

Azetidine Cyclic Ureas

This application claims priority to International Patent Application No. PCT/CN2020/091416, filed on May 20, 2020, the entire contents of which
5 are incorporated herein by reference.

Introduction

Tumor necrosis factor alpha (TNF- α)-induced NF- κ B activation plays a central role in the immune system and inflammatory responses.
10 Receptor-interacting protein 1 (RIP1) is a multi-functional signal transducer involved in mediating nuclear factor κ B (NF- κ B) activation, apoptosis, and necroptosis. The kinase activity of RIP1 is critically involved in mediating necroptosis, a caspase-independent pathway of necrotic cell death. Holler et al. Nat Immunol 2000; 1: 489–495; Degterev
15 et al. Nat Chem Biol 2008; 4: 313–321.

Necroptosis plays a role in various pathological forms of cell death, including ischemic brain injury, neurodegenerative diseases and viral infections. Dunai, et al., Dec 2011, Pathol. Oncol. Res.: POR 17 (4): 791–800. Necrostatin-1 (Nec-1), a small molecule inhibitor of RIP1 kinase
20 activity, can block necroptosis. Degterev et al. Nat Chem Biol 2005; 1: 112–119.

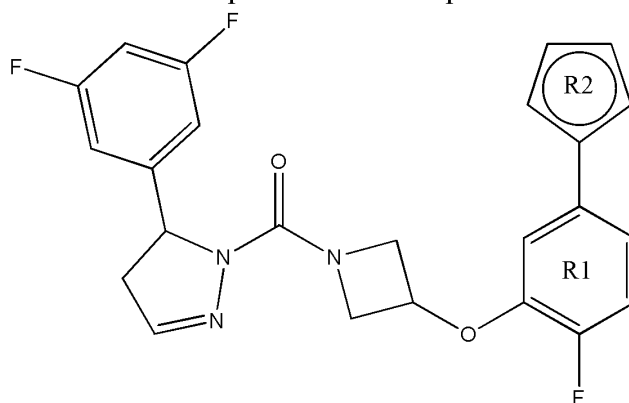
RIP1 can contribute to D-1 immunotherapy resistance (e.g. Manguso et al., 2017 Nature 547, 413–418) and can act as a checkpoint kinase governing tumor immunity (e.g. Wang et al, Cancer Cell 34, 757–774, Nov
25 12, 2018).

Related patent publications include: US 9974762, US 10092529, US6756394, US8278344, US20120122889, US20090099242, US20100317701, US20110144169, US20030083386, US201200309795, WO2009023272, WO2010075290, WO2010075561, WO2012125544, and
30 WO 2020/103884.

Summary of the Invention

The invention provides compounds that are inhibitors of necrosis, necroptosis, ferroptosis, human receptor interacting protein 1 kinase (RIP1) or related indications, and prodrugs thereof, which are hydrolyzed, typically in the gut or blood, to yield the corresponding inhibitors. In
 5 embodiments the inhibitors provide unexpectedly exceptional metabolic stability, evidenced by liver microsome data and PK data.

In an aspect the invention provides a compound of formula I:



10

I,

wherein:

R1 is 1-F substituted C6 aryl comprising 0, 1 or 2 N heteroatoms; and

R2 is C5 aryl comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N
 15 heteroatoms and an O or S heteroatom, substituted with 0-3 substituents
 selected from halide, optionally-substituted N, S or O, and optionally-
 substituted hydrocarbyl;

or a salt, hydrate or stereoisomer thereof.

In embodiments:

the R2 substituents are independently C0-C6: aldehyde, aldimine,
 20 alkanoyloxy, alkoxy, alkoxy carbonyl, alkyloxy, alkyl, alkenyl, alkynyl,
 amine, azo, halogens, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl,
 ester, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, iscyante, N-
 tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate,

phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl or trifluoromethyl ether (OCF₃);

R1 comprises N2, N4 or N2/N4 ("/" means "and", unless otherwise specified);

5 R2 comprises N1, N1/N2, N2/N3, N3/N4, N2/N5; N2/N4, S2/N4, N2/S4, S3/N4, N2/S3, N3/O4, N2/N3/S5, N2/N3/O5, N2/N3/N5 or N2/N3/N4; or

any combination of the foregoing substituents.

