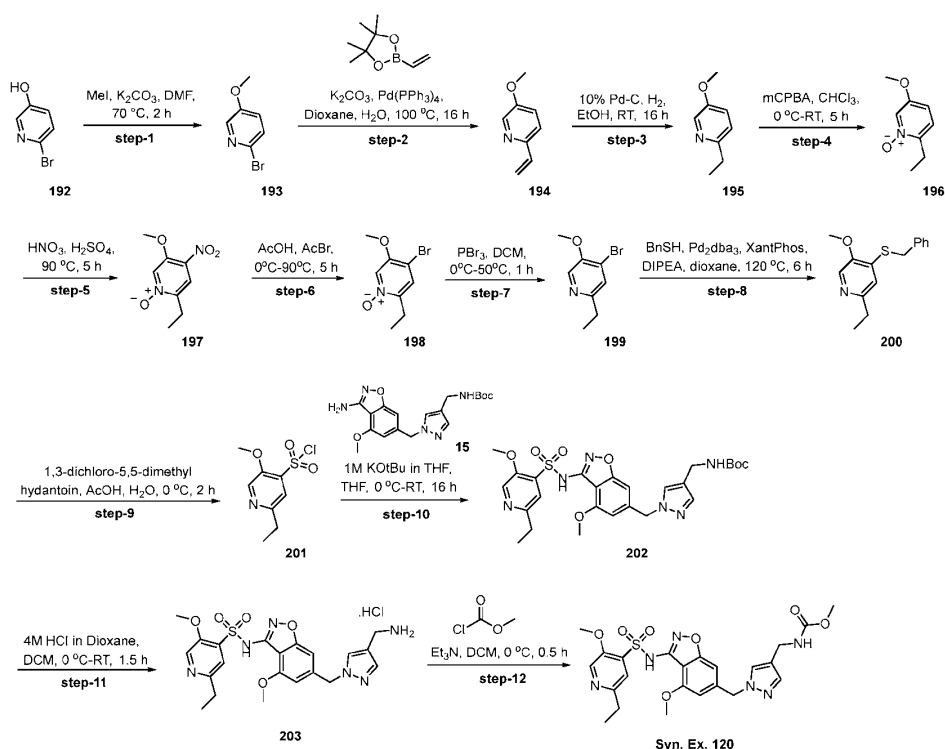
[2120] **Synthesis of N-((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)-2-fluoroacrylamide (Syn. Ex. 119)**

[2121] To a stirred solution of 2-fluoroacrylic acid (0.04 g, 0.522 mmol) in DCM (5 mL) were added DIPEA (0.22 mL, 1.306 mmol) and HATU (0.15 g, 0.391 mmol) followed by the addition of compound **191** (0.15 g, 0.261 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford N-((1-((3-((2-((1H-imidazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-

yl)methyl)-2-fluoroacrylamide (**Syn. Ex. 119**; 8 mg, 4.96%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 120

[2122] **Scheme 75: Synthesis of methyl ((1-((3-((2-ethyl-5-methoxypyridine)-4-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 120**)**



[2123] **Synthesis of 2-bromo-5-methoxypyridine (193)**

[2124] To a stirred solution of compound **192** (15 g, 86.206 mmol) in DMF (150 mL) were added K_2CO_3 (35.74 g, 258.620 mmol) and MeI (6.44 mL, 103.448 mmol). The reaction mixture was stirred at 70 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with Et₂O. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford title compound **193** (10 g, 56.75%) as a pale-yellow oil. LCMS calculated for C_6H_6BrNO : 186.96; Found: 188 (M+2).

[2125] **Synthesis of 5-methoxy-2-vinylpyridine (194)**

[2126] To a stirred solution of compound **193** (10 g, 53.185 mmol) in 1,4-Dioxane (100 mL) were added K_2CO_3 (22.05 g, 159.557 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (9.82 g, 63.822 mmol) and water (20 mL). The reaction mixture was degassed with Argon for 3 min followed by addition of $Pd(PPh_3)_4$ (3.16 g, 2.659 mmol). The reaction mixture was stirred at 100 °C for 16 h. After completion (monitored by TLC), the mixture was filtered through celite bed, washed with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 30% EtOAc/Heptane to afford title compound **194** (8 g, 85.90%) as a pale-yellow liquid. LCMS calculated for C_8H_9NO : 135.07; Found: 136.20 (M+1)

[2127] **Synthesis of 2-ethyl-5-methoxypyridine (195)**

[2128] To a stirred solution of compound **194** (8 g, 59.184 mmol) in EtOH (100 mL) was added 10% Pd-C (75.58 g, 71.021 mmol). The reaction mixture was stirred at room temperature for 16 h under H_2 atmosphere. After completion (monitored by TLC), the reaction mixture was filtered through a celite bed and concentrated under reduced pressure to afford title compound **195** (10 g, 83.13%) as a brown oil. 1H NMR (400 MHz, $CHCl_3$) δ ppm 8.22 (br s, 1 H), 7.04 - 7.10 (m, 2 H), 3.83 (s, 3 H), 2.77 (q, $J=7.46$ Hz, 2 H), 1.28 (br t, $J=7.46$ Hz, 3 H).

[2129] **Synthesis of 2-ethyl-5-methoxypyridine 1-oxide (196)**

[2130] To a stirred solution of compound **195** (8 g, 58.317 mmol) in $CHCl_3$ (200 mL) was added mCPBA (15.88 g, 87.476 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the mixture was quenched with saturated $NaHCO_3$ and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford title compound **196** (7 g, 51.71%) as a pale-yellow solid. LCMS calculated for $C_8H_{11}NO_2$: 153.08; Found: 154 (M+1)

[2131] **Synthesis of 2-ethyl-5-methoxy-4-nitropyridine 1-oxide (197)**

[2132] To a stirred solution of compound **196** (7 g, 45.697 mmol) in H_2SO_4 (20 mL) was added HNO_3 (16 mL). The reaction mixture was stirred at 90 °C for 5 h under N_2 atmosphere. After completion (monitored by TLC), the mixture was quenched with ice-cold water (100 mL), basified with 1N NaOH and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a title compound **197** (3 g, 32.39%) as a yellow oil. LCMS calculated for $C_8H_{10}N_2O_4$: 198.06; Found: 198.80 (M+1)

[2133] **Synthesis of 4-bromo-2-ethyl-5-methoxypyridine 1-oxide (198)**

[2134] To a stirred solution of mixture of compound **197** (4.50 g, 22.706 mmol) in AcOH (30 mL) was added AcBr (20 mL) at 0 °C. The reaction mixture was stirred at 90 °C for 5 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water (60 mL), basified with 2N NaOH and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **198** (4 g, 74.15%) as a pale-yellow solid. LCMS calculated for C₈H₁₀BrNO₂: 230.99; Found: 232 (M+2)

[2135] Synthesis of 4-bromo-2-ethyl-5-methoxypyridine (199)

[2136] To a stirred solution of compound **198** (4 g, 17.235 mmol) in DCM (50 mL) was added PBr₃ (10 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, basified with 2N NaOH and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **199** (3.50 g, 87.87%) as a pale-yellow oil. LCMS calculated for C₈H₁₀BrNO: 214.99; Found: 216 (M+2).

[2137] Synthesis of 4-(benzylthio)-2-ethyl-5-methoxypyridine (200)

[2138] To a stirred solution of compound **199** (3.50 g, 16.197 mmol) in 1,4-Dioxane (100 mL) were added BnSH (2.01 g, 16.197 mmol) and DIPEA (8.63 mL, 48.593 mmol) followed by XantPhos (0.77 g, 1.295 mmol). The reaction mixture was degassed with Argon for 10 min. followed by addition of Pd₂(dba)₃ (0.76 g, 0.809 mmol). The reaction mixture was stirred at 120 °C for 6 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 10-15% EtOAc/Heptane to afford title compound **200** (3 g, 71.19%) as a pale-yellow solid. LCMS calculated for C₁₅H₁₇NOS: 259.10; Found: 260.10 (M+1).

[2139] Synthesis of 2-ethyl-5-methoxypyridine-4-sulfonyl chloride (201)

[2140] To a stirred solution of compound **200** (0.50 g, 1.927 mmol) in AcOH (5 mL) and H₂O (1 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (0.77 g, 3.855 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 10% EtOAc/Heptane to afford title compound **201** (0.37 g, 44.79%) as a colourless sticky solid. LCMS calculated for C₈H₁₀ClNO₃S: 235.01; Found: 236 (M+1).

[2141] Synthesis of tert-Butyl ((1-((3-((2-ethyl-5-methoxypyridine)-4-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (202)

[2142] To a stirred solution of compound **15** (0.30 g, 0.803 mmol) in THF (20 mL) were added 1M KOtBu in THF (2.41 mL, 2.410 mmol) and compound **201** (0.28 g, 1.205 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was washed with Et₂O to afford title compound **202** (0.27 g, 27.58%) as a pale-yellow solid. LCMS calculated for C₂₆H₃₂N₆O₇S: 572.21; Found: 571.20 (M-1).

[2143] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-ethyl-5-methoxypyridine-4-sulfonamide hydrochloride (203)

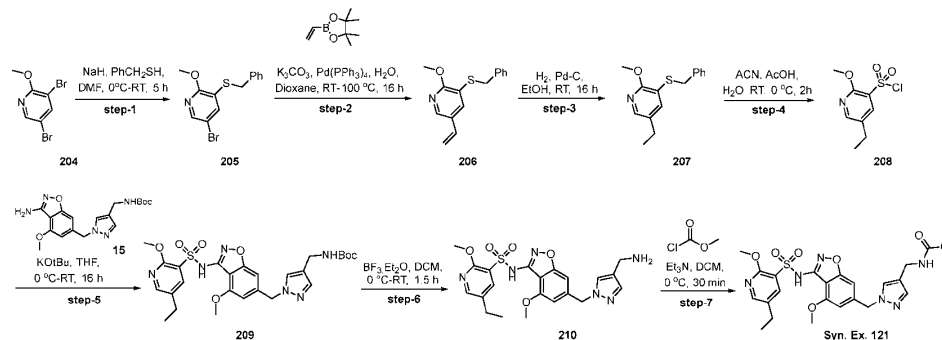
[2144] To a stirred solution of compound **202** (0.26 g, 0.454 mmol) in DCM (mL) was added 4M HCl in Dioxane (9.90 mL, 39.628 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was washed with Et₂O and concentrated under reduced pressure to afford title compound **203** (0.23 g, 43.20%) as a pale-yellow solid. LCMS calculated for C₂₁H₂₄N₆O₅S: 472.15; Found: 471.10 (M-1).

[2145] Synthesis of methyl ((1-((3-((2-ethyl-5-methoxypyridine)-4-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 120)

[2146] To a solution of compound **203** (0.20 g, 0.392 mmol) in DCM (20 mL) were added Et₃N (0.16 mL, 1.179 mmol) and methyl chloroformate (0.04 g, 0.471 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((2-ethyl-5-methoxypyridine)-4-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 120**; 20 mg, 9.20%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 121

[2147] Scheme 76: Synthesis of methyl ((1-((3-((5-ethyl-2-methoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 121)



[2148] Synthesis of 3-(benzylthio)-5-bromo-2-methoxypyridine (205)

[2149] To a stirred solution of compound **204** (13 g, 48.703 mmol) in DMF (60 mL) were added 60% NaH in Oil (2.33 g, 58.444 mmol) and PhCH₂SH (6.27 mL, 53.574 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and stirred at 0 °C for 10 min. The solid precipitate was filtered and dried under reduced pressure to afford title compound **205** (10 g, 64.20%) as a pale-yellow solid. LCMS calculated for C₁₃H₁₂BrNOS: 308.98; Found: 310 (M+2).

[2150] Synthesis of 3-(benzylthio)-2-methoxy-5-vinylpyridine (206)

[2151] To a stirred solution of compound **205** (5 g, 16.118 mmol) in 1,4-Dioxane (40 mL) and water (10 mL) were added K₂CO₃ (4.45 g, 32.236 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.72 g, 24.177 mmol) at room temperature. The reaction mixture was degassed with N₂ for 10 min followed by addition of PdCl₂(PPh₃)₂ (0.56 g, mmol). The reaction mixture was stirred at 100 °C for 16 h. After completion (monitored by TLC), the mixture was filtered through a celite bed and washed with EtOAc. The filtrate was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **206** (3.50 g, 69.19%) as a colourless liquid. LCMS calculated for C₁₅H₁₅NOS: 257.09; Found: 258.10 (M+1).

[2152] Synthesis of 3-(benzylthio)-5-ethyl-2-methoxypyridine (207)

[2153] To a stirred solution of compound **206** (3.80 g, 14.765 mmol) in EtOH (40 mL) was added 10% Pd-C (0.37 g, 3.543 mmol). The reaction mixture was stirred at room temperature for 16 h under H₂ atmosphere. After completion (monitored by TLC), the reaction mixture

was filtered through a celite bed and washed with MeOH. The filtrate was concentrated under reduced pressure to afford title compound **207** (3 g, 74.41%) as a reddish semi-solid. LCMS calculated for C₁₅H₁₇NOS: 259.10; Found: 260.10 (M+1).

[2154] Synthesis of 5-ethyl-2-methoxypyridine-3-sulfonyl chloride (208)

[2155] To a stirred solution of compound **207** (0.50 g, 1.927 mmol) in ACN (10 mL) were added water (1.50 mL) and AcOH (2.50 mL) followed by the addition of 1,3-dichloro-5,5-dimethylhydantoin (0.75 g, 3.855 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 20% EtOAc/Heptane to title compound **208** (0.25 g, 36.86%) as an off-white sticky solid. LCMS calculated for C₈H₁₀ClNO₃S: 235.01; Found: 236.10 (M+1)

[2156] Synthesis of tert-Butyl ((1-((3-((5-ethyl-2-methoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (209)

[2157] To a stirred solution of compound **15** (0.25 g, 0.669 mmol) in THF (10 mL) was added 1M KOtBu in THF (2 mL, 2.008 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by addition of 5-ethyl-2-methoxypyridine-3-sulfonyl chloride (0.31 g, 1.339 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with citric acid and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 70% EtOAc/Heptane to afford compound **209** (0.20 g, 42.93%) as an off-white solid. LCMS calculated for C₂₆H₃₂N₆O₇S: 572.21; Found: 571.30 (M-1)

[2158] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxypyridine-3-sulfonamide (210)

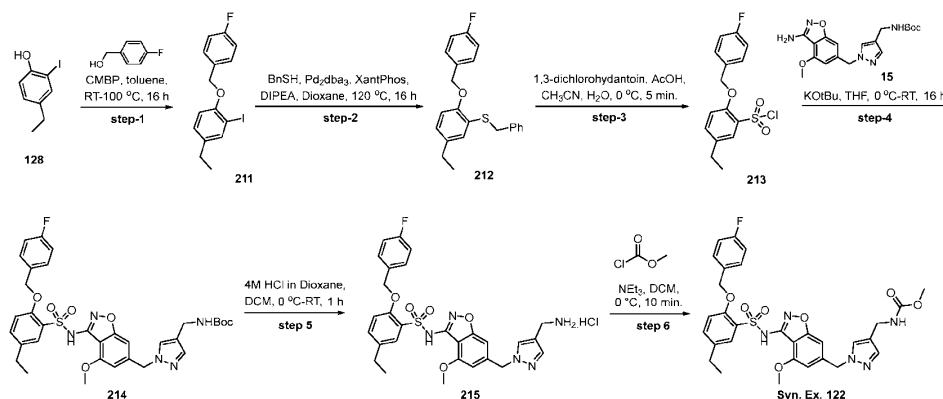
[2159] To a stirred solution of compound **209** (0.18 g, 0.314 mmol) in DCM (10 mL) was added BF₃.Et₂O (0.50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The solid residue was washed Et₂O and dried under reduced pressure to afford title compound **210** (0.15 g, 88.07%) as a pale-yellow solid. LCMS calculated for C₂₁H₂₄N₆O₅S: 472.15; Found: 471.20 (M-1)

[2160] Synthesis of methyl ((1-((3-((5-ethyl-2-methoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 121)

[2161] To a stirred solution of compound **210** (0.10 g, 0.211 mmol) in DCM (10 mL) were added Et₃N (0.08 mL, 0.634 mmol) and methyl chloroformate (0.02 g, 0.253 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl((1-((3-((5-ethyl-2-methoxypyridine)-3-sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 121; 20 mg, 17.65%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 122

[2162] Scheme 77: Synthesis of methyl ((1-((3-((5-ethyl-2-((4-fluorobenzyl)oxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 122)



[2163] Synthesis of 4-ethyl-1-((4-fluorobenzyl)oxy)-2-iodobenzene (211)

[2164] To a stirred solution of compound **128** (5 g, 20.156 mmol) in toluene (50 mL) were added (4-fluorophenyl)methanol (3.81 g, 30.235 mmol) and cyanomethylenetriethylphosphorane (CMPB, 7.44 g, 30.235 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and by combi-flash column chromatography using 5% EtOAc/Heptane to afford title compound **211** (3 g, 41.78%) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.62 (br s, 1 H), 7.53 (br t, J=6.26 Hz, 2 H), 7.14 - 7.28 (m, 3 H), 6.99 (br d, J=8.22 Hz, 1 H), 5.13 (s, 2 H), 1.13 (br t, J=7.43 Hz, 3 H).

[2165] Synthesis of benzyl(5-ethyl-2-((4-fluorobenzyl)oxy)phenyl)sulfane (212)

[2166] To a stirred solution of compound **211** (3 g, 8.422 mmol) in 1,4-Dioxane (50 mL) were added DIPEA (3.24 mL, 18.529 mmol), XantPhos (0.40 g, 0.673 mmol) and BnSH (1.04 g, 8.422 mmol). The reaction mixture was degassed with N₂ for 10 min followed by addition of Pd₂(dba)₃ (0.38 g, 0.421 mmol). The reaction mixture was stirred at 120 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 5% EtOAc/Heptane to afford title compound **212** (2.70 g, 47.29%) as a pale-yellow solid. LCMS calculated for C₂₂H₂₁FOS: 352.13; Found: 353.26 (M+1).

[2167] Synthesis of 5-ethyl-2-((4-fluorobenzyl)oxy)benzenesulfonyl chloride (213)

[2168] To a stirred solution of compound **212** (1 g, 2.837 mmol) in ACN (30 mL), AcOH (1 mL) and water (1 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (0.84 g, 4.255 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 5% EtOAc/Heptane to afford title compound **213** (0.65 g, 21.11%) as a white solid. The crude was carried forward to the next step without purification.

[2169] Synthesis of tert-Butyl ((1-((3-((5-ethyl-2-((4-fluorobenzyl)oxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (214)

[2170] To a stirred solution of compound **15** (0.20 g, 0.535 mmol) in THF (15 mL) were added 1M K⁺OT⁻Bu in THF (1.60 mL, 1.606 mmol) and compound **213** (0.35 g, 1.071 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with aqueous citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 5% EtOAc/Heptane to afford title compound **214** (0.19 g, 47.96%) as a white solid. LCMS calculated for C₃₃H₃₆FN₅O₇S: 665.23; Found: 664.30 (M-1)

[2171] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-((4-fluorobenzyl)oxy)benzenesulfonamide hydrochloride (215)

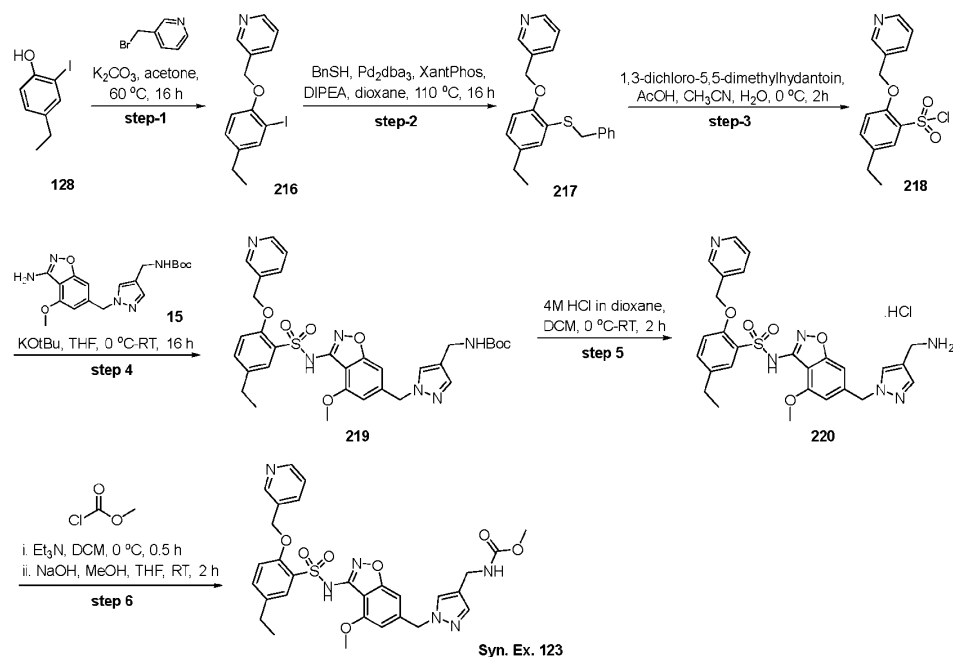
[2172] To a stirred solution of compound **214** (0.03 g, 0.045 mmol) in DCM (2 mL) was added 4M HCl in Dioxane (0.30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The solid residue was washed with Et₂O and dried under reduced pressure to afford title compound **215** (0.02 g, 68.72%) as an off-white solid. LCMS calculated for C₂₈H₂₈FN₅O₅S: 565.18; Found: 564.20 (M-1)

[2173] **Synthesis of methyl ((1-((3-((5-ethyl-2-((4-fluorobenzyl)oxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 122)**

[2174] To a stirred solution of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-((4-fluorobenzyl)oxy)benzenesulfonamide hydrochloride (**215**) (0.15 g, 0.216 mmol) in DCM (5 mL) were added Et₃N (0.09 mL, 0.650 mmol) and methyl carbonochloridate (0.02 g, 0.260 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 10 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc (2 x 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-((4-fluorobenzyl)oxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 122**; 8 mg, 5.82%) as a white solid. (See analytical data in Table 1).

EXAMPLE 123

[2175] **Scheme 78: Synthesis of methyl ((1-((3-((5-ethyl-2-(pyridin-3-ylmethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 123)**



[2176] Synthesis of 3-((4-ethyl-2-iodophenoxy)methyl)pyridine (216)

[2177] To a stirred solution of compound **128** (2 g, 8.062 mmol) in acetone (25 mL) were added K_2CO_3 (2.78 g, 20.156 mmol) and 3-(bromomethyl)pyridine (1.52 g, 8.868 mmol). The reaction mixture was stirred at 60 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 20-25% EtOAc/Heptane to afford title compound **216** (1.60 g, 57.86%) as a brown oil. LCMS calculated for $C_{14}H_{14}INO$: 339.01; Found: 340 (M+1).

[2178] Synthesis of 3-((2-(benzylthio)-4-ethylphenoxy)methyl)pyridine (217)

[2179] To a stirred solution of compound **216** (1.60 g, 4.717 mmol) in 1,4-Dioxane (20 mL) were added DIPEA (1.80 mL, 10.377 mmol), BnSH (0.58 g, 4.717 mmol) and XantPhos (0.22 g, 0.377 mmol). The reaction mixture was degassed with Argon purging for 10 min followed by addition of $Pd_2(dba)_3$ (0.22 g, 0.235 mmol). The reaction mixture was stirred at 110 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 35-40% EtOAc/Heptane to afford title compound

217 (1.50 g, 93.75%) as a pale-yellow solid. LCMS calculated for C₂₁H₂₁NOS: 335.13; Found: 336.10 (M+1).

[2180] Synthesis of 5-ethyl-2-(pyridin-3-ylmethoxy)benzenesulfonyl chloride (218)

[2181] To a stirred solution of compound **217** (0.80 g, 2.384 mmol) in ACN (32 mL), AcOH (1.60 mL) and H₂O (0.80 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (0.94 g, 4.769 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **218** (0.83 g, 31.20%) as a brown gummy solid. The crude was carried in the next step without purification.

[2182] Synthesis of tert-Butyl ((1-((3-((5-ethyl-2-(pyridin-3-ylmethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (219)

[2183] To a stirred solution of compound **15** (0.30 g, 0.80 mmol) in THF (4 mL) were added compound **218** (0.37 g, 1.20 mmol) and 1M KOtBu in THF (2.41 mL, 2.41 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with saturated citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 2-5% MeOH/DCM to afford title compound **219** (0.11 g, 15.32%) as a brown solid. LCMS calculated for C₃₂H₃₆N₆O₇S: 648.24; Found: 649.30 (M+1).

[2184] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-(pyridin-3-ylmethoxy)benzenesulfonamide hydrochloride (220)

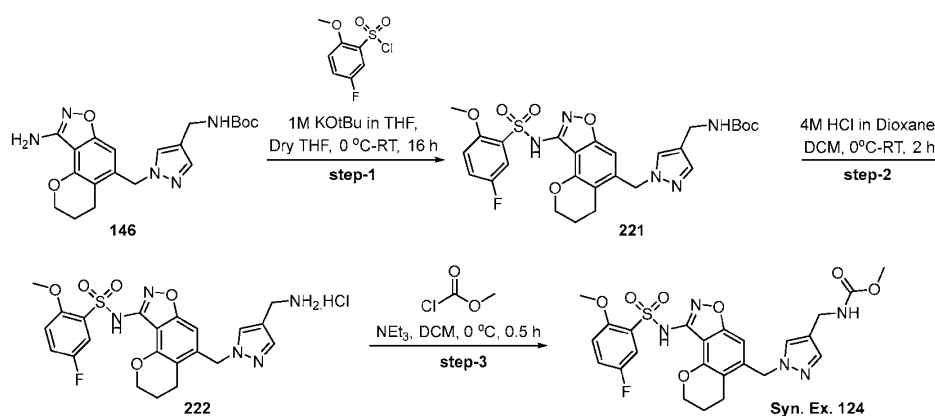
[2185] To a stirred solution of compound **219** (0.08 g, 0.123 mmol) in DCM (4 mL) was added 4M HCl in Dioxane (0.15 mL, 0.616 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure and triturated with Et₂O to afford title compound **220** (0.075 g, 74.47%) as a brown solid. LCMS calculated for C₂₇H₂₈N₆O₅S: 548.18; Found: 547.20 (M-1).

[2186] Synthesis of methyl ((1-((3-((5-ethyl-2-(pyridin-3-ylmethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 123)

[2187] To a stirred solution of compound **220** (0.075 g, 0.128 mmol) in DCM (4 mL) were added Et₃N (0.05 mL, 0.384 mmol) and methyl carbonochloridate (0.01 g, 0.153 mmol) at 0 °C while maintaining the pH at 7-8. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was concentrated under reduced pressure to afford crude. The crude was dissolved in solution of MeOH:THF (6 mL; 2:1) followed by addition of NaOH (10 mg). The mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(pyridin-3-yl)methoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 123**; 19.5 mg, 25.16%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 124

[2188] **Scheme 79: Synthesis of methyl ((1-((9-((5-fluoro-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 124**)**



[2189] **Synthesis of tert-Butyl ((1-((9-((5-fluoro-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**221**)**

[2190] To a stirred solution of compound **146** (1 g, 2.503 mmol) in dry THF (10 mL) were added 1M KOtBu in THF (7.51 mL, 7.510 mmol) and 5-fluoro-2-methoxybenzenesulfonyl chloride (1.12 g, 5.006 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to adjust the

pH ~ 6 and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **221** (1 g, 37.38%) as a brown solid. LCMS calculated for C₂₇H₃₀FN₅O₇S: 587.18; Found: 586.20 (M-1).

[2191] Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-9-yl)-5-fluoro-2-methoxybenzenesulfonamide hydrochloride (222)

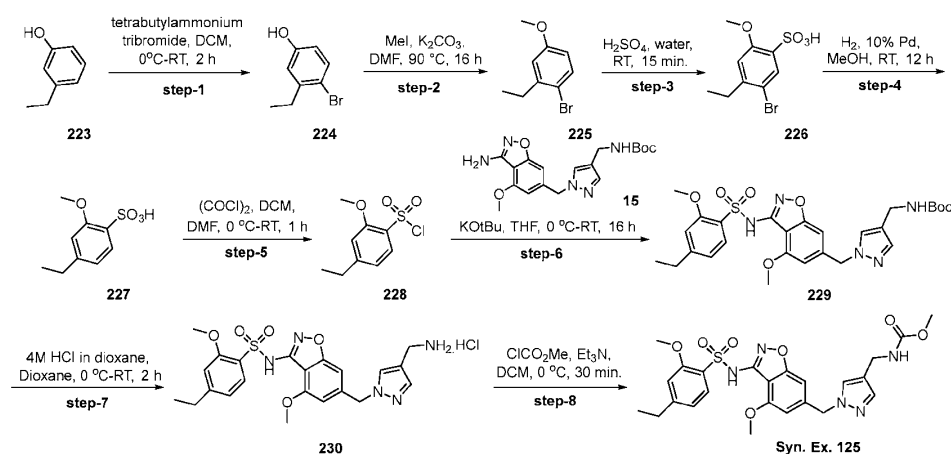
[2192] To a stirred solution of compound **221** (1 g, 1.701 mmol) in DCM (10 mL) was added 4M HCl in Dioxane (2.12 mL, 8.508 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The solid residue was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **222** (0.50 g, 46.54%) as an off-white solid. LCMS calculated for C₂₂H₂₂FN₅O₅S: 487.13; Found: 486.10 (M-1).

[2193] Synthesis of methyl ((1-((9-((5-fluoro-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 124)

[2194] To a stirred solution of compound **222** (0.20 g, 0.381 mmol) in DCM (10 mL) were added NEt₃ (0.10 mL, 0.763 mmol) and methyl chloroformate (0.05 g, 0.572 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was diluted with water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((9-((5-fluoro-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 124**; 7 mg, 3.26 %) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 125

[2195] Scheme 80: methyl ((1-((3-((4-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate



[2196] Synthesis of 4-bromo-3-ethylphenol (224)

[2197] To a stirred solution of 3-ethylphenol **223** (10 g, 81.853 mmol) in DCM (100 mL) was added tetrabutylammonium tribromide (39.46 g, 81.853 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with DCM, co-distilled with Et₂O and dried under reduced pressure to afford title compound **224** (10 g, 43.14%) as a liquid. LCMS calculated for C₈H₉BrO: 199.98; Found: 201.10 (M+1).

[2198] Synthesis of 1-bromo-2-ethyl-4-methoxybenzene (225)

[2199] To a stirred solution of compound **224** (10 g, 49.736 mmol) in DMF (100 mL) were added K₂CO₃ (13.74 g, 99.472 mmol) and MeI (6.19 mL, 99.472 mmol). The reaction mixture was stirred at 90 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **225** (10 g, 93.47%) as a liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.44 (br d, *J*=8.77 Hz, 1 H), 6.92 (br d, *J*=1.75 Hz, 1 H), 6.74 (br dd, *J*=8.55, 2.41 Hz, 1 H), 3.74 (s, 3 H), 2.65 (q, *J*=7.45 Hz, 2 H), 1.15 (br t, *J*=7.23 Hz, 3 H).

[2200] Synthesis of 5-bromo-4-ethyl-2-methoxybenzenesulfonic acid (226)

[2201] Compound **225** (2 g, 9.298 mmol) in was dissolved in H₂SO₄ (50 mL). The reaction mixture was stirred at room temperature for 15 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water (50 mL), filtered and washed with heptane. The solid precipitate was dried under reduced pressure to afford title compound **226** (2.50 g, 91.09%) as a white solid. LCMS calculated for C₉H₁₁BrO₄S: 293.96; Found: 295 (M+1).

[2202] Synthesis of 4-ethyl-2-methoxybenzenesulfonic acid (227)

[2203] To a stirred solution of 5-bromo-4-ethyl-2-methoxybenzenesulfonic acid **226** (5 g, 16.940 mmol) in MeOH (60 mL) was added 10% Pd (0.54 g, 0.508 mmol). The reaction mixture was stirred at room temperature for 12 h under H₂ atmosphere (50 psi). After completion (monitored by TLC), the reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to afford 4-ethyl-2-methoxybenzenesulfonic acid **227** (2 g, 51.31%) as a brown solid. LCMS calculated for C₉H₁₂O₄S: 216.05; Found: 215.10 (M-1).

[2204] Synthesis of 4-ethyl-2-methoxybenzenesulfonyl chloride (228)

[2205] To a solution of 4-ethyl-2-methoxybenzenesulfonic acid **227** (0.60 g, 2.774 mmol) in DCM (10 mL) and DMF (0.02 mL, 0.277 mmol) was added (COCl)₂ (2.42 mL, 27.745 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **228** (0.45 g, 45.61%) as a brown liquid. ¹H NMR (401 MHz, DMSO-*d*₆) δ ppm 7.56 (d, *J*=7.82 Hz, 1 H), 6.81 (s, 1 H), 6.70 (d, *J*=7.58 Hz, 1 H), 3.74 (s, 3 H), 2.58 (q, *J*=7.58 Hz, 2 H), 1.17 (t, *J*=7.58 Hz, 3 H).

[2206] Synthesis of *tert*-Butyl ((1-((3-((4-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (229)

[2207] To a stirred solution of compound **15** (0.30 g, 0.803 mmol) in THF (10 mL) was added 1M KO^tBu in THF (2.41 mL, 2.410 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 10 min. followed by compound **228** (0.37 g, 1.606 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **229** (0.15 g, 23.51%) as a brown solid. LCMS calculated for C₂₇H₃₃N₅O₇S: 571.21; Found: 570.20 (M-1).

[2208] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-4-ethyl-2-methoxybenzenesulfonamide hydrochloride (230)

[2209] To a stirred solution of compound **229** (0.15 g, 0.262 mmol) in 1,4-Dioxane (5 mL) was added 4M HCl in Dioxane (0.32 mL, 1.311 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was

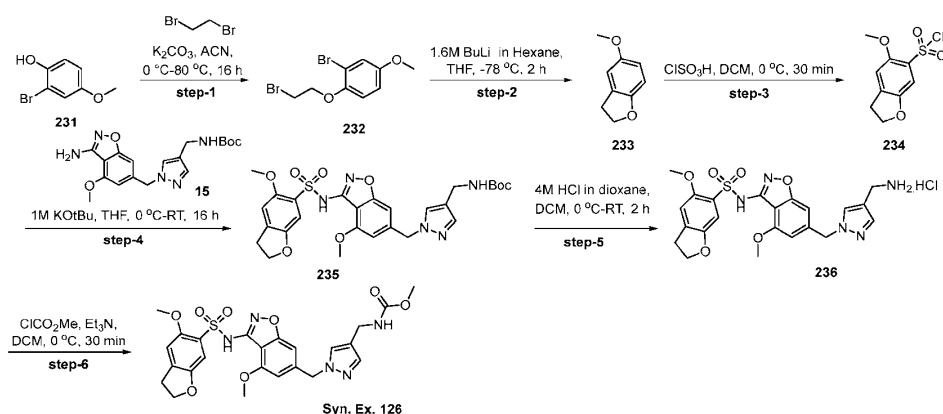
concentrated under reduced pressure. The crude was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **230** (0.12 g, 69.32%) as an off-white solid. LCMS calculated for C₂₂H₂₅N₅O₅S: 471.16; Found: 470.20 (M-1).

[2210] Synthesis of methyl ((1-((3-((4-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 125)

[2211] To a stirred solution of compound **230** (0.12 g, 0.236 mmol) in DCM (10 mL) were added Et₃N (0.06 mL, 0.472 mmol) and methyl chloroformate (0.02 g, 0.283 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((4-ethyl-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 125**; 8.00 mg, 6.33%) as an off-white solid. See analytical data in Table 1.

EXAMPLE 126

[2212] Scheme 81: Synthesis of methyl ((1-((4-methoxy-3-((5-methoxy-2,3-dihydrobenzofuran)-6-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 126)



[2213] Synthesis of 2-bromo-1-(2-bromoethoxy)-4-methoxybenzene (232)

[2214] To a stirred solution of compound **231** (10 g, 49.251 mmol) in ACN (100 mL) were added K₂CO₃ (14.64 g, 147.754 mmol) at 0 °C and 1,2-dibromoethane (27.71 g, 147.754 mmol). The reaction mixture was stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic

layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure.

The crude was purified by combi-flash column chromatography using 10-20%

EtOAc/Heptane to afford title compound **232** (6 g, 38.51%) as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.18 (d, *J*=3.07 Hz, 1 H), 7.09 (d, *J*=9.21 Hz, 1 H), 6.92 (dd, *J*=8.99, 2.85 Hz, 1 H), 4.31 (t, *J*=5.48 Hz, 2 H), 3.78 (t, *J*=5.48 Hz, 2 H), 3.72 (s, 3 H).

[2215] Synthesis of 5-methoxy-2,3-dihydrobenzofuran (233)

[2216] To a stirred solution of compound **232** (5 g, 16.130 mmol) in THF (50 mL) was added BuLi (1.6 mol/L) in Hexane (12.09 mL, 19.356 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **233** (2.30 g, 86.40%) as a colourless liquid; LCMS calculated for C₉H₁₀O₂: 150.07; Found: 151.20 (M+1).

[2217] Synthesis of 5-methoxy-2,3-dihydrobenzofuran-7-sulfonyl chloride (234)

[2218] To a stirred solution of compound **233** (0.30 g, 1.997 mmol) in DCM (3 mL) was added ClSO₃H (0.41 mL, 5.992 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 25-35% EtOAc/Heptane to afford title compound **234** (0.12 g, 23.43%) as an off-white semi-solid; LCMS calculated for C₉H₉ClO₄S: 247.99; Found: 248.74 (M+1).

[2219] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((5-methoxy-2,3-dihydrobenzofuran)-6-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (235)

[2220] To a stirred solution of compound **15** (0.30 g, 0.803 mmol) in THF (5 mL) were added 1M KO^tBu in THF (2.41 mL, 2.410 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min followed by addition of compound **234** (0.29 g, 1.205 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with saturated citric acid and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 80-100% EtOAc/Heptane to afford title compound **235** (0.18 g, 24.10%) as a pale-brown solid; LCMS calculated for C₂₇H₃₁N₅O₈S: 585.19; Found: 584.40 (M-1).

[2221] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-methoxy-2,3-dihydrobenzofuran-6-sulfonamide hydrochloride (236)

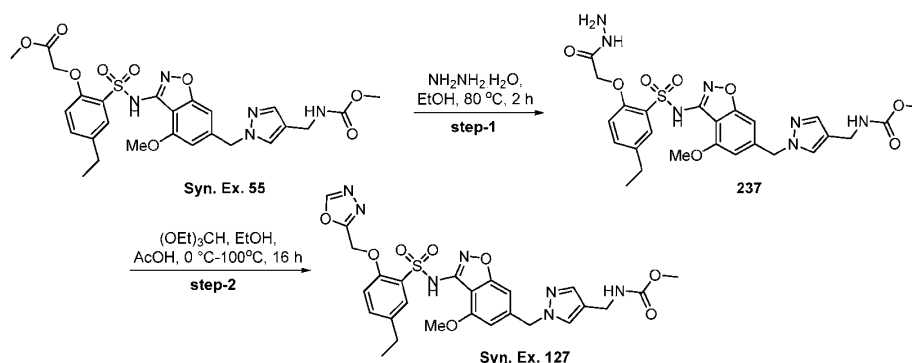
[2222] To a stirred solution of compound **235** (0.15 g, 0.256 mmol) in DCM (2 mL) was added 4M HCl in Dioxane (0.64 mL, 2.561 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O and concentrated under reduced pressure to afford title compound **236** (0.16 g, 75.40%) as an off-white solid; LCMS calculated for C₂₂H₂₃N₅O₆S: 485.14; Found: 486.22 (M+2).

[2223] Synthesis of methyl ((1-((4-methoxy-3-((5-methoxy-2,3-dihydrobenzofuran)-6-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 126)

[2224] To a stirred solution of compound **236** (0.15 g, 0.287 mmol) in DCM (5 mL) was added Et₃N (0.08 mL, 0.574 mmol) and ClCO₂Me (0.02 g, 0.287 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl ((1-((4-methoxy-3-((5-methoxy-2,3-dihydrobenzofuran)-6-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 126**; 0.009 g, 5.70%) as an off-white solid. See analytical data in Table 1.

EXAMPLE 127

[2225] Scheme 82: Synthesis of methyl ((1-((3-((2-((1,3,4-oxadiazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 127)



[2226] Synthesis of methyl ((1-((3-((5-ethyl-2-(2-hydrazinyl-2-oxoethoxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (237)

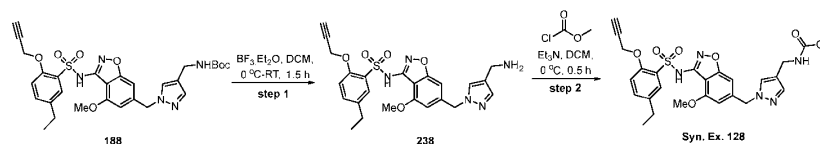
[2227] To a solution of **Syn. Ex. 55** (0.12 g, 0.204 mmol) in EtOH (5 mL) was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (0.01 g, 0.245 mmol). The reaction mixture was stirred at 80 °C for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure and washed with Et₂O to afford title compound **237** (0.10 g, 69.20%) as a sticky solid. LCMS calculated for C₂₅H₂₉N₇O₈S: 587.18; Found: 588.51 (M+1).

[2228] Synthesis of methyl ((1-((3-((2-((1,3,4-oxadiazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 127**)

[2229] To a stirred solution of compound **237** (0.20 g, 0.183 mmol) in mixture of EtOH (2 mL) were added AcOH (0.99 mL, 17.293 mmol) and (OEt)₃CH (2 mL, 11.904 mmol). The reaction mixture was stirred at 110 °C for 16 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was purified by prep. HPLC to afford title compound methyl ((1-((3-((2-((1,3,4-oxadiazol-2-yl)methoxy)-5-ethylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 127**; 5 mg, 4.41%) as an off-white solid. See analytical data in Table 1.

EXAMPLE 128

[2230] Scheme 83: Synthesis of methyl ((1-((3-((5-ethyl-2-(prop-2-yn-1-yloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 128**)



[2231] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-(prop-2-yn-1-yloxy)benzenesulfonamide (**238**)

[2232] To a stirred solution of compound **188** (50 mg, 0.083 mmol) in DCM (10 mL) was added $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.02 g, 0.083 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed Et₂O and dried under reduced pressure to

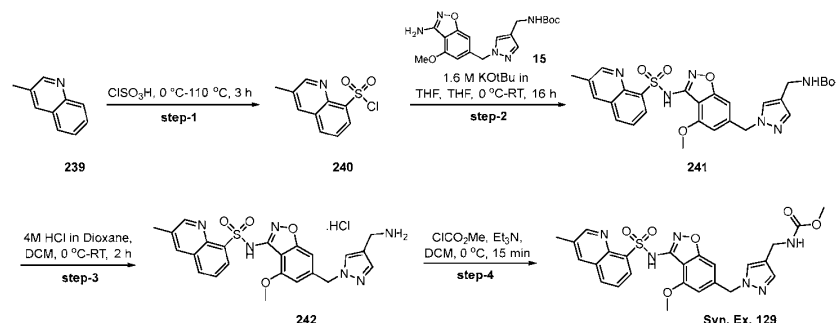
afford title compound **238** (30 mg, 32.25%) as a pale-yellow solid. LCMS calculated for C₂₄H₂₅N₅O₅S: 495.16; Found: 496.20 (M+1)

[2233] Synthesis of methyl ((1-((3-((5-ethyl-2-(prop-2-yn-1-yloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 128)

[2234] To a stirred solution of compound **238** (0.15 g, 0.302 mmol) in DCM (10 mL) were added Et₃N (0.12 mL, 0.908 mmol) and methyl chloroformate (0.02 mL, 0.363 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-(prop-2-yn-1-yloxy)phenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 128**; 5 mg, 2.98%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 129

[2235] Scheme 84: Synthesis of methyl ((1-((4-methoxy-3-((3-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 129)



[2236] Synthesis of 3-methylquinoline-8-sulfonyl chloride (240)

[2237] A solution of compound **239** (2 g, 13.967 mmol) in ClSO₃H (20 mL) was stirred at 110 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **240** (2.20 g, 59.44%) as a brown solid. LCMS calculated for C₁₀H₈ClNO₂S: 241.00; Found: 242.10 (M+1)

[2238] **Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((3-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (241)**

[2239] To a stirred solution of compound **15** (0.30 g, 0.803 mmol) in THF (20 mL) was added 1.6M KOtBu in THF (1.50 mL, 2.410 mmol) at 0 °C. The reaction mixture was stirred for 10 min. followed by addition of compound **240** (0.33 g, 1.365 mmol) in THF. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 70-72% EtOAc/Heptane to afford title compound **241** (0.11 g, 18.45%) as an off-white solid. TLC: 80% EtOAc/Heptane (R_f: 0.4). LCMS calculated for C₂₈H₃₀N₆O₆S: 578.19; Found: 577.20 (M-1)

[2240] **Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-3-methylquinoline-8-sulfonamide hydrochloride (242)**

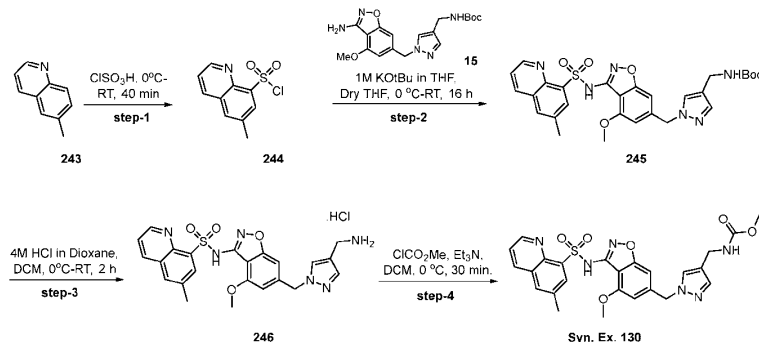
[2241] To a solution of compound **241** (0.11 g, 0.190 mmol) in DCM (2 mL) was added 4M HCl in dioxane (1.09 mL, 4.398 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, washed with Et₂O and dried under reduced pressure to afford title compound **242** (0.09 g, 69.87%) as an off-white solid. LCMS calculated for C₂₃H₂₂N₆O₄S: 478.14; Found: 479.20 (M+1)

[2242] **Synthesis of methyl ((1-((4-methoxy-3-((3-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 129)**

[2243] To a stirred solution of compound **242** (90 mg, 0.174 mmol) in DCM (2 mL) were added triethylamine (0.07 mL, 0.524 mmol) and methyl chloroformate (0.01 g, 0.209 mmol) in DCM at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((4-methoxy-3-((3-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 129**) (8 mg, 8.44%) as a white solid. (See analytical data in Table 1).

EXAMPLE 130

[2244] Scheme 85: Synthesis of methyl ((1-((4-methoxy-3-((6-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 130)



[2245] Synthesis of 6-methylquinoline-8-sulfonyl chloride (244)

[2246] A solution of compound **243** (2 g, 13.967 mmol) in ClSO_3H (2.80 mL) was stirred at room temperature for 40 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford compound **244** (1.50 g, 36.88%) as an off-white solid. LCMS calculated for $\text{C}_{10}\text{H}_8\text{ClNO}_2\text{S}$: 241.00; Found: 242.10 (M+1)

[2247] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((6-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**245**)

[2248] To a stirred solution of compound **15** (0.50 g, 1.339 mmol) in THF (20 mL) was added 1M KOtBu in THF (4.01 mL, 4.017 mmol) at 0 °C. The reaction mixture was stirred for 10 min. followed by addition of compound **244** (0.48 g, 2.008 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to ~ pH 6 and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **245** (0.70 g, 52.40%) as a brown solid. LCMS calculated for $\text{C}_{28}\text{H}_{30}\text{N}_6\text{O}_6\text{S}$: 578.19; Found: 579.40 (M+1)

[2249] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-6-methylquinoline-8-sulfonamide hydrochloride (**246**)

[2250] To a solution of compound **245** (0.70 g, 1.209 mmol) in 1,4-dioxane (4 mL) and DCM (4 mL) was added 4M HCl in Dioxane (1.512 mL, 6.048 mmol) at 0 °C. The reaction

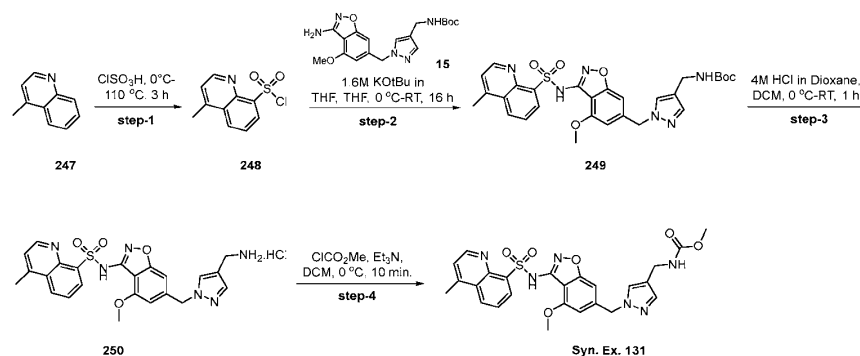
mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **246** (0.20 g, 22.15%) as an off-white solid. LCMS calculated for C₂₃H₂₂N₆O₄S: 478.14; Found: 479.20 (M+1)

[2251] Synthesis of methyl ((1-((4-methoxy-3-((6-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 130)

[2252] To a stirred solution of compound **246** (0.30 g, 0.582 mmol) in DCM (10 mL) were added NEt₃ (0.16 mL, 1.165 mmol) and methyl chloroformate (0.05 mL, 0.699 mmol) in DCM at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((4-methoxy-3-((6-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 130**; 20 mg, 6.33%) as a white solid. (See analytical data in Table 1).

EXAMPLE 131

[2253] Scheme 86: Synthesis of methyl ((1-((4-methoxy-3-((4-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 131)



[2254] Synthesis of 4-methylquinoline-8-sulfonyl chloride (248)

[2255] A solution of compound **247** (2 g, 13.967 mmol) in ClSO₃H (20 mL) was stirred at 110 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title

compound **248** (2 g, 32.96%) as a brown solid. LCMS calculated for C₁₀H₈CINO₂S: 241; Found: 242.10 (M+1)

[2256] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((4-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (249)

[2257] To a stirred solution of compound **15** (0.20 g, 0.535 mmol) in THF (20 mL) was added 1.6M KOtBu in THF (1 mL, 1.607 mmol) at 0 °C. The reaction mixture was stirred for 5 min. followed by addition of compound **248** (0.23 g, 0.964 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with aqueous citric acid and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **249** (0.35 g, 51.52%) as a yellow solid. LCMS calculated for C₂₈H₃₀N₆O₆S: 578.19; Found: 579.36 (M+1)

[2258] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-4-methylquinoline-8-sulfonamide hydrochloride (250)

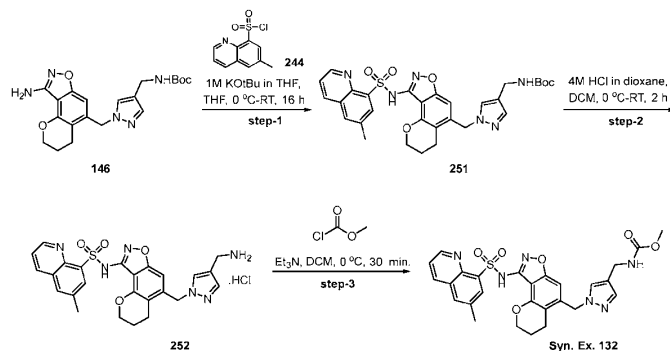
[2259] To a stirred solution of compound **249** (0.25 g, 0.432 mmol) in DCM (3 mL) was added 4M HCl in dioxane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, washed with Et₂O and dried under reduced pressure to afford title compound **250** (0.15 g, 40.14%) as an off-white solid. LCMS calculated for C₂₃H₂₂N₆O₄S: 478.14; Found: 479.20 (M+1)

[2260] Synthesis of methyl ((1-((4-methoxy-3-((4-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 131)

[2261] To a stirred solution of compound **250** (0.10 g, 0.194 mmol) in DCM (10 mL) were added NEt₃ (0.08 mL, 0.582 mmol) and methyl chloroformate (0.02 g, 0.233 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((4-methoxy-3-((4-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 131**; 10 mg, 9.51%) as a white solid. (See analytical data in Table 1).

EXAMPLE 132

[2262] **Scheme 87: Synthesis of methyl ((1-((4-methoxy-3-((4-methylquinoline)-8-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 132)**



[2263] **Synthesis of *tert*-Butyl ((1-((9-((6-methylquinoline)-8-sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**251**)**

[2264] To a stirred solution compound **146** (0.30 g, 0.751 mmol) in THF (10 mL) was added 1M KOtBu in THF (2.25 mL, 2.253 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by addition of compound **244** (0.36 g, 1.502 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to adjust the pH ~6 and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **251** (0.50 g, 44.03%) as a brown solid. LCMS calculated for C₃₀H₃₂N₆O₆S: 604.21; Found: 605.30 (M+1)

[2265] **Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-9-yl)-6-methylquinoline-8-sulfonamide hydrochloride (**252**)**

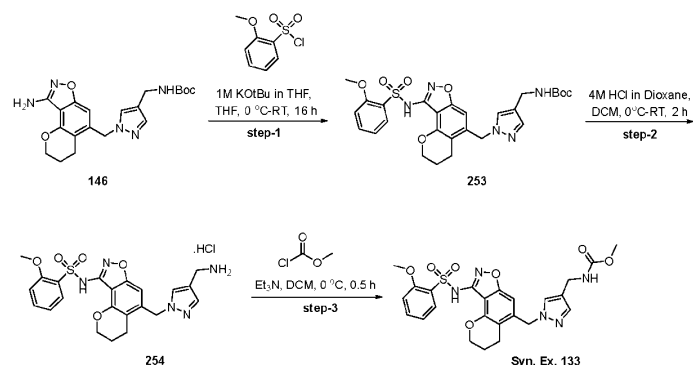
[2266] To a stirred solution of compound **251** (0.50 g, 0.826 mmol) in DCM (mL) was added 4M HCl in dioxane (1.03 mL, 4.134 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford compound **252** (0.30 g, 46.27%) as an off-white solid. LCMS calculated for C₂₅H₂₄N₆O₄S: 504.16; Found: 505.20 (M+1)

[2267] Synthesis of methyl ((1-((9-((6-methylquinoline)-8-sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 132)

[2268] To a stirred solution of compound **252** (0.40 g, 0.739 mmol) in DCM (6 mL) were added Et₃N (0.20 mL, 1.478 mmol) and methyl chloroformate (0.06 mL, 0.887 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((9-((6-methylquinoline)-8-sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 132**; 10 mg, 2.35%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 133

[2269] Scheme 88: Synthesis of methyl ((1-((9-((2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 133)



[2270] Synthesis of *tert*-Butyl ((1-((9-((2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (253**)**

[2271] To a solution of compound **146** (0.15 g, 0.375 mmol) in THF (10 mL) was added 1M KOtBu in THF (1.12 mL, 1.126 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. followed by addition of 2-methoxybenzenesulfonyl chloride (0.11 g, 0.563 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to adjust the pH 6 and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated

under reduced pressure to afford title compound **253** (0.20 g, 93.50%) as a brown solid.

LCMS calculated for C₂₇H₃₁N₅O₇S: 569.19; Found: 568.20 (M-1)

[2272] Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-9-yl)-2-methoxybenzenesulfonamide hydrochloride (254)

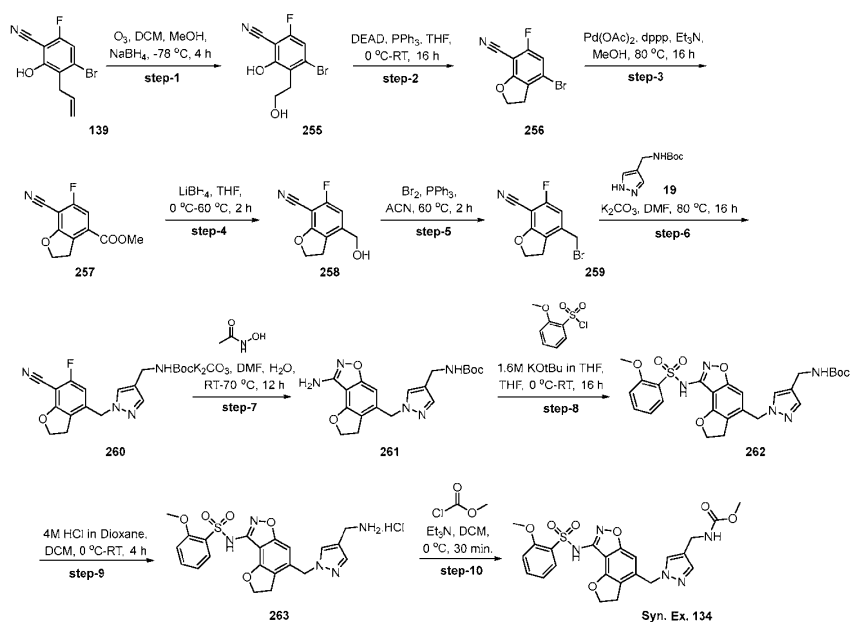
[2273] To a stirred solution of compound **253** (0.20 g, 0.351 mmol) in 1,4-dioxane (5 mL) and DCM (5 mL) was added 4M HCl in dioxane (0.43 mL, 1.755 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, washed with DCM, co-distilled with Et₂O and dried under reduced pressure to afford title compound **254** (0.15 g, 48.98%) as an off-white solid. LCMS calculated for C₂₂H₂₃N₅O₅S: 469.14; Found: 468.20 (M-1)

[2274] Synthesis of methyl ((1-((9-((2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 133)

[2275] To a stirred solution of compound **254** (0.20 g, 0.395 mmol) in DCM (10 mL) were added triethylamine (0.11 mL, 0.790 mmol) and methyl chloroformate (0.04 g, 0.474 mmol) in DCM at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((9-((2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 133**; 10 mg, 4.65%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 134

[2276] Scheme 89: Synthesis of methyl ((1-((8-((2-methoxyphenyl)sulfonamido)-2,3-dihydrobenzofuro[7,6-d]isoxazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 134)



[2277] Synthesis of 4-bromo-6-fluoro-2-hydroxy-3-(2-hydroxyethyl)benzonitrile (255)

[2278] To a stirred solution of compound **139** (2 g, 7.810 mmol) in DCM (10 mL) and MeOH (10 mL) ozone gas was purged for 5 min at -78 °C followed by addition of NaBH₄ (0.59 g, 15.620 mmol). The reaction was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was quenched with 1N HCl, extracted with DCM and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 25% ethyl acetate /Heptane to afford title compound **255** (0.90 g, 28.53%) as an off-white solid. LCMS calculated for C₉H₇BrFNO₂: 258.96; Found: 258 (M-1)

[2279] Synthesis of 4-bromo-6-fluoro-2,3-dihydrobenzofuran-7-carbonitrile (256)

[2280] To a solution of compound **255** (0.20 g, 0.769 mmol) in THF (10 mL) were added PPh₃ (0.30 g, 1.153 mmol) and DEAD (1.49 g, 7.306 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, extracted with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 20% EtOAc/Heptane and concentrated under reduced pressure to afford title compound **256** (0.10 g, 53.73%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.31 (d, *J*=9.54 Hz, 1 H), 4.87 (t, *J*=8.71 Hz, 2 H), 3.22 (br t, *J*=8.71 Hz, 2 H).

[2281] Synthesis of methyl 7-cyano-6-fluoro-2,3-dihydrobenzofuran-4-carboxylate (257)

[2282] To a stirred solution of compound **256** (0.30 g, 1.239 mmol) in MeOH (10 mL) was added Pd(OAc)₂ (0.01 g, 0.061 mmol), 1,3-Bis(diphenylphosphino)propane (0.05 g, 0.123 mmol) and triethylamine (0.34 mL, 2.478 mmol) and purged with N₂ for 10 min. The reaction mixture was stirred at 80 °C for 16 h under carbon monoxide gas (110 psi). After completion (monitored by TLC), the mixture was cooled at room temperature, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 20% EtOAc/Hexane to afford title compound **257** (0.15 g, 54.7%) as an off-white solid. ¹H NMR (401 MHz, DMSO-*d*₆) δ 7.29 (d, *J*=10.27 Hz, 1 H), 4.86 (t, *J*=8.74 Hz, 2 H), 3.87 (s, 3 H), 3.50 (td, *J*=8.74, 1.71 Hz, 2 H)

[2283] Synthesis of 6-fluoro-4-(hydroxymethyl)-2,3-dihydrobenzofuran-7-carbonitrile (258)

[2284] To a stirred solution of compound **257** (3 g, 13.563 mmol) in THF (160 mL) was added LiBH₄ (0.62 g, 28.482 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was cooled at room temperature, quenched with water, extracted with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 50% EtOAc/Heptane to afford title compound **258** (1.50 g, 55.70%) as an off-white solid. LCMS calculated for C₁₀H₈FN₂O: 193.05; Found: 194.10 (M+1).

[2285] Synthesis of 4-(bromomethyl)-6-fluoro-2,3-dihydrobenzofuran-7-carbonitrile (259)

[2286] To a stirred solution of compound **258** (0.50 g, 2.588 mmol) in acetonitrile (20 mL) were added triphenylphosphine (1.10 g, 4.141 mmol) and bromine (0.21 mL, 4.141 mmol). The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with Na₂S₂O₃, extracted with EtOAc, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 15% EtOAc/Heptane to afford title compound **259** (0.30 g, 45.26%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.03 (br d, *J*=10.37 Hz, 1 H), 4.86 (br t, *J*=8.71 Hz, 2 H), 4.64 (s, 2 H), 3.26 (br t, *J*=8.71 Hz, 2 H).

[2287] Synthesis of *tert*-Butyl ((1-((7-cyano-6-fluoro-2,3-dihydrobenzofuran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (260)

[2288] To a stirred solution of compound **19** (1.10 g, 5.584 mmol) in DMF (30 mL) were added K₂CO₃ (1.78 g, 12.887 mmol) and compound **259** (1.10 g, 4.295 mmol). The reaction

mixture was stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was cooled at room temperature, quenched with water, extracted with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 40% EtOAc/Hexane to afford title compound **260** (0.90 g, 37.75%) as an off-white solid. LCMS calculated for C₁₉H₂₁N₄O₃: 372.16; Found: 373.30 (M+1)

[2289] Synthesis of *tert*-Butyl ((1-((8-amino-2,3-dihydrobenzofuro[7,6-d]isoxazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (261)

[2290] To a stirred solution of compound **260** (0.40 g, 1.074 mmol) in DMF (6 mL) and water (1 mL) were added K₂CO₃ (0.89 g, 6.445 mmol) and acetohydroxamic acid (0.48 g, 6.445 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 12 h. After completion (monitored by TLC), the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 60% EtOAc/Hexane to afford title compound **261** (0.25 g, 48.30%) as an off-white solid. LCMS calculated for C₁₉H₂₃N₅O₄: 385.18; Found: 386.28 (M+1)

[2291] Synthesis of *tert*-Butyl ((1-((2-methoxyphenyl)sulfonamido)-2,3-dihydrobenzofuro[7,6-d]isoxazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (262)

[2292] To a stirred solution compound **261** (0.05 g, 0.129 mmol) in dry THF (5 mL) was added 1.6 M KOtBu in THF (0.24 mL, 0.389 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by addition of 2-methoxybenzenesulfonyl chloride (0.05 g, 0.259 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl to adjust the pH 6 and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **262** (0.04 g, 22.11%) as a brown solid. LCMS calculated for C₂₆H₂₉N₅O₇S: 555.18; Found: 556.38 (M+1)

[2293] Synthesis of N-(4-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-2,3-dihydrobenzofuro[7,6-d]isoxazol-8-yl)-2-methoxybenzenesulfonamide hydrochloride (263)

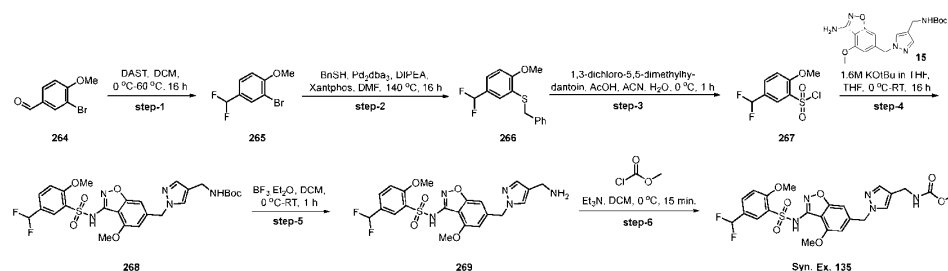
[2294] To a solution of compound **262** (40 mg, 0.071 mmol) in DCM (2 mL) was added 4M HCl in 1,4-dioxane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure triturated with Et₂O to afford title compound **263** (30 mg, 21.67%) as a brown solid. LCMS calculated for C₂₁H₂₁N₅O₅S: 455.13; Found: 457.20 (M+2)

[2295] **Synthesis of methyl ((1-((8-((2-methoxyphenyl)sulfonamido)-2,3-dihydrobenzofuro[7,6-d]isoxazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 134)**

[2296] To a stirred solution of compound **263** (30 mg, 0.060 mmol) in DCM (3 mL) were added triethylamine (0.02 mL, 0.182 mmol) and methyl chloroformate (0.6 mg, 0.073 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((8-((2-methoxyphenyl)sulfonamido)-2,3-dihydrobenzofuro[7,6-d]isoxazol-4-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 134**, 3 mg, 9.42%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 135

[2297] **Scheme 90: Synthesis of methyl ((1-((3-((5-(difluoromethyl)-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 135)**



[2298] **Synthesis of 2-bromo-4-(difluoromethyl)-1-methoxybenzene (265)**

[2299] To a stirred solution of compound **264** (5 g, 23.250 mmol) in DCM (50 mL) was added DAST (11.83 g, 69.751 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 7-9% EtOAc/Hexane to afford title compound **265** (4.50 g, 79.20%) as a yellow liquid. TLC: 20% EtOAc/Hexane (*R_f*: 0.6); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.75 - 7.80 (m, 1 H), 7.58 (dt, *J*=8.60, 0.89 Hz, 1 H), 7.24 (d, *J*=8.63 Hz, 1 H), 6.79 - 7.15 (m, 1 H), 3.90 (s, 3 H)

[2300] **Synthesis of benzyl(5-(difluoromethyl)-2-methoxyphenyl)sulfane (266)**

[2301] To a stirred solution of compound **265** (0.50 g, 2.109 mmol) in DMF (5 mL) were added DIPEA (1.10 mL, 6.328 mmol) and XantPhos (0.25 g, 0.421 mmol). The reaction mixture was degassed with N₂ for 10 min followed by addition of benzyl mercaptan (1.04 g, 8.437 mmol) and Pd₂(dba)₃ (0.19 g, 0.210 mmol). The reaction mixture was stirred at 140 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 0-2% EtOAc/Hexane to afford title compound **266** (0.30 g, 33.49%) as a yellow semisolid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.44 (s, 1 H), 7.35 - 7.40 (m, 3 H), 7.21 - 7.34 (m, 3 H), 7.04 - 7.12 (m, 1 H), 6.91 (s, 1 H), 4.20 (s, 2 H), 3.86 (s, 3 H).

[2302] **Synthesis of 5-(difluoromethyl)-2-methoxybenzenesulfonyl chloride (267)**

[2303] To a stirred solution of compound **266** (0.30 g, 1.070 mmol) in ACN (6 mL), water (0.10 mL) and AcOH (0.20 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (0.43 g, 2.141 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **267** (0.20 g, 40.05%) as a yellow semiliquid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.76 - 7.92 (m, 1 H), 7.50 (br d, *J*=8.33 Hz, 1 H), 7.19 - 7.37 (m, 1 H), 6.74 - 7.13 (m, 1 H), 3.90 (s, 3 H).

[2304] **Synthesis of *tert*-Butyl ((1-((3-((5-(difluoromethyl)-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (268)**

[2305] To a stirred solution of compound **15** (0.15 g, 0.401 mmol) in THF (5 mL) was added 1.6M KO^tBu in THF (0.75 mL, 1.205 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min followed by addition of compound **267** (0.20 g, 0.803 mmol) in THF. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 70-72% EtOAc/Pet ether to afford title compound **268** (0.12 g, 26.67%) as an off-white solid. TLC: 80% EtOAc/Hexane (*R*_f: 0.4). LCMS calculated for C₂₆H₂₉F₂N₅O₇S: 593.18; Found: 594.30 (M+1).

[2306] **Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-5-(difluoromethyl)-2-methoxybenzenesulfonamide (269)**

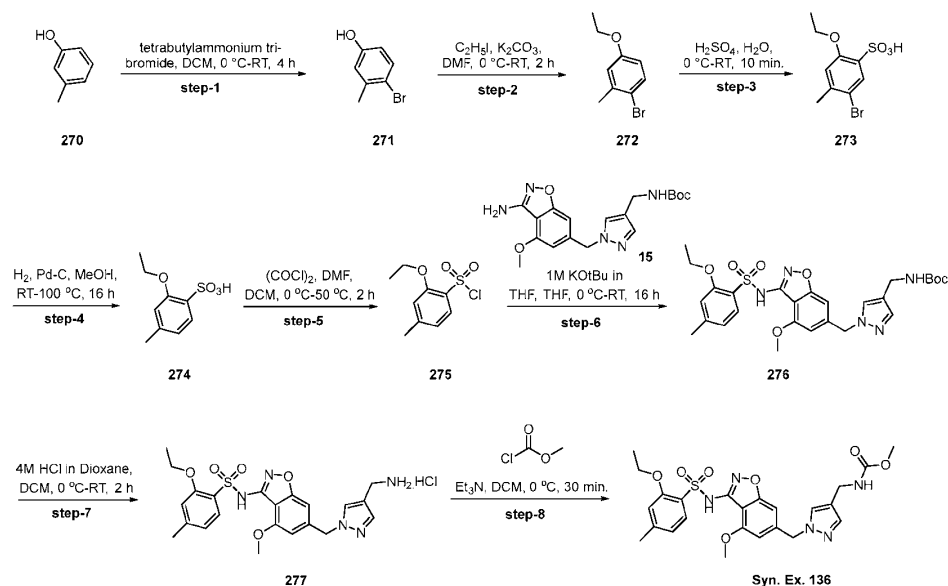
[2307] To a solution of compound **268** (0.12 g, 0.202 mmol) in DCM (2 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.03 mL, 0.303 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed Et_2O and concentrated under reduced pressure to afford title compound **269** (0.10 g, 53.13%) as an off-white solid. LCMS calculated for $\text{C}_{21}\text{H}_{21}\text{F}_2\text{N}_5\text{O}_5\text{S}$: 493.12; Found: 492.20 (M-1)

[2308] **Synthesis of methyl ((1-((3-((5-(difluoromethyl)-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 135)**

[2309] To a solution of compound **269** (0.13 g, 0.263 mmol) in DCM (5 mL) were added NEt_3 (0.11 mL, 0.790 mmol) in DCM (0.20 mL) and methyl chloroformate (0.02 mL, 0.316 mmol) in DCM (0.20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((3-((5-(difluoromethyl)-2-methoxyphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 135**; 5.00 mg, 3.34% yield) as an off-white solid. TLC: 5% MeOH/DCM (R_f : 0.4). (See analytical data in Table 1).