10 In an aspect the invention provides a compound having a structure disclosed herein.

In an aspect the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound, a salt, hydrate or stereoisomer thereof, disclosed herein and one or more pharmaceutically acceptable excipients, in predetermined, unit dosage
15 form.

In an aspect the invention provides use of a compound, a salt, hydrate or stereoisomer thereof, or composition disclosed herein in the manufacture of a medicament for inhibiting necrosis, necroptosis, ferroptosis, human RIP1, or related indications, in a person in need thereof.

20 In an aspect the invention provides a compound, a salt, hydrate or stereoisomer thereof, or composition disclosed herein for use in inhibiting necrosis, necroptosis, ferroptosis, human RIP1, or related indications in a person in need thereof, or in the manufacture of a medicament thereof in a person in need thereof.

25 In an aspect the invention provides a method of using a compound, a salt, hydrate or stereoisomer thereof, or composition disclosed herein for to inhibit necrosis, necroptosis, ferroptosis, human RIP1, or related indications in a person in need thereof, or in the manufacture of a medicament thereof in a person in need thereof.

The invention encompasses all combination of the particular embodiments recited herein, as if each combination had been laboriously recited.

5 **Description of particular embodiments of the invention**

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the
10 appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

The term "alkyl" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups of 1-18, or 1-12, or 1-6, or 1-3
15 carbon atoms. Examples of the alkyl group include methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu"). Other examples of the alkyl group include 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-
20 methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl groups.

Lower alkyl means 1-8, preferably 1-6, more preferably 1-4 carbon
25 atoms, e.g., 1-3 carbon atoms, lower alkenyl or alkynyl means 2-8, 2-6 or 2-4 carbon atoms.

The term "alkenyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkenyl
30 group may be selected from ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-

methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups.

The term "alkynyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one $C\equiv C$ triple bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butynyl, 2-butynyl, and 3-butynyl groups.

The term "cycloalkyl" refers to a hydrocarbon group selected from saturated and partially unsaturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups. For example, the cycloalkyl group may be of 3-12, or 3-8, or 3-6, or 3-4, carbon atoms. Even further for example, the cycloalkyl group may be a monocyclic group of 3-12, or 3-8, or 3-6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. Examples of the bicyclic cycloalkyl groups include those having 7-12 ring atoms arranged as a bicycle ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. The ring may be saturated or have at least one double bond (i.e. partially unsaturated), but is not fully conjugated, and is not aromatic, as aromatic is defined herein.

The term "aryl" herein refers to a group selected from: 5- and 6-membered carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected, for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. 5- or 6-membered "aryl"

may comprise 0, 1, 2 or 3 heteroatoms selected from the group consisting of N, S or O.

For example, the aryl group is selected from 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

The term "halogen" or "halo" refers to F, Cl, Br or I.

The term "heteroalkyl" refers to alkyl comprising at least one heteroatom.

The term "heteroaryl" refers to a group selected from:

5- to 7-membered aromatic, e.g., 5- to 6-membered aromatic, monocyclic rings comprising 1, 2, 3 or 4 heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon;

8- to 12-membered bicyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and

11- to 14-membered tricyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms

being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

For example, the heteroaryl group includes a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring.

- 5 For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring.

When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some
10 embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-
15 pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl,
20 triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as 1H-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as 1H-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-
25 thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinoline.

The term "heterocyclic" or "heterocycle" or "heterocyclyl" refers to a
30 ring selected from 4- to 12-membered, e.g., 3- to 6-membered, or 3 to 5-membered, or 4 to 5-membered, or 5 to 6-membered, or 4- to 6-membered,

monocyclic, bicyclic and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atoms in addition to 1, 2, 3 or 4 heteroatoms, selected from oxygen, sulfur, and nitrogen. "Heterocycle" also refers to a 5- to 7-membered heterocyclic ring comprising at least one
 5 heteroatom selected from N, O, and S fused with 5-, 6-, and/or 7-membered cycloalkyl, carbocyclic aromatic or heteroaromatic ring, provided that the point of attachment is at the heterocyclic ring when the heterocyclic ring is fused with a carbocyclic aromatic or a heteroaromatic ring, and that the point of attachment can be at the cycloalkyl or
 10 heterocyclic ring when the heterocyclic ring is fused with cycloalkyl.