EXAMPLE 136

[2310] **Scheme 91: Synthesis of methyl ((1-((3-((2-ethoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 136)**



[2311] Synthesis of 4-bromo-3-methylphenol (271)

[2312] To a stirred solution of m-cresol **270** (3 g, 27.742 mmol) in DCM (30 mL) was added tetrabutylammonium tribromide (13.37 g, 27.742 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 20-30% of EtOAc/Heptane to afford title compound **271** (4.50 g, 64%) as a white semisolid. TLC: 30% EtOAc/Heptane (*R_f*: 0.3). LCMS calculated for C₇H₇BrO: 185.97; Found: 185.20 (M-1)

[2313] Synthesis of 1-bromo-4-ethoxy-2-methylbenzene (272)

[2314] To a stirred solution of compound **271** (4.50 g, 24.059 mmol) in DMF (40 mL) was added K₂CO₃ (4.76 g, 48.118 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min followed by addition of ethyl iodide (2.96 mL, 36.088 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with cold water, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford title compound **272** (3.50 g, 54.78%) as a colourless liquid. TLC: 20% EtOAc/Heptane (*R_f*: 0.8); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.42 (d, *J*=8.71 Hz, 1 H), 6.94 (br s, 1 H), 6.71 (br dd, *J*=8.71, 2.07 Hz, 1 H), 3.99 (q, *J*=6.77 Hz, 2 H), 2.29 (s, 3 H), 1.30 (t, *J*=7.05 Hz, 3 H)

[2315] Synthesis of 5-bromo-2-ethoxy-4-methylbenzenesulfonic acid (273)

[2316] A solution of compound **272** (2 g, 9.298 mmol) in H₂SO₄ (20 mL) was stirred at room temperature for 10 min. The reaction was quenched by addition of water at 0 °C. The solid residue was filtered, washed with Heptane and dried under reduced pressure to afford title compound **273** (2.30 g, 81.29%) as a pale-brown solid. LCMS calculated for C₉H₁₁BrO₄S: 293.96; Found: 293.10 (M-1)

[2317] Synthesis of 2-ethoxy-4-methylbenzenesulfonic acid (274)

[2318] To a stirred solution of compound **273** (2.30 g, 7.792 mmol) in MeOH (50 mL) was added 10% Pd-C (1.49 g, 1.402 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h under H₂ atmosphere (100 psi). After completion (monitored by TLC), the mixture was filtered through celite pad, washed with MeOH and concentrated under reduced pressure. The crude was washed with ether and dried under reduced pressure to afford title compound **274** (1.60 g, 93.05%) as brown semisolid. TLC: 20% MeOH/DCM (R_f: 0.4). LCMS calculated for C₉H₁₂O₄S: 216.05; Found: 215.30 (M-1)

[2319] Synthesis of 2-ethoxy-4-methylbenzenesulfonyl chloride (275)

[2320] To a stirred solution of compound **274** (0.40 g, 1.849 mmol) in DCM (4 mL) were added oxalyl chloride (3.99 mL, 45.706 mmol) and DMF (0.04 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 2 h under N₂. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **275** (0.42 g, 96.75%) as a colorless liquid. TLC: 50% EtOAc/Heptane (R_f: 0.8); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.54 (br d, *J*=7.46 Hz, 1 H), 6.75 (s, 1 H), 6.63 (br d, *J*=7.46 Hz, 1 H), 3.98 - 4.04 (m, 2 H), 2.27 (s, 3 H), 1.29 (br t, *J*=6.84 Hz, 3 H)

[2321] Synthesis of *tert*-Butyl ((1-((3-((2-ethoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (276)

[2322] To a stirred solution of compound **15** (0.30 g, 0.803 mmol) in THF (10 mL) was added 1M KOtBu in THF (2.41 mL, 2.410 mmol) at 0 °C. The reaction mixture was stirred for 5 min. followed by addition of compound **275** (0.37 g, 1.607 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The solid residue was washed with ether and dried under reduced pressure to afford title compound **276** (0.32 g, 29.26%) as pale-yellow semisolid. TLC: EtOAc (R_f: 0.2). LCMS calculated for C₂₇H₃₃N₅O₇S: 571.21; Found: 570.20 (M-1)

[2323] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-2-ethoxy-4-methylbenzenesulfonamide hydrochloride (277)

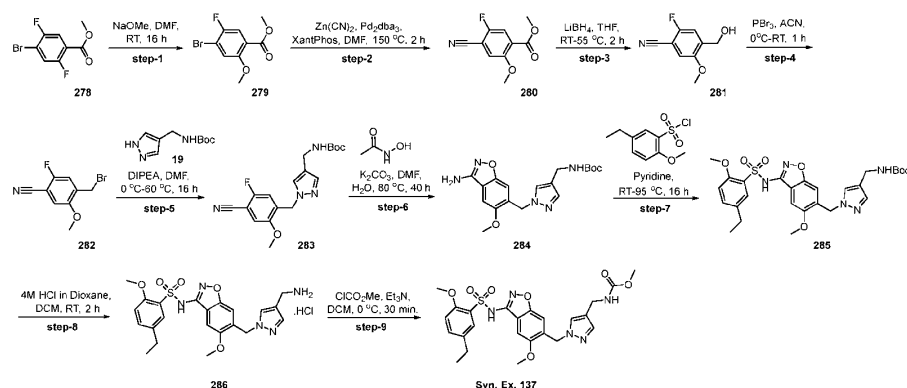
[2324] To a stirred solution of compound **276** (0.30 g, 0.524 mmol) in DCM (5 mL) was added 4M HCl in dioxane (1.31 mL, 5.248 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with ether and dried under reduced pressure to afford title compound **277** (0.25 g, 52.52%) as pale-yellow solid. LCMS calculated for C₂₂H₂₅N₅O₅S: 471.16; Found: 470.30 (M-1).

[2325] Synthesis of methyl ((1-((3-((2-ethoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 136)

[2326] To a stirred solution of compound **277** (0.16 g, 0.314 mmol) in DCM (3 mL) was added Et₃N (0.08 mL, 0.629 mmol) and methyl chloroformate (0.03 g, 0.314 mmol) in DCM (1 mL) at 0°C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water (10 mL) and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford methyl ((1-((3-((2-ethoxy-4-methylphenyl)sulfonamido)-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 136**; 5.00 mg, 2.96%) as an off-white solid. TLC: 10% MeOH/DCM (R_f: 0.7). (See analytical data in Table 1).

EXAMPLE 137

[2327] Scheme 92: Synthesis of methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 137)



[2328] Synthesis of methyl 4-bromo-5-fluoro-2-methoxybenzoate (279)

[2329] To a stirred solution of compound **278** (2 g, 8 mmol) in DMF (20 mL) was added NaOMe (0.54 g, 9.60 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **279** (1 g, 47%) as a white solid. TLC: 10% EtOAc/Heptane (*R_f*: 0.4). LCMS calculated for C₉H₈BrFO₃: 261.96; Found: 263 (M+1)

[2330] Synthesis of methyl 4-cyano-5-fluoro-2-methoxybenzoate (280)

[2331] To a stirred solution of compound **279** (50 mg, 0.190 mmol) in DMF (2 mL) was added Zn(CN)₂ (g, 0.285 mmol). The reaction mixture was degassed with N₂ for 5 min followed by addition of XantPhos (0.01 g, 0.019 mmol) and Pd₂(dba)₃ (0.0087 g, 0.009 mmol). The reaction mixture was stirred at 150 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **280** (26 mg, 64.66%) as a brown solid. TLC: 30% EtOAc/Heptane; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 - 7.77 (m, 2 H) 3.84 (d, *J*=13.13 Hz, 6 H)

[2332] Synthesis of 2-fluoro-4-(hydroxymethyl)-5-methoxybenzonitrile (281)

[2333] To a stirred solution of compound **280** (100 mg, 0.478 mmol) in THF (4 mL) was added LiBH₄ (2 mol/L) in THF (0.72 mL, 1.434 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold saturated aq. NH₄Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced

pressure. The crude was triturated with DCM/Heptane (9:1 ratio) to afford title compound **281** (82 mg, 91.59%) as a white solid. TLC: 40% EtOAc/Heptane, (R_f: 0.45); ¹H NMR (401 MHz, DMSO-*d*₆) δ 7.47 (d, *J*=5.14 Hz, 1 H) 7.40 (d, *J*=9.90 Hz, 1 H) 5.50 (t, *J*=5.56 Hz, 1 H) 4.49 - 4.54 (m, 2 H) 3.83 (s, 3 H)

[2334] Synthesis of 4-(bromomethyl)-2-fluoro-5-methoxybenzonitrile (282)

[2335] To a solution of compound **281** (80 mg, 0.441 mmol) in CH₃CN (3 mL) was added PBr₃ (0.08 mL, 0.883 mmol) at 0 °C. The reaction mixture was warm to room temperature and stirred for 1 h. After completion (monitored by TLC), the mixture was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 6-10% EtOAc/Heptane to afford title compound **282** (60 mg, 54.82%) as a white solid. TLC: 10% EtOAc/Heptane, (R_f: 0.4); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 (d, *J*=9.65 Hz, 1 H) 7.60 (d, *J*=5.26 Hz, 1 H) 4.62 (s, 2 H) 3.90 (s, 3 H)

[2336] Synthesis of *tert*-Butyl ((1-(4-cyano-5-fluoro-2-methoxybenzyl)-1H-pyrazol-4-yl)methyl)carbamate (283)

[2337] To a stirred solution of compound **19** (1.20 g, 5.90 mmol) in DMF (15 mL) were added DIPEA (2.60 mL, 15 mmol) and compound **282** (1.20 g, 4.90 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 40-52% EtOAc/Heptane to afford title compound **283** (0.90 g, 46%) as a brown gummy oil. TLC: 50% EtOAc/Heptane, (R_f: 0.4). LCMS calculated for C₁₈H₂₁FN₄O₃: 360.16; Found: 361.10 (M+1)

[2338] Synthesis of *tert*-Butyl ((1-((3-amino-5-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (284)

[2339] To a stirred solution of compound **283** (0.10 g, 0.277 mmol) in DMF (3 mL) and water (0.60 mL) were added N-hydroxyacetamide (0.062 g, 0.832 mmol) and K₂CO₃ (0.19 g, 1.387 mmol). The reaction mixture was stirred at 80 °C for 40 h. After completion (monitored by TLC), the mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was triturated with Et₂O and dried to afford title compound **284** (0.03 g, 20.61%) as a brown solid. LCMS calculated for C₁₈H₂₃N₅O₄: 373.18; Found: 374.20 (M+1)

[2340] Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (285)

[2341] To a solution of compound **284** (0.25 g, 0.669 mmol) in Pyridine (3 mL) was added 5-ethyl-2-methoxybenzenesulfonyl chloride (0.18 g, 0.80 mmol) at room temperature. The reaction mixture was stirred at 95 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 50-60% EtOAc/Heptane to afford title compound **285** (0.05 g, 12.93%) as a brown solid. LCMS calculated for C₂₇H₃₃N₅O₇S: 571.21; Found: 572.40 (M+1)

[2342] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (286)

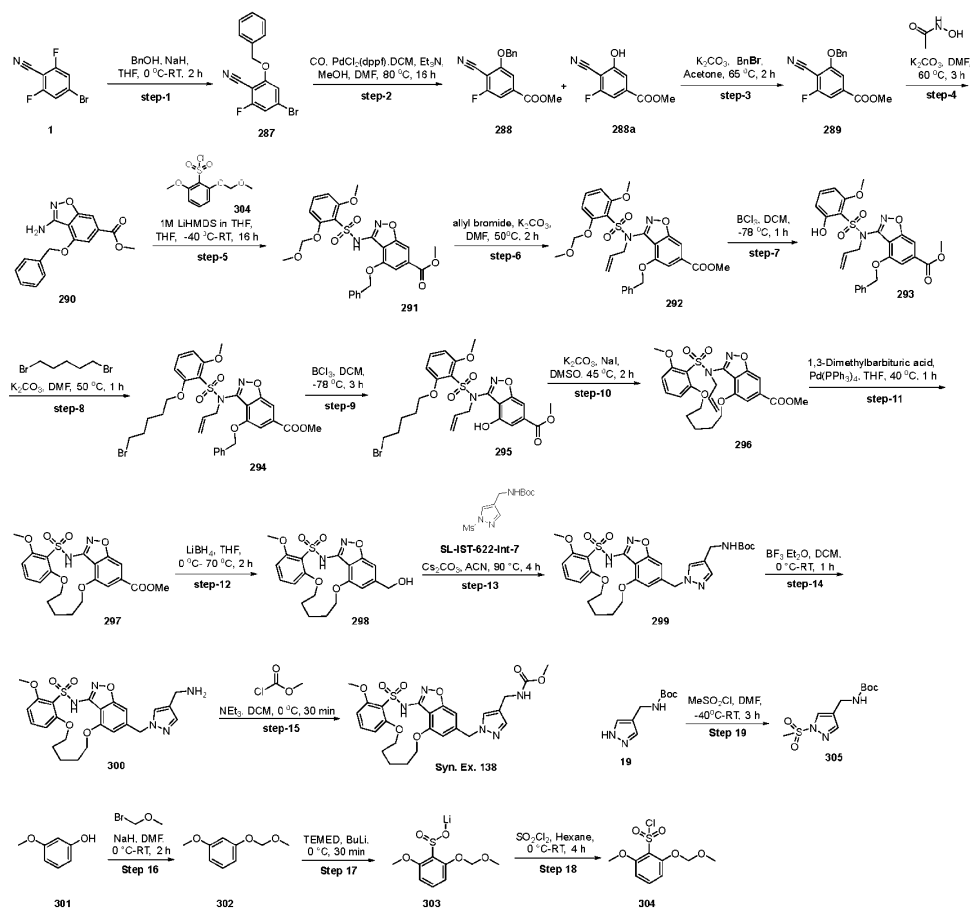
[2343] To a stirred solution of compound **285** (0.095 g, 0.166 mmol) in DCM (4 mL) was added 4M HCl in 1,4-Dioxane (0.20 mL, 0.831 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **286** (0.08 g, 83.07%) as a brown solid. LCMS calculated for C₂₂H₂₅N₅O₅S: 471.16; Found: 470.30 (M-1)

[2344] Synthesis of methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 137)

To a stirred solution compound **286** (0.07 g, 0.148 mmol) in DCM (5 mL) was added Et₃N (0.066 mL, 0.445 mmol) and methyl chloroformate (0.012 mL, 0.163 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford title compound (**Syn. Ex. 137**; 7.00 mg, 8.82%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 138

[2345] Scheme 93: Synthesis of methyl ((1-((14-methoxy-15,15-dioxido-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]inden-2-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 138)



[2346] Synthesis of 2-(benzyloxy)-4-bromo-6-fluorobenzonitrile (287)

[2347] To a stirred solution of 60% NaH in mineral oil (2.20 g, 55.05 mmol) in THF (200 mL) was added BnOH (4.75 mL, 45.87 mmol) in THF (5 mL) at 0°C . The reaction mixture was stirred at room temperature for 1 h followed by addition of compound 1 (10 g, 45.87 mmol) in THF (50 mL) at 0°C . The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc . The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 12-23% EtOAc/Heptane to afford title compound **287** (8 g, 57%) as a white solid; $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.30 - 7.58 (m, 7 H), 5.35 (s, 2 H).

[2348] Synthesis of methyl 3-(benzyloxy)-4-cyano-5-fluorobenzoate (288) and methyl 4-cyano-3-fluoro-5-hydroxybenzoate (288a)

[2349] A solution of compound **287** (10.50 g, 34.30 mmol) in MeOH (150 mL) and DMF (150 mL) was degassed with nitrogen for 10 min followed by addition of PdCl₂(dppf).DCM (2.83 g, 3.43 mmol) and Et₃N (14.40 mL, 103 mmol). The reaction mixture was stirred at 80 °C for 16 h under CO atmosphere (80 psi). After completion (monitored by TLC), the mixture was cooled at room temperature, filtered, and concentrated under reduced pressure to afford the mixture of compound **288** and compound **288a** (17 g, 88.70%) as a brown gummy oil.

[2350] Synthesis of methyl 3-(benzyloxy)-4-cyano-5-fluorobenzoate (289)

[2351] To a stirred solution of mixture of compound **288** and compound **288a** (16 g, 33.30 mmol) in acetone (160 mL) were added K₂CO₃ (6.90 g, 50 mmol) and BnBr (2.37 mL, 20 mmol). The reaction mixture was stirred 65 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 12-16% EtOAc/Heptane to afford title compound **289** (10 g, 99.50%) as a brown solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.65 (s, 1 H), 7.35 - 7.57 (m, 6 H), 5.42 (s, 2 H), 3.91 (s, 3 H)

[2352] Synthesis of methyl 3-amino-4-(benzyloxy)benzo[d]isoxazole-6-carboxylate (290)

[2353] To a solution of compound **289** (5 g, 18 mmol) in DMF (75 mL) were added N-hydroxyacetamide (4 g, 53 mmol) and K₂CO₃ (12 g, 88 mmol). The reaction mixture was stirred 60 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was washed with pentane, IPA and filtered to afford title compound (**290**) (2.30 g, 40%) as a white solid. LCMS calculated for C₁₆H₁₄N₂O₄: 298.10; Found: 299.10 (M+1)

[2354] Synthesis of methyl 4-(benzyloxy)-3-((2-methoxy-6-(methoxymethoxy)phenyl)sulfonamido)benzo[d]isoxazole-6-carboxylate (291)

[2355] To a stirred solution of compound **290** (2 g, 6.70 mmol) in THF (80 mL) was added 1M LiHMDS in THF (20 mL, 20 mmol) at - 40 °C. The reaction mixture was stirred at - 40 °C for 1 h followed by addition of compound **304** (3.60 g, 13 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and

concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 40-43% EtOAc/Heptane to afford title compound **291** (0.72 g, 19%) as a brown gummy oil. LCMS calculated for C₂₅H₂₄N₂O₉S: 528.12; Found: 527.20 (M-1)

[2356] Synthesis of methyl 3-((N-allyl-2-methoxy-6-(methoxymethoxy)phenyl)sulfonamido)-4-(benzyloxy)benzo[d]isoxazole-6-carboxylate (292)

[2357] To a stirred solution of compound **291** (1.20 g, 2.27 mmol) in DMF (20 mL) were added K₂CO₃ (1.57 g, 11.40 mmol) and 3-bromoprop-1-ene (1.37 g, 11.40 mmol). The reaction mixture was stirred at 50 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 38-46% of EtOAc/Heptane to afford title compound **292** (0.75 g, 53.80%) as a brown solid. LCMS calculated for C₂₈H₂₈N₂O₉S: 568.15; Found: 569.30 (M+1)

[2358] Synthesis of methyl 3-((N-allyl-2-hydroxy-6-methoxyphenyl)sulfonamido)-4-(benzyloxy)benzo[d]isoxazole-6-carboxylate (293)

[2359] To a stirred solution of compound **292** (0.90 g, 1.583 mmol) in DCM (85 mL) was added 1M BCl₃ in Toluene (2.53 mL, 2.533 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 36-45% of EtOAc/Heptane to afford title compound **293** (0.63 g, 70.73%) as a brown gummy oil. LCMS calculated for C₂₆H₂₄N₂O₈S: 524.13; Found: 525.10 (M+1).

[2360] Synthesis of methyl 3-((N-allyl-2-((5-bromopentyl)oxy)-6-methoxyphenyl)sulfonamido)-4-(benzyloxy)benzo[d]isoxazole-6-carboxylate (294)

[2361] To a stirred solution of compound **293** (0.63 g, 1.201 mmol) in DMF (16 mL) were added K₂CO₃ (0.74 g, 5.405 mmol) and 1,5-dibromopentane (0.49 mL, 3.603 mmol). The reaction mixture was stirred at 50 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 39-42% EtOAc/Heptane to afford title compound **294** (0.85 g, 89.34%) as a brown solid. LCMS calculated for C₃₁H₃₃BrN₂O₈S: 672.11; Found: 673.20 (M+1)

[2362] Synthesis of methyl 3-((N-allyl-2-((5-bromopentyl)oxy)-6-methoxyphenyl)sulfonamido)-4-hydroxybenzo[d]isoxazole-6-carboxylate (295)

[2363] To a stirred solution of compound **294** (0.85 g, 1.262 mmol) in DCM (25 mL) was added 1M BCl₃ in toluene (8.80 mL, 8.833 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 3 h. After completion (monitored by TLC), the mixture was quenched with ice-cold aqueous NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 36-45% EtOAc/Heptane to afford title compound **295** (0.63 g, 81.75%) as a brown gummy oil. LCMS calculated for C₂₄H₂₇BrN₂O₈S: 582.07; Found: 583.20 (M+1)

[2364] Synthesis of methyl 16-allyl-14-methoxy-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]indene-2-carboxylate 15,15-dioxide (296)

[2365] To a stirred solution of compound **295** (0.63 g, 1.080 mmol) in DMSO (60 mL) were added K₂CO₃ (0.29 g, 2.160 mmol) and NaI (0.08 g, 0.539 mmol). The reaction mixture was stirred at 45 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 36-45% EtOAc/Heptane to afford title compound **296** (0.32 g, 56.34%) as a brown gummy oil. LCMS calculated for C₂₄H₂₆N₂O₈S: 502.14; Found: 503.30 (M+1)

[2366] Synthesis of methyl 14-methoxy-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]indene-2-carboxylate 15,15-dioxide (297)

[2367] To a stirred solution of compound **296** (0.32 g, 0.636 mmol) in THF (32 mL) were added 1,3-dimethylbarbituric acid (0.33 g, 2.101 mmol) and Pd(PPh₃)₄ (0.33 g, 0.280 mmol). The reaction mixture stirred at 40 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 55-80% EtOAc/Heptane to afford title compound **297** (0.28 g, 84.65%) as a brown solid. LCMS calculated for C₂₁H₂₂N₂O₈S: 462.11; Found: 463.20 (M+1).

[2368] **Synthesis of 2-(hydroxymethyl)-14-methoxy-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]indene 15,15-dioxide (298)**

[2369] To a stirred solution of compound **297** (0.28 g, 0.605 mmol) in THF (5 mL) was added 2M LiBH₄ in THF (0.91 mL, 1.816 mmol) at 0 °C. The reaction mixture was stirred at 70 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was triturated with 9% DCM/pentane to afford title compound **298** (0.20 g, 65.20%) as a brown solid. LCMS calculated for C₂₀H₂₂N₂O₇S: 434.11; Found: 435.30 (M+1).

[2370] **Synthesis of *tert*-Butyl ((1-((14-methoxy-15,15-dioxido-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]inden-2-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (299)**

[2371] To a stirred solution of compound **298** (0.18 g, 0.414 mmol) in CH₃CN (8 mL) were added Cs₂CO₃ (0.53 g, 1.657 mmol) and compound **305** (0.22 g, 0.828 mmol). The reaction mixture was stirred at 90 °C for 4 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 10% MeOH/DCM to afford title compound **299** (80 mg, 18.80%) as a brown solid. LCMS calculated for C₂₉H₃₅N₅O₈S: 613.22; Found: 612.30 (M-1).

[2372] **Synthesis of 2-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-14-methoxy-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]indene 15,15-dioxide (300)**

[2373] To a stirred solution of compound **299** (0.08 g, 0.130 mmol) in DCM (2 mL) was added BF₃·Et₂O (0.37 mL, 0.195 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **300** (0.07 g, 62.87%) as a brown gummy oil. LCMS calculated for C₂₄H₂₇N₅O₆S: 513.17; Found: 514.70 (M+1).

[2374] **Synthesis of methyl ((1-((14-methoxy-15,15-dioxido-6,7,8,9-tetrahydro-5H,16H-4,10,18-trioxa-15-thia-16,17-diazabenz[11,12]cyclotetradeca[1,2,3-cd]inden-2-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 138)**

[2375] To a stirred solution of compound **300** (0.07 g, 0.136 mmol) in DCM (3 mL) were added NEt₃ (0.06 mL, 0.408 mmol) and methyl chloroformate (0.01 mL, 0.149 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford title compound (**Syn. Ex. 138**; 9.00 mg, 11% yield) as an off-white solid. (See analytical data in Table 1).

[2376] Synthesis of 1-methoxy-3-(methoxymethoxy)benzene (302)

[2377] To a stirred solution of 60% NaH in oil (8.37 g, 209.44 mmol) in DMF (200 mL) were added 3-methoxyphenol **301** (20 g, 161.11 mmol) and bromo(methoxy)methane (24.15 g, 193.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 12-15% of EtOAc/Heptane to afford title compound **302** (22 g, 78.53%) as a colourless oil. LCMS calculated for C₉H₁₂O₃: 168.08; Found: 169.20 (M+1).

[2378] Synthesis of lithium 2-methoxy-6-(methoxymethoxy)benzenesulfinate (303)

[2379] To a stirred solution of compound **302** (10 g, 59.50 mmol) in Hexane (200 mL) were added tetramethylethylenediamine (9.91 mL, 65.40 mmol) and 1.6M BuLi in Hexane (40.87 mL, 65.40 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The mixture was cooled at -70 °C, purged with SO₂ for 20 min. and warmed at 10 °C. After completion (monitored by TLC), the mixture was filtered, washed with Et₂O and concentrated under reduced pressure to afford title compound **303** (13.50 g, 86.20%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.10 (br t, *J*=8.11 Hz, 1 H), 6.52 - 6.67 (m, 2 H), 5.11 - 5.19 (m, 2 H), 3.72 (s, 3 H), 3.36 (s, 3 H)

[2380] Synthesis of 2-methoxy-6-(methoxymethoxy)benzenesulfonyl chloride (304)

[2381] To a stirred solution of compound **303** (7.50 g, 31 mmol) in Hexane (75 mL) was added SO₂Cl₂ (2.60 mL, 31 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford title compound **304** (3.60 g, 43%) as a brown solid; ¹H NMR (401 MHz,

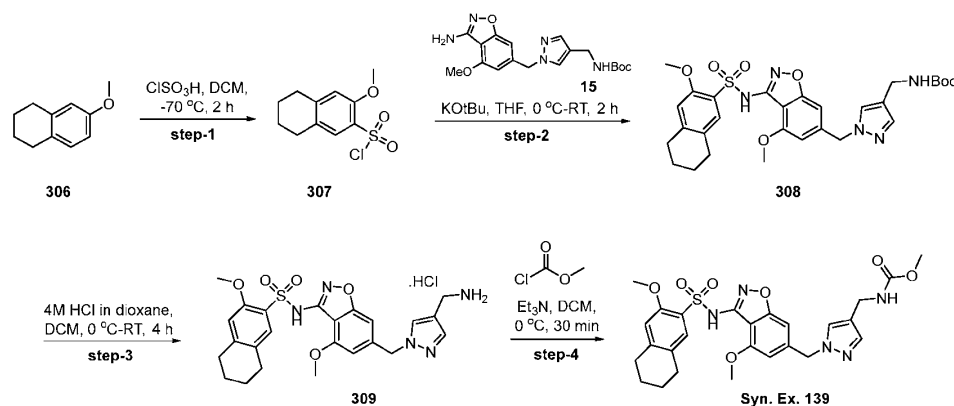
CHLOROFORM-*d*) δ ppm 7.47 - 7.57 (m, 1 H), 6.87 (br d, $J=8.31$ Hz, 1 H), 6.70 (br d, $J=8.44$ Hz, 1 H), 5.33 (br s, 2 H), 3.98 (br s, 3 H), 3.55 (s, 3 H).

[2382] Synthesis of *tert*-Butyl ((1-(methylsulfonyl)-1H-pyrazol-4-yl)methyl)carbamate (305)

[2383] To a stirred solution of compound **19** (1 g, 5.070 mmol) in DMF (16 mL) were added sodium bis(trimethylsilyl)amide (1 mol/L) in THF (5.07 mL, 5.070 mmol) and MeSO₂Cl (0.44 mL, 5.577 mmol) at -40 °C. The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the mixture was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 35-60% EtOAc/Heptane to afford title compound **305** (0.60 g, 28.30%) as a white solid. LCMS calculated for C₁₀H₁₇N₃O₄S: 275.09; Found: 275.92 (M+1).

EXAMPLE 139

[2384] Scheme 94: Synthesis of methyl ((1-((4-methoxy-3-((3-methoxy-5,6,7,8-tetrahydronaphthalene)-2-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 139)



[2385] Synthesis of 3-methoxy-5,6,7,8-tetrahydronaphthalene-2-sulfonyl chloride (307)

[2386] To a stirred solution of compound **306** (1 g, 6.164 mmol) in DCM (30 mL) was added ClSO₃H (1.30 mL, 18.492 mmol) at -70 °C. The reaction mixture was stirred at -70 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with saturated aqueous NaHCO₃ and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **307**

(0.65 g, 40.44%) as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.38 (s, 1 H), 6.68 (s, 1 H), 3.71 (s, 3 H), 2.59 - 2.73 (m, 4 H), 1.70 (br t, *J*=2.87 Hz, 4 H).

[2387] Synthesis of *tert*-Butyl ((1-((4-methoxy-3-((3-methoxy-5,6,7,8-tetrahydronaphthalene)-2-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (308)

[2388] To a stirred solution of compound **15** (0.35 g, 0.959 mmol) in THF (20 mL) were added 1.6M KOtBu in THF (2.39 mL, 3.836 mmol) and compound **307** (0.50 g, 1.918 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **308** (0.20 g, 6.93%). LCMS calculated for C₂₉H₃₅N₅O₇S: 597.23; Found: 596.30 (M-1).

[2389] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-4-methoxybenzo[d]isoxazol-3-yl)-3-methoxy-5,6,7,8-tetrahydronaphthalene-2-sulfonamide hydrochloride (309)

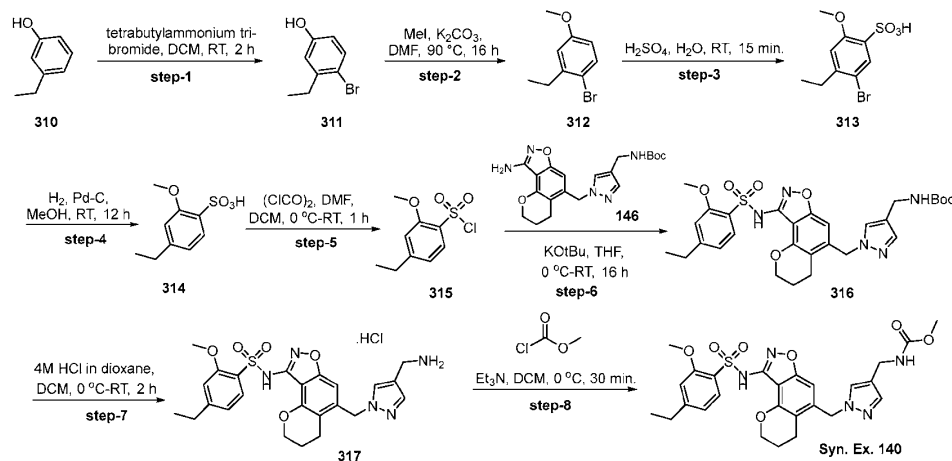
[2390] To a solution of compound **308** (0.20 g, 0.334 mmol) in DCM (5 mL) was added 4M HCl in dioxane (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **309** (0.15 g, 83.98%) as an off-white solid. LCMS calculated for C₂₄H₂₇N₅O₅S: 497.17; Found: 495.20 (M-2)

[2391] Synthesis of methyl ((1-((4-methoxy-3-((3-methoxy-5,6,7,8-tetrahydronaphthalene)-2-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 139)

[2392] To a stirred solution of compound **309** (0.15 g, 0.280 mmol) in DCM (5 mL) were added NEt₃ (0.11 mL, 0.842 mmol) methyl chloroformate (0.02 mL, 0.308 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((4-methoxy-3-((3-methoxy-5,6,7,8-tetrahydronaphthalene)-2-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 139**; 40 mg, 25.25%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 140

[2393] **Scheme 94: Synthesis of methyl ((1-((9-((4-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 140)**



[2394] **Synthesis of 4-bromo-3-ethylphenol (311)**

[2395] To a solution of 3-ethylphenol **310** (5 g, 40.930 mmol) in DCM (50 mL) was added tetrabutylammonium tribromide (19.73 g, 40.930 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **311** (5 g, 60.75%) as a liquid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.58 (s, 1 H), 7.31 (br d, *J*=8.77 Hz, 1 H), 6.73 (br d, *J*=1.75 Hz, 1 H), 6.45 - 6.61 (m, 1 H), 2.58 (q, *J*=7.45 Hz, 2 H), 1.12 (br t, *J*=7.24 Hz, 3 H).

[2396] **Synthesis of 1-bromo-2-ethyl-4-methoxybenzene (312)**

[2397] To a solution of compound **311** (8 g, 39.789 mmol) in DMF (80 mL) were added K₂CO₃ (10.99 g, 79.578 mmol) and MeI (4.95 mL, 79.578 mmol). The reaction mixture was stirred at 90 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **312** (8 g, 93.47%) as a liquid; ¹H NMR (401 MHz, DMSO-*d*₆) δ ppm 7.45 (d, *J*=8.68 Hz, 1 H), 6.93 (d, *J*=3.06 Hz, 1 H), 6.74 (dd, *J*=8.68, 3.06 Hz, 1 H), 3.75 (s, 3 H), 2.65 (q, *J*=7.50 Hz, 2 H), 1.15 (t, *J*=7.52 Hz, 3 H).

[2398] **Synthesis of 5-bromo-4-ethyl-2-methoxybenzenesulfonic acid (313)**

[2399] A solution of compound **312** (3 g, 13.948 mmol) in H₂SO₄ (30 mL) was stirred at room temperature for 15 min. After completion (monitored by TLC), the mixture was quenched with ice-cold water (30 mL), concentrated under reduced pressure, filtered, washed with Heptane, and dried under reduced pressure to afford title compound **313** (4 g, 97.16%) as a white solid. LCMS calculated for C₉H₁₁BrO₄S: 293.96; Found: 295 (M+1)

[2400] Synthesis of 4-ethyl-2-methoxybenzenesulfonic acid (314)

[2401] To a solution of compound **313** (6 g, 20.329 mmol) in MeOH (150 mL) was added 10% Pd-C (1 g, 0.939 mmol). The reaction mixture was stirred at room temperature for 12 h under H₂ atmosphere (50 psi). After completion (monitored by TLC), the mixture was filtered through celite pad and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 0-5% MeOH/DCM to afford title compound **314** (4 g, 66.42%) as a brown colored liquid. LCMS calculated for C₉H₁₂O₄S: 216.05; Found: 215.20 (M-1)

[2402] Synthesis of 4-ethyl-2-methoxybenzenesulfonyl chloride (315)

[2403] To a stirred solution compound **314** (2 g, 9.248 mmol) in DCM (20 mL) and DMF (0.07 mL) was added oxalyl chloride (8.09 mL, 92.486 mmol) at 0 °C. The reaction was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford title compound **315** (0.25 g, 11.51%) as a brown liquid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.56 (br d, *J*=7.88 Hz, 1 H), 6.80 (s, 1 H), 6.69 (br d, *J*=7.46 Hz, 1 H), 3.77 (br s, 3 H), 2.54 - 2.62 (m, 2 H), 1.17 (br t, *J*=7.46 Hz, 3 H)

[2404] Synthesis of *tert*-Butyl ((1-((9-((4-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (316)

[2405] To a stirred solution compound **146** (0.30 g, 0.751 mmol) in dry THF (10 mL) was added 1.6M K₂CO₃ in THF (1.40 mL, 2.253 mmol) at 0 °C. The reaction was stirred at 0 °C for 10 min. followed by addition of compound **315** (0.35 g, 1.502 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The aqueous layer was acidified with 1N HCl to pH ~ 6 and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under

reduced pressure to afford title compound **316** (0.40 g, 58.80%) as a brown solid. LCMS calculated for C₂₉H₃₅N₅O₇S: 597.23; Found: 596.30 (M-1)

[2406] Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-9-yl)-4-ethyl-2-methoxybenzenesulfonamide hydrochloride (317)

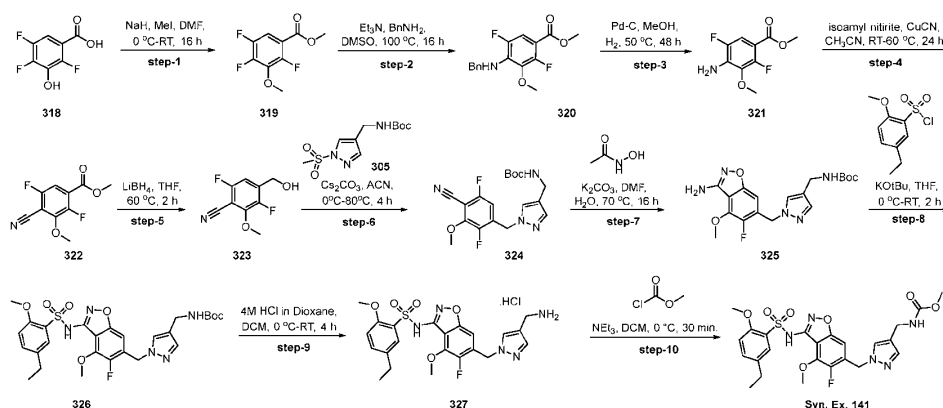
[2407] To a solution of compound **316** (0.40 g, 0.669 mmol) in DCM (10 mL) was added 4M HCl in dioxane (0.83 mL, 3.346 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with DCM, co-distilled with Et₂O and concentrated under reduced pressure to afford title compound **317** (0.20 g, 32.43%) as an off-white solid. LCMS calculated for C₂₄H₂₇N₅O₅S: 497.17; Found: 498.60 (M+1)

[2408] Synthesis of methyl ((1-((9-((4-ethyl-2-methoxyphenyl)sulfonamido)-3,4-dihydro-2H-chromeno[8,7-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 140)

[2409] To a solution of compound **317** (0.20 g, 0.374 mmol) in DCM (10 mL) were added NEt₃ (0.15 mL, 1.123 mmol) and methyl chloroformate (0.03 mL, 0.486 mmol) in DCM at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified using prep. HPLC to afford title compound (**Syn. Ex. 140**; 14 mg, 6.52%) as an off-white solid.