"Heterocycle" also refers to an aliphatic spirocyclic ring comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have at least one double bond (i.e. partially unsaturated). The heterocycle
 15 may be substituted with oxo. The point of the attachment may be carbon or heteroatom in the heterocyclic ring. A heterocycle is not a heteroaryl as defined herein.

Examples of the heterocycle include, but not limited to, (as numbered from the linkage position assigned priority 1) 1-pyrrolidinyl, 2-pyrrolidinyl,
 20 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl,
 25 homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl and 1,4-diazepane 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl,
 30 tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl,

pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1, 1-dioxo-1-thiomorpholinyl.

The term "fused ring" herein refers to a polycyclic ring system, e.g., a bicyclic or tricyclic ring system, in which two rings share only two ring atoms and one bond in common. Examples of fused rings may comprise a fused bicyclic cycloalkyl ring such as those having from 7 to 12 ring atoms arranged as a bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems as mentioned above; a fused bicyclic aryl ring such as 7 to 12 membered bicyclic aryl ring systems as mentioned above, a fused tricyclic aryl ring such as 10 to 15 membered tricyclic aryl ring systems mentioned above; a fused bicyclic heteroaryl ring such as 8- to 12-membered bicyclic heteroaryl rings as mentioned above, a fused tricyclic heteroaryl ring such as 11- to 14-membered tricyclic heteroaryl rings as mentioned above; and a fused bicyclic or tricyclic heterocyclyl ring as mentioned above.

In embodiments substituents are selected from optionally substituted heteroatom and optionally substituted, optionally hetero-, optionally cyclic C1-C18 hydrocarbyl, particularly wherein the optionally substituted, optionally hetero-, optionally cyclic C1-C18 hydrocarbyl is optionally-substituted, optionally hetero-, optionally cyclic alkyl, alkenyl or alkynyl, or optionally-substituted, optionally hetero- aryl; and/or the optionally substituted heteroatom is halogen, optionally substituted hydroxyl (such as alkoxy, aryloxy), optionally substituted acyl (such as formyl, alkanoyl, carbamoyl, carboxyl, amido), optionally substituted amino (such as amino, alkylamino, dialkylamino, amido, sulfamidyl), optionally substituted thiol (such as mercapto, alkylthiol, aryl thiol), optionally substituted sulfinyl or

sulfonyl (such as alkylsulfinyl, arylsulfinyl, alkyl sulfonyl, arylsulfonyl), nitro, or cyano.

In embodiments, substituents are selected from: halogen, -R', -OR', =O, =NR', =N-OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R',
 5 -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR'-SO₂NR''', -NR''CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂, -N₃, -CH(Ph)₂, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl, in a number ranging from zero to three, with those groups having zero, one or
 10 two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C1-C8)alkyl and heteroalkyl, (C1-C8)alkyl and heteroalkyl substituted with one to three halogens, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C1-C4)alkyl
 15 groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. Hence, -NR'R'' includes 1-pyrrolidinyl and 4-morpholinyl, "alkyl" includes groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃), and when the aryl group is 1,2,3,4-tetrahydronaphthalene, it may be substituted with a
 20 substituted or unsubstituted (C3-C7)spirocycloalkyl group. The (C3-C7)spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl".

Preferred substituents are selected from: halogen, -R', -OR', =O, -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -
 25 OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'-SO₂NR''R''', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl, where R' and R'' are as defined above.

Preferred substituents are disclosed herein and exemplified in the tables, structures, examples, and claims, and may be applied across
 30 different compounds of the invention, i.e. substituents of any given compound may be combinatorically used with other compounds.

In particular embodiments applicable substituents are independently substituted or unsubstituted heteroatom, substituted or unsubstituted, 0-3 heteroatom C1-C6 alkyl, C1-C3 alkyl, or C1-C2 alkyl, substituted or unsubstituted, 0-3 heteroatom C2-C6 alkenyl, substituted or unsubstituted, 5 0-3 heteroatom C2-C6 alkynyl, or substituted or unsubstituted, 0-3 heteroatom C6-C14 aryl, or C5-C6 aryl, wherein each heteroatom is independently oxygen, phosphorus, sulfur or nitrogen.

In more particular embodiments, applicable substituents are independently aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, 10 alkyloxy, alkyl, alkenyl, alkynyl, amine, azo, halogen, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl, ester, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, iscyante, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl or trifluoromethyl ether 15 (OCF₃). It shall be noted that, when used in the context of substituents, terms such as aldehyde, aldimine, amine, azo, ester, imine, isocyanide, iscyante, nitrate, nitrile, nitrite, phosphate, sulfide or trifluoromethyl ether equal to aldehyde group, aldimine group, amino, azo group, ester group, imino, isocyanide group, iscyante group, nitrate group, nitrile group, nitrite 20 group, phosphate group, sulfide group or trifluoromethyl ether group, respectively.

Combinations of substituents as disclosed herein are those that result in the formation of stable or chemically feasible compounds. For abbreviation or according to common practice, certain hydrogen atoms 25 attached to a certain atom (e.g., a carbon atom C or a nitrogen atom N) are not specifically spelled out in a chemical structure, formula, or notation; hydrogen atoms are deemed to be present to the extent the valences of the certain atom (e.g., C or N) are completed.

The compounds may contain an asymmetric center and may thus exist 30 as enantiomers. Where the compounds possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and

diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds and/or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

The term “substantially pure” means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer(s). In some embodiments, the term “substantially pure” means that the target stereoisomer contains no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer(s).

When compounds contain olefin double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

Some of the compounds may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl $-\text{CH}_2\text{C}(\text{O})-$ groups (keto forms) may undergo tautomerism to form hydroxyl $-\text{CH}=\text{C}(\text{OH})-$ groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods

including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as
5 techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by
10 methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the
15 diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as
20 formation of diastereomers using optically active resolving agents. Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric
25 compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

"Pharmaceutically acceptable salts" include, but are not limited to
30 salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates, hydrobromates, sulfates, sulfinates, and nitrates;

as well as salts with organic acids, selected, for example, from malates, maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates, p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with
5 $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium.

In addition, if a compound is obtained as an acid addition salt, the free
10 base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts
15 from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

"Treating," "treat," or "treatment" refers to administering at least one compound and/or at least one stereoisomer thereof, and/or at least one
20 hydrate thereof, and/or at least one pharmaceutically acceptable salt thereof to a subject in recognized need thereof.

An "effective amount" refers to an amount of at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof effective to "treat" a disease or
25 disorder in a subject, and that will elicit, to some significant extent, the biological or medical response of a tissue, system, animal or human that is being sought, such as when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective
30 amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

The term "at least one substituent" includes, for example, from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents. For example, "at least one substituent R¹⁶" herein includes from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents selected from the list of R¹⁶ as described
5 herein.

The subject compounds and stereoisomers thereof, hydrates thereof, and pharmaceutically acceptable salts thereof may be employed alone or in combination with at least one other therapeutic agent for treatment. In some embodiments, the compounds, stereoisomers thereof, hydrates
10 thereof, and pharmaceutically acceptable salts thereof can be used in combination with at least one additional therapeutic agent. The compound and/or one pharmaceutically acceptable salt disclosed herein may be administered with the at least one other therapeutic agent in a single dosage form or as a separate dosage form. When administered as a
15 separate dosage form, the at least one other therapeutic agent may be administered prior to, at the same time as, or following administration of the compound and/or one pharmaceutically acceptable salt disclosed herein.

Also provided is a composition comprising a subject compound and stereoisomers thereof, hydrates thereof, and pharmaceutically acceptable
20 salts thereof, and at least one pharmaceutically acceptable carrier.