EXAMPLE 141

[2410] Scheme 95: Synthesis of methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-fluoro-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 141)



[2411] Synthesis of methyl 2,4,5-trifluoro-3-methoxybenzoate (319)

[2412] To a stirred solution of compound **318** (5 g, 26 mmol) in DMF (50 mL) was added NaH (3 g, 110 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min followed by addition of MeI (2 g, 14 mmol). The reaction mixture was stirred at room temperature 12 h. After completion (monitored by TLC), the mixture was acidified with citric acid and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 10-15% EtOAc/Hexane and concentrated under reduced pressure to afford title compound **319** (3.50 g, 61.07%) as colourless liquid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56 - 7.68 (m, 1 H), 4.01 (s, 3 H), 3.86 (s, 3 H)

[2413] Synthesis of methyl 4-(benzylamino)-2,5-difluoro-3-methoxybenzoate (320)

[2414] To a stirred solution of compound **319** (18 g, 81.766 mmol) in DMSO (180 mL) was added BnNH₂ (14 mL, 122.65 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. followed by addition of Et₃N (34.40 mL, 245.30 mmol). The reaction mixture was stirred at 100 °C for 12 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 10-15% EtOAc in Hexane to afford title compound **320** (12 g, 41.50%) as a colourless liquid. LCMS calculated for C₁₆H₁₅F₂NO₃: 307.10; Found: 308.20 (M+1)

[2415] Synthesis of methyl 4-amino-2,5-difluoro-3-methoxybenzoate (321)

[2416] To a stirred solution of compound **320** (2.40 g, 7.80 mmol) in MeOH (24 mL) was added 10% Pd-C (0.50 g) at room temperature. The reaction mixture was stirred at 50 °C for 48 h under H₂ atmosphere (50 psi). After completion (monitored by TLC), the mixture was

filtered through celite bed, washed with MeOH (10 mL) and concentrated under reduced pressure to afford title compound **321** (1.40 g, 75%) as an off-white solid. LCMS calculated for C₉H₉F₂NO₃: 217.06; Found: 218.20 (M+1)

[2417] Synthesis of methyl 4-cyano-2,5-difluoro-3-methoxybenzoate (322)

[2418] To a stirred solution of compound **321** (6 g, 27.628 mmol) in ACN (60 mL) was added CuCN (7.49 g, 82.884 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 24 h followed by addition of isoamyl nitrite (10.01 g, 82.884 mmol). After completion (monitored by TLC), the mixture was filtered through celite bed, washed with MeOH and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 20% EtOAc/Hexane to afford title compound **322** (3 g, 47.79%) as a brown solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 - 7.63 (m, 1 H), 4.12 - 4.18 (m, 3 H), 3.86 - 3.92 (m, 3 H)

[2419] Synthesis of 3,6-difluoro-4-(hydroxymethyl)-2-methoxybenzonitrile (323)

[2420] To a stirred solution of compound **322** (3 g, 13 mmol) in THF (30 mL) was added LiBH₄ (0.58 g, 26 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice cold water, extracted with EtOAc and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 50% EtOAc/Heptane to afford title compound **323** (2.10 g, 79.84%) as an off-white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.04 (dd, *J*=8.63, 4.75 Hz, 1 H), 4.81 (s, 2 H), 4.15 (s, 3 H)

[2421] Synthesis of *tert*-Butyl ((1-(4-cyano-2,5-difluoro-3-methoxybenzyl)-1H-pyrazol-4-yl)methyl)carbamate (324)

[2422] To a stirred solution of compound **305** (10 mg, 0.05 mmol) in ACN (4 mL) were added Cs₂CO₃ (0.04 g, 0.15 mmol) and compound **323** (0.01 g, 0.05 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 4 h. After completion (monitored by TLC), the mixture was cooled at room temperature, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 50% EtOAc/Hexane to afford title compound **324** (8 mg, 42.32%) as an off-white solid. LCMS calculated for C₁₈H₂₀F₂N₄O₃: 378.15; Found: 379 (M+1)

[2423] Synthesis of 6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-fluoro-4-methoxybenzo[d]isoxazol-3-amine (325)

[2424] To a stirred solution of compound **324** (0.05 g, 0.1321 mmol) in DMF (4 mL) were added K₂CO₃ (0.05 g, 0.396 mmol), acetohydroxamic acid (0.02 g, 0.396 mmol) and water (2 mL). The reaction mixture was stirred at 70 °C for 16 h. After completion (monitored by

TLC), the mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 70-80% EtOAc/Hexane to afford title compound **325** (30 mg, 28.54%) as a pale-yellow solid. LCMS calculated for C₁₈H₂₂FN₅O₄: 391.17; Found: 392 (M+1)

[2425] Synthesis of *tert*-Butyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-fluoro-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (326)

[2426] To a stirred solution of compound **325** (0.03 g, 0.0766 mmol) in THF (5 mL) were added 1.6M KOtBu in THF (0.09 mL, 0.153 mmol) and 5-ethyl-2-methoxybenzenesulfonyl chloride (0.02 g, 0.076 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford title compound **326** (0.03 g, 25.10%) as an off-white solid. LCMS calculated for C₂₇H₃₂FN₅O₇S: 589.20; Found: 590 (M+1)

[2427] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-fluoro-4-methoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (327)

[2428] To a solution of compound **326** (30 mg, 0.050 mmol) in DCM (4 mL) was added 4M HCl in dioxane (0.05 mL, 0.203 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and dried under reduced pressure to afford title compound **327** (25 mg, 31.84% yield) as an off-white solid. LCMS calculated for C₂₂H₂₄FN₅O₅S: 489.15; Found: 488.20 (M-1)

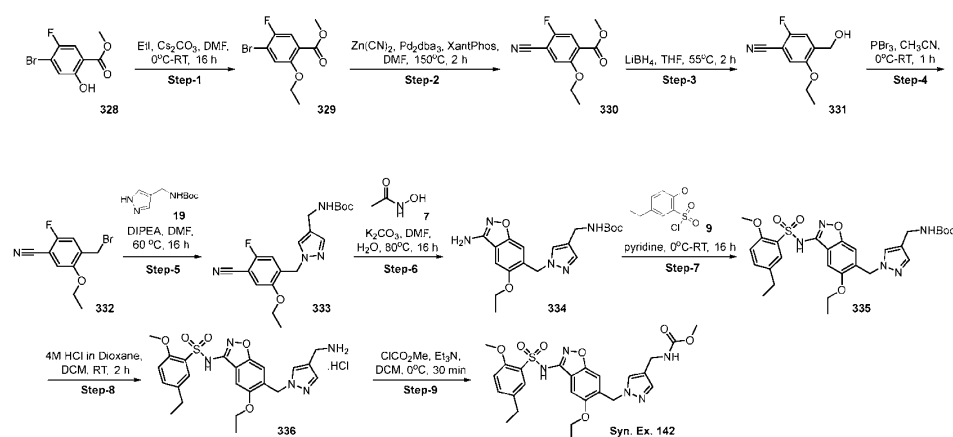
[2429] Synthesis of methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-fluoro-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 141)

[2430] To a solution of compound **327** (25 mg, 0.047 mmol) in DCM (2 mL) were added NEt₃ (0.01 mL, 0.142 mmol) and methyl chloroformate (0.003 mL, 0.047 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-

fluoro-4-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 141**; 8 mg, 30.18%) as an off-white solid. (See analytical data in Table 1).

EXAMPLE 142

[2431] **Scheme 95: Synthesis of methyl ((1-((5-ethoxy-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 142**)**



[2432] **Synthesis of methyl 4-bromo-2-ethoxy-5-fluorobenzoate (329)**

[2433] To a stirred solution of compound **328** (1 g, 4 mmol) in DMF (12 mL) were added Cs_2CO_3 (2 g, 6.0 mmol) and iodoethane (0.95 g, 6.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **329** (1.1 g, 98%) as a white solid. TLC: 10% EtOAc/Heptane (R_f : 0.4). LCMS calculated for $\text{C}_{10}\text{H}_{10}\text{BrFO}_3$: 275.98; Found: 277.0 ($M+1$)

[2434] **Synthesis of methyl 4-cyano-2-ethoxy-5-fluorobenzoate (330)**

[2435] To a stirred solution of compound **329** (6.5 g, 23 mmol) in DMF (80 mL) was added $\text{Zn}(\text{CN})_2$ (4.2g, 35 mmol). The reaction mixture was degassed with N_2 for 5 min. followed by addition of XantPhos (1.4 g, 2.3 mmol) and $\text{Pd}_2(\text{dba})_3$ (1.1 g, 1.2 mmol) and again degassed for 2 min. The reaction mixture was stirred at 150 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 19-26% EtOAc/Heptane to afford title compound **330** (4.4 g, 83%) as a brown solid. TLC: 25%

EtOAc/Heptane (R_f: 0.4); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 - 7.78 (m, 2H) 4.13 (q, *J* = 6.91 Hz, 2H) 3.83 (s, 3H) 1.31 (t, *J* = 7.05 Hz, 3H)

[2436] Synthesis of 5-ethoxy-2-fluoro-4-(hydroxymethyl)benzonitrile (331)

[2437] To a stirred solution of methyl 4-cyano-2-ethoxy-5-fluorobenzoate **330** (4.3 g, 19 mmol) in THF (50 mL) was added 2M LiBH₄ in THF (29 mL, 58 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 2 h. After completion (monitored by TLC), the mixture was added to ice-cold aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was triturated with DCM/Heptane (9:1) to afford title compound **331** (3.4 g, 86%) as a white solid. TLC: 40% EtOAc/Heptane, (R_f: 0.45); ¹H NMR (401 MHz, DMSO-*d*₆) δ ppm 7.45 (d, *J* = 5.14 Hz, 1H) 7.39 (d, *J* = 9.78 Hz, 1H) 4.52 (d, *J* = 5.38 Hz, 2H) 4.08 (q, *J* = 6.93 Hz, 2H) 1.32 (t, *J* = 6.85 Hz, 3H)

[2438] Synthesis of 4-(bromomethyl)-5-ethoxy-2-fluorobenzonitrile (332)

[2439] To a stirred solution of compound **331** (3.4 g, 17 mmol) in ACN (40 mL) was added PBr₃ (3.3 mL, 35 mmol) at 0 °C. Then reaction mixture was warm to room temperature and stirred for 1 h. After completion (monitored by TLC), the mixture was added to saturated NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 15-20% EtOAc/Heptane to afford title compound **332** (2.45 g, 54%) as a white solid. TLC: 10% EtOAc/Heptane, (R_f: 0.4); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.65 (d, *J* = 9.54 Hz, 1H) 7.58 (d, *J* = 5.39 Hz, 1H) 4.62 (s, 2H) 4.16 (q, *J* = 7.05 Hz, 2H) 1.36 (t, *J* = 6.84 Hz, 3H).

[2440] Synthesis of *tert*-butyl ((1-(4-cyano-2-ethoxy-5-fluorobenzyl)-1H-pyrazol-4-yl)methyl)carbamate (333)

[2441] To a stirred solution of compound **332** (2 g, 7.7 mmol) in DMF (20 mL) were added DIPEA (4.1 mL, 23 mmol) and compound **19** (1.8 g, 9.3 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 40-51% EtOAc/Heptane to afford title compound **333** (1.25 g, 39%) as a white solid. TLC: 50% EtOAc/Heptane, (R_f: 0.4). LCMS calculated for C₁₉H₂₃FN₄O₃: 374.18; Found: 375.2 (M+1)

[2442] Synthesis of *tert*-butyl ((1-((3-amino-5-ethoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (334)

[2443] To a stirred solution of compound **333** (1.25 g, 3.34 mmol) in DMF (36 mL) and water (9 mL) were added acetohydroxamic acid (0.75 g, 10.0 mmol) and K₂CO₃ (2.3 g, 16.7 mmol). The reaction mixture was stirred at 80 °C for 16 h. After completion (monitored by TLC), the mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 50-62% EtOAc/Heptane to afford title compound **334** (0.32 g, 13.1%) as a brown solid. LCMS calculated for C₁₉H₂₅N₅O₄: 387.19; Found: 388.3 (M+1)

[2444] **Synthesis of *tert*-butyl ((1-((5-ethoxy-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (335)**

[2445] To a stirred solution of compound **334** (0.4 g, 1.033 mmol) in pyridine (3 mL) was added 5-ethyl-2-methoxybenzenesulfonyl chloride (0.29 g, 1.239 mmol) at room temperature. The reaction mixture was stirred at 95 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography using 50-60% EtOAc/Heptane to afford title compound **335** (75 mg, 1.66%) as a brown solid. LCMS calculated for C₂₈H₃₅N₅O₇S: 585.23; Found: 586.4 (M+1)

[2446] **Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-ethoxybenzo[d]isoxazol-3-yl)-5-ethyl-2-methoxybenzenesulfonamide hydrochloride (336)**

[2447] To a stirred solution of compound **335** (115 mg, 0.1963 mmol) in DCM (3 mL) was added 4M HCl in 1,4-Dioxane (0.24 mL, 0.981 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The crude was triturated with Et₂O to afford title compound **336** (95 mg, 84.48%) as a brown solid. LCMS calculated for C₂₃H₂₇N₅O₅S: 485.17; Found: 484.0 (M-1)

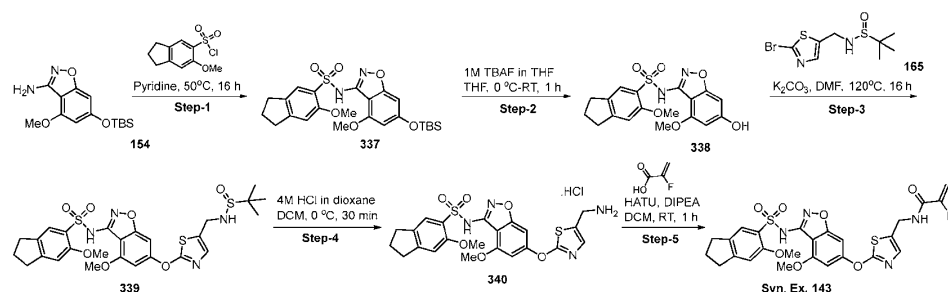
[2448] **Synthesis of methyl ((1-((5-ethoxy-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 142)**

[2449] To a stirred solution compound **336** (80 mg, 0.164 mmol) in DCM (3 mL) was added Et₃N (0.073 mL, 0.4942 mmol) and methyl chloroformate (0.012, 0.163 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by

TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((5-ethoxy-3-((5-ethyl-2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 142**; 20 mg, 21.58%) as an off-white solid.

EXAMPLE 143

[2450] Scheme 96: Synthesis of 2-fluoro-N-((2-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)acrylamide (Syn. Ex. 143**)**



[2451] Synthesis of N-(6-((tert-butyldimethylsilyl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide (337)

[2452] To a stirred solution of compound **154** (1 g, 3.4 mmol) in Pyridine (10 mL) was added 6-methoxy-2,3-dihydro-1H-indene-5-sulfonyl chloride (2.2 g, 8.9 mmol). The reaction mixture was stirred at 50 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **337** (0.48 g, 25%) as a brown solid. LCMS calculated for C₂₄H₃₂N₂O₆SSi: 504.18; Found: 505.0 (M+1).

[2453] Synthesis of N-(6-hydroxy-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide (338)

[2454] To a stirred solution of compound **337** (0.48 g, 0.951 mmol) in THF (8 mL) was added 1M TBAF in THF (1.1 mL, 1.141 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to

afford title compound **138** (0.25 g, 63.04%) as a brown solid. LCMS calculated for $C_{18}H_{18}N_2O_6S$: 390.09; Found: 391.0 (M+1)

[2455] Synthesis of N-(6-(((5-(((tert-butylsulfinyl)amino)methyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide (339)

[2456] To a stirred solution of compound **338** (0.5 g, 1.281 mmol) in DMF (5 mL) were added K_2CO_3 (0.53 g, 3.842 mmol) and compound **165** (0.45 g, 1.537 mmol). The reaction mixture was stirred at 120 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **339** (0.13 g, 9.53%) as an off white solid. LCMS calculated for $C_{26}H_{30}N_4O_7S_3$: 606.13; Found: 607.0 (M+1)

[2457] Synthesis of N-(6-(((5-(aminomethyl)thiazol-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide hydrochloride (340)

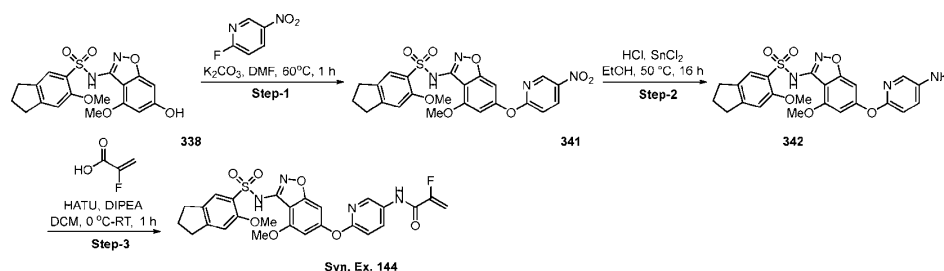
[2458] To a stirred solution of compound **339** (0.13 g, 0.214 mmol) in DCM (3 mL) was added 4M HCl in 1,4-Dioxane (0.11 mL, 0.4285 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After completion (monitored by TLC), the mixture was concentrated under reduced pressure. The residue was washed with Et₂O and concentrated under vacuum to afford title compound **340** (0.15 g, 65.46%) as a brown gummy. LCMS calculated for $C_{22}H_{22}N_4O_6S_2$: 502.10; Found: 504.27 (M+2).

[2459] Synthesis of 2-fluoro-N-((2-(((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)acrylamide (Syn. Ex. 143)

[2460] To a stirred solution of compound **340** (0.14 g, 0.278 mmol) in DCM (2 mL) were added DIPEA (0.1 g, 0.835 mmol), HATU (0.16 g, 0.417 mmol) and 2-fluoroacrylic acid (0.03 g, 3343 mmol) at rt. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 2-fluoro-N-((2-(((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)acrylamide **Syn. Ex. 143** (0.013 g, 8.09%) as an off white solid.

EXAMPLE 144

[2461] **Scheme 97: Synthesis of 2-fluoro-N-(6-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)acrylamide (Syn. Ex. 144)**



[2462] **Synthesis of 6-methoxy-N-(4-methoxy-6-((5-nitropyridin-2-yl)oxy)benzo[d]isoxazol-3-yl)-2,3-dihydro-1H-indene-5-sulfonamide (341)**

[2463] To a stirred solution of compound **338** (0.22 g, 0.563 mmol) in DMF (3 mL) were added K_2CO_3 (0.15 g, 1.127 mmol) and 2-fluoro-5-nitropyridine (0.096 g, 0.676 mmol). The reaction mixture was stirred at 60 °C for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water, acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **341** (0.15 g, 38.26%) as a brown solid. LCMS calculated for $C_{23}H_{20}N_4O_8S$: 512.10; Found: 512.9 (M+1)

[2464] **Synthesis of N-(6-((5-aminopyridin-2-yl)oxy)-4-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide (342)**

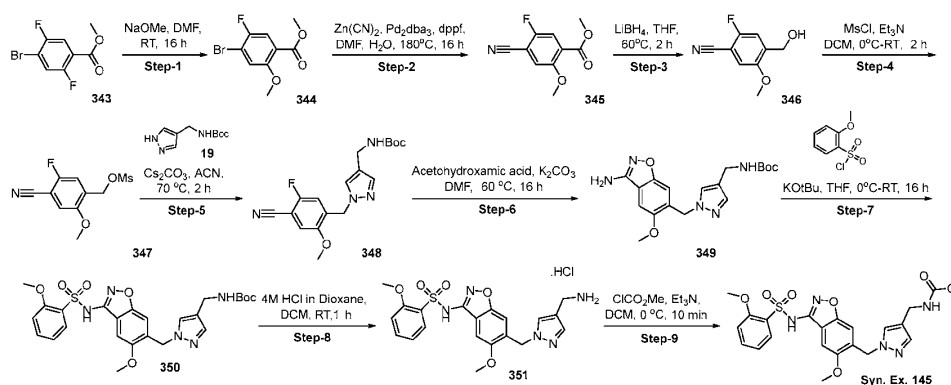
[2465] To a stirred solution of compound **341** (0.18 g, 0.351 mmol) in EtOH (3 mL) were added HCl (0.026 mL, 1.054 mmol) and Tin(II) chloride (0.206 g, 1.054 mmol). The reaction mixture was stirred at 50 °C for 16 h. After completion (monitored by TLC), the mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was washed with Et_2O to afford title compound **342** (0.15 g, 69.3%) as a brown solid. LCMS calculated for $C_{23}H_{22}N_4O_6S$: 482.13; Found: 483.1 (M+1).

[2466] **Synthesis of 2-fluoro-N-(6-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)acrylamide (Syn. Ex. 144)**

[2467] To a stirred solution of compound **342** (0.06 g, 0.124 mmol) in DCM (2 mL) were added DIPEA (0.064 mL, 0.373 mmol), HATU (0.073 g, 0.186 mmol) and 2-fluoroacrylic acid (0.013 g, 0.149 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 2-fluoro-N-((6-((4-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)oxy)pyridin-3-yl)acrylamide **Syn. Ex. 144** (9.00 mg, 13%) as an off white solid.

EXAMPLE 145

[2468] **Scheme 98: Synthesis of methyl ((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 145**)**



[2469] **Synthesis of methyl 4-bromo-5-fluoro-2-methoxybenzoate (344)**

[2470] To a stirred solution of compound **343** (10 g, 39.837 mmol) in DMF (100 mL) was added NaOMe (2.83 g, 49.797 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with cold water and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **344** (10.2 g, 89.1%) as a white solid. LCMS calculated for C₉H₈BrFO₃: 261.96; Found: 264.6 (M+2)

[2471] **Synthesis of methyl 4-cyano-5-fluoro-2-methoxybenzoate (345)**

[2472] To a stirred solution of compound **344** (8.5 g, 32 mmol) in DMF (100 mL) was added Zn(CN)₂ (5.7 g, 48 mmol). The reaction mixture was degassed with N₂ for 5 min.

followed by addition of XantPhos (1.9 g, 3.2 mmol) and $\text{Pd}_2(\text{dba})_3$ (1.5 g, 1.6 mmol) and again degassed for 2 min. The reaction mixture was stirred at 150 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford methyl 4-cyano-5-fluoro-2-methoxybenzoate **345** (5.5 g, 75%) as a brown solid. TLC: 25% EtOAc/Heptane (R_f: 0.4). LCMS calculated for $\text{C}_{10}\text{H}_8\text{FNO}_3$: 209.05; Found: 209.8 (M+1)

[2473] Synthesis of 2-fluoro-4-(hydroxymethyl)-5-methoxybenzonitrile (346)

[2474] To a stirred solution of compound **345** (6 g, 28.685 mmol) in THF (60 mL) was added 2M LiBH_4 in THF (43 mL, 43.027 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **346** (3.75 g, 70.3%) as a white solid. TLC: 40% EtOAc/Heptane, (R_f: 0.45). ^1H NMR (401 MHz, $\text{DMSO}-d_6$) δ = 7.46 (d, J = 5.1 Hz, 1H), 7.40 (d, J = 9.8 Hz, 1H), 5.49 (t, J = 5.5 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 3.83 (s, 3H).

[2475] Synthesis of 4-cyano-5-fluoro-2-methoxybenzyl methanesulfonate (347)

[2476] To a stirred solution of compound **346** (3 g, 16.56 mmol) in DCM (30 mL) were added MsCl (1.54 mL, 19.872 mmol) and Et_3N (4.65 mL, 33.120 mmol) at 0 °C. Then reaction mixture was warm to room temperature and stirred for 2h at room temperature. After completion, the mixture was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford title compound **347** (4 g, 48.17 %) as a white solid. TLC: 60% EtOAc/Heptane, (R_f: 0.7). ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ = 7.12 - 6.96 (m, 2H), 4.63 (s, 2H), 3.92 (s, 3H), 3.12 (s, 3H)

[2477] Synthesis of tert-butyl ((1-(4-cyano-5-fluoro-2-methoxybenzyl)-1H-pyrazol-4-yl)methyl)carbamate (348)

[2478] To a stirred solution of compound **347** (4 g, 15.429 mmol) in CH_3CN (40 mL) were added Cs_2CO_3 (15 g, 46.287 mmol) and compound **19** (3.65 g, 18.515 mmol) at 0 °C. The reaction mixture stirred at 70 °C for 2 h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title

compound **348** (2.5 g, 37%) as a pale-yellow liquid. TLC: 60% EtOAc/Heptane, (R_f: 0.6).

LCMS calculated for C₁₈H₂₁N₄O₃: 360.16; Found: 361.1 (M+1)

[2479] Synthesis of tert-butyl ((1-((3-amino-5-methoxybenzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (349)

[2480] To a stirred solution of compound **348** (2 g, 5.549 mmol) in DMF (20 mL) were added acetohydroxamic acid (1.7 g, 22.20 mmol) and K₂CO₃ (4.6 g, 33.30 mmol). The reaction mixture was stirred at 60 °C for 16 h. After completion, the mixture was quenched with cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **349** (1.2 g, 52%) as an off white solid. LCMS calculated for C₁₈H₂₃N₅O₄: 373.18; Found: 374.1 (M+1).

[2481] Synthesis of tert-butyl ((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (350)

[2482] To a stirred solution of compound **349** (0.6 g, 1.607 mmol) in THF (6 mL) were added KOtBu in THF (4 mL) and 2-methoxybenzenesulfonyl chloride (0.59 g, 2.892 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion, the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **350** (0.4 g, 33.47%) as an off white solid. LCMS calculated for C₂₅H₂₉N₅O₇S: 543.18; Found: 544.4 (M+1).

[2483] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-methoxybenzo[d]isoxazol-3-yl)-2-methoxybenzenesulfonamide hydrochloride (351)

[2484] To a stirred solution of compound **350** (0.4 g, 0.735 mmol) in DCM (4 mL) was added 4M HCl in 1,4-Dioxane (4 mL, 16 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion, the mixture was concentrated, triturated with Et₂O and dried under reduced pressure to afford title compound **351** (0.3 g, 85.65%) as a yellow solid. LCMS calculated for C₂₀H₂₁N₅O₅S: 443.13; Found: 442.8 (M-1).

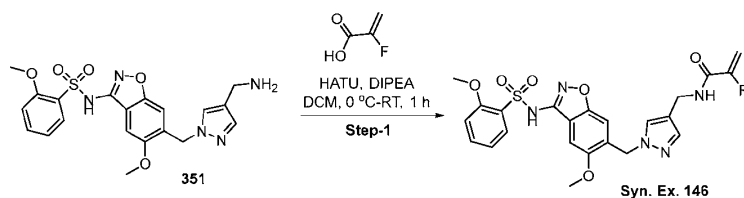
[2485] Synthesis of methyl ((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 145)

[2486] To a stirred solution compound **351** (0.12 g, 0.271 mmol) in DCM (2 mL) were added Et₃N (0.117 mL, 0.813 mmol) and ClCO₂Me (0.025 mL, 0.325 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. After completion (monitored by TLC), the

mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate **Syn. Ex. 145** (20 mg, 14.68%) as a white solid.

EXAMPLE 146

[2487] **Scheme 99: Synthesis 2-fluoro-N-((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)acrylamide (Syn. Ex. 146)**

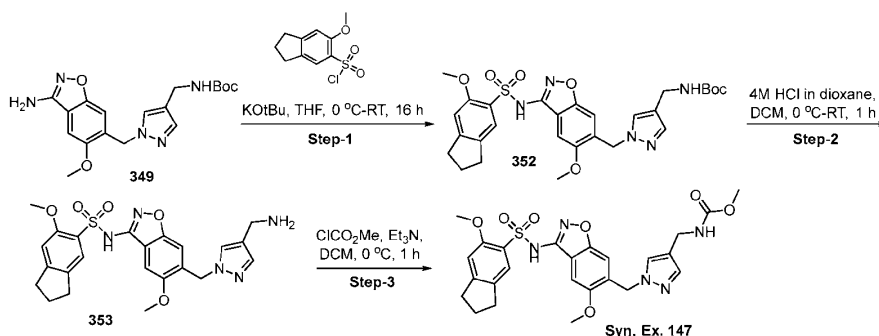


[2488] To a stirred solution of compound **351** (0.1 g, 0.225 mmol) in DCM (4 mL) were added DIPEA (0.117 mL, 0.6764 mmol), HATU (0.13 g, 0.338 mmol) and 2-fluoroacrylic acid (**2**) (0.024 g, 0.2706 mmol). The reaction mixture was stirred at room temperature for 1 h. After completion, the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford 2-fluoro-N-((1-((5-methoxy-3-((2-methoxyphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl) acrylamide **Syn. Ex. 146** (35 mg, 29.84%) as an off white solid.

EXAMPLE 147

[2489] **Scheme 100: Synthesis of methyl ((1-((5-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-**

yl)methyl)carbamate (Syn. Ex. 147)



[2490] Synthesis of tert-butyl ((1-((5-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (352)

[2491] To a stirred solution of compound **349** (0.3 g, 0.803 mmol) in THF (4 mL) were added 1M KOtBu in THF (2 mL, 3.214 mmol) and 6-methoxy-2,3-dihydro-1H-indene-5-sulfonyl chloride (0.35 g, 1.446 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion (monitored by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by combi-flash chromatography to afford title compound **352** (0.15 g, 27.73%) as an off white solid. LCMS calculated for C₂₈H₃₃N₅O₇S: 583.21; Found: 584.1 (M+1).

[2492] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-methoxybenzo[d]isoxazol-3-yl)-6-methoxy-2,3-dihydro-1H-indene-5-sulfonamide hydrochloride (353)

[2493] To a stirred solution of compound **352** (0.12 g, 0.2056 mmol) in DCM (2 mL) was added 4M HCl in 1,4-Dioxane (1.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the mixture was concentrated under reduced pressure, triturated with Et₂O and concentrated under reduced pressure to afford title compound **353** (80 mg, 73.49%) as a pale yellow solid. LCMS calculated for C₂₃H₂₅N₅O₅S: 483.16; Found: 482.1 (M-1)

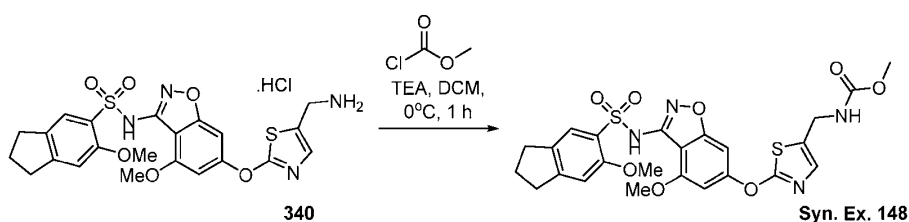
[2494] Synthesis of methyl ((1-((5-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn. Ex. 147)

[2495] To a stirred solution compound **353** (0.07 g, 0.1448 mmol) in DCM (4 mL) were added Et₃N (0.062 mL, 0.4343 mmol) and ClCO₂Me (0.0135 mL, 0.1737 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. After completion (monitored by TLC), the

mixture was quenched with ice-cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by prep. HPLC to afford methyl ((1-((5-methoxy-3-((6-methoxy-2,3-dihydro-1H-indene)-5-sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate **Syn. Ex. 147** (10 mg, 12.55%) as a white solid.

EXAMPLE 148

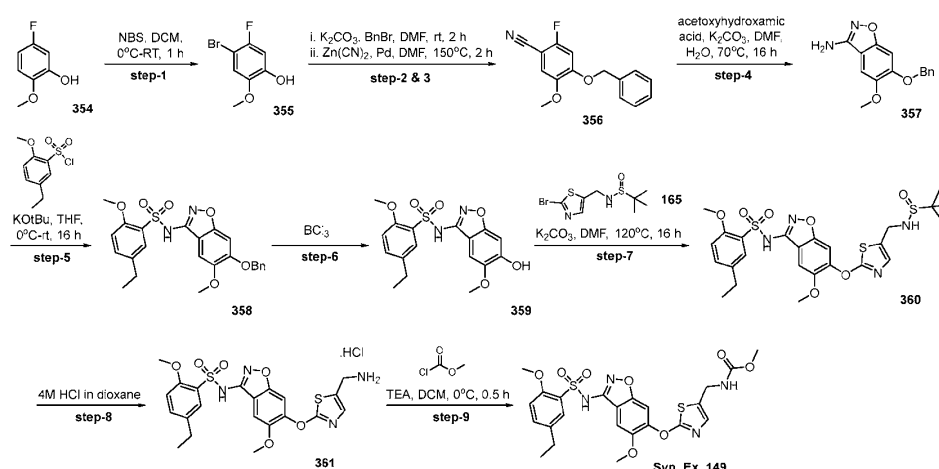
[2496] **Scheme 101: Synthesis of N-[[2-[[4-methoxy-3-[(6-methoxyindan-5-yl)sulfonylamino]-1,2-benzoxazol-6-yl]oxy]thiazol-5-yl]methyl]carbamate (Syn. Ex. 148)**



[2497] To a stirred solution of compound **340** (67 mg, 0.133 mmol) in DCM (2 mL) was added Triethylamine (0.052 mL, 0.399 mmol) and methyl carbonochloridate (0.013 g, 0.1466 mmol) at 0°C and was stirred for 30 min. After completion (monitored by TLC), reaction mixture was quenched with ice cold water and extracted with DCM. Combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by prep-HPLC to afford N-[[2-[[4-methoxy-3-[(6-methoxyindan-5-yl)sulfonylamino]-1,2-benzoxazol-6-yl]oxy]thiazol-5-yl]methyl]carbamate (**Syn. Ex. 148**; 11 mg, 0.019 mmol, 14.68% yield) as an off white solid.

EXAMPLE 149

Scheme 102: Synthesis of methyl ((2-((3-((5-ethyl-2-methoxyphenyl)sulfonamido)-5-methoxybenzo[d]isoxazol-6-yl)oxy)thiazol-5-yl)methyl)carbamate (Syn. Ex. 149)



[2498] Synthesis of 4-bromo-5-fluoro-2-methoxyphenol (355)

[2499] To a stirred solution of compound **354** (10.0 g, 70.4 mmol) in DCM (120 mL) was added NBS (12.53 g, 70.4 mmol, 98 mass%) portion wise over 10 min. The reaction mixture continued to stir at room temperature for 1h. After completion (monitored by TLC), the mixture was quenched with ice cold water and was extracted with DCM. The combined organic layer was washed with brine solution and was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound purified by combi flash to afford title compound **355** (13.3 g, 38.5 mmol, 54.7% Yield) as a white solid. LCMS calculated for C₇H₆BrFO₂: 221.02; Found: 220.8 (M-1). Regiochemistry of bromine addition was confirmed by NMR.

[2500] Synthesis of 1-benzyloxy-4-bromo-5-fluoro-2-methoxy-benzene (356)

[2501] To a stirred solution of compound **355** (13.2 g, 59.7 mmol) in acetonitrile (150 mL) was added potassium carbonate (24.8 g, 179 mmol) and benzyl bromide (11.7 g, 65.7 mmol) at 0°C. The reaction was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice cold water and was extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated. The crude was purified by combi flash to afford title compound (9.1 g, 29 mmol, 48%) as a white solid. LCMS calculated for C₁₅H₁₂FNO₂: 257.085; Found: 258.10 (M+1). This intermediate (5.0 g, 16 mmol) was dissolved in DMF (50 mL) and zinc cyanide (24 mmol) was added. The reaction was purged with nitrogen for 10 min followed by addition of Xantphos (0.96 g, 1.6 mmol) and Pd₂(dba)₃ (0.74 g, 0.80 mmol). The reaction mixture was stirred at 140°C for 16h. After completion (monitored by LCMS), the mixture quenched with ice cold water and was extracted with ethyl acetate. The combined

organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound purified by combi flash to afford title compound **356** (1.6 g, 5.3 mmol, 33%) as a brown solid. LCMS calculated for C₁₅H₁₂FNO₂: 257.3; Found: 256.0 (M-1).

[2502] Synthesis of 6-benzyloxy-5-methoxy-1,2-benzoxazol-3-amine (357)

[2503] To a solution of compound **356** (1.60 g, 6.22 mmol) in DMF (35 mL) was added acetohydroxamic acid (1.43 g, 18.7 mmol) and potassium carbonate (3.44 g, 24.9 mmol). The reaction mixture was stirred at 70°C for 16h. After completion, the mixture was quenched with ice-cold water and extracted with ethyl acetate. Combined organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated. The crude compound was triturated with diethyl ether to afford title compound **357** (1.0 g, 3.3 mmol, 53% Yield) as a white solid. LCMS calculated for C₁₅H₁₄N₂O₃: 270.3; Found: 271.1 (M+1).

[2504] Synthesis of ~{N}-(6-benzyloxy-5-methoxy-1,2-benzoxazol-3-yl)-5-ethyl-2-methoxy-benzenesulfonamide (358)

[2505] To a stirred solution of compound **357** in THF (15 mL) was added 1M solution of potassium tert-butoxide in THF (15.0 mL, 15.0 mmol) at 0°C and stirred for 10 min. followed by addition of 5-ethyl-2-methoxy-benzenesulfonyl chloride (1.76 g, 7.49 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 16h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with ethyl acetate. Combined organic layer was washed with brine solution, dried over sodium sulphate filtered and concentrated under reduced pressure. The crude was purified by combi flash to afford title compound **358** (1.2 g, 2.3 mmol, 46% Yield) as a brown solid. LCMS calculated for C₂₄H₂₄N₂O₆S: 468.5; Found: 469.3 (M+1)

[2506] Synthesis of 5-ethyl~{N}-(6-hydroxy-5-methoxy-1,2-benzoxazol-3-yl)-2-methoxy-benzenesulfonamide (359)

[2507] To a stirred solution of compound **358** (1.75 g, 3.74 mmol) in DCM (50.00 mL) was added 1M boron trichloride solution in toluene (26 mL, 26.1 mmol) at -78°C. The reaction mixture was stirred at -78°C for 2h. After completion (monitored by TLC), the mixture was quenched with ice-cold sodium bicarbonate solution and extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was triturated with diethyl ether to afford title compound **359** (1.1 g, 2.8 mmol, 74% Yield) as a brown solid. LCMS calculated for C₁₇H₁₈N₂O₆S: 378.4; Found: 379.1 (M+1)

[2508] **Synthesis of ~{N}-[6-[5-[(~{tert}-butylsulfinylamino)methyl]thiazol-2-yl]oxy-5-methoxy-1,2-benzoxazol-3-yl]-5-ethyl-2-methoxy-benzenesulfonamide (360)**

[2509] To a stirred solution of compound **359** (500 mg, 1.321 mmol) in DMF (5 mL) was added potassium carbonate (0.369 gr, 2.643 mmol) and compound **165** (0.589 gm, 1.982 mmol) at room temperature. The reaction mixture was stirred at 120°C for 24h. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by combi flash to afford title compound **360** (100 mg, 0.135 mmol, 10.22%) as a brown solid. LCMS calculated for C₂₅H₃₀N₄O₇S₃: 594.7; Found: 595.5 (M+1).