The composition comprising a subject compound and stereoisomers thereof, hydrates thereof, and pharmaceutically acceptable salts thereof can be administered in various known manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir,
25 although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal,
30 intralesional and intracranial injection or infusion techniques. The

compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art.

The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosage forms that can also be used to administer the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules containing the compound and/or the at least one pharmaceutically acceptable salt thereof disclosed herein and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like, can also be used. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can further comprise at least one agent selected from coloring and flavoring agents to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols can be examples of suitable carriers for parenteral solutions. Solutions for parenteral administration may comprise a water
5 soluble salt of the at least one compound describe herein, at least one suitable stabilizing agent, and if necessary, at least one buffer substance. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, can be examples of suitable stabilizing agents. Citric acid and its salts and sodium EDTA can also be used as
10 examples of suitable stabilizing agents. In addition, parenteral solutions can further comprise at least one preservative, selected, for example, from benzalkonium chloride, methyl- and propylparaben, and chlorobutanol.

A pharmaceutically acceptable carrier is, for example, selected from carriers that are compatible with active ingredients of the composition (and
15 in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which can form specific, more soluble complexes with the at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein), can be utilized as
20 pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in the art.

For administration by inhalation, the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof may
30 also be delivered as powders, which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler

device. One exemplary delivery system for inhalation can be metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a subject compound and stereoisomers thereof, hydrates thereof, and pharmaceutically acceptable salts thereof disclosed herein in at least
5 one suitable propellant, selected, for example, from fluorocarbons and hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percentage of a solution or suspension of the subject compound and stereoisomers thereof, hydrates
10 thereof, and pharmaceutically acceptable salts thereof in an appropriate ophthalmic vehicle, such that the subject compound and stereoisomers thereof, hydrates thereof, and at least one pharmaceutically acceptable salts thereof is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and
15 internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

20 The dosage administered will be dependent on factors, such as the age, health and weight of the recipient, the extent of disease, type of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. In general, a daily dosage of the active ingredient can vary, for example, from 0.1 to 2000 milligrams per day. For example, 10- 500
25 milligrams once or multiple times per day may be effective to obtain the desired results.

In some embodiments, a large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with, for example, 100 milligrams of the subject compound and stereoisomers
30 thereof, hydrates thereof, and pharmaceutically acceptable salt thereof

disclosed herein in powder, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

In some embodiments, a mixture of the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

In some embodiments, a large number of tablets can be prepared by conventional procedures so that the dosage unit comprises, for example, 100 milligrams of the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

In some embodiments, a parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of the compound and/or at least an enantiomer, a diastereomer, or pharmaceutically acceptable salt thereof disclosed herein in 10% by volume propylene glycol. The solution is made to the expected volume with water for injection and sterilized.

In some embodiment, an aqueous suspension can be prepared for oral administration. For example, each 5 milliliters of an aqueous suspension comprising 100 milligrams of finely divided compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin can be used.

The same dosage forms can generally be used when the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof are

administered stepwise or in conjunction with at least one other therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is
5 understood to include the administration of at least two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the at least two active components.

The compounds, stereoisomers thereof, hydrates thereof, and pharmaceutically acceptable salts thereof disclosed herein can be
10 administered as the sole active ingredient or in combination with at least one second active ingredient.

The subject compounds, stereoisomers thereof, hydrates thereof, and/or pharmaceutically acceptable salts are incorporated into pharmaceutical compositions or formulations. The compositions will
15 contain pharmaceutically acceptable diluents and/or carriers, i. e. diluents or carriers that are physiologically compatible and substantially free from pathogenic impurities. Suitable excipients or carriers and methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in such publications as
20 Remington's Pharmaceutical Science, Mack Publishing Co, NJ (1991). The compositions may also be in the form of controlled release or sustained release compositions as known in the art. For many applications the subject compounds are administered for morning/daytime dosing, with off period at night.

25 The subject compounds may be used per se, or in the form of their pharmaceutically acceptable salts, such as hydrochlorides, hydrobromides, acetates, sulfates, citrates, carbonates, trifluoroacetates and the like. When compounds contain relatively acidic functionalities, salts can be obtained by addition of the desired base, either neat or in a suitable inert solvent.
30 Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium

salts, or the like. When compounds contain relatively basic functionalities, salts can be obtained by addition of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, 5 hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, 10 lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1- 15 19).

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid, and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar 20 solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of this invention.

In addition to salt forms, this invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under 25 physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch 30 reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than

the parent drug. They may, for instance, be more bioavailable by oral administration than the parent drug. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely
5 on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity.

Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated
10 forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the invention.
15

Some of the subject compounds possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds, such as deuterium, e.g. $-CD_3$, CD_2H or CDH_2 in place of methyl. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (^{125}I) or carbon-14
20 (^{14}C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.
25

The compounds are generally administered in a "therapeutically effective amount", i.e. the amount of the subject compound that will elicit
30 the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other

clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective
5 amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

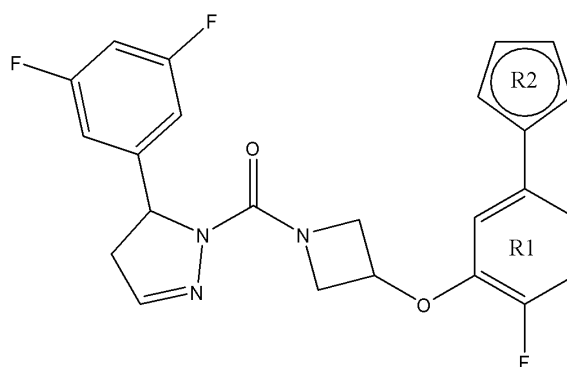
The contacting is generally effected by administering to the subject an effective amount of one or more compounds having the general formula I (supra), including the various embodiments described above. Generally
10 administration is adjusted to achieve a therapeutic dosage of about 0.1 to 50, preferably 0.5 to 10, more preferably 1 to 10 mg/kg, though optimal dosages are compound specific, and generally empirically determined for each compound.

The term "unit dosage forms" refers to physically discrete units
15 suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills,
20 tablets, capsules, lozenges or the like in the case of solid compositions. In such compositions, the mimetic is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form. Unit dosage
25 formulations are preferably about of 5, 10, 25, 50, 100, 250, 500, or 1,000 mg per unit. In a particular embodiment, unit dosage forms are packaged in a multipack adapted for sequential use, such as blisterpack comprising sheets of at least 6, 9 or 12 unit dosage forms.

The subject compositions may also be coformulated and/or
30 coadministered with a different compound to treat applicable indications, or to treat programmed cell death. In embodiments applicable indications

include brain injury, neurodegenerative diseases, viral infections, immune tolerance, and cancer e.g. promote tumor immunity in pancreatic cancer and melanoma.

In one embodiment, a compound of this disclosure is a compound of
5 the following structural formula I:

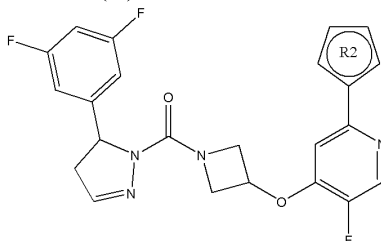


I

R1 is 1-F substituted C6 aryl comprising 0, 1 or 2 N heteroatoms; and
R2 is C5 aryl comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms
10 and an O or S heteroatom, substituted with 0-3 substituents selected from
halide, optionally-substituted N, S or O, and optionally-substituted
hydrocarbyl; or a salt, hydrate or stereoisomer thereof.

In one embodiment, the R2 substituents are independently C0-C6:
aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, alkyloxy, alkyl,
15 alkenyl, alkynyl, amine, azo, halogens, carbamoyl, carbonyl, carboxamido,
carboxyl, cyanyl, ester, haloformyl, hydroperoxyl, hydroxyl, imine,
isocyanide, iscyante, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro,
nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol,
thiocyanyl, trifluoromethyl or trifluoromethyl ether (OCF₃); R1 comprises
20 N2, N4 or N2/N4; R2 comprises N1, N1/N2, N2/N3, N3/N4, N2/N5;
N2/N4, S2/N4, N2/S4, S3/N4, N2/S3, N3/O4, N2/N3/S5, N2/N3/O5,
N2/N3/N5 or N2/N3/N4; or any combination of the foregoing substituents.