[2510] **Synthesis of ~{N}-[6-[5-(aminomethyl)thiazol-2-yl]oxy-5-methoxy-1,2-benzoxazol-3-yl]-5-ethyl-2-methoxy-benzenesulfonamide (361)**

[2511] To a stirred solution of compound **360** (100 mg, 0.1682 mmol) in DCM (5 mL) was added 4M HCl in dioxane (0.21 mL, 0.8408 mmol) at 0°C. Then reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the reaction was concentrated and triturated with diethyl ether to afford title compound **361** (82 mg, 0.1549 mmol, 92.11% Y) as a brown solid. LCMS calculated for C₂₁H₂₂N₄O₆S₂: 490.6; Found: 489.0 (M-1).

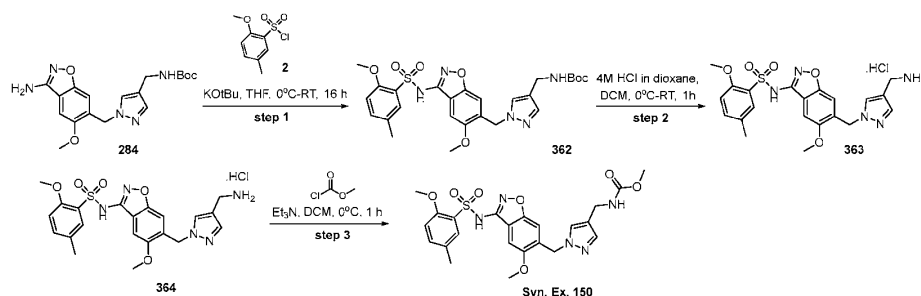
[2512] **Synthesis of methyl ~{N}-[[2-[[3-[(5-ethyl-2-methoxy-phenyl)sulfonylamino]-5-methoxy-1,2-benzoxazol-6-yl]oxy]thiazol-5-yl]methyl]carbamate (Syn. Ex. 149)**

[2513] To a stirred solution of compound **361** (80 mg, 0.15 mmol) in DCM (4 mL) was added triethylamine (0.064 mL, 0.455 mmol) in (0.2 mL of DCM) and methyl carbonochloridate (0.0129 mL, 0.166 mmol) in (0.2 mL of DCM) simultaneously while maintaining (pH~7-8) at 0°C. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by prep-HPLC purification to afford title compound (**Syn. Ex. 149**; 21 mg, 0.037 mmol, 24.67%) as an off white solid.

EXAMPLE 150

[2514] **Scheme 103: Synthesis of methyl-{N}-[[1-[[5-methoxy-3-[(2-methoxy-5-methyl-phenyl)sulfonylamino]-1,2-benzoxazol-6-yl]methyl]pyrazol-4-yl] methyl]carbamate**

(Syn. Ex. 150)



[2515] Synthesis of tert-butyl ((1-((5-methoxy-3-((2-methoxy-5-methylphenyl)sulfonamido)benzo[d]isoxazol-6-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (362)

[2516] To a stirred solution of compound **284** (200 mg, 0.535 mmol) in THF (4 mL) was added 1.6M potassium tert-butoxide in THF (1.0 mL, 1.607 mmol) at 0°C. The reaction was stirred for 5 min followed by addition of 2-methoxy-5-methylbenzenesulfonyl chloride (200 mg, 0.910 mmol) at 0°C. The reaction mixture was stirred at RT for 16 h. After completion (monitored by TLC), the mixture was quenched with aqueous solution of citric acid and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound **362** (220 mg, 0.211 mmol, 39.53%) as pale yellow solid. LCMS calculated for C₂₆H₃₁N₅O₇S: 557.6; Found: 558.0 (M+1).

[2517] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-methoxybenzo[d]isoxazol-3-yl)-2-methoxy-5-methylbenzenesulfonamide (363)

[2518] To a stirred solution of compound **362** (200 mg, 0.358 mmol) in DCM (2 mL) was added 4M HCl in 1,4-dioxane (2 mL, 8 mmol). The reaction mixture was stirred at room temperature for 1h. After completion (monitored by TLC), then reaction mixture was concentrated under reduced pressure. The crude compound was triturated with diethyl ether to afford title compound **363** (220 mg, 0.270 mmol, 75.48% Yield) as a brown solid. LCMS calculated for C₂₁H₂₃N₅O₅S: 457.5; Found: 456.1 (M-1).

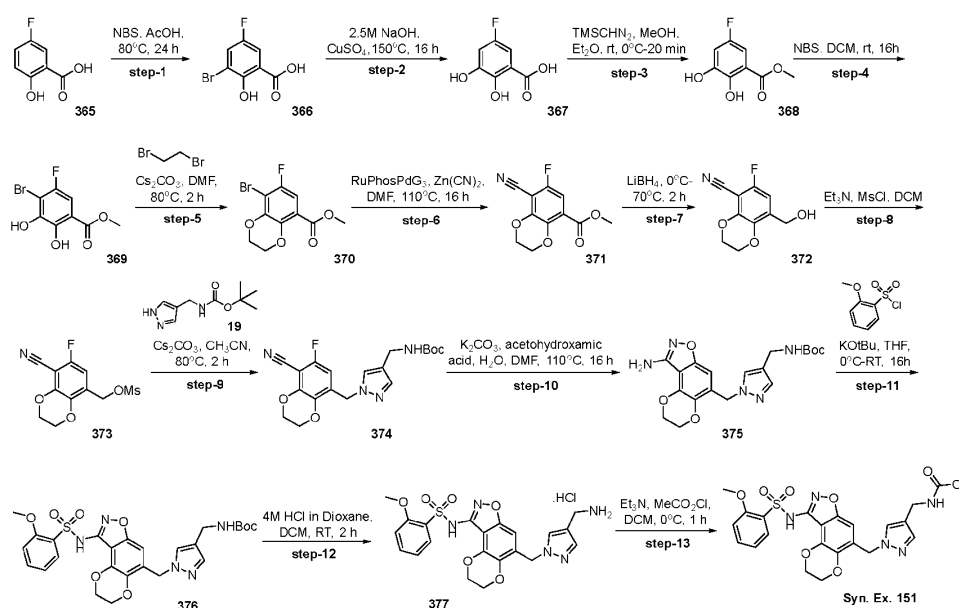
[2519] Synthesis of N-(6-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-5-methoxybenzo[d]isoxazol-3-yl)-2-methoxy-5-methylbenzenesulfonamide (Syn. Ex. 150)

[2520] To a solution of compound **363** (150 mg, 0.3279 mmol) in DCM (5 mL) was added triethylamine (0.141 mL, 0.983 mmol) in 0.3 mL of DCM and methyl carbonochloridate (0.0381 mL, 0.491 mmol) in (0.3 mL of DCM) was added simultaneously while maintaining (pH~7-8) at 0°C. The reaction was stirred for 10 min. After completion (monitored by TLC),

the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by prep-HPLC purification to afford title compound (**Syn. Ex. 150**; 8 mg, 0.0147 mmol, 4.51%) as an off-white solid.

EXAMPLE 151

[2521] **Scheme 104: Synthesis of methyl ((1-((9-((2-methoxyphenyl)sulfonamido)-2,3-dihydro-[1,4]dioxino[2',3':5,6]benzo[1,2-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (**Syn. Ex. 151**)**



[2522] **Synthesis of 3-bromo-5-fluoro-2-hydroxy-benzoic acid (366)**

[2523] To a stirred solution of compound **365** (30.0 g, 192 mmol) in acetic acid (300 mL) was added N-bromosuccinimide (34.9 g, 192 mmol) at room temperature. The reaction mixture was stirred at 80°C for 24h. After completion, the mixture was quenched with ice cold water and was extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude was triturated with 2% EA/Heptane to afford title compound **366** (30 g, 127.65 mmol, 66.4% Yield) as a brown solid. LCMS calculated for C₇H₄BrFO₃: 235.01; Found: 232.8 (M-2).

[2524] **Synthesis of 5-fluoro-2,3-dihydroxy-benzoic acid (367)**

[2525] To a solution of 2.5M sodium hydroxide in H₂O (210 mL, 521 mmol) was added copper (II) sulfate (0.238g, 1.49 mmol). The mixture was stirred at room temperature for 1h, then filtered. Compound **366** (17.5 g, 74.5 mmol) was added to the filtrate. The reaction mixture was stirred at 150 °C for 16h. After completion, the reaction mixture was cooled and acidified with 2.0 M HCl to pH < 2, then diluted with H₂O (500 mL) and was extracted with Ethyl acetate. The combined organic layer was washed with brine solution and dried over sodium sulphate filtered and concentrated under reduced pressure. The crude compound was triturated with 5% EA/Heptane to afford title compound **367** (9.2 g, 48 mmol, 64.0% Yield) as a brown solid. LCMS calculated for C₇H₅FO₄: 172.11; Found: 170.9 (M-1).

[2526] **Synthesis of 5-fluoro-2,3-dihydroxy-benzoic acid (368)**

[2527] To a stirred solution of compound **367** (5.0 g, 29 mmol) in methanol (50 mL) and diethyl ether (20 mL) was added 2M (trimethylsilyl)diazomethane in hexanes (38 mL, 76 mmol) drop wise over 10 min at room temperature. The reaction was stirred at room temperature for 20 min. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The crude compound purified by combi flash to afford title compound **368** (3.74 g, 19.6 mmol, 68% Yield) as a brown solid. LCMS calculated for C₈H₇FO₄: 186.14; Found: 185.0 (M-1).

[2528] **Synthesis of methyl 4-bromo-5-fluoro-2,3-dihydroxy-benzoate (369)**

[2529] To a stirred solution of compound **368** (5.0 g, 27 mmol) in DCM (150 mL) was added N-bromosuccinimide (5.9 g, 32 mmol) at 0°C portion wise over 5 min. The reaction mixture was stirred at room temperature for 16h. After completion (monitored by TLC), the mixture was quenched with ice cold water and extracted with DCM. The combined organic layer was washed with brine solution and dried over sodium sulphate filtered and concentrated under reduced pressure. The crude compound purified by combi flash to afford title compound **369** (3.2 g, 9.9 mmol, 37% Yield) as a brown solid. LCMS calculated for C₈H₆BrFO₄: 265.03; Found: 266.1 (M+H).

[2530] **Synthesis of methyl 5-bromo-6-fluoro-2,3-dihydro-1,4-benzodioxine-8-carboxylate (370)**

[2531] To a stirred solution of compound **369** (2.5 g, 9.4 mmol) in N,N-dimethylformamide (25.00 mL) was added cesium carbonate (6.2 g, 19 mmol) and 1,2-dibromoethane (1.3 mL, 15 mmol). The reaction mixture was stirred at 80°C for 2h. After completion (monitored by TLC), the mixture quenched with ice cold water and stirred for 10 min to afford a solid. The solid was filtered to afford title compound **370** (2.3 g, 7.0 mmol,

75% Yield) as a brown solid. LCMS calculated for C₁₀H₈BrFO₄: 291.07; Found: 293.2 (M+2).

[2532] Synthesis of methyl 5-cyano-6-fluoro-2,3-dihydro-1,4-benzodioxine-8-carboxylate (371)

[2533] To a stirred solution of compound **370** (3.00 g, 10.3 mmol) in N,N-dimethylformamide (50.00 mL) was added zinc cyanide (3.09 g, 25.8 mmol) and RuPhos Pd G3 (1.36, 1.55 mmol). The solution was purged with nitrogen for 3 min. The reaction mixture was stirred at 110°C for 16h. After completion (monitored by TLC), the reaction was quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound purified by combi flash to afford title compound **371** (1.50 g, 6.32 mmol, 61.4% Yield) as a brown solid. LCMS calculated for C₁₁H₈FN₂O₄: 237.044 found: 238.1 (M+1).

[2534] Synthesis of 6-fluoro-8-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxine-5-carbonitrile (372)

[2535] To a stirred solution of compound **371** (1.5 g, 6.3 mmol) in tetrahydrofuran (20 mL) was added 1M lithium borohydride in THF (13 mL, 13 mmol) at 0°C. The reaction mixture was stirred at 65°C for 2h. After completion (monitored by TLC), the reaction was quenched with sat. ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford title compound **372** (1.3 g, 5.2 mmol, 83% Yield) as a white solid. LCMS calculated for C₁₀H₈FN₂O₃: 209.049 found 210.2 (M+H).

[2536] Synthesis of (5-cyano-6-fluoro-2,3-dihydro-1,4-benzodioxin-8-yl)methyl methane sulfonate (373)

[2537] To a stirred solution of compound **372** (1.3 g, 6.2 mmol) in DCM (30 mL) was added triethylamine (4.4 mL, 31 mmol) and methanesulfonyl chloride (0.98 mL, 12 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), the reaction was quenched with ice cold water and extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford title compound **373** (1.3 g, 3.4 mmol, 55% Yield) as a brown semi solid. LCMS calculated for C₁₁H₁₀FN₂O₅S: 287.026 found 288.2 (M+H).

[2538] Synthesis of tert-butyl ((1-((8-cyano-7-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (374)

[2539] To a stirred solution compound **373** (1.3 g, 4.5 mmol) in acetonitrile (15.00 mL) was added cesium carbonate (3.0 g, 9.0 mmol) and stirred for 5 min. Compound (**10**) (1.3 g, 6.8 mmol) was added at room temperature. The reaction was stirred at 70°C for 3h. After completion (monitored by TLC), the reaction was concentrated under reduced pressure, quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by combi flash to afford title compound **374** (460 mg, 1.03 mmol, 23% Yield) as a brown gummy liquid. LCMS calculated for C₁₉H₂₁FN₄O₄: 388.4; Found: 389.0 (M+1).

[2540] **Synthesis of tert-butyl ((1-((9-amino-2,3-dihydro-[1,4]dioxino[2',3':5,6]benzo[1,2-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (375)**

[2541] To a stirred solution of compound **374** (260.00 mg, 0.669 mmol) in N,N-dimethylformamide (5 mL) was added potassium carbonate (555 mg, 4.016 mmol), water (0.7 mL, 40 mmol) and acetoxy hydroxamic acid (150.8 mg, 2.008 mmol). The reaction mixture was stirred at 110°C for 16h. After completion (monitored by LCMS), the reaction was quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by combi flash to afford title compound (**375**) (150.00 mg, 0.32 mmol, 48.10% Yield) as a brown solid. LCMS calculated for C₁₉H₂₃N₅O₅: 401.4; Found: 402.0 (M+1).

[2542] **Synthesis of tert-butyl ((1-((9-((2-methoxyphenyl)sulfonamido)-2,3-dihydro-[1,4]dioxino[2',3':5,6]benzo[1,2-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (376)**

[2543] To a stirred solution of compound **375** (225 mg, 0.5605 mmol) in THF (5 mL) was added 1.6 M potassium tert-butoxide in THF (1.1 mL, 1.682 mmol) at 0°C. The reaction was stirred for 5 min followed by addition of 2-methoxybenzenesulfonyl chloride (173.8 mg, 0.8408 mmol) at 0°C. The reaction was stirred at room temperature for 16h. After completion (monitored by LCMS), the reaction was quenched with ice cold water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by combi flash to afford title compound **376** (160 mg, 0.2799 mmol, 49.94% Yield) as a brown solid. LCMS calculated for C₂₆H₂₉N₅O₈S: 571.6; Found: 572.0 (M+1).

[2544] Synthesis of N-(5-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)-2,3-dihydro-[1,4]dioxino[2',3':5,6]benzo[1,2-d]isoxazol-9-yl)-2-methoxybenzenesulfonamide.HCl (377)

[2545] To a stirred solution of compound **376** (80.00 mg, 0.1400 mmol) in DCM (2.0 mL) was added 4M hydrochloric acid in dioxane (0.17 mL, 0.6998 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2h. After completion (monitored by TLC), reaction was concentrated under reduced pressure. The crude compound was triturated with diethyl ether to afford title compound **377** (68.00 mg, 0.1370 mmol, 97.89% Yield) as a brown solid. LCMS calculated for C₂₁H₂₁N₅O₆S: 471.5; Found: 470.0 (M-1).

[2546] Synthesis methyl ((1-((9-((2-methoxyphenyl)sulfonamido)-2,3-dihydro-[1,4]dioxino[2',3':5,6]benzo[1,2-d]isoxazol-5-yl)methyl)-1H-pyrazol-4-yl)methyl)carbamate (Syn.Ex.151)

[2547] To a stirred solution of **377** (66 mg, 0.1400 mmol) in DCM (2 mL) was added Triethylamine (0.059 mL, 0.419 mmol) in dichloromethane (0.2 mL) and methyl carbonochloridate (0.012 mL, 0.154 mmol) in dichloromethane (0.2 mL) simultaneously while maintaining (pH~7-8) at 0°C. The reaction was stirred for 30 min. at 0°C. After completion (monitored by TLC), the mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was washed with brine solution and was dried over sodium sulphate, filtered and concentrated under reduced pressure and purified by preparative HPLC to afford **Syn. Ex. 151** (28 mg, 0.139 mmol, 38% yield).

[2548] Table 1. Analytical data for compounds provided herein.

Compound	Mass Spec. Found (m/z)/ Mass Spec. Calculated	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆ , unless otherwise stated)
Syn. Ex. 1	542.1 (M+1)/ 541.08 for C ₂₄ H ₂₀ CIN ₅ O ₆ S	δ 9.57 (s, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.38 - 7.31 (m, 1H), 7.27 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.02 (s, 3H), 3.79 (s, 6H), 3.61 (br d, J = 2.4 Hz, 3H), 3.29 - 3.23 (m, 3H), 3.20 (br s, 2H), 2.40 - 2.33 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H).
Syn. Ex. 2	542.1 (M+1)/ 541.08 for C ₂₄ H ₂₀ CIN ₅ O ₆ S	δ 11.36 - 10.26 (m, 1H), 7.82 - 7.56 (m, 3H), 7.21 (br s, 1H), 6.97 - 6.68 (m, 2H), 5.41 (br s, 2H), 4.71 (br s, 2H), 4.56 (br d, J = 5.6 Hz, 1H), 4.43 (br s, 2H), 4.01 - 3.72 (m, 6H).
Syn. Ex. 3	512.1 (M+1)/ 511.15 for C ₂₄ H ₂₅ N ₅ O ₆ S	δ 10.14 (s, 1H), 7.80 (br d, J = 6.8 Hz, 1H), 7.62 (br t, J = 7.6 Hz, 1H), 7.34 (d, J = 3.0 Hz, 1H), 7.19 (br d, J = 8.1 Hz, 1H), 7.09 (br t, J = 7.4 Hz, 1H), 6.90 (br d, J = 17.6 Hz, 1H), 6.77 (br d, J = 5.6 Hz, 1H), 5.38 (br d, J = 2.6 Hz, 2H), 4.63 - 4.46 (m, 2H), 4.34 (br d, J = 4.3 Hz, 2H), 3.84 (d, J = 4.9 Hz, 3H), 3.79 (d, J = 4.5 Hz, 3H), 2.38 - 2.21 (m, 2H), 1.00 (br t, J = 7.3 Hz, 3H).
Syn. Ex. 4	538.1 (M+1)/ 537.13 for C ₂₅ H ₂₃ N ₅ O ₇ S	δ 10.20 (s, 1H), 7.35 (d, J = 0.9 Hz, 1H), 7.31 (d, J = 3.1 Hz, 1H), 7.22 (dd, J = 0.7, 3.1 Hz, 1H), 7.21 - 7.18 (m, 1H), 7.16 (s, 1H), 7.13 (d, J = 0.7 Hz, 1H), 5.39 (d, J = 9.9 Hz, 2H), 4.77 (s, 1H), 4.65 (s, 1H), 4.57 (d, J = 4.2 Hz, 1H), 4.44 (s, 1H), 4.39 (s, 1H), 3.85 (d, J = 2.1 Hz, 3H), 3.74 (s, 3H), 3.73 (d, J = 0.6 Hz, 3H).
Syn. Ex. 5	538.28 (M+1)/ 537.13 for C ₂₅ H ₂₃ N ₅ O ₇ S	δ 10.19 (s, 1H), 7.76 (s, 1H), 7.30 (d, J = 3.1 Hz, 1H), 7.23 - 7.18 (m, 1H), 7.16 - 7.11 (m, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 5.42 (s, 2H), 4.71 (d, J = 1.5 Hz, 2H), 4.56 (d, J = 6.5 Hz, 1H), 4.42 (s, 2H), 3.85 (s, 3H), 3.74 (d, J = 4.2 Hz, 6H).
Syn. Ex. 6	522.0 (M+1)/ 521.10 for C ₂₁ H ₂₃ N ₅ O ₇ S ₂	δ 10.12 (s, 1H), 7.89 - 7.77 (m, 2H), 7.62 (br t, J = 7.1 Hz, 1H), 7.45 (s, 1H), 7.29 - 7.25 (m, 1H), 7.19 (br d, J

		= 8.1 Hz, 1H), 7.09 (br t, J = 7.7 Hz, 1H), 6.85 (s, 1H), 6.75 (s, 1H), 5.39 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.80 (d, J = 16.9 Hz, 6H), 2.82 (s, 3H).
Syn. Ex. 7	502.28 (M+1)/ 501.13 for C ₂₂ H ₂₃ N ₅ O ₇ S	δ 10.11 (s, 1H), 7.80 (dd, J = 1.7, 7.8 Hz, 1H), 7.71 (s, 1H), 7.65 - 7.59 (m, 1H), 7.43 (br s, 1H), 7.37 (s, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.52 (s, 3H).
Syn. Ex. 8	514.1 (M+1)/ 513.17 for C ₂₄ H ₂₇ N ₅ O ₆ S	δ 10.02 (br s, 1H), 8.25 - 7.98 (m, 1H), 7.72 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.53 - 7.42 (m, 1H), 7.37 (s, 1H), 7.10 (br d, J = 8.5 Hz, 1H), 6.92 - 6.71 (m, 2H), 5.36 (s, 2H), 4.06 (d, J = 5.5 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 2.60 (q, J = 7.5 Hz, 2H), 1.79 (s, 3H), 1.19 - 1.10 (m, 3H).
Syn. Ex. 9	564.1 (M+1)/ 563.18 for C ₂₈ H ₂₉ N ₅ O ₆ S	δ 10.03 (s, 1H), 7.61 (dd, J = 1.8, 8.3 Hz, 2H), 7.45 (br d, J = 6.1 Hz, 1H), 7.11 (br d, J = 8.3 Hz, 1H), 6.88 (br s, 1H), 6.74 (br s, 1H), 5.27 (s, 2H), 4.56 (s, 1H), 3.92 - 3.76 (m, 5H), 3.76 - 3.72 (m, 3H), 3.62 - 3.52 (m, 2H), 2.86 - 2.79 (m, 1H), 2.74 - 2.66 (m, 2H), 2.63 - 2.55 (m, 3H), 1.14 (t, J = 7.5 Hz, 3H).
Syn. Ex. 10	552.1 (M+1)/ 551.11 for C ₂₂ H ₂₅ N ₅ O ₈ S ₂	δ 9.83 - 9.70 (m, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H), 7.27 (t, J = 5.9 Hz, 1H), 6.83 (br s, 1H), 6.74 (br s, 1H), 6.66 - 6.60 (m, 2H), 5.39 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.81 (s, 3H).
Syn. Ex. 11	550.2 (M+1)/ 549.17 for C ₂₇ H ₂₇ N ₅ O ₆ S	δ 10.01 - 9.27 (m, 1H), 7.66 (s, 1H), 7.45 (br d, J = 8.6 Hz, 1H), 7.33 (s, 1H), 7.11 (br dd, J = 3.3, 8.4 Hz, 1H), 6.97 (s, 1H), 6.77 (br d, J = 4.4 Hz, 1H), 5.38 (br d, J = 8.8 Hz, 2H), 4.63 (br s, 2H), 4.38 (br d, J = 11.0 Hz, 2H), 3.88 (d, J = 4.2 Hz, 3H), 3.79 (d, J = 4.9 Hz, 3H), 2.62 (q, J = 7.6 Hz, 2H), 2.16 - 1.91 (m, 3H), 1.17 (t, J = 7.5 Hz, 3H).

Syn. Ex. 12	550.03(M+1)/ 549.17 for C27H27N5O6S	δ 10.03 (s, 1H), 7.74 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.57 - 7.42 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 5.41 (s, 2H), 4.67 (s, 2H), 4.39 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.60 (q, J = 7.7 Hz, 2H), 2.09 - 2.01 (m, 3H), 1.14 (t, J = 7.5 Hz, 3H).
Syn. Ex. 13	556.12 (M+1)/ 555.16 for C26H26FN5O6S	δ 9.48 (br s, 1H), 7.66 (s, 1H), 7.44 (br d, J = 8.3 Hz, 1H), 7.33 (br s, 1H), 7.11 (br d, J = 8.6 Hz, 1H), 6.95 (br s, 1H), 6.77 (s, 1H), 5.51 (br d, J = 3.5 Hz, 1H), 5.38 (s, 2H), 5.29 (br dd, J = 3.1, 17.3 Hz, 1H), 4.77 - 4.48 (m, 4H), 3.87 (s, 3H), 3.78 (s, 3H), 2.62 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H).
Syn. Ex. 14	544.66 (M+1)/ 543.16 for C25H26FN5O6S	δ 10.96 - 9.86 (m, 1H), 9.19 - 8.64 (m, 1H), 7.74 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.45 (br d, J = 6.4 Hz, 1H), 7.39 (s, 1H), 7.10 (br d, J = 8.6 Hz, 1H), 6.87 (br s, 1H), 6.73 (br s, 1H), 5.57 (d, J = 3.4 Hz, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.69 - 2.56 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 15	538.61 (M+1)/ 537.17 for C26H27N5O6S	δ 10.00 (br s, 1H), 8.77 (br t, J = 5.5 Hz, 1H), 7.71 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.36 (s, 1H), 7.20 - 7.02 (m, 1H), 6.84 (br s, 1H), 6.72 (br s, 1H), 5.36 (s, 2H), 4.09 (d, J = 5.8 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.67 - 2.57 (m, 2H), 1.93 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 16	544.44(M+1)/ 543.18 for C25H29N5O7S	δ 10.03 (s, 1H), 7.70 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.46 (dd, J = 2.1, 8.6 Hz, 1H), 7.42 - 7.32 (m, 2H), 7.11 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 3.99 (dd, J = 6.4, 13.4 Hz, 4H), 3.82 (s, 3H), 3.74 (s, 3H), 2.60 (q, J = 7.6 Hz, 2H), 1.13 (dt, J = 3.4, 7.3 Hz, 6H).
Syn. Ex. 17	530.4 (M+1)/ 529.16 for C24H27N5O7S	δ 10.01 (br s, 1H), 7.71 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.43 (br d, J = 5.0 Hz, 2H), 7.37 (s, 1H), 7.10 (br d, J = 7.5 Hz, 1H), 6.85 (br s, 1H), 6.74 (br s, 1H), 5.37 (s,

		2H), 4.01 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 2.59 (q, J = 7.4 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 18	594.71 (M+1)/ 593.16 for C ₂₅ H ₃₁ N ₅ O ₈ S ₂	δ 10.43 - 9.74 (m, 1H), 7.79 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.36 (t, J = 5.9 Hz, 1H), 7.10 (br d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 6.76 (s, 1H), 5.39 (s, 2H), 4.00 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.60 - 3.51 (m, 3H), 3.22 - 3.16 (m, 7H), 2.69 - 2.55 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 19	524.07 (M+1)/ 523.15 for C ₂₅ H ₂₅ N ₅ O ₆ S	δ 9.78 (br s, 1H), 9.03 (br t, J = 5.3 Hz, 1H), 7.74 (s, 1H), 7.54 (s, 1H), 7.38 (s, 1H), 6.99 (br s, 1H), 6.85 (br s, 1H), 6.74 (br s, 1H), 5.37 (s, 2H), 4.24 - 4.04 (m, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H).
Syn. Ex. 20	550.03 (M+1)/ 549.14 for C ₂₃ H ₂₇ N ₅ O ₇ S ₂	δ 9.79 (br s, 1H), 7.80 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.27 (t, J = 5.9 Hz, 1H), 6.99 (br s, 1H), 6.84 (br s, 1H), 6.75 (br s, 1H), 5.39 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.81 (s, 3H), 2.25 (s, 3H), 2.18 (s, 4H).
Syn. Ex. 21	544.31(M+1)/ 543.10 for C ₂₄ H ₂₂ CIN ₅ O ₆ S	δ 11.03 - 10.28 (m, 1H), 9.03 (br t, J = 5.8 Hz, 1H), 8.26 - 7.51 (m, 2H), 7.38 (s, 1H), 7.25 (br s, 1H), 6.88 (br s, 1H), 6.75 (s, 1H), 5.38 (s, 2H), 4.20 - 4.05 (m, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 2.38 (s, 3H).
Syn. Ex. 22	569.98 (M+1)/ 569.08 for C ₂₂ H ₂₄ CIN ₅ O ₇ S ₂	δ 10.47 (br s, 1H), 7.80 (s, 1H), 7.71 (s, 1H), 7.46 (s, 1H), 7.33 - 7.21 (m, 2H), 6.87 (br s, 1H), 6.75 (s, 1H), 5.40 (s, 2H), 4.02 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 2.82 (s, 3H), 2.38 (s, 3H).
Syn. Ex. 23	536.33 (M+1)/ 535.15 for C ₂₆ H ₂₅ N ₅ O ₆ S	δ 10.27 - 9.47 (m, 1H), 9.03 (br t, J = 5.4 Hz, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 6.75 (s, 1H), 5.37 (s, 2H), 4.18 - 4.04 (m, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 2.98 - 2.77 (m, 4H), 2.12 - 1.96 (m, 2H)
Syn. Ex. 24	562.00(M+1)/ 561.14 for C ₂₄ H ₂₇ N ₅ O ₇ S ₂	δ 9.76 (br s, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.45 (s, 1H), 7.27 (t, J = 6.0 Hz, 1H), 7.06 (br s, 1H), 6.89 - 6.72 (m,

		2H), 5.39 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 2.95 - 2.76 (m, 7H), 2.02 (quin, J = 7.4 Hz, 2H).
Syn. Ex. 25	542.2 (M+1)/ 541.16 for C ₂₅ H ₂₇ N ₅ O ₇ S	δ 9.75 (br s, 1H), 7.71 (s, 1H), 7.63 (s, 1H), 7.42 (br s, 1H), 7.37 (s, 1H), 7.06 (br s, 1H), 6.83 (br s, 1H), 6.74 (br s, 1H), 5.36 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 3.08 - 2.76 (m, 4H), 2.20 - 1.94 (m, 2H).
Syn. Ex. 26	533.22 (M+1)/ 532.12 for C ₂₅ H ₂₀ N ₆ O ₆ S	δ 10.89 (br s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.77 (s, 1H), 7.58 (br d, J = 7.9 Hz, 1H), 7.36 (s, 1H), 6.97 (d, J = 12.7 Hz, 1H), 6.79 (s, 1H), 5.40 (br d, J = 9.6 Hz, 2H), 4.88 - 4.78 (m, 1H), 4.65 (s, 1H), 4.57 (d, J = 4.4 Hz, 1H), 4.41 (br d, J = 19.7 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H).
Syn. Ex. 27	538.10 (M+1)/ 537.17 for C ₂₆ H ₂₇ N ₅ O ₆ S	δ 9.78 (s, 1H), 8.85 - 8.68 (t, 1H), 7.72 (s, 1H), 7.54 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.84 (s, 1H), 6.79 - 6.69 (s, 1H), 5.39 - 5.38 (s, 2H), 4.09 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.25 (s, 3H), 2.22 - 2.15 (m, 3H), 1.93 - 1.93 (s, 3H).
Syn. Ex. 28	544.30 (M+1) / 543.16 for C ₂₅ H ₂₆ FN ₅ O ₆ S	δ 9.78 (br s, 1H), 8.86 (br s, 1H), 7.74 (s, 1H), 7.54 (s, 1H), 7.39 (s, 1H), 6.97 (br s, 1H), 6.83 (br s, 1H), 6.71 (br s, 1H), 5.45 (s, 1H), 5.36 (s, 2H), 5.27 - 5.20 (m, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.85 (s, 3H), 3.73 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H).
Syn. Ex. 29	550.11 (M+1)/ 549.17 for C ₂₇ H ₂₇ N ₅ O ₆ S	δ 9.75 (s, 1H), 8.77 (br t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.36 (s, 1H), 7.07 (s, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 5.37 (s, 2H), 4.09 (d, J = 5.8 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 2.96 - 2.77 (m, 4H), 2.12 - 2.00 (m, 2H), 1.93 (s, 3H).
Syn. Ex. 30	556.08 (M+1) / 555.16 for C ₂₆ H ₂₆ FN ₅ O ₆ S	δ 9.75 (s, 1H), 8.86 (t, J = 5.3 Hz, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 7.39 (s, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 5.62 - 5.41 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.19 (d, J = 6.0 Hz, 2H), 3.86 (s,

		3H), 3.76 (s, 3H), 2.90 - 2.77 (m, 4H), 2.02 (t, J = 7.4 Hz, 2H).
Syn. Ex. 31	659.33 (M+1)/ 658.24 for C ₃₀ H ₃₈ N ₆ O ₉ S	δ 10.00 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.49 - 7.40 (m, 2H), 7.37 (s, 1H), 7.10 (br d, J = 7.8 Hz, 1H), 6.85 (br s, 2H), 6.74 (br s, 1H), 5.37 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.91 (br t, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.10 (br d, J = 5.5 Hz, 2H), 2.59 (q, J = 7.6 Hz, 2H), 1.36 (s, 9H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 32	559.85 (M+1) / 558.19 for C ₂₅ H ₃₀ N ₆ O ₇ S	δ 10.04 (s, 1H), 7.94 (br s, 3H), 7.74 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.40 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 6.78 (s, 1H), 5.38 (s, 2H), 4.12 (br t, J = 5.5 Hz, 2H), 4.08 - 4.01 (d, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.09 - 2.95 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 33	578.45 (M+1)/ 577.17 for C ₂₅ H ₃₁ N ₅ O ₇ S ₂	δ 10.09 (s, 1H), 7.90 - 7.74 (m, 2H), 7.64 (br d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.27 (t, J = 5.9 Hz, 1H), 7.11 (br d, J = 8.8 Hz, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 5.39 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 2.82 (s, 3H), 1.25 (s, 9H).
Syn. Ex. 34	560.35(M+1)/ 559.174 for C ₂₅ H ₂₉ N ₅ O ₈ S	δ 10.00 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.37 (s, 1H), 7.11 (br d, J = 8.4 Hz, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 4.68 (br t, J = 4.9 Hz, 1H), 4.01 (d, J = 5.9 Hz, 2H), 3.95 (br t, J = 5.1 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.52 (q, J = 5.1 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 35	560.31 (M+1)/ 559.12 for C ₂₅ H ₂₆ CIN ₅ O ₆ S	δ 10.01 (s, 1H), 8.75 (br t, J = 5.7 Hz, 1H), 7.75 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.52 - 7.42 (m, 1H), 7.40 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.88 (s, 1H), 6.73 (s, 1H), 6.31 (d, J = 1.9 Hz, 1H), 5.90 (d, J = 1.9 Hz, 1H), 5.37 (s, 2H), 4.18 (d, J = 5.9 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.60 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).