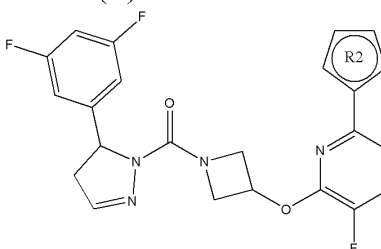
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula II(1):



5 II(1)

wherein R2 (Ring 2) is C5 aryl (5-membered aryl) comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms and an O or S heteroatom, substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

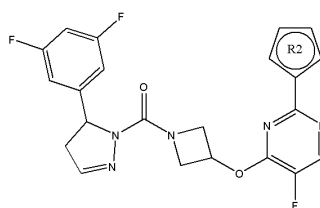
10 In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula II(2):



15 II(2)

wherein R2 (Ring 2) is C5 aryl (5-membered aryl) comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms and an O or S heteroatom, substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

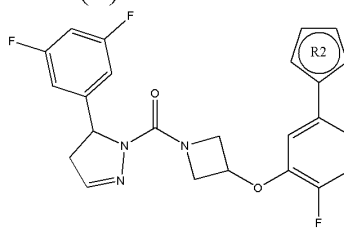
20 In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula II(3):



II(3)

wherein R2 (Ring 2) is C5 aryl (5-membered aryl) comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms and an O or S heteroatom, substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

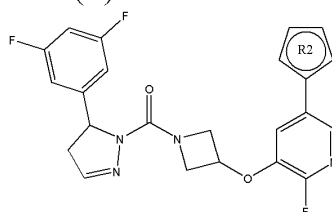
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula II(4):



II(4)

wherein R2 (Ring 2) is C5 aryl (5-membered aryl) comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms and an O or S heteroatom, substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

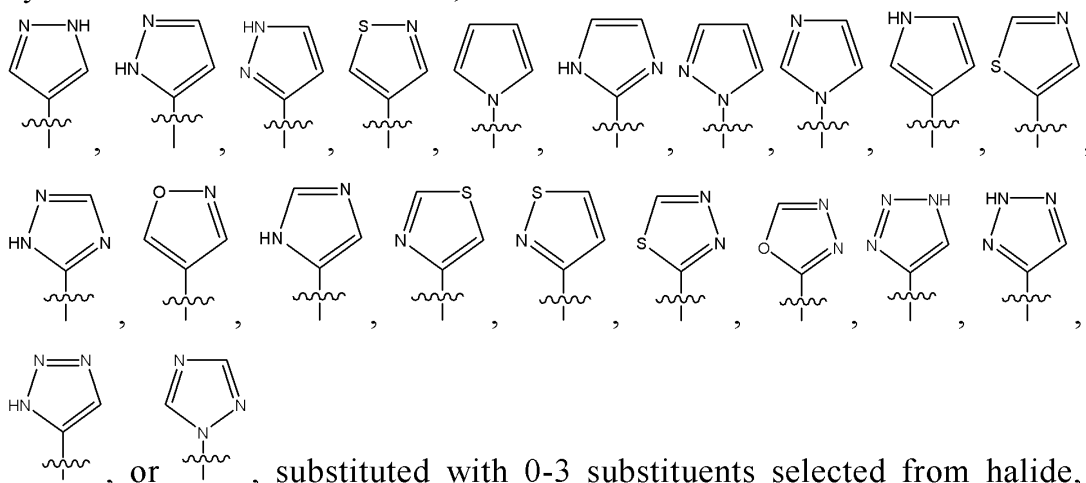
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula II(5):



II(5)

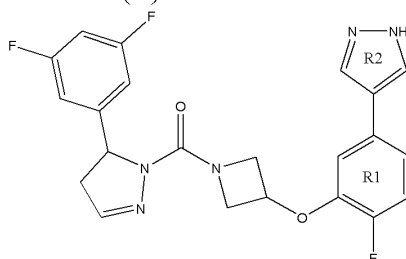
wherein R2 (Ring 2) is C5 aryl (5-membered aryl) comprising 1, 2 or 3 N heteroatoms, or 1 or 2 N heteroatoms and an O or S heteroatom, substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

- 5 In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein R2 is



- 10 optionally-substituted N, S or O, and optionally-substituted hydrocarbyl, and all other variables not specifically defined herein are as defined in any one of the appropriate preceding embodiments.