Syn. Ex. 36	592.34(M+1)/ 591.15 for C ₂₉ H ₂₆ FN ₅ O ₆ S	(δ 9.94 (s, 1H), 8.86 (br t, J = 5.4 Hz, 1H), 7.86 (dd, J = 1.6, 7.9 Hz, 1H), 7.75 (s, 1H), 7.64 - 7.50 (m, 1H), 7.40 (s, 1H), 7.36 (br s, 2H), 7.25 - 7.17 (m, 4H), 7.09 (br t, J = 6.8 Hz, 1H), 6.82 (br s, 1H), 6.70 (br s, 1H), 5.57 (d, J = 3.4 Hz, 1H), 5.45 (d, J = 3.4 Hz, 1H), 5.36 (s, 2H), 5.29 - 5.24 (m, 2H), 4.19 (d, J = 5.9 Hz, 2H), 3.65 (s, 3H).
Syn. Ex. 37	598.39 (M+1)/ 597.13 for C ₂₇ H ₂₇ N ₅ O ₇ S ₂	δ 9.96 (br s, 1H), 7.86 (dd, J = 1.5, 7.9 Hz, 1H), 7.80 (s, 1H), 7.59 - 7.53 (m, 1H), 7.46 (s, 1H), 7.38 (br s, 2H), 7.28 (br t, J = 5.9 Hz, 1H), 7.24 - 7.19 (m, 4H), 7.08 (br s, 1H), 6.86 - 6.69 (m, 2H), 5.38 (s, 2H), 5.26 (br s, 2H), 4.02 (d, J = 5.9 Hz, 2H), 3.67 (br s, 3H), 2.81 (s, 3H).
Syn. Ex. 38	564.36 (M+1)/ 563.15 for C ₂₄ H ₂₉ N ₅ O ₇ S ₂	δ 10.04 (s, 1H), 7.80 (s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.50 (br d, J = 7.1 Hz, 1H), 7.45 (s, 1H), 7.27 (t, J = 5.9 Hz, 1H), 7.11 (br d, J = 8.4 Hz, 1H), 6.87 (br s, 1H), 6.75 (br s, 1H), 5.39 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 2.98 - 2.88 (m, 1H), 2.82 (s, 3H), 1.16 (d, J = 6.9 Hz, 6H).
Syn. Ex. 39	558.20 (M+1)/ 557.17 for C ₂₆ H ₂₈ FN ₅ O ₆ S	δ 10.04 (br s, 1H), 7.86 (s, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.45 (s, 2H), 7.09 (br d, J = 7.3 Hz, 1H), 6.86 (br s, 1H), 6.70 (br s, 1H), 5.39 (s, 2H), 5.24 (d, J = 3.9 Hz, 1H), 5.15 (d, J = 4.0 Hz, 1H), 4.37 (br s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.01 - 2.79 (m, 3H), 2.59 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 40	516.58 (M+1)/ 515.12 for C ₂₃ H ₂₂ FN ₅ O ₆ S	δ 10.13 (s, 1H), 8.87 (s, 1H), 7.80 (dd, J = 1.7, 7.9 Hz, 1H), 7.75 (s, 1H), 7.67 - 7.59 (m, 1H), 7.39 (s, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 5.60 - 5.43 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.7 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H).
Syn. Ex. 41	546.63 (M+1)/ 545.13 for C ₂₄ H ₂₄ FN ₅ O ₇ S	δ 10.19 (s, 1H), 8.87 (br t, J = 6.5 Hz, 1H), 7.75 (s, 1H), 7.39 (s, 1H), 7.30 (d, J = 3.1 Hz, 1H), 7.25 - 7.11 (m, 2H), 6.88 (s, 1H), 6.75 (s, 1H), 5.71 - 5.42 (m, 1H), 5.38

		(s, 2H), 5.23 (dd, J = 3.4, 15.7 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.73 (d, J = 8.9 Hz, 6H).
Syn. Ex. 42	526.52(M+1)/ 525.16 for C ₂₅ H ₂₇ N ₅ O ₆ S	δ 10.49 - 9.67 (m, 1H), 8.35 (br t, J = 5.3 Hz, 1H), 7.75 (s, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.40 (s, 1H), 7.14 - 7.08 (m, 1H), 6.87 (br d, J = 1.8 Hz, 1H), 6.75 (br s, 1H), 6.25 - 6.17 (m, 1H), 6.10 (d, J = 2.4 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 5.37 (s, 2H), 4.17 (d, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 43	569.80(M+1)/ 568.58 for C ₂₆ H ₂₅ FN ₆ O ₆ S	δ 10.48 (br s, 1H), 8.87 (br t, J = 5.4 Hz, 1H), 7.74 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.54 (br dd, J = 1.3, 5.9 Hz, 1H), 7.39 (s, 1H), 7.29 (br d, J = 5.0 Hz, 1H), 6.86 (br s, 1H), 6.73 (br s, 1H), 5.62 - 5.42 (m, 1H), 5.37 (s, 2H), 5.29 - 5.15 (m, 3H), 4.18 (d, J = 5.9 Hz, 2H), 3.81 (s, 3H), 2.74 - 2.59 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H).
Syn. Ex. 44	555.39 (M+1)/ 554.58 for C ₂₅ H ₂₆ N ₆ O ₇ S	δ 10.48 (br s, 1H), 7.88 - 7.65 (m, 2H), 7.61 - 7.54 (m, 1H), 7.43 (br s, 1H), 7.37 (s, 1H), 7.29 (br d, J = 7.5 Hz, 1H), 6.84 (br s, 1H), 6.73 (br s, 1H), 5.36 (s, 2H), 5.23 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.51 (s, 3H), 2.66 - 2.60 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H).
Syn. Ex. 45	587.37 (M+1)/ 586.60 for C ₂₆ H ₂₇ FN ₆ O ₇ S	δ 10.78 - 10.40 (m, 1H), 8.86 (br t, J = 5.4 Hz, 1H), 7.74 (s, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.59 - 7.51 (m, 1H), 7.48 (br d, J = 7.3 Hz, 1H), 7.39 (s, 1H), 7.33 - 7.24 (m, 1H), 7.13 - 7.07 (m, 1H), 6.93 - 6.85 (m, 1H), 6.77 - 6.67 (m, 1H), 5.57 (d, J = 3.4 Hz, 1H), 5.45 (d, J = 3.4 Hz, 1H), 5.35 (br s, 2H), 4.55 - 4.48 (m, 2H), 4.18 (d, J = 5.9 Hz, 2H), 3.78 (s, 3H), 2.59 (q, J = 7.8 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 46	540.65 (M+1)/ 539.56 for C ₂₅ H ₂₅ N ₅ O ₇ S	δ 9.77 (br s, 1H), 8.77 (br t, J = 5.8 Hz, 1H), 8.06 - 7.54 (m, 2H), 7.36 (s, 1H), 7.01 - 6.38 (m, 4H), 5.36 (s, 2H), 4.09 (d, J = 5.8 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 1.93 (s, 3H).

Syn. Ex. 47	546.29 (M+1)/ 545.59 for C ₂₅ H ₂₈ FN ₅ O ₆ S	δ 10.01 (s, 1H), 8.46 (br t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.45 (br d, J = 6.8 Hz, 1H), 7.38 (s, 1H), 7.10 (br d, J = 8.3 Hz, 1H), 6.85 (br s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 5.04 (q, J = 6.7 Hz, 1H), 4.13 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 1.43 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 47a	546.29 (M+1)/ 545.59 for C ₂₅ H ₂₈ FN ₅ O ₆ S	δ 10.01 (s, 1H), 8.46 (br t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.45 (br d, J = 6.8 Hz, 1H), 7.38 (s, 1H), 7.10 (br d, J = 8.3 Hz, 1H), 6.85 (br s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 5.04 (q, J = 6.7 Hz, 1H), 4.13 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 1.43 (d, J = 6.6 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).
Syn. Ex. 47b	546.29 (M+1)/ 545.59 for C ₂₅ H ₂₈ FN ₅ O ₆ S	δ 10.01 (s, 1H), 8.46 (br t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.45 (br d, J = 6.8 Hz, 1H), 7.38 (s, 1H), 7.10 (br d, J = 8.3 Hz, 1H), 6.85 (br s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 5.04 (q, J = 6.7 Hz, 1H), 4.13 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 1.43 (d, J = 6.6 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).
Syn. Ex. 48	601.83 (M+1)/ 600.20 for C ₂₇ H ₃₂ N ₆ O ₈ S	δ 10.02 (s, 1H), 7.91 (br s, 1H), 7.71 (s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.46 (br d, J = 6.7 Hz, 2H), 7.38 (s, 1H), 7.11 (d, J = 8.6 Hz, 1H), 6.86 (s, 1H), 6.75 (s, 1H), 5.37 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.93 (t, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.21 (q, J = 5.7 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.78 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 49	554.37(M+1)/ 553.59 for C ₂₆ H ₂₇ N ₅ O ₇ S	δ 10.03 (br s, 1H), 8.92 (br t, J = 5.7 Hz, 1H), 7.73 (s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.53 - 7.43 (m, 1H), 7.37 (s, 1H), 7.10 (br d, J = 8.3 Hz, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 4.19 (s, 2H), 4.11 (d, J = 5.9 Hz,

		3H), 3.82 (s, 3H), 3.74 (s, 3H), 2.60 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H).
Syn. Ex. 50	568.17 (M+1)/ 567.12 for C ₂₃ H ₂₃ F ₂ N ₅ O ₈ S	δ 10.85 - 9.97 (m, 1H), 7.74 (s, 1H), 7.54 - 7.38 (m, 3H), 7.32 - 7.03 (m, 3H), 6.77 (d, J = 8.5 Hz, 2H), 5.44 (s, 2H), 4.02 (d, J = 5.9 Hz, 2H), 3.75 (s, 6H), 3.52 (s, 3H).
Syn. Ex. 51	557.2 (M+1)/ 556.14 for C ₂₆ H ₂₅ FN ₄ O ₇ S	δ 10.05 (s, 1H), 9.10 (br t, J = 5.8 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 2.4, 8.4 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.54 - 7.45 (m, 1H), 7.13 (br d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.91 (br s, 1H), 6.65 (br s, 1H), 5.64 - 5.45 (m, 1H), 5.28 (dd, J = 3.4, 15.7 Hz, 1H), 4.34 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.64 - 2.57 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H).
Syn. Ex. 52	580.20(M+1)/ 579.14 for C ₂₅ H ₂₄ F ₃ N ₅ O ₆ S	δ 11.11 - 10.19 (m, 1H), 8.86 (br t, J = 5.8 Hz, 1H), 7.77 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.46 (br d, J = 7.6 Hz, 1H), 7.41 (s, 1H), 7.25 (br s, 2H), 7.11 (br d, J = 8.4 Hz, 1H), 7.01 (br s, 1H), 5.61 - 5.45 (m, 1H), 5.43 (s, 2H), 5.23 (dd, J = 3.4, 15.6 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.71 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 53	560.22(M+1)/ 559.13 for C ₂₅ H ₂₃ F ₂ N ₅ O ₆ S	δ 11.11 - 10.38 (m, 1H), 9.04 (br t, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.40 (s, 1H), 7.32 - 7.26 (m, 1H), 7.23 (br s, 1H), 7.11 (br d, J = 8.6 Hz, 1H), 7.02 (br s, 1H), 5.43 (s, 2H), 4.28 - 4.06 (m, 3H), 3.71 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 54	602.20 (M+1)/ 601.16 for C ₂₇ H ₂₈ FN ₅ O ₈ S	δ 9.59 (s, 1H), 9.26 - 8.68 (m, 1H), 7.74 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.54 - 7.42 (m, 1H), 7.38 (s, 1H), 7.09 - 7.01 (m, 1H), 6.88 (br s, 1H), 6.73 (br s, 1H), 5.59 - 5.42 (m, 1H), 5.36 (s, 2H), 5.23 (dd, J = 3.4, 15.7 Hz, 1H), 4.90 (br s, 2H), 4.18 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.52 (s, 3H), 2.64 - 2.58 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H).

Syn. Ex. 55	588.20 (M+1)/ 587.17 for C ₂₆ H ₂₉ N ₅ O ₉ S	δ = 9.59 (s, 1H), 7.70 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.42 (br s, 2H), 7.36 (s, 1H), 7.10 - 7.02 (m, 1H), 6.86 (br s, 1H), 6.74 (br s, 1H), 5.36 (s, 2H), 4.90 (br s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.85 (s, 3H), 3.51 (s, 6H), 2.64 - 2.58 (m, 2H), 1.15 (t, J = 7.5 Hz, 3H).
Syn. Ex. 56	543.20 (M+1)/ 542.15 for C ₂₅ H ₂₆ N ₄ O ₈ S	δ 10.05 (br s, 1H), 8.07 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 2.3, 8.4 Hz, 1H), 7.72 - 7.67 (m, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.46 (br d, J = 7.6 Hz, 1H), 7.12 (br d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.89 (br s, 1H), 6.63 (br s, 1H), 4.16 (br d, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.54 (s, 3H), 2.61 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 57	551.2(M+1)/ 550.15 for C ₂₇ H ₂₆ N ₄ O ₇ S	δ 10.05 (s, 1H), 9.01 (t, J = 6.0 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 2.4, 8.4 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.47 (br d, J = 6.1 Hz, 1H), 7.13 (br d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.90 (br s, 1H), 6.64 (br s, 1H), 4.24 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.61 (q, J = 7.5 Hz, 2H), 1.95 (s, 3H), 1.15 (t, J = 7.6 Hz, 3H).
Syn. Ex. 58	540.53(M+1)/ 539.15 for C ₂₅ H ₂₅ N ₅ O ₇ S	δ 10.18 (s, 1H), 8.78 (br t, J = 5.6 Hz, 1H), 7.72 (s, 1H), 7.37 (s, 1H), 7.30 (d, J = 3.2 Hz, 1H), 7.22 - 7.17 (m, 1H), 7.16 - 7.11 (m, 1H), 6.86 (br s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 4.09 (d, J = 5.7 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 1.93 (s, 3H).
Syn. Ex. 59	558.72(M+1)/ 557.17 for C ₂₆ H ₂₈ FN ₅ O ₆ S	δ 10.03 (s, 1H), 8.86 (br t, J = 5.8 Hz, 1H), 7.74 (s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.39 (s, 1H), 7.11 (br d, J = 8.5 Hz, 1H), 6.88 (s, 1H), 6.73 (s, 1H), 5.62 - 5.41 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 2.95 - 2.86 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H).

Syn. Ex. 60	546.58(M+1)/ 545.14 for C ₂₄ H ₂₄ FN ₅ O ₇ S	δ 9.77 (s, 1H), 8.86 (br t, J = 5.6 Hz, 1H), 8.10 - 7.51 (m, 2H), 7.39 (s, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 6.68 - 6.59 (m, 2H), 5.62 - 5.43 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.6 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H).
Syn. Ex. 61	537.20 (M+1)/ 536.14 for C ₂₆ H ₂₄ N ₄ O ₇ S	δ 10.05 (br s, 1H), 9.26 (br t, J = 5.8 Hz, 1H), 8.07 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 2.3, 8.4 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.54 - 7.42 (m, 1H), 7.19 - 7.03 (m, 2H), 6.91 (br s, 1H), 6.64 (br s, 1H), 4.27 (d, J = 6.0 Hz, 2H), 4.18 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.61 (q, J = 7.4 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).
Syn. Ex. 62	574.20 (M+1)/ 573.15 for C ₂₅ H ₂₇ N ₅ O ₉ S	δ 7.71 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.43 (br dd, J = 1.9, 8.2 Hz, 2H), 7.37 (s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.82 (s, 1H), 6.72 (s, 1H), 5.36 (s, 2H), 4.75 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.51 (s, 3H), 2.64 - 2.57 (m, 2H), 1.15 (t, J = 7.5 Hz, 3H) exchangeable protons not observed.
Syn. Ex. 63	564.30 (M-1) / 565.14 for C ₂₄ H ₂₅ F ₂ N ₅ O ₇ S	δ 10.73 - 10.51 (m, 1H), 7.73 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.44 (br d, J = 4.8 Hz, 2H), 7.38 (s, 1H), 7.22 (br s, 1H), 7.10 (br d, J = 7.3 Hz, 1H), 7.01 (br d, J = 1.1 Hz, 1H), 5.43 (s, 2H), 4.02 (d, J = 5.9 Hz, 2H), 3.71 (s, 3H), 3.52 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).
Syn. Ex. 64	560.20 (M+1) / 559.17 for C ₂₅ H ₂₉ N ₅ O ₈ S	δ 9.89 - 9.80 (m, 1H), 7.71 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.43 (br s, 2H), 7.36 (s, 1H), 7.15 (br d, J = 3.0 Hz, 1H), 6.84 (br s, 1H), 6.72 (br s, 1H), 5.36 (s, 2H), 5.06 (m, 1H), 4.07 - 3.99 (m, 4H), 3.82 (s, 3H), 3.70 - 3.63 (m, 2H), 3.51 (s, 3H), 2.62 - 2.59 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H).
Syn. Ex. 65	554.32 (M+1) / 553.16 for C ₂₆ H ₂₇ N ₅ O ₇ S	δ 9.85 (br s, 1H), 9.03 (br t, J = 5.5 Hz, 1H), 7.75 (s, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.45 (br d, J = 4.8 Hz, 1H), 7.38 (s, 1H), 7.16 (br d, J = 8.0 Hz, 1H), 6.85 (br d, J = 9.6 Hz, 1H), 6.73 (br s, 1H), 5.37 (s, 2H), 5.08

		(br s, 1H), 4.13 - 4.09 (m, 2H), 4.05 (t, $J = 4.8$ Hz, 2H), 3.82 (s, 3H), 3.76 - 3.61 (m, 3H), 2.61 (q, $J = 7.5$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 66	643.39 (M+1) / 642.21 for C ₂₉ H ₃₄ N ₆ O ₉ S	δ 10.12 (s, 1H), 7.72 (d, $J = 1.0$ Hz, 1H), 7.63 (s, 1H), 7.49 (t, $J = 1.0$ Hz, 1H), 7.41 (br s, 1H), 7.37 (d, $J = 1.0$ Hz, 1H), 7.14 (br d, $J = 8.3$ Hz, 1H), 6.86 (br s, 1H), 6.75 (d, $J = 1.0$ Hz, 1H), 5.36 (s, 2H), 4.99 (br s, 2H), 4.01 (br d, $J = 5.8$ Hz, 2H), 3.85 (s, 3H), 3.52 (br s, 8H), 3.40 (br s, 3H), 2.62 (q, $J = 1.0$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 67	588.20 (M+1) / 587.15 for C ₂₆ H ₂₆ FN ₅ O ₈ S	δ 8.85 (br t, $J = 5.5$ Hz, 1H), 7.71 (s, 1H), 7.55 (d, $J = 1.4$ Hz, 1H), 7.37 (s, 1H), 7.26 (dd, $J = 2.2, 8.3$ Hz, 1H), 7.20 - 7.08 (m, 2H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.71 (s, 1H), 6.58 (s, 1H), 5.61 - 5.42 (m, 1H), 5.32 (s, 2H), 5.22 (dd, $J = 3.4, 15.8$ Hz, 1H), 4.45 (br s, 2H), 4.18 (d, $J = 5.9$ Hz, 2H), 3.76 (br s, 3H), 2.61 - 2.53 (m, 2H), 1.15 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 68	657.30 (M+1) / 656.21 for C ₃₀ H ₃₃ FN ₆ O ₈ S	δ 10.14 (br s, 1H), 8.86 (br s, 1H), 7.74 (s, 1H), 7.63 (br s, 1H), 7.49 - 7.46 (m, 1H), 7.38 (s, 1H), 7.16 - 7.14 (m, 1H), 6.90 - 6.71 (m, 2H), 5.58 - 5.44 (m, 1H), 5.36 (s, 2H), 5.23 (dd, $J = 3.4, 15.6$ Hz, 1H), 5.00 - 4.98 (m, 2H), 4.18 (d, $J = 5.9$ Hz, 2H), 3.84 (s, 3H), 3.52 (br s, 4H), 3.40 (br s, 4H), 2.63 - 2.60 (m, 2H), 1.16 (t, $J = 7.5$ Hz, 3H)
Syn. Ex. 69	549.28 (M+1) / 548.15 for C ₂₆ H ₂₄ N ₆ O ₆ S	δ 10.47 (s, 1H), 9.03 (br s, 1H), 7.73 (s, 1H), 7.69 (br d, $J = 1.9$ Hz, 1H), 7.38 (m, 1H), 7.29 - 7.22 (m, 1H), 6.87 - 6.68 (m, 2H), 6.51 (s, 1H), 5.35 (br s, 2H), 5.21 (br s, 2H), 4.14 - 4.08 (m, 2H), 3.82 (s, 3H), 3.69 (br s, 1H), 2.69 - 2.57 (m, 2H), 1.15 (br t, $J = 7.5$ Hz, 3H)
Syn. Ex. 70	592.20 (M+1) / 591.16 for C ₂₆ H ₂₅ N ₉ O ₆ S	δ 9.02 (br t, $J = 5.7$ Hz, 1H), 7.73 (s, 1H), 7.69 (d, $J = 2.4$ Hz, 1H), 7.50 (dd, $J = 2.2, 8.4$ Hz, 1H), 7.37 (s, 1H), 7.33 (d, $J = 8.5$ Hz, 1H), 6.83 (s, 1H), 6.70 (s, 1H), 5.54

		(s, 2H), 5.36 (s, 2H), 4.12 - 4.10 (m, 3H), 3.79 (s, 3H), 2.64 (m, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 71	598.30 (M+1) / 597.18 for C ₂₅ H ₂₇ N ₉ O ₇ S	δ 7.68 (m, 2H), 7.42 (dd, $J = 2.2, 8.3$ Hz, 2H), 7.36 - 7.25 (m, 2H), 6.74 (s, 1H), 6.64 (s, 1H), 5.44 (s, 2H), 5.33 (s, 2H), 4.00 (d, $J = 5.9$ Hz, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 2.67 - 2.60 (m, 2H), 1.18 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 72	612.27 (M+1) / 611.17 for C ₂₆ H ₂₆ FN ₉ O ₆ S	δ 10.12 (br s, 1H), 8.87 (br t, $J = 5.4$ Hz, 1H), 7.75 (s, 1H), 7.69 (d, $J = 2.1$ Hz, 1H), 7.53 (dd, $J = 2.2, 8.4$ Hz, 1H), 7.40 - 7.33 (m, 2H), 6.86 (s, 1H), 6.72 (s, 1H), 5.59 - 5.43 (m, 3H), 5.36 (s, 2H), 5.23 (dd, $J = 3.4, 15.6$ Hz, 1H), 4.18 (br d, $J = 5.9$ Hz, 2H), 3.77 (s, 3H), 2.69 - 2.60 (m, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 73	612.20 (M+1) / 611.16 for C ₂₇ H ₂₆ FN ₇ O ₇ S	δ 9.68 (s, 1H), 9.55 (s, 1H), 8.86 (br t, $J = 5.3$ Hz, 1H), 7.75 (s, 1H), 7.70 (d, $J = 2.1$ Hz, 1H), 7.51 (br d, $J = 8.1$ Hz, 1H), 7.39 (s, 1H), 7.29 (br d, $J = 8.0$ Hz, 1H), 6.86 (br s, 1H), 6.71 (s, 1H), 5.60 - 5.35 (m, 5H), 5.23 (dd, $J = 3.4, 15.6$ Hz, 1H), 4.19 (d, $J = 6.0$ Hz, 2H), 3.81 (s, 3H), 2.63 (br d, $J = 7.5$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H).
Syn. Ex. 74	598.20 (M+1) / 597.16 for C ₂₆ H ₂₇ N ₇ O ₈ S	δ 9.58 (s, 1H), 8.15 (s, 1H), 7.68 (s, 2H), 7.42 (br s, 1H), 7.35 (s, 1H), 7.25 - 6.96 (m, 2H), 6.66 - 6.49 (m, 2H), 5.33 - 5.23 (m, 4H), 4.01 (d, $J = 5.9$ Hz, 2H), 3.80 (s, 3H), 3.51 (s, 3H), 2.56 (br s, 2H), 1.13 (t, $J = 7.6$ Hz, 3H).
Syn. Ex. 75	559.20 (M+1) / 558.19 for C ₂₅ H ₃₀ N ₆ O ₇ S	δ 8.50 - 8.00 (m, 2H), 7.68 (s, 1H), 7.65 (d, $J = 2.3$ Hz, 1H), 7.46 - 7.43 (m, 1H), 7.34 (s, 1H), 7.23 (dd, $J = 2.4, 8.3$ Hz, 1H), 7.00 (d, $J = 8.1$ Hz, 1H), 6.67 (s, 1H), 6.57 (s, 1H), 5.29 (s, 2H), 4.08 (t, $J = 4.8$ Hz, 2H), 4.00 (d, $J = 5.9$ Hz, 2H), 3.85 (s, 3H), 3.51 (s, 3H), 3.09 (t, $J = 4.8$ Hz, 2H), 2.61 (q, $J = 7.6$ Hz, 2H), 1.19 (t, $J = 7.6$ Hz, 3H).

Syn. Ex. 76	573.20 (M+1) / 572.19 for C26H29FN6O6S	δ 8.86 (br t, J = 5.1 Hz, 1H), 8.32 (br s, 3H), 7.72 (s, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.37 (s, 1H), 7.23 (dd, J = 2.4, 8.3 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 5.61 - 5.41 (m, 1H), 5.30 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.17 (d, J = 6.0 Hz, 2H), 4.08 (t, J = 4.9 Hz, 2H), 3.85 (s, 3H), 3.10 (br t, J = 4.8 Hz, 2H), 2.61 (q, J = 7.5 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H).
Syn. Ex. 77	629 (M+1) / 628.20 for C28H32N6O9S	δ 9.74 (s, 1H), 7.71 (s, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.37 (s, 1H), 7.12 (br d, J = 8.1 Hz, 1H), 6.90 - 6.71 (m, 2H), 5.36 (s, 2H), 4.26 - 4.18 (m, 2H), 4.13 (br s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.66 - 3.59 (m, 2H), 3.51 (s, 4H), 2.61 (q, J = 7.5 Hz, 3H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 78	643.30 (M+1) / 642.19 for C29H31FN6O8S	δ 9.74 (s, 1H), 8.86 (br t, J = 5.8 Hz, 1H), 7.75 (s, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.47 (br d, J = 7.8 Hz, 1H), 7.39 (s, 1H), 7.12 (br d, J = 8.3 Hz, 1H), 6.87 (br s, 1H), 6.73 (br s, 1H), 5.58 - 5.43 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.6 Hz, 1H), 4.26 - 4.09 (m, 6H), 3.82 (s, 3H), 3.62 (br d, J = 6.0 Hz, 2H), 3.53 - 3.48 (m, 2H), 2.61 (q, J = 7.7 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).
Syn. Ex. 79	631.30 (M+1) / 630.19 for C28H31FN6O8S	δ 9.96 (br s, 1H), 8.86 (br t, J = 5.3 Hz, 1H), 7.75 (s, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.45 (br d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.27 (br t, J = 5.6 Hz, 1H), 7.09 (br d, J = 8.6 Hz, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 5.58 - 5.44 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.18 (d, J = 5.9 Hz, 2H), 3.98 (br t, J = 4.9 Hz, 2H), 3.84 (s, 3H), 3.51 (s, 3H), 3.37 (br d, J = 5.1 Hz, 2H), 2.62 (q, J = 7.4 Hz, 2H), 1.16 (t, J = 1.0 Hz, 3H)
Syn. Ex. 80	611.24 (M+1) / 610.18 for C27H27FN8O6S	δ 14.18 - 14.04 (m, 1H), 10.45 (br s, 1H), 8.85 (br t, J = 5.7 Hz, 1H), 8.53 - 8.45 (m, 1H), 7.74 (s, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.49 (br d, J = 6.9 Hz, 1H), 7.40 - 7.33 (m, 2H), 6.90 - 6.65 (m, 2H), 5.58 - 5.43 (m, 1H), 5.36 (s, 2H), 5.28 - 5.19 (m, 3H), 4.18 (d, J = 5.9 Hz, 2H),

		3.85 (s, 3H), 2.63 (q, $J = 7.7$ Hz, 2H), 1.17 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 81	601.30 (M+1) / 600.20 for C ₂₇ H ₃₂ N ₆ O ₈ S	δ 10.00 (s, 1H), 8.03 (br t, $J = 5.6$ Hz, 1H), 7.71 (s, 1H), 7.64 (d, $J = 2.3$ Hz, 1H), 7.48 - 7.40 (m, 2H), 7.37 (s, 1H), 7.09 (d, $J = 8.6$ Hz, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 5.37 (s, 2H), 4.03 - 3.97 (m, 4H), 3.82 (s, 3H), 3.51 (s, 3H), 3.43 (q, $J = 5.3$ Hz, 2H), 2.61 (q, $J = 7.5$ Hz, 2H), 1.81 (s, 3H), 1.15 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 82	615.30 (M+1) / 614.20 for C ₂₈ H ₃₁ FN ₆ O ₇ S	δ 10.01 (br s, 1H), 8.86 (br t, $J = 5.7$ Hz, 1H), 8.16 - 8.00 (m, 1H), 7.74 (s, 1H), 7.64 (d, $J = 1.9$ Hz, 1H), 7.39 (s, 2H), 7.08 (br d, $J = 4.4$ Hz, 1H), 6.72 (br d, $J = 1.8$ Hz, 2H), 5.58 - 5.44 (m, 1H), 5.36 (br s, 2H), 5.23 (dd, $J = 3.4, 15.8$ Hz, 1H), 4.26 - 3.95 (m, 2H), 4.03 - 3.87 (m, 2H), 3.81 (s, 3H), 3.52 - 3.34 (m, 2H), 2.70 - 2.57 (m, 2H), 1.81 (s, 3H), 1.15 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 83	569.39 (M+1) / 568.17 for C ₂₆ H ₂₈ N ₆ O ₇ S	δ 7.71 - 7.63 (m, 2H), 7.42 (br s, 1H), 7.38 - 7.34 (m, 2H), 7.10 (br s, 1H), 6.76 - 6.63 (m, 2H), 5.33 (s, 2H), 4.19 (br s, 2H), 4.01 (d, $J = 5.8$ Hz, 2H), 3.82 (s, 3H), 3.51 (s, 3H), 2.96 (t, $J = 6.3$ Hz, 2H), 2.59 (q, $J = 7.5$ Hz, 2H), 1.15 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 84	583.20 (M+1) / 582.17 for C ₂₇ H ₂₇ FN ₆ O ₆ S	δ 9.92 (s, 1H), 8.87 (br t, $J = 5.7$ Hz, 1H), 7.75 (s, 1H), 7.66 (d, $J = 2.2$ Hz, 1H), 7.48 (br d, $J = 7.2$ Hz, 1H), 7.39 (s, 1H), 7.20 (br d, $J = 8.3$ Hz, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 5.59 - 5.44 (m, 1H), 5.37 (s, 2H), 5.23 (dd, $J = 3.4, 15.7$ Hz, 1H), 4.27 (br t, $J = 6.0$ Hz, 2H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.81 (s, 3H), 3.00 (t, $J = 6.1$ Hz, 2H), 2.62 (q, $J = 7.6$ Hz, 2H), 1.15 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 85	527.25 (M+1) / 526.13 for C ₂₃ H ₂₂ N ₆ O ₇ S	δ 9.03 (br t, $J = 5.6$ Hz, 1H), 8.12 (d, $J = 1.0$ Hz, 1H), 7.74 (s, 1H), 7.38 (s, 1H), 6.79 (d, $J = 1.0$ Hz, 2H), 6.65 (s, 1H), 6.51 (s, 1H), 5.35 (s, 2H), 4.11 (t, $J = 1.0$ Hz, 3H), 3.83 (s, 3H), 3.75 (br s, 6H)

Syn. Ex. 86	533.20 (M+1) / 532.14 for C ₂₂ H ₂₄ N ₆ O ₈ S	δ 8.25 - 8.11 (d, 1H), 7.72 (s, 1H), 7.48 - 7.35 (d, 2H), 6.95 - 6.83 (t, 2H), 6.75 (s, 1H), 6.46 (s, 1H), 5.38 (s, 2H), 4.02 (d, J = 5.9 Hz, 2H), 3.83 (d, J = 1.0 Hz, 9H), 3.52 (s, 3H)
Syn. Ex. 87	547.20 (M+1) / 546.13 for C ₂₃ H ₂₃ FN ₆ O ₇ S	δ 10.18 (s, 1H), 8.86 (br t, J = 5.7 Hz, 1H), 8.22 (br d, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.40 (s, 1H), 6.95 - 6.86 (m, 2H), 6.75 (s, 1H), 5.59 - 5.44 (m, 1H), 5.38 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.19 (d, J = 5.9 Hz, 2H), 3.82 (s, 9H)
Syn. Ex. 88	516.25 (M+1) / 515.15 for C ₂₃ H ₂₅ N ₅ O ₇ S	δ 10.02 (br s, 1H), 7.71 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.48 - 7.33 (m, 3H), 7.06 (br d, J = 7.0 Hz, 1H), 6.90 - 6.62 (m, 2H), 5.36 (s, 2H), 4.01 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.51 (s, 3H), 2.28 (s, 3H)
Syn. Ex. 89	530.20 (M+1) / 529.14 for C ₂₄ H ₂₄ FN ₅ O ₆ S	δ 9.98 (s, 1H), 8.86 (br t, J = 5.8 Hz, 1H), 7.75 (s, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.09 (d, J = 8.5 Hz, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 5.60 - 5.44 (m, 1H), 5.37 (s, 2H), 5.23 (dd, J = 3.4, 15.8 Hz, 1H), 4.19 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 2.29 (s, 3H)
Syn. Ex. 90	515.30 (M+1) / 514.16 for C ₂₃ H ₂₆ N ₆ O ₆ S	δ 10.01 (m, 1H), 7.69 (s, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.47 - 7.43 (m, 1H), 7.37 (s, 1H), 7.10 (br d, J = 8.3 Hz, 1H), 6.85 (br s, 1H), 6.75 (br s, 1H), 6.12 (br t, J = 5.2 Hz, 1H), 5.44 - 5.34 (m, 4H), 3.99 (d, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.60 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H)
Syn. Ex. 91	529.30 (M+1) / 528.18 for C ₂₄ H ₂₈ N ₆ O ₆ S	δ 10.03 - 9.99 (br s, 1H), 7.67 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.42 - 7.30 (m, 2H), 7.06 (br s, 1H), 6.81 (br s, 1H), 6.70 (br s, 1H), 6.06 (br t, J = 5.4 Hz, 1H), 5.68 - 5.64 (m, 1H), 5.35 (s, 2H), 4.01 (d, J = 5.8 Hz, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 2.58 (q, J = 7.4 Hz, 2H), 2.53 (d, J = 4.6 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H)

Syn. Ex. 92	620.20 (M+1) / 619.19 for C31H30FN5O6S	δ 9.85 (s, 1H), 8.86 (br t, $J = 5.6$ Hz, 1H), 7.75 (s, 1H), 7.68 (d, $J = 2.3$ Hz, 1H), 7.40 (s, 2H), 7.36 - 7.32 (m, 2H), 7.22 - 7.18 (m, 3H), 7.12 (br d, $J = 8.4$ Hz, 1H), 6.84 (s, 1H), 6.70 (s, 1H), 5.59 - 5.43 (m, 1H), 5.36 (s, 2H), 5.27 - 5.19 (m, 3H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.63 (s, 3H), 2.59 (q, $J = 7.5$ Hz, 2H), 1.13 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 93	606.30 (M+1) / 605.19 for C30H31N5O7S	δ 9.85 (s, 1H), 7.71 (s, 1H), 7.69 (d, $J = 2.4$ Hz, 1H), 7.41 (br d, $J = 9.3$ Hz, 2H), 7.39 - 7.33 (m, 3H), 7.23 - 7.19 (m, 3H), 7.12 (d, $J = 8.6$ Hz, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 5.36 (s, 2H), 5.22 (s, 2H), 4.02 (d, $J = 5.9$ Hz, 2H), 3.64 (s, 3H), 3.51 (s, 3H), 2.59 (q, $J = 7.5$ Hz, 2H), 1.14 (t, $J = 7.6$ Hz, 3H).
Syn. Ex. 94	651.33 (M+1) / 650.20 for C31H31FN6O7S	δ 10.14 (br s, 1H), 8.87 (br t, $J = 5.5$ Hz, 1H), 7.99 (br d, $J = 3.0$ Hz, 1H), 7.75 - 7.68 (m, 2H), 7.39 (s, 2H), 7.09 - 7.02 (m, 1H), 6.91 (br d, $J = 4.1$ Hz, 1H), 6.82 - 6.62 (m, 3H), 5.59 - 5.43 (m, 1H), 5.34 (s, 2H), 5.26 - 5.15 (m, 3H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.77 (s, 3H), 3.65 (br s, 3H), 2.62 - 2.54 (m, 2H), 1.14 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 95	637.26 (M+1) / 636.20 for C30H32N6O8S	δ 10.12 (br s, 1H), 8.00 (br d, $J = 4.8$ Hz, 1H), 7.72 - 7.68 (m, 2H), 7.42 (br d, $J = 5.5$ Hz, 1H), 7.37 (s, 1H), 7.05 (br s, 1H), 6.92 (br s, 1H), 6.78 (br s, 2H), 6.67 (br d, $J = 2.4$ Hz, 1H), 5.34 (s, 2H), 5.19 (br s, 2H), 4.02 (d, $J = 5.9$ Hz, 2H), 3.77 (s, 3H), 3.66 (br s, 3H), 3.51 (s, 3H), 2.59 (q, $J = 7.3$ Hz, 2H), 1.14 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 96	570.30 (M+1) / 569.17 for C27H28FN5O6S	δ 9.82 (s, 1H), 8.86 (br t, $J = 5.5$ Hz, 1H), 7.65 (s, 1H), 7.62 (d, $J = 2.1$ Hz, 1H), 7.46 (dd, $J = 2.3, 8.5$ Hz, 1H), 7.40 (s, 1H), 7.22 - 7.05 (m, 1H), 6.54 (s, 1H), 5.59 - 5.43 (m, 1H), 5.34 (s, 2H), 5.23 (dd, $J = 3.4, 15.8$ Hz, 1H), 4.21 - 4.15 (m, 4H), 3.76 (br s, 3H), 2.71 - 2.66 (m, 2H), 2.60 (q, $J = 7.5$ Hz, 2H), 2.00 - 1.94 (m, 2H), 1.14 (t, $J = 7.6$ Hz, 3H)

Syn. Ex. 97	556.25 (M+1) / 555.18 for C ₂₆ H ₂₉ N ₅ O ₇ S	δ 9.82 (s, 1H), 7.62 (s, 2H), 7.45 (br t, J = 8.1 Hz, 2H), 7.38 (s, 1H), 7.12 (br d, J = 8.4 Hz, 1H), 6.52 (s, 1H), 5.34 (s, 2H), 4.19 - 4.16 (m, 2H), 4.02 (d, J = 5.9 Hz, 2H), 3.77 (s, 3H), 3.51 (s, 3H), 2.71 - 2.66 (m, 2H), 2.63 - 2.56 (m, 2H), 2.02 - 1.93 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H)
Syn. Ex. 98	579.30 (M+1) / 578.15 for C ₂₅ H ₃₀ N ₄ O ₈ S ₂	δ 7.64 (d, J = 2.3 Hz, 1H), 7.35 - 7.25 (m, 1H), 7.10 (br dd, J = 4.1, 7.4 Hz, 1H), 7.03 - 6.98 (m, 1H), 6.90 (s, 1H), 6.79 - 6.67 (m, 1H), 5.80 (t, J = 5.63 Hz, 1H), 4.14 (d, J = 5.6 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.57 (br d, J = 7.5 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H), 1.11 (s, 9H)
Syn. Ex. 99	547.26 (M+1) / 546.12 for C ₂₄ H ₂₃ FN ₄ O ₈ S	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.81 (d, J = 2.0 Hz, 1H), 7.37 - 7.28 (d, 1H), 7.01 (d, 2H), 6.86 - 6.81 (d, 1H), 6.73 (br s, 1H), 5.70 - 5.16 (m, 1H), 4.48 - 4.20 (d, 2H), 3.97 - 3.92 (d, 3H), 3.80 (s, 3H), 2.62 (q, J = 7.6 Hz, 2H), 1.21 (m, 3H)
Syn. Ex. 100	533.10 (M+1) / 532.13 for C ₂₃ H ₂₄ N ₄ O ₉ S	δ 10.18 (br s, 1H), 7.70 - 7.63 (m, 2H), 7.45 (br d, J = 1.3 Hz, 1H), 7.31 (br s, 1H), 7.10 (d, J = 1.0 Hz, 1H), 6.89 (br s, 1H), 6.84 (s, 1H), 4.18 (d, J = 5.6 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 2.63 - 2.59 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 101	549.20 (M+1) / 548.10 for C ₂₃ H ₂₄ N ₄ O ₈ S ₂	δ 10.17 (br s, 1H), 7.76 (br s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.23 (br d, J = 0.9 Hz, 1H), 7.16 (s, 1H), 7.12 (br d, J = 8.4 Hz, 1H), 6.85 (br s, 1H), 4.25 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.54 (s, 3H), 2.62 - 2.59 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 102	563.21 (M+1) / 562.10 for C ₂₄ H ₂₃ FN ₄ O ₇ S ₂	δ 10.16 (br s, 1H), 9.18 (br t, J = 5.9 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.46 (br d, J = 7.1 Hz, 1H), 7.24 - 7.20 (m, 2H), 7.11 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 5.63 - 5.48 (m, 1H), 5.29 (dd, J = 3.6, 15.7 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.62 - 2.59 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H)

Syn. Ex. 103	543.20 (M+1)/ 542.09 for C ₂₄ H ₂₂ N ₄ O ₇ S ₂	δ 10.17 (br s, 1H), 9.35 (br t, J = 5.8 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.45 (br d, J = 2.5 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.19 (s, 1H), 7.13 - 7.09 (m, 1H), 6.85 (br s, 1H), 4.35 (d, J = 5.6 Hz, 2H), 4.20 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 2.61 (q, J = 7.7 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 104	549.33 (M+1)/ 548.10 for C ₂₃ H ₂₄ N ₄ O ₈ S ₂	δ 10.18 (s, 1 H), 7.64 (br d, J = 2.1 Hz, 2H), 7.50 - 7.44 (s, 1H), 7.28 (br s, 1H), 7.12 (br d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.87 (br s, 1H), 4.10 (br d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.54 (s, 3H), 2.61 (q, J = 7.4 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 105	563.10 (M+1)/ 562.10 for C ₂₄ H ₂₃ FN ₄ O ₇ S ₂	δ 10.19 (s, 1 H), 9.00 (br t, J = 5.75 Hz, 1 H), 7.64 (d, J = 2.3 Hz, 1H), 7.48 (dd, J = 2.3, 8.5 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 1.6 Hz, 1H), 5.63 - 5.46 (m, 1H), 5.28 (dd, J = 3.4, 15.7 Hz, 1H), 4.27 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.61 (d, J = 7.5 Hz, 2H), 1.16 (t, J = 7.6 Hz, 3H)
Syn. Ex. 106	543.20 (M+1)/ 542.15 for C ₂₅ H ₂₆ N ₄ O ₈ S	δ 7.78 - 7.70 (m, 2H), 7.63 (br t, J = 6.1 Hz, 1H), 7.41 - 7.19 (m, 2H), 7.09 (td, J = 1.5, 2.6 Hz, 1H), 6.98 (br d, J = 7.3 Hz, 2H), 6.76 - 6.64 (m, 2H), 4.10 (d, J = 6.1 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 3.52 (s, 3H), 2.57 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 107	543.33 (M+1)/ 542.13 for C ₂₅ H ₂₃ FN ₄ O ₇ S	δ 10.54 (s, 1 H), 10.05 (br s, 1 H), 8.50 (d, J = 2.5 Hz, 1H), 8.20 (dd, J = 2.6, 8.8 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.49 - 7.41 (s, 1H), 7.13 (br d, J = 8.6 Hz, 2H), 6.93 - 6.85 (s, 1H), 6.63 (br s, 1H), 5.81 - 5.65 (m, 1H), 5.50 - 5.42 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.61 (br d, J = 7.5 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H)
Syn. Ex. 108	523.21 (M+1)/ 522.12 for C ₂₅ H ₂₂ N ₄ O ₇ S	δ 10.99 (s, 1H), 8.37 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H), 8.06 (dd, J = 2.8, 8.9 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.28 - 7.16 (m, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.93 (br d, J = 7.1 Hz, 1H), 6.62 (br s, 1H), 6.42 (br s, 1H), 4.46

		(s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 2.55 (m, 2H), 1.14 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 109	529.26 (M+1)/ 528.13 for C ₂₄ H ₂₄ N ₄ O ₈ S	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.25 (d, $J = 2.6$ Hz, 1H), 8.02 (dd, $J = 2.5, 8.6$ Hz, 1H), 7.80 (d, $J = 2.3$ Hz, 1H), 7.44 (dd, $J = 2.2, 8.4$ Hz, 1H), 7.07 - 7.01 (m, 2H), 6.68 (d, $J = 1.6$ Hz, 1H), 6.58 (d, $J = 1.5$ Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 2.66 (d, $J = 7.6$ Hz, 2H), 1.23 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 110	543.29 (M+1)/ 542.15 for C ₂₅ H ₂₆ N ₄ O ₈ S	δ 12.99 (br s, 1H), 8.06 (d, $J = 5.1$ Hz, 1H), 7.79 (br t, $J = 6.1$ Hz, 1H), 7.71 (d, $J = 2.3$ Hz, 1H), 7.38 (dd, $J = 1.8, 8.3$ Hz, 1H), 7.08 - 7.00 (m, 3H), 6.84 (s, 2H), 4.21 (d, $J = 6.3$ Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.56 (s, 3H), 2.61 (q, $J = 7.5$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 111	557.30 (M+1)/ 556.14 for C ₂₆ H ₂₅ FN ₄ O ₇ S	δ 12.99 (br s, 1H), 9.16 (br t, $J = 6.1$ Hz, 1H), 8.07 (d, $J = 5.1$ Hz, 1H), 7.71 (d, $J = 2.3$ Hz, 1H), 7.39 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 7.02 (d, $J = 5.3$ Hz, 1H), 6.99 (br s, 1H), 6.86 (s, 1H), 6.82 (br s, 1H), 5.65 - 5.49 (m, 1H), 5.31 (dd, $J = 3.5, 15.6$ Hz, 1H), 4.38 (d, $J = 6.1$ Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 2.61 (q, $J = 7.6$ Hz, 2H), 1.16 (t, $J = 7.6$ Hz, 3H)
Syn. Ex. 112	526.29 (M+1)/ 525.13 for C ₂₄ H ₂₃ N ₅ O ₇ S	δ 10.80 (br s, 1H), 7.97 - 7.93 (m, 2H), 7.71 (s, 1H), 7.45 - 7.41 (m, 1H), 7.37 (s, 1H), 7.25 (br d, $J = 8.0$ Hz, 1H), 6.83 (br s, 1H), 6.73 (br s, 1H), 5.37 (s, 2H), 4.41 (s, 1H), 4.01 (d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.51 (s, 3H)
Syn. Ex. 113	574.49 (M+1)/ 573.17 for C ₂₆ H ₂₈ FN ₅ O ₇ S	δ 10.07 (s, 1H), 8.87 (br t, $J = 5.7$ Hz, 1H), 7.74 (s, 1H), 7.63 (d, $J = 2.2$ Hz, 1H), 7.38 (s, 1H), 7.21 - 7.04 (m, 1H), 6.88 - 6.62 (m, 1H), 6.51 (s, 1H), 6.37 - 6.36 (m, 1H), 5.68 - 5.41 (m, 2H), 5.35 (s, 2H), 5.23 (dd, $J = 3.4, 15.7$ Hz, 1H), 4.18 (d, $J = 5.9$ Hz, 2H), 4.04 (br t, $J = 4.5$ Hz, 2H), 3.81 (s, 3H), 3.64 (br d, $J = 1.1$ Hz, 2H), 2.62 - 2.54 (m, 2H), 1.15 (t, $J = 7.5$ Hz, 3H).

Syn. Ex. 114	611.20 (M+1)/ 610.18 for C ₂₇ H ₂₇ FN ₈ O ₆ S	δ ppm 14.85 (br s, 1 H), 8.85 (br t, J=5.44 Hz, 1 H), 7.74 (s, 1 H), 7.66 (d, J=2.13 Hz, 1 H), 7.36 - 7.45 (m, 2 H), 7.22 - 7.28 (m, 1 H), 6.81 (br s, 1 H), 6.68 (br s, 1 H), 5.43 - 5.58 (m, 1 H), 5.35 (s, 2 H), 5.19 - 5.31 (m, 3 H), 4.18 (d, J=5.88 Hz, 2 H), 3.74 (br s, 3 H), 2.57 - 2.64 (m, 2 H), 1.15 (t, J=7.57 Hz, 3 H)
Syn. Ex. 115	588.20 (M+1)/ 587.18 for C ₂₅ H ₂₉ N ₇ O ₈ S	δ ppm 9.35 (br s, 1 H), 7.71 (s, 1 H), 7.61 (d, J=2.25 Hz, 1 H), 7.39 - 7.47 (m, 2 H), 7.37 (s, 1 H), 7.20 (d, J=8.50 Hz, 1 H), 6.85 (s, 1 H), 6.73 (s, 1 H), 5.60 (br s, 2 H), 5.36 (s, 2 H), 4.61 (s, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.82 (s, 3 H), 3.51 (s, 3 H), 2.60 (q, J=7.55 Hz, 2 H), 1.14 (t, J=7.57 Hz, 3 H)
Syn. Ex. 116	596.30 (M+1)/ 595.18 for C ₂₇ H ₂₉ N ₇ O ₇ S	δ ppm 7.65 - 7.69 (m, 2 H), 7.33 - 7.43 (m, 3 H), 7.22 (d, J=8.38 Hz, 1 H), 7.11 (s, 2 H), 6.73 (s, 1 H), 6.64 (s, 1 H), 5.32 (s, 2 H), 5.14 (s, 2 H), 4.00 (br d, J=5.75 Hz, 2 H), 3.87 (s, 3 H), 3.54 (s, 3 H), 2.59 - 2.65 (m, 2 H), 1.18 (t, J=7.57 Hz, 3 H)
Syn. Ex. 117	597.20 (M+1)/ 596.18 for C ₂₆ H ₂₈ N ₈ O ₇ S	δ ppm 14.10 (br s, 1 H), 10.38 - 10.52 (m, 1 H), 7.71 (s, 1 H), 7.65 (d, J=2.00 Hz, 1 H), 7.49 (br d, J=7.88 Hz, 1 H), 7.34 - 7.45 (m, 3 H), 6.84 (br s, 1 H), 6.72 (br s, 1 H), 5.36 (s, 2 H), 5.27 (s, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.86 (s, 3 H), 3.51 (s, 3 H), 2.59 - 2.65 (m, 2 H), 1.16 (t, J=7.57 Hz, 3 H)
Syn. Ex. 118	602.20 (M+1)/ 601.18 for C ₂₆ H ₂₈ FN ₇ O ₇ S	δ ppm 9.31 (br s, 1 H), 8.86 (br t, J=4.94 Hz, 1 H), 7.74 (s, 1 H), 7.62 (d, J=2.00 Hz, 1 H), 7.39 (s, 2 H), 7.17 (br d, J=5.38 Hz, 1 H), 6.83 (br s, 1 H), 6.70 (br s, 1 H), 5.41 - 5.68 (m, 3 H), 5.36 (s, 2 H), 5.23 (dd, J=15.76, 3.38 Hz, 1 H), 4.57 (br s, 2 H), 4.19 (d, J=5.88 Hz, 2 H), 3.82 (s, 3 H), 2.59 (q, J=7.63 Hz, 2 H), 1.14 (t, J=7.57 Hz, 3 H)
Syn. Ex. 119	610.20 (M+1)/ 609.18 for C ₂₈ H ₂₈ FN ₇ O ₆ S	δ ppm 8.85 (br t, J=5.38 Hz, 1 H), 7.72 (s, 1 H), 7.66 (d, J=2.25 Hz, 1 H), 7.35 - 7.42 (m, 2 H), 7.25 (d, J=8.38 Hz, 1 H), 7.14 (s, 2 H), 6.77 (s, 1 H), 6.66 (s, 1 H), 5.42

		- 5.59 (m, 1 H), 5.33 (s, 2 H), 5.16 - 5.26 (m, 3 H), 4.17 (d, J=5.88 Hz, 2 H), 3.86 (s, 3 H), 2.63 (q, J=7.60 Hz, 2 H), 1.18 (t, J=7.57 Hz, 3 H)
Syn. Ex. 120	531.32 (M+1)/ 530.16 for C ₂₃ H ₂₆ N ₆ O ₇ S	δ ppm 10.89 (br s, 1 H), 8.49 (br s, 1 H), 7.71 (s, 1 H), 7.55 (s, 1 H), 7.42 (br d, J=5.88 Hz, 1 H), 7.37 (s, 1 H), 6.87 (br s, 1 H), 6.72 (br s, 1 H), 5.37 (s, 2 H), 4.01 (d, J=5.75 Hz, 2 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.52 (s, 3 H), 2.76 (q, J=7.63 Hz, 2 H), 1.19 (t, J=7.57 Hz, 3 H)
Syn. Ex. 121	531.20 (M+1)/ 530.16 for C ₂₃ H ₂₆ N ₆ O ₇ S	δ ppm 10.70 (br s, 1 H), 8.26 (br s, 1 H), 8.01 (d, J=2.20 Hz, 1 H), 7.71 (s, 1 H), 7.43 (br t, J=5.20 Hz, 1 H), 7.37 (s, 1 H), 6.63 - 6.94 (m, 2 H), 5.37 (s, 2 H), 4.01 (d, J=5.87 Hz, 2 H), 3.78 (d, J=14.43 Hz, 6 H), 3.51 (s, 3 H), 2.62 (q, J=7.54 Hz, 2 H), 1.15 (t, J=7.58 Hz, 3 H)
Syn. Ex. 122	624.20 (M+1)/ 623.18 for C ₃₀ H ₃₀ FN ₅ O ₇ S	δ ppm 9.94 (s, 1 H), 7.71 (s, 1 H), 7.68 (d, J=2.20 Hz, 1 H), 7.33 - 7.45 (m, 5 H), 7.05 (br t, J=8.80 Hz, 2 H), 6.68 - 6.82 (m, 2 H), 5.36 (s, 2 H), 5.17 (s, 2 H), 4.01 (d, J=5.99 Hz, 2 H), 3.66 (s, 3 H), 3.51 (s, 3 H), 2.59 (q, J=7.58 Hz, 2 H), 1.14 (t, J=7.58 Hz, 3 H)
Syn. Ex. 123	607.20 (M+1)/ 606.19 for C ₂₉ H ₃₀ N ₆ O ₇ S	δ ppm 10.02 (br s, 1 H), 8.63 (br s, 1 H), 8.44 (dd, J=4.69, 1.31 Hz, 1 H), 7.64 - 7.84 (m, 3 H), 7.33 - 7.48 (m, 3 H), 7.07 - 7.24 (m, 2 H), 6.57 - 6.76 (m, 2 H), 5.33 (s, 2 H), 5.19 (br s, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.69 (br s, 3 H), 3.51 (s, 3 H), 2.55 - 2.62 (m, 2 H), 1.14 (t, J=7.57 Hz, 3 H)
Syn. Ex. 124	546.36 (M+1)/ 545.14 for C ₂₄ H ₂₄ FN ₅ O ₇ S	δ ppm 10.40 (br s, 1 H), 7.61 (s, 1 H), 7.56 (dd, J=8.19, 3.06 Hz, 1 H), 7.43 (t, J=1.00 Hz, 1 H), 7.38 (s, 1 H), 7.23 (br s, 1 H), 6.51 (br s, 1 H), 5.33 (s, 2 H), 4.16 (t, J=1.00 Hz, 2 H), 4.02 (d, J=5.88 Hz, 2 H), 3.77 (s, 3 H), 3.52 (s, 3 H), 2.64 - 2.71 (m, 2 H), 1.93 - 2.01 (m, 2 H)
Syn. Ex. 125	530.33 (M+1)/ 529.16 for C ₂₄ H ₂₇ N ₅ O ₇ S	δ ppm 9.93 (br s, 1 H), 7.67 - 7.73 (m, 2 H), 7.44 (br t, J=4.80 Hz, 1 H), 7.37 (s, 1 H), 7.02 (br s, 1 H), 6.93 (br d, J=7.13 Hz, 1 H), 6.84 (br s, 1 H), 6.74 (br s, 1 H), 5.37 (s, 2 H), 4.02 (d, J=5.75 Hz, 2 H), 3.85 (s, 3 H), 3.78 (s,

		3 H), 3.52 (s, 3 H), 2.65 (q, J=1.00 Hz, 2 H), 1.19 (t, J=7.63 Hz, 3 H)
Syn. Ex. 126	544.10 (M+1)/ 543.14 for C ₂₄ H ₂₅ N ₅ O ₈ S	δ 9.93 (br s, 1 H), 7.71 (s, 1 H), 7.43 (br s, 1 H), 7.37 (s, 1 H), 7.14 (br s, 1 H), 7.09 (s, 1 H), 6.84 (br s, 1 H), 6.74 (br s, 1 H), 5.37 (s, 2 H), 4.54 (t, J=8.63 Hz, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.87 (s, 3 H), 3.73 (s, 3 H), 3.52 (s, 3 H), 3.22 (br t, J=8.63 Hz, 2 H)
Syn. Ex. 127	598.20 (M+1)/ 597.16 for C ₂₆ H ₂₇ N ₇ O ₈ S	δ 10.14 (br s, 1 H), 9.14 (s, 1 H), 7.72 (s, 1 H), 7.68 (d, J=2.13 Hz, 1 H), 7.51 (br d, J=8.13 Hz, 1 H), 7.40 - 7.45 (m, 1 H), 7.37 (s, 1 H), 7.31 (br d, J=8.13 Hz, 1 H), 6.85 (s, 1 H), 6.72 (s, 1 H), 5.53 (s, 2 H), 5.37 (s, 2 H), 4.01 (d, J=5.75 Hz, 2 H), 3.79 (s, 3 H), 3.51 (s, 3 H), 2.59 - 2.65 (m, 2 H), 1.16 (t, J=7.57 Hz, 3 H)
Syn. Ex. 128	554.20 (M+1)/ 553.16 for C ₂₆ H ₂₇ N ₅ O ₇ S	δ 9.92 (br s, 1 H), 7.71 (s, 1 H), 7.67 (d, J=2.25 Hz, 1 H), 7.40 - 7.51 (m, 2 H), 7.37 (s, 1 H), 7.18 (br d, J=8.00 Hz, 1 H), 6.84 (br s, 1 H), 6.73 (br s, 1 H), 5.37 (s, 2 H), 4.87 (br s, 2 H), 4.02 (d, J=5.88 Hz, 2 H), 3.86 (s, 3 H), 3.52 (s, 3 H), 3.40 (t, J=2.31 Hz, 1 H), 2.61 (q, J=7.50 Hz, 2 H), 1.16 (t, J=7.57 Hz, 3 H)
Syn. Ex. 129	537.31 (M+1)/ 536.15 for C ₂₅ H ₂₄ N ₆ O ₆ S	δ 8.91 (d, J=1.25 Hz, 1 H), 8.29 - 8.36 (m, 2 H), 8.24 (br d, J=7.38 Hz, 1 H), 7.74 (br t, J=7.63 Hz, 1 H), 7.68 (s, 1 H), 7.40 (br s, 1 H), 7.34 (s, 1 H), 6.80 (br s, 1 H), 6.70 (s, 1 H), 5.32 (s, 2 H), 3.99 (d, J=5.75 Hz, 2 H), 3.83 (s, 3 H), 3.51 (s, 3 H), 2.53 (s, 3 H)
Syn. Ex. 130	537.34 (M+1)/ 536.15 for C ₂₅ H ₂₄ N ₆ O ₆ S	δ 8.99 (br d, J=2.75 Hz, 1 H), 8.44 (br d, J=7.88 Hz, 1 H), 8.27 (d, J=1.88 Hz, 1 H), 8.10 (br s, 1 H), 7.60 - 7.69 (m, 2 H), 7.40 (br s, 1 H), 7.34 (s, 1 H), 6.80 (s, 1 H), 6.70 (s, 1 H), 5.32 (s, 2 H), 3.99 (d, J=5.88 Hz, 2 H), 3.84 (s, 3 H), 3.51 (s, 3 H), 2.57 (s, 3 H)
Syn. Ex. 131	537.34 (M+1)/ 536.15 for C ₂₅ H ₂₄ N ₆ O ₆ S	δ 8.91 (br d, J=4.25 Hz, 1 H), 8.36 - 8.49 (m, 2 H), 7.79 (br t, J=7.94 Hz, 1 H), 7.67 (s, 1 H), 7.54 (br d, J=3.25 Hz, 1 H), 7.36 - 7.44 (m, 1 H), 7.34 (s, 1 H), 6.78 (br s,

		1 H), 6.69 (s, 1 H), 5.31 (s, 2 H), 3.99 (d, J=5.75 Hz, 2 H), 3.85 (s, 3 H), 3.51 (s, 3 H), 2.72 (s, 3 H)
Syn. Ex. 132	563.32 (M+1)/ 562.16 for C ₂₇ H ₂₆ N ₆ O ₆ S	δ 9.01 (br d, J=2.88 Hz, 1 H), 8.44 (br d, J=8.00 Hz, 1 H), 8.27 (d, J=1.50 Hz, 1 H), 8.10 (br s, 1 H), 7.67 (br dd, J=8.19, 4.19 Hz, 1 H), 7.58 (s, 1 H), 7.33 - 7.43 (m, 2 H), 6.45 (s, 1 H), 5.28 (s, 2 H), 4.17 - 4.21 (m, 2 H), 3.99 (br d, J=5.75 Hz, 2 H), 3.50 (s, 3 H), 2.63 (br t, J=6.32 Hz, 2 H), 2.57 (s, 3 H), 1.91 - 1.99 (m, 2 H)
Syn. Ex. 133	528.20 (M+1)/ 527.15 for C ₂₄ H ₂₅ N ₅ O ₇ S	δ 9.97 (br s, 1 H), 7.79 (br d, J=6.36 Hz, 1 H), 7.62 (s, 2 H), 7.35 - 7.48 (m, 2 H), 6.99 - 7.25 (m, 2 H), 6.50 (br s, 1 H), 5.33 (s, 2 H), 4.17 (br t, J=4.83 Hz, 2 H), 4.02 (br d, J=5.75 Hz, 2 H), 3.80 (s, 3 H), 3.51 (s, 3 H), 2.63 - 2.72 (m, 2 H), 1.93 - 2.02 (m, 2 H)
Syn. Ex. 134	514.33 (M+1)/ 513.13 for C ₂₃ H ₂₃ N ₅ O ₇ S	δ 10.80 (br s, 1 H), 7.73 (dd, J=7.82, 1.69 Hz, 1 H), 7.66 (s, 1 H), 7.59 - 7.64 (m, 1 H), 7.38 - 7.47 (m, 1 H), 7.36 (s, 1 H), 7.21 (br d, J=6.00 Hz, 1 H), 7.00 - 7.09 (m, 1 H), 6.72 (br s, 1 H), 5.34 (s, 2 H), 4.70 (br t, J=8.88 Hz, 2 H), 4.01 (d, J=5.75 Hz, 2 H), 3.78 (s, 3 H), 3.52 (s, 3 H), 3.11 (br t, J=9.01 Hz, 2 H)
Syn. Ex. 135	552.37 (M+1)/ 551.13 for C ₂₃ H ₂₃ F ₂ N ₅ O ₇ S	δ 8.11 (s, 1 H), 7.76 (br d, J=8.63 Hz, 1 H), 7.65 (s, 1 H), 7.47 (s, 1 H), 7.22 (d, J=8.76 Hz, 1 H), 6.59 - 6.94 (m, 3 H), 5.38 (s, 2 H), 4.14 (s, 2 H), 3.90 (s, 3 H), 3.84 (s, 3 H), 3.62 (s, 3 H), 2.02 (s, 1 H)
Syn. Ex. 136	530.20 (M+1)/ 529.16 for C ₂₄ H ₂₇ N ₅ O ₇ S	δ 9.52 (s, 1 H), 7.65 - 7.75 (m, 2 H), 7.43 (br s, 1 H), 7.37 (s, 1 H), 7.00 (s, 1 H), 6.89 (br d, J=7.63 Hz, 1 H), 6.84 (s, 1 H), 6.75 (s, 1 H), 5.37 (s, 2 H), 4.07 (q, J=7.00 Hz, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.85 (s, 3 H), 3.51 (s, 3 H), 2.25 - 2.38 (m, 3 H), 1.21 (t, J=6.94 Hz, 3 H)
Syn. Ex. 137	530.20 (M+1)/ 529.16 for C ₂₄ H ₂₇ N ₅ O ₇ S	δ 11.53 (s, 1 H) 7.68 (d, J=2.13 Hz, 1 H) 7.64 (s, 1 H) 7.58 (s, 1 H) 7.42 - 7.47 (m, 2 H) 7.37 (s, 1 H) 7.08 (d, J=8.63 Hz, 1 H) 6.86 (s, 1 H) 5.32 (s, 2 H) 4.02 (d, J=5.75 Hz, 2 H) 3.86 (s, 3 H) 3.75 (s, 3 H) 3.51 (s, 3 H) 2.60 (q, J=7.50 Hz, 2 H) 1.14 (t, J=7.57 Hz, 3 H).

Syn. Ex. 138	572.20 (M+1)/ 571.17 for C ₂₆ H ₂₉ N ₅ O ₈ S	δ 8.52 (br s, 1 H), 7.71 (s, 1 H), 7.39 - 7.52 (m, 2 H), 7.37 (s, 1 H), 6.74 - 6.88 (m, 4 H), 5.36 (s, 2 H), 4.34 (br s, 2 H), 4.11 (br s, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.86 (s, 3 H), 3.51 (s, 3 H), 1.82 - 1.97 (m, 2 H), 1.74 - 1.79 (m, 2 H), 1.63 - 1.70 (m, 2 H)
Syn. Ex. 139	556.20 (M+1)/ 555.18 for C ₂₆ H ₂₉ N ₅ O ₇ S	δ 7.67 (s, 1 H), 7.47 (s, 1 H), 7.40 - 7.45 (m, 1 H), 7.35 (s, 1 H), 6.60 (s, 1 H), 6.58 (s, 1 H), 6.50 (s, 1 H), 6.04 (br s, 1 H), 5.29 (s, 2 H), 4.01 (d, J=5.88 Hz, 2 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.51 (s, 3 H), 2.67 (br dd, J=3.56, 1.56 Hz, 2 H), 2.61 (br s, 2 H), 1.70 (br t, J=3.06 Hz, 4 H)
Syn. Ex. 140	556.20 (M+1)/ 555.18 for C ₂₆ H ₂₉ N ₅ O ₇ S	δ 9.75 (s, 1 H), 7.69 (d, J=8.00 Hz, 1 H), 7.62 (s, 1 H), 7.44 (br s, 1 H), 7.38 (s, 1 H), 7.04 (s, 1 H), 6.93 (br d, J=8.00 Hz, 1 H), 6.50 (s, 1 H), 5.34 (s, 2 H), 4.20 (br t, J=4.88 Hz, 2 H), 4.02 (d, J=5.75 Hz, 2 H), 3.81 (s, 3 H), 3.51 (s, 3 H), 2.60 - 2.71 (m, 4 H), 2.31 - 2.34 (m, 2 H), 1.94 - 2.03 (m, 3 H)
Syn. Ex. 141	548.37 (M+1)/ 547.15 for C ₂₄ H ₂₆ N ₅ O ₇ S	δ 10.49 (br s, 1 H), 7.68 (br s, 1 H), 7.62 (s, 1 H), 7.32 - 7.48 (m, 3 H), 7.09 - 7.19 (m, 1 H), 6.91 - 6.96 (m, 1 H), 5.40 (br s, 2 H), 4.05 - 4.15 (m, 2 H), 4.01 (br d, J=5.88 Hz, 3 H), 3.72 (br s, 3 H), 3.52 (s, 3 H), 2.53 - 2.59 (m, 2 H), 1.14 (t, J=7.57)
Syn. Ex. 142	544.43 (M+1)/ 543.18 for C ₂₅ H ₂₉ N ₅ O ₇ S	δ 11.51 (s, 1H) 7.68 (d, J = 2.00 Hz, 1H) 7.64 (s, 1H) 7.39 - 7.49 (m, 3H) 7.35 (s, 1H) 7.05 (d, J = 8.25 Hz, 1 H) 6.90 (s, 1H) 5.31 (s, 2H) 4.07 (q, J = 6.92 Hz, 2H) 4.02 (d, J = 5.75 Hz, 2H) 3.72 (s, 3H) 3.52 (s, 3H) 2.59 (q, J = 7.67 Hz, 2H) 1.40 (t, J = 6.88 Hz, 3H) 1.14 (t, J = 7.63 Hz, 3H)
Syn. Ex. 143	575.26 (M+1)/ 574.10 for C ₂₅ H ₂₃ N ₄ O ₇ S ₂	δ = 9.18 (t, J = 5.8 Hz, 1H), 8.15 (s, 1H), 7.64 (s, 1H), 7.20 (s, 1H), 7.11 - 6.66 (m, 3H), 5.69 - 5.46 (m, 1H), 5.29 (dd, J = 3.5, 15.8 Hz, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 3.01 - 2.70 (m, 4H), 2.07 - 1.90 (m, 2H)

Syn. Ex. 144	555.28 (M+1)/ 554.13 for C ₂₆ H ₂₃ FN ₄ O ₇ S	δ = 10.54 (s, 1H), 9.84 - 9.74 (m, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.20 (dd, J = 2.6, 8.9 Hz, 1H), 7.65 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.09 - 6.54 (m, 3H), 5.84 - 5.55 (m, 1H), 5.47 (dd, J = 3.8, 15.5 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.96 - 2.75 (m, 4H), 2.14 - 1.91 (m, 2H)
Syn. Ex. 145	502.36 (M+1)/ 501.13 for C ₂₂ H ₂₃ N ₅ O ₇ S	δ = 11.59 (s, 1H), 7.86 (dd, J = 1.4, 7.9 Hz, 1H), 7.65 (s, 1H), 7.62 - 7.49 (m, 2H), 7.49 - 7.40 (m, 1H), 7.37 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.84 (s, 1H), 5.33 (s, 2H), 4.02 (d, J = 5.8 Hz, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 3.52 (s, 3H)
Syn. Ex. 146	516.37 (M+1)/ 515.13 for C ₂₃ H ₂₂ FN ₅ O ₆ S	δ = 11.59 (s, 1H), 8.87 (t, J = 5.8 Hz, 1H), 7.85 (dd, J = 1.5, 7.8 Hz, 1H), 7.67 (s, 1H), 7.59 - 7.46 (m, 2H), 7.38 (s, 1H), 7.25 - 6.96 (m, 2H), 6.83 (s, 1H), 5.69 - 5.41 (m, 1H), 5.32 (s, 2H), 5.23 (dd, J = 3.4, 15.6 Hz, 1H), 4.19 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H)
Syn. Ex. 147	542.44 (M+1)/ 541.16 for C ₂₅ H ₂₇ N ₅ O ₇ S	δ = 8.24 (s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 6.86 (s, 1H), 6.67 (s, 1H), 5.28 (s, 2H), 4.02 (d, J = 5.8 Hz, 1H), 3.84 (s, 2H), 3.65 (s, 2H), 3.52 (s, 2H), 2.92 - 2.72 (m, 3H), 2.13 - 1.86 (m, 2H).
Syn. Ex. 148	561.29 (M+1)/ 560.10 for C ₂₄ H ₂₄ N ₄ O ₈ S ₂	δ = 7.69 - 7.83 (m, 1 H) 7.62 - 7.67 (m, 1 H) 6.86 - 7.21 (m, 3 H) 6.63 - 6.83 (m, 1 H) 4.25 (d, J=6.00 Hz, 2 H) 3.88 (s, 3 H) 3.74 (s, 3 H) 3.55 (s, 3 H) 2.76 - 2.94 (m, 4 H) 1.91 - 2.05 (m, 2 H)
Syn. Ex. 149	549.30 (M+1)/ 548.60 for C ₂₃ H ₂₄ N ₄ O ₈ S ₂	δ = 11.65 (s, 1 H) 7.64 - 7.79 (m, 4 H) 7.41 (s, 1 H) 6.97 - 7.15 (m, 2 H) 4.20 (d, J=1.00 Hz, 2 H) 3.79 (s, 3 H) 3.75 (s, 3 H) 3.53 (s, 3 H) 2.55 - 2.68 (m, 2 H) 1.17 (t, J=1.00 Hz, 3 H)
Syn. Ex. 150	516.4 (M+1)/ 515.5 for C ₂₃ H ₂₅ N ₅ O ₇ S	δ = 7.62 (s, 2 H) 7.44 (t, J=1.00 Hz, 1 H) 7.35 (s, 1 H) 7.12 - 7.30 (m, 2 H) 6.90 (d, J=1.00 Hz, 1 H) 6.71 (s, 1 H) 5.30 (s, 2 H) 4.03 (d, J=1.00 Hz, 2 H) 3.83 - 3.87 (m, 3 H) 3.66 (s, 3 H) 3.52 (s, 3 H) 2.25 (s, 3 H)

Syn. Ex. 151	530.3 (M+1)/ 529.12 for C ₂₃ H ₂₃ N ₅ O ₈ S	δ = 7.76 (dd, J=7.75, 1.38 Hz, 1 H) 7.63 (s, 1 H) 7.44 (br s, 1 H) 7.36 (s, 1 H) 7.13 (br s, 1 H) 7.01 (br s, 1 H) 6.40 (br s, 1 H) 5.28 (s, 2 H) 4.32 (s, 4 H) 4.02 (d, J=5.75 Hz, 2 H) 3.77 (s, 3 H) 3.52 (s, 3 H)
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EXAMPLE 152**[2549] KAT6A AlphaLISA Inhibition Screening Assay**

[2550] The Kat6a inhibitory activity of test compounds was determined using an Alpha Screen-based detection method. The assay reactions were conducted in a volume of 10 μ L in Alpha Plate, White 384 well plate (cat # 6008280, Perkin Elmer). The enzymatic reactions were performed in assay buffer pH 8.0 (50 mM Tris-HCl, 0.1 mM EDTA, 0.01% Tween-20, 1 mM Dithiothreitol, 0.1% BSA (fatty acid free) and 330 nM TSA (Trichostatin A)). 10 μ L reaction volume consisting of 25 nM of Recombinant KAT6A / MOZ (488-778) protein (Active motif, Catalog #81223), 400 nM Acetyl coenzyme A (Catalog #A2056, Sigma), 200 nM of Histone H3 peptide [(amino acids 1-21), biotin-labeled (BPS Biosciences, Catalog #52011)]. Test compounds were screened at different doses starting with 10 μ M, 3 fold dilution and 10 point Dose response curve. Enzyme and compounds solution were pre-incubated in assay plate for 60 or 10 min at room temperature then substrate and Acetyl coenzyme A solution were added to the plate. After addition, the plate was sealed with adhesive seals and incubated for 120 minutes at room temperature.

[2551] After 120 minutes of incubation, 5 μ L (10 μ g/mL) of AlphaLISA anti-acetyl-Lysine acceptor beads (Perkin Elmer, Catalog # AL143C) were added to the plate and it was incubated for 60 minutes at room temperature. Then 10 μ L (10 μ g/mL) of Alpha Streptavidin donor beads (Perkin Elmer, Catalog # 6760002S) were added to the plate which was further incubated for 60 minutes at room temperature. After incubation, the alpha signal was recorded by using Perkin Elmer Envision multi-mode reader. Percent inhibition of enzyme activity by test compounds were determined relative to vehicle control. Results are shown in Table 2 below.

[2552] Table 2. Kat6A % Inhibition.

Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M	Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M
1	100	100	72	100	100
2	100	71	73	100	100
3	100	100	74	100	100
4	100	100	75	92	59
5	100	83	76	96	74
6	100	99	77	98	96
7	99	97	78	100	100
8	100	99	79	100	99
9	100	61	80	100	100
10	100	100	81	99	91
11	100	100	82	99	94
12	97	38	83	99	98
13	100	99	84	100	100
14	100	100	85	95	91
15	100	100	86	100	86
16	98	98	87	100	95
17	100	99	88	98	99
18	98	97	89	100	100
19	98	100	90	100	99
20	100	100	91	100	99
21	99	100	92	100	100
22	100	100	93	98	90
23	100	100	94	100	100
24	100	99	95	100	100
25	100	100	96	100	100
26	100	99	97	100	100
27	100	100	98	92	78
28	100	100	99	100	91

Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M		Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M
29	100	100		100	100	92
30	100	100		101	100	100
31	99	86		102	100	99
32	97	75		103	99	97
33	100	96		104	92	25
34	100	86		105	99	68
35	100	100		106	44	10
36	97	93		107	100	100
37	100	100		108	100	99
38	99	100		109	98	95
39	100	92		110	58	9
40	99	99		111	54	0
41	100	87		112	98	70
42	100	93		113	100	98
43	98	96		114	100	100
44	100	97		115	100	100
45	99	85		116	100	100
46	100	98		117	100	100
47	96	98		118	100	97
47a	100	100		119	100	100
47b	100	96		120	100	100
48	100	96		121	94	100
49	100	94		122	100	100
50	96	98		123	100	100
51	100	89		124	100	100
52	100	100		125	101	100
53	100	98		126	100	101
54	97	97		127	100	101

Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M		Syn. Ex. #	Average Kat6A % inhibition @ 10 μ M	Average Kat6A % inhibition @ 1 μ M
55	100	100		128	100	101
56	99	78		129	102	102
57	100	70		130	102	100
58	97	91		131	100	99
59	100	100		132	99	100
60	100	93		133	103	100
61	100	60		134	101	97
62	100	100		135	97	96
63	96	95		136	99	99
64	100	94		137	89	98
65	100	100		138	114	111
66	100	93		139	114	119
67	100	100		140	104	106
68	100	96		141	91	104
69	99	96		142	99	110
70	100	100		143	99	101
71	100	100		144	99	101
				145	108	108
				146	101	99
				147	101	101
				148	117	115
				149	102	101
				150	103	101

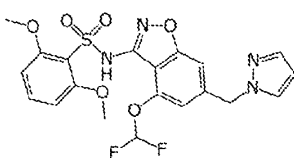
EXAMPLE 153

[2553] KAT6A and Kat6B IC50 using FLAG-tagged Kat6A and GST-tagged Kat6B

[2554] Compounds were suspended in as a stock of 10 mM in DMSO. Compounds were diluted and tested in 10-doses with 3-fold serial dilutions starting with 10 μ M as the highest

concentration. Compounds were preincubated in the reaction mixture with the enzyme (5 nM KAT6A, amino acids 488-778 with an N-terminal FLAG tag incorporated; 10 nM KAT6B protein, amino acids 657-1069 with an N-terminal GST tag). This preincubation was for 60 minutes prior to the addition of substrate. Inhibition of KAT6A/MSYT3 activity was tested on a Histone H3 peptide substrate and inhibition of KAT6B/MYST4 activity was tested on a Histone H4 peptide substrate, both in the presence of 1 μ M Acetyl-CoA. Reactions were performed in reaction buffer 50 mM Tris-HCl, pH 8.0, 50 mM NaCl, 0.1 mM EDTA, 1 mM EDTA, 1% DMSO and the reactions initiated with the addition of Acetyl-CoA as a co-factor, with histone acetylation measured with a radiometric activity assay using a radioisotope-based filtration assay. Inhibition of acetylation was calculated using with standard curve-fitting model and IC₅₀ determination. Results are shown in Table 3.

[2555] **Table 3: IC₅₀ of selected compounds assayed for inhibition of Kat6A and Kat6B.** This data demonstrates that a substituent on the 5-position of thiazoles (**Syn. Ex. 101**, **Syn. Ex. 102**), 5-position of pyridine (**Syn. Ex. 107**) and 4-position of pyrazole (**Syn. Ex. 52**, **Syn. Ex. 50**, **Syn. Ex. 7**, **Syn. Ex. 14**, **Syn. Ex. 15**, **Syn. Ex. 25**) result in poor Kat6B potency and thus confer selectivity against Kat6B. For comparison, data for known unsubstituted heteroaryl compounds (WO 2023/088233 and WO 2020/254946) is also provided.

Synthetic example / reference	Biochemical assay:Kat6A IC ₅₀ (nM)	Biochemical assay:Kat6B IC ₅₀ (nM)
Compound 59, WO 2023/088233	1	25.5
Syn. Ex. 101	4	2490
Syn. Ex. 102	2	2530
Compound 9, WO 2023/088233	1	332
Syn. Ex. 107	2	1630
	2	144

Synthetic example / reference	Biochemical assay:Kat6A IC ₅₀ (nM)	Biochemical assay:Kat6B IC ₅₀ (nM)
Claim 83 of WO 2023/088233		
Syn. Ex. 52	12	3670
Syn. Ex. 50	34	2396
Example 98, WO 2020/254946	1	40
Example 45, WO 2020/254946	1	24
Syn. Ex. 7	22	571
Syn. Ex. 14	2	878
Syn. Ex. 15	5	1025
Syn. Ex. 25	2	722

EXAMPLE 154**[2556] Cell Titer-Glo® Luminescent Cell Viability Assay in ZR-75-1 cells**

[2557] The CellTiter-Glo® Luminescent Cell Viability Assay is a homogeneous method employed to determine the number of metabolically active cells in culture. On day 0, ZR-75-1 cells were detached completely from the culture flasks using 0.25% trypsin-EDTA (Catalog # 25200056, Gibco). ZR-75-1 cells were seeded into white opaque-96 well culture plate (Catalog # 6005680, Perkin Elmer) at a density of 1500 cells per well in 200 µL of RPMI 1640 medium (Catalog # A1049101, Gibco) supplemented with 10% Fetal Bovine Serum (Catalog # 16000044, Gibco) and 1X Penicillin-Streptomycin (Catalog # 15140122, Gibco). The plates were incubated at 37 °C with 5% CO₂ for 24 hours. On day 1, the spent media was removed from each well of the plate and 180 µL of fresh RPMI 1640 complete media was added. Test compounds were diluted in 100% DMSO followed by complete media. 20 µL of media containing compounds were added to each well so that the final DMSO concentration was 0.5%. The test compounds were tested for 10 points DRC (10 µM top concentration, 3-fold dilution). The assay plates were incubated at 37 °C with 5% CO₂ for 48 hours. The test compounds and media were replenished every 48 hours till day 10.

[2558] On day 10, the CellTiter-Glo® 2.0 reagent (Catalog #G9242, Promega) was thawed and equilibrated to room temperature. Assay plates were removed from the incubator and

equilibrated to room temperature for about 30 minutes. 100 µL of spent media was removed from each well and then 50 µL of CellTiter-Glo® 2.0 Reagent was added. The plates were incubated on an orbital shaker at room temperature for 10 minutes to induce cell lysis and stabilize luminescent signal. The luminescent signal was recorded using Perkin Elmer Envision multi-mode plate reader. Percent cytotoxicity induced by test compounds was determined relative to vehicle control. EC₅₀ value for test compounds was calculated using GraphPad Prism software (four parameter-variable slope equation). Results are shown in Table 4 below.

[2559] **Table 4.** ZR-75-1 cell viability ranges for selected compounds provided herein. A < 0.1 µM; B 0.1-1 µM; C 1-10 µM.

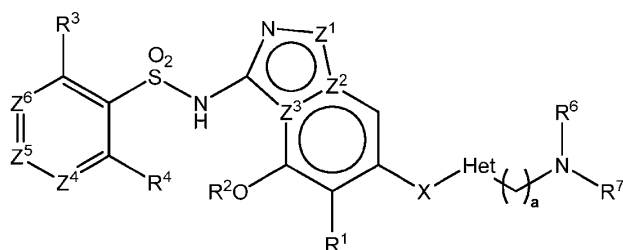
Syn. Ex. #	ZR-75-1: EC ₅₀ (µM)	Syn. Ex. #	ZR-75-1: EC ₅₀ (µM)
7	A	50	B
14	A	51	B
15	B	52	B
19	A	53	C
23	A	54	A
25	A	55	A
46	B	56	B
47	B		

[2560] This disclosure is not to be limited in scope by the embodiments disclosed in the examples which are intended as single illustrations of individual aspects, and any equivalents are within the scope of this disclosure. Various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[2561] Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated by reference herein in their entireties.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R¹ and R² together form alkylene;

R³ is -O-(CH₂)_b-R⁸;

b is 1-4;

R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

R¹² is alkyl or NR¹⁴R¹⁵;

R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R⁴ is H or alkoxy;

Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

(i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

(ii) Z¹ is NH or O, and Z² and Z³ are C, or

(iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

Z⁴, Z⁵ and Z⁶ are selected from (i), (ii), (iii) or (iv):

(i) Z⁴ is N, Z⁵ is CR⁵, and Z⁶ is CH,

(ii) Z⁴ is CR¹⁶, Z⁵ is N, and Z⁶ is CH,

(iii) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is N, or

(iv) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is CH;

R⁵ and R¹⁶ are selected from (i) or (ii):

(i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is O, $S(O)_x$ or CH_2 , where x is 0-2;

Het and R^6 are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

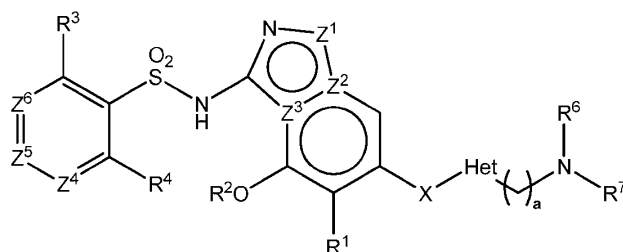
R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl,

alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.

2. A compound of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 are selected from (i) or (ii):

(i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

(ii) R^1 and R^2 together form alkylene;

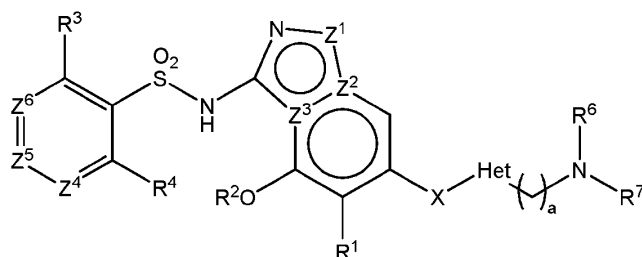
R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
 R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
 R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
 R^{12} is alkyl or $NR^{14}R^{15}$;
 R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
 R^4 is H or alkoxy;
 Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
 (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
 (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
 (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
 Z^4 is CR^{16} ;
 Z^5 is CR^5 ;
 Z^6 is N or CH;
 R^5 and R^{16} together form alkylene or heteroalkylene;
 X is O, $S(O)_x$ or CH_2 , where x is 0-2;
 Het and R^6 are selected from (i) or (ii):
 (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
 (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
 R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
 R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;
 and
 R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

3. A compound of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 are selected from (i) or (ii):

(i) R^1 is H, alkyl, haloalkyl or halo; and R^2 is alkyl, cycloalkyl or haloalkyl, or

(ii) R^1 and R^2 together form alkylene;

R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

R^{12} is alkyl or $NR^{14}R^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R^4 is H or alkoxy;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

(iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

(i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

(ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

(iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

(iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH ;

R^5 and R^{16} are selected from (i) or (ii):

(i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is O or $S(O)_x$, where x is 0-2;

Het and R^6 are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

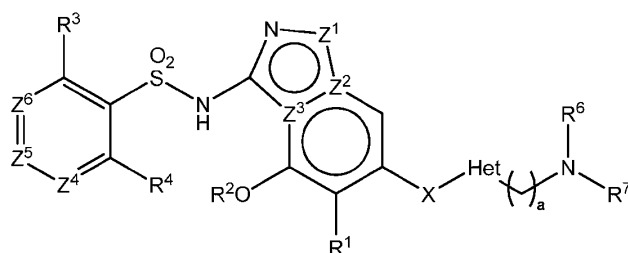
R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl,

alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

4. A compound of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

R^2 and R^4 together form heteroalkylene;

R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

R^{12} is alkyl or $NR^{14}R^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

(iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

(i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

(ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

(iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

(iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;

R^5 and R^{16} are selected from (i) or (ii):

(i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is O, $S(O)_x$ or CH_2 , where x is 0-2;

Het and R^6 are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

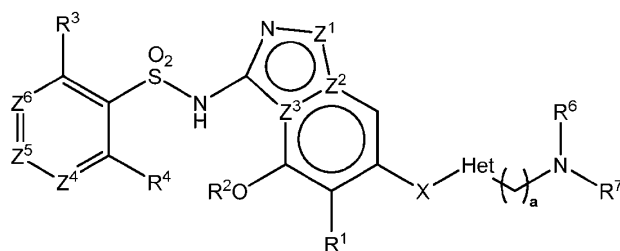
aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-\text{NH}-(\text{CH}_2)_2-\text{R}^{19}$, $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$ or $-\text{NR}^{20}\text{R}^{21}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-\text{NR}^9\text{R}^{10}$.

5. A compound of Formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 is H, alkyl, haloalkyl or halo;

R^2 is alkyl, cycloalkyl or haloalkyl;

R^3 is $-\text{O}-(\text{CH}_2)_b-\text{R}^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $\text{C}(\text{O})\text{R}^{11}$, $\text{C}(=\text{NH})(\text{R}^{12})$ or $\text{C}(=\text{N}-\text{O}-\text{R}^9)(\text{R}^{12})$;

R^9 and R^{10} are each independently H, alkyl or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $\text{NR}^{14}\text{R}^{15}$;

R^{12} is alkyl or $\text{NR}^{14}\text{R}^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R^4 is H or alkoxy;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

(iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

- (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
 (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
 (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
 (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;

R^5 and R^{16} are selected from (i) or (ii):

- (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

- (ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is $CR^{22}R^{23}$, where R^{22} and R^{23} are each independently H or alkyl;

Het and R^6 are selected from (i) or (ii):

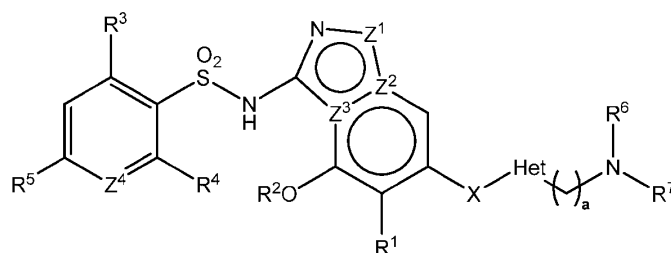
- (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

- (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$; and

R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-O-(CH_2)_2-R^{19}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$.

6. The compound of any one of claims 1-5 that has Formula Ia:



or a pharmaceutically acceptable derivative thereof.

7. The compound of any one of claims 1-6, wherein:

R^1 is H;

R^2 is alkyl, cycloalkyl or haloalkyl;

R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;

R^{11} is alkyl or alkoxy;

X is CH_2 ; and

R^{17} is alkoxy.

8. The compound of any one of claims 1-7, wherein:

R^1 is H;

R^2 is alkyl or haloalkyl;

R^8 is H, CN, OH, aryl, NR^9R^{10} or $C(O)R^{11}$;

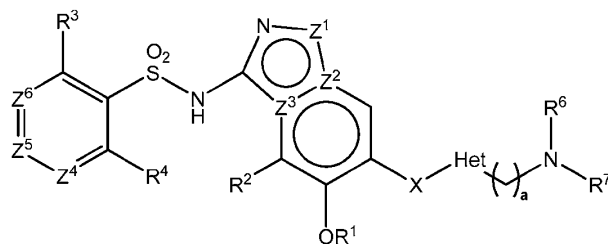
R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl;

R^{11} is alkoxy;

X is CH_2 ; and

R^{17} is alkoxy.

9. A compound of Formula II:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 together form alkylene;

R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

R^{12} is alkyl or $NR^{14}R^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R^4 is H or alkoxy;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

(iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

(i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

(ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

(iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

(iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH ;

R^5 and R^{16} are selected from (i) or (ii):

(i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is O, $S(O)_x$ or CH_2 , where x is 0-2;

Het and R^6 are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

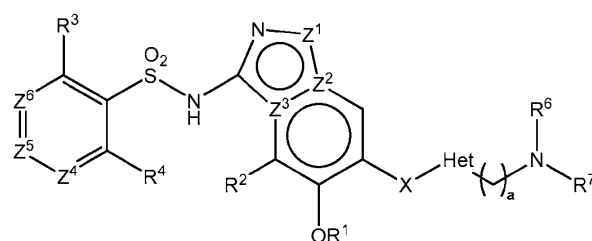
R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl,

alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^{20}R^{21}$.

10. A compound of Formula II:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 are selected from (i) or (ii);

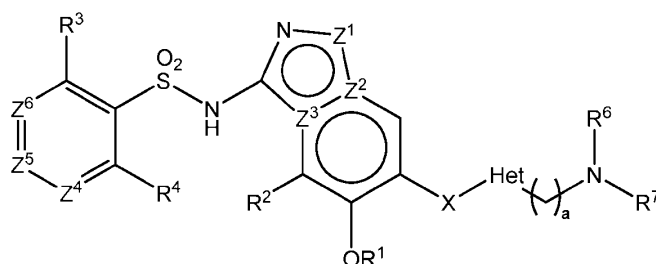
- (i) R^1 is alkyl, cycloalkyl or haloalkyl; and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or
- (ii) R^1 and R^2 together form alkylene;
- R^3 is $-O-(CH_2)_b-R^8$;
- b is 1-4;
- R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
- R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
- R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
- R^{12} is alkyl or $NR^{14}R^{15}$;
- R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
- R^4 is H or alkoxy;
- Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
- (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
- (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
- (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
- Z^4 is CR^{16} ;
- Z^5 is CR^5 ;
- Z^6 is N or CH;
- R^5 and R^{16} together form alkylene or heteroalkylene;
- X is O, $S(O)_x$ or CH_2 , where x is 0-2;
- Het and R^6 are selected from (i) or (ii):
- (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
- (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
- R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
- R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19}

is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

11. A compound of Formula II:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 are selected from (i) or (ii):

(i) R^1 is alkyl, cycloalkyl or haloalkyl, and R^2 is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo, or

(ii) R^1 and R^2 together form alkylene;

R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

R^{12} is alkyl or $NR^{14}R^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

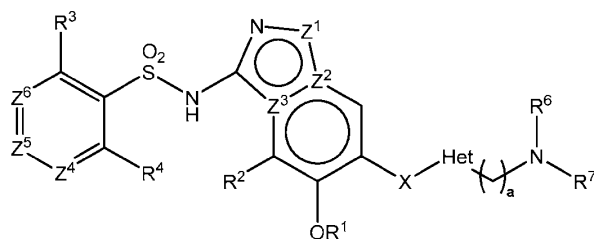
R^4 is H or alkoxy;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

- (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
 Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):
 (i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,
 (ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,
 (iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or
 (iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH;
 R^5 and R^{16} are selected from (i) or (ii):
 (i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or
 (ii) R^5 and R^{16} together form alkylene or heteroalkylene;
 X is O or $S(O)_x$, where x is 0-2;
 Het and R^6 are selected from (i) or (ii):
 (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
 (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
 R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
 R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;
 and
 R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxyethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.
12. A compound of Formula II:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R¹ is alkyl, cycloalkyl or haloalkyl;

R² is H, alkyl, haloalkyl, alkoxy, cycloalkoxy, haloalkoxy or halo;

R³ is -O-(CH₂)_b-R⁸;

b is 1-4;

R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹,

C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

R¹² is alkyl or NR¹⁴R¹⁵;

R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R⁴ is H or alkoxy;

Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

(i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

(ii) Z¹ is NH or O, and Z² and Z³ are C, or

(iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

Z⁴, Z⁵ and Z⁶ are selected from (i), (ii), (iii) or (iv):

(i) Z⁴ is N, Z⁵ is CR⁵, and Z⁶ is CH,

(ii) Z⁴ is CR¹⁶, Z⁵ is N, and Z⁶ is CH,

(iii) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is N, or

(iv) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is CH;

R⁵ and R¹⁶ are selected from (i) or (ii):

(i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

X is $\text{CR}^{22}\text{R}^{23}$, where R^{22} and R^{23} are each independently H or alkyl;

Het and R^6 are selected from (i) or (ii):

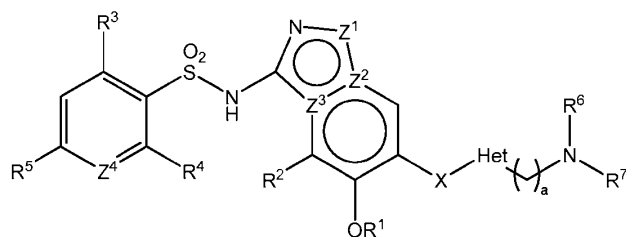
(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(\text{CH}_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-\text{C}(\text{O})\text{R}^{17}$; and

R^{17} is alkoxy, alkenyloxy, alkynyloxy or $-\text{O}-(\text{CH}_2)_2-\text{R}^{19}$; where R^{19} is $-\text{OR}^9$ or $-\text{NR}^9\text{R}^{10}$.

13. A compound of any one of claims 9-12, wherein the compound has Formula IIa:



or a pharmaceutically acceptable derivative thereof.

14. The compound of any one of claims 9-13, wherein:

R^1 is alkyl, cycloalkyl or haloalkyl;

R^2 is H;

R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $\text{C}(\text{O})\text{R}^{11}$;

R^9 and R^{10} are each independently H or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl or alkoxy;

R^{11} is alkyl or alkoxy;

X is CH_2 ; and

R^{17} is alkoxy.

15. The compound of any one of claims 9-13, wherein:

R^1 is alkyl or haloalkyl;

R^2 is H;

R^8 is H, CN, OH, aryl, NR^9R^{10} or $\text{C}(\text{O})\text{R}^{11}$;

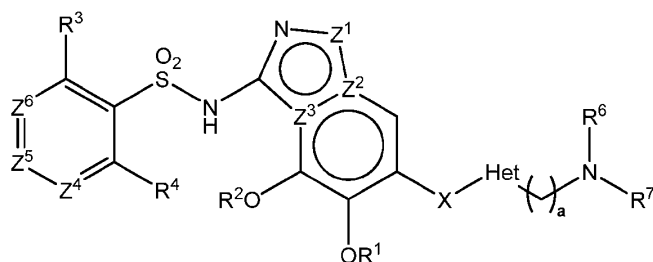
R^9 and R^{10} are each independently H or $\text{C}(\text{O})\text{R}^{13}$; where R^{13} is alkyl;

R^{11} is alkoxy;

X is CH_2 ; and

R^{17} is alkoxy.

16. A compound of Formula III:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R¹ and R² together form alkylene;

R³ is -O-(CH₂)_b-R⁸;

b is 1-4;

R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹, C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or NR¹⁴R¹⁵;

R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

R¹² is alkyl or NR¹⁴R¹⁵;

R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R⁴ is H or alkoxy;

Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

(i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

(ii) Z¹ is NH or O, and Z² and Z³ are C, or

(iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

Z⁴, Z⁵ and Z⁶ are selected from (i), (ii), (iii) or (iv):

(i) Z⁴ is N, Z⁵ is CR⁵, and Z⁶ is CH,

(ii) Z⁴ is CR¹⁶, Z⁵ is N, and Z⁶ is CH,

(iii) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is N, or

(iv) Z⁴ is CR¹⁶, Z⁵ is CR⁵, and Z⁶ is CH;

R⁵ and R¹⁶ are selected from (i) or (ii):

(i) R⁵ and R¹⁶ are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R⁵ and R¹⁶ together form alkylene or heteroalkylene;

X is O, S(O)_x or CH₂, where x is 0-2;

Het and R⁶ are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R⁶ is -(CH₂)₁₋₂-, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R⁷ is -C(O)R¹⁷, -S(O)R¹⁸ or -SO₂R¹⁸;

R¹⁷ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, -NH-(CH₂)₂-R¹⁹, -O-(CH₂)₂-R¹⁹ or -NR²⁰R²¹; where R¹⁹

is -OR⁹ or -NR⁹R¹⁰, and R²⁰ and R²¹ are each independently H, alkyl, cycloalkyl or haloalkyl;

and

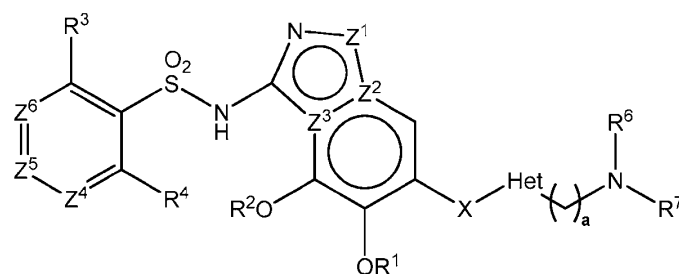
R¹⁸ is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl,

alkoxymethylalkynyl, aminomethylalkynyl, or -NR²⁰R²¹.

17. A compound of Formula III:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R¹ and R² are selected from (i) or (ii):

(i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

(ii) R¹ and R² together form alkylene;

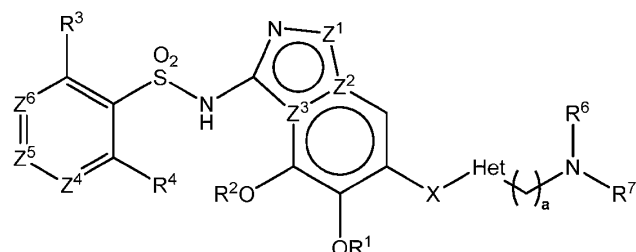
R³ is -O-(CH₂)_b-R⁸;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$, $C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;
 R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;
 R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;
 R^{12} is alkyl or $NR^{14}R^{15}$;
 R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;
 R^4 is H or alkoxy;
 Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):
 (i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,
 (ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or
 (iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;
 Z^4 is CR^{16} ;
 Z^5 is CR^5 ;
 Z^6 is N or CH;
 R^5 and R^{16} together form alkylene or heteroalkylene;
 X is O, $S(O)_x$ or CH_2 , where x is 0-2;
 Het and R^6 are selected from (i) or (ii):
 (i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or
 (ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;
 R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;
 R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;
 and
 R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxyethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

18. A compound of Formula III:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R^1 and R^2 are selected from (i) or (ii):

(i) R^1 and R^2 are each independently alkyl, cycloalkyl or haloalkyl, or

(ii) R^1 and R^2 together form alkylene;

R^3 is $-O-(CH_2)_b-R^8$;

b is 1-4;

R^8 is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR^9R^{10} , $C(O)R^{11}$,

$C(=NH)(R^{12})$ or $C(=N-O-R^9)(R^{12})$;

R^9 and R^{10} are each independently H, alkyl or $C(O)R^{13}$; where R^{13} is alkyl, alkoxy or $NR^{14}R^{15}$;

R^{11} is hydroxy, alkyl, alkoxy or $NR^{14}R^{15}$;

R^{12} is alkyl or $NR^{14}R^{15}$;

R^{14} and R^{15} are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R^4 is H or alkoxy;

Z^1 , Z^2 and Z^3 are selected from (i), (ii) or (iii):

(i) Z^1 is N, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N,

(ii) Z^1 is NH or O, and Z^2 and Z^3 are C, or

(iii) Z^1 is CH, one of Z^2 and Z^3 is C and the other of Z^2 and Z^3 is N;

Z^4 , Z^5 and Z^6 are selected from (i), (ii), (iii) or (iv):

(i) Z^4 is N, Z^5 is CR^5 , and Z^6 is CH,

(ii) Z^4 is CR^{16} , Z^5 is N, and Z^6 is CH,

(iii) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is N, or

(iv) Z^4 is CR^{16} , Z^5 is CR^5 , and Z^6 is CH ;

R^5 and R^{16} are selected from (i) or (ii):

(i) R^5 and R^{16} are each independently H, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl or haloalkyl, or

(ii) R^5 and R^{16} together form alkylene or heteroalkylene;

X is O or $S(O)_x$, where x is 0-2;

Het and R^6 are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R^6 is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R^6 is $-(CH_2)_{1-2}-$, and R^6 and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$, $-S(O)R^{18}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl,

haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl,

aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy,

haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl;

and

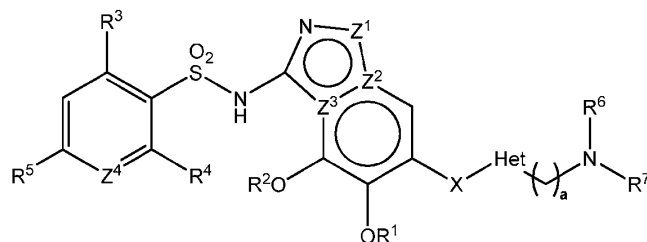
R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl,

haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl,

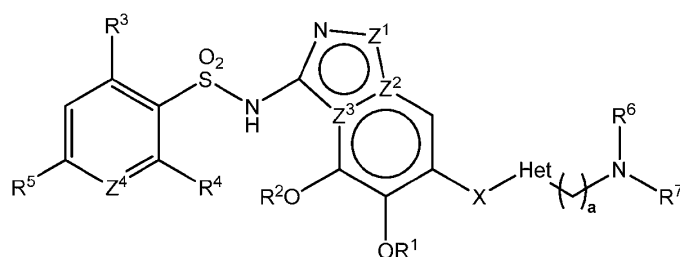
aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl,

alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

19. The compound of any one of claims 16-18, wherein the compound has Formula IIIa:



20. A compound of Formula IIIa:



or a pharmaceutically acceptable derivative thereof, wherein:

a is 0-2;

R¹ and R² are selected from (i) or (ii):

(i) R¹ and R² are each independently alkyl, cycloalkyl or haloalkyl, or

(ii) R¹ and R² together form alkylene;

R³ is -O-(CH₂)_b-R⁸;

b is 1-4;

R⁸ is H, CN, OH, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, NR⁹R¹⁰, C(O)R¹¹,

C(=NH)(R¹²) or C(=N-O-R⁹)(R¹²);

R⁹ and R¹⁰ are each independently H, alkyl or C(O)R¹³; where R¹³ is alkyl, alkoxy or

NR¹⁴R¹⁵;

R¹¹ is hydroxy, alkyl, alkoxy or NR¹⁴R¹⁵;

R¹² is alkyl or NR¹⁴R¹⁵;

R¹⁴ and R¹⁵ are each independently H, OH, alkoxy or alkyl, or together with the nitrogen atom to which they are attached form heterocyclyl;

R⁴ is H or alkoxy;

Z¹, Z² and Z³ are selected from (i), (ii) or (iii):

(i) Z¹ is N, one of Z² and Z³ is C and the other of Z² and Z³ is N,

(ii) Z¹ is NH or O, and Z² and Z³ are C, or

(iii) Z¹ is CH, one of Z² and Z³ is C and the other of Z² and Z³ is N;

Z⁴ is N or CR¹⁶, where R¹⁶ is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

R⁵ is H, alkyl, haloalkyl, alkoxy, halo, alkenyl or alkynyl;

X is O, S(O)_x or CH₂, where x is 0-2;

Het and R⁶ are selected from (i) or (ii):

(i) Het is a 5- or 6-membered heteroaryl, and R⁶ is H, alkyl or haloalkyl, or

(ii) Het is a 5- or 6-membered heteroaryl, R⁶ is -(CH₂)₁₋₂-, and R⁶ and Het together with the atoms to which they are attached form a 5,5-, 5,6-, 5,7-, 6,5-, 6,6- or 6,7-bicyclic ring system;

R^7 is $-C(O)R^{17}$ or $-SO_2R^{18}$;

R^{17} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, methylaminomethylalkenyl, dimethylaminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, methylaminomethylalkynyl, dimethylaminomethylalkynyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, $-NH-(CH_2)_2-R^{19}$, $-O-(CH_2)_2-R^{19}$ or $-NR^{20}R^{21}$; where R^{19} is $-OR^9$ or $-NR^9R^{10}$, and R^{20} and R^{21} are each independently H, alkyl, cycloalkyl or haloalkyl; and

R^{18} is alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, cyanoalkenyl, hydroxymethylalkenyl, alkoxymethylalkenyl, aminomethylalkenyl, alkynyl, haloalkynyl, cyanoalkynyl, hydroxymethylalkynyl, alkoxymethylalkynyl, aminomethylalkynyl, or $-NR^9R^{10}$.

21. The compound of any one of claims 16-20, wherein:

R^1 and R^2 are selected from (i) or (ii):

(i) R^1 and R^2 are each alkyl, or

(ii) R^1 and R^2 together form alkylene;

R^8 is H, CN, OH, aryl, heteroaryl, NR^9R^{10} or $C(O)R^{11}$;

R^9 and R^{10} are each independently H or $C(O)R^{13}$; where R^{13} is alkyl or alkoxy;

R^{11} is alkyl or alkoxy;

R^5 and R^{16} together form alkylene;

X is O or CH_2 ;

R^{17} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl; and

R^{18} is alkyl, haloalkyl, alkoxyalkyl, aminoalkyl, alkenyl, haloalkenyl, alkynyl or hydroxymethylalkynyl.

22. The compound of any one of claims 1-4, 6, 9-11, 13 and 16-21, wherein X is O.

23. The compound of any one of claims 1, 2, 4-10 and 11-21, wherein X is CH_2 .

24. The compound of any one of claims 1-23, wherein a is 0 or 1.

25. The compound of any one of claims 1-8, wherein R^2 is alkyl.

26. The compound of any one of claims 1-8, wherein R^2 is haloalkyl.

27. The compound of any one of claims 1-8, wherein R^2 is difluoromethyl.

28. The compound of any one of claims 9-15, wherein R^1 is alkyl.

29. The compound of any one of claims 9-15, wherein R^1 is haloalkyl.

30. The compound of any one of claims 9-15, wherein R¹ is difluoromethyl.
31. The compound of any one of claims 1-6, wherein R¹ is H.
32. The compound of any one of claims 9-15, wherein R² is H.
33. The compound of any one of claims 16-21, wherein R¹ and R² together form C₁-alkylene optionally substituted with one or more halo or methyl.
34. The compound of any one of claims 1-33, wherein b is 1 or 2.
35. The compound of any one of claims 1-6, 9-13 and 16-21, wherein R⁸ is H, phenyl, 4-fluorophenyl, morpholinyl, COOH, COOMe, C(=NH)NHOH, tetrazolyl, oxadiazolyl, triazolyl, pyridyl, imidazolyl, oxazolidinyl, NHC(O)OMe, cyano, hydroxy, amino or acetylamino.
36. The compound of any one of claims 1-35, wherein R⁸ is hydrogen.
37. The compound of any one of claims 1-36, wherein R⁴ is H.
38. The compound of any one of claims 1-37, wherein R⁴ is methoxy.
39. The compound of any one of claims 1-38, wherein Z¹ is NH or O, and Z² and Z³ are C.
40. The compound of any one of claims 1-39, wherein Z¹ is O, and Z² and Z³ are C.
41. The compound of any one of claims 1-40, wherein Z⁴ is N.
42. The compound of any one of claims 1-40, wherein Z⁴ is CR¹⁶.
43. The compound of any one of claims 1-42, wherein R⁵ is H, cyano, alkoxy or alkyl, and R¹⁶ is H, alkyl, alkoxy, halo or alkynyl.
44. The compound of any one of claims 1-43, wherein R⁵ is H, cyano, methoxy or methyl, and R¹⁶ is H, methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, fluoro, ethynyl or propynyl.
45. The compound of any one of claims 1-44, wherein Het is a 5- or 6-membered heteroaryl, and R⁶ is H or alkyl.
46. The compound of any one of claims 1-45, wherein Het is a 5-membered heteroaryl, and R⁶ is H or methyl.
47. The compound of any one of claims 1-46, wherein Het is pyrazolyl, oxazolyl, thiazolyl or pyridyl, and R⁶ is H or methyl.
48. The compound of any one of claims 1-47, wherein Het is pyrazolyl, and R⁶ is H or methyl.
49. The compound of any one of claims 1-48, wherein R⁷ is -C(O)R¹⁷.
50. The compound of any one of claims 1-48, wherein R⁷ is -S(O)R¹⁸.
51. The compound of any one of claims 1-48, wherein R⁷ is -SO₂R¹⁸.

52. The compound of any one of claims 1-6, 9-13 and 16-21, wherein R¹⁷ is alkyl, alkoxy, alkenyl, haloalkenyl, alkynyl, NR²⁰R²¹ or hydroxyalkynyl.
53. The compound of any one of claims 1-6, 9-13 and 16-21, wherein R¹⁷ is methyl, methoxy, NHMe, ethenyl, 1-fluoro-1-ethenyl, ethynyl or 1-propyn-1-yl.
54. The compound of any one of claims 1-53, wherein R¹⁸ is methyl or tert-butyl.
55. The compound of any one of claims 1-54, wherein the compound is any one of the compounds disclosed herein.
56. A pharmaceutical composition, comprising the compound of any one of claims 1-55 and a pharmaceutically acceptable carrier.
57. A method of treating a subject having cancer, comprising administering to the subject the compound of any one of claims 1-55 or the pharmaceutical composition of claim 56.
58. A method of treating a subject having a myc-driven cancer, comprising administering to the subject the compound of any one of claims 1-55 or the pharmaceutical composition of claim 56.