- 15 In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula III(1):

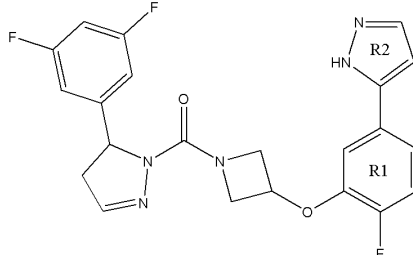


III(1)

wherein R1 (Ring 1) is 1-F substituted C6 aryl (6-membered aryl) comprising 0, 1 or 2 N heteroatoms; and wherein R2 (Ring 2) is a C5 aryl

as set forth in structural formula III(1), substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

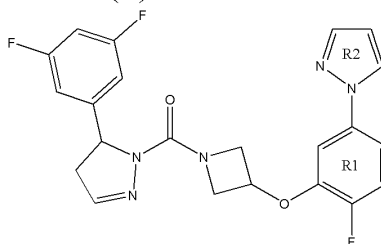
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula III(2):



III(2)

wherein R1 (Ring 1) is 1-F substituted C6 aryl (6-membered aryl) comprising 0, 1 or 2 N heteroatoms; and wherein R2 (Ring 2) is a C5 aryl as set forth in structural formula III(2), substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has the following structural formula III(3):

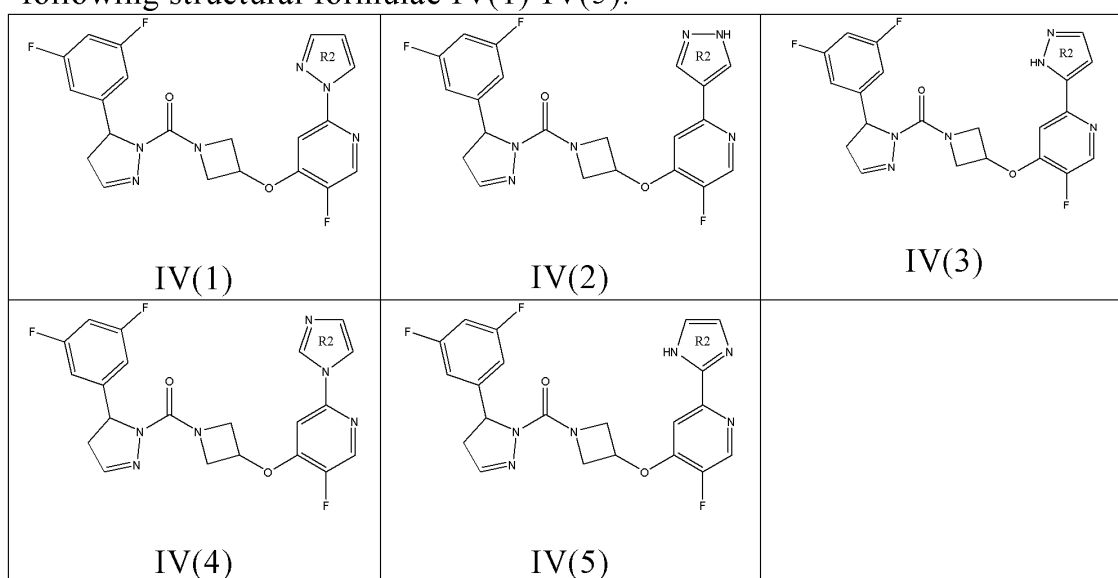


III(3)

wherein R1 (Ring 1) is 1-F substituted C6 aryl (6-membered aryl) comprising 0, 1 or 2 N heteroatoms; and wherein R2 (Ring 2) is a C5 aryl as set forth in structural formula III (3), substituted with 0-3 substituents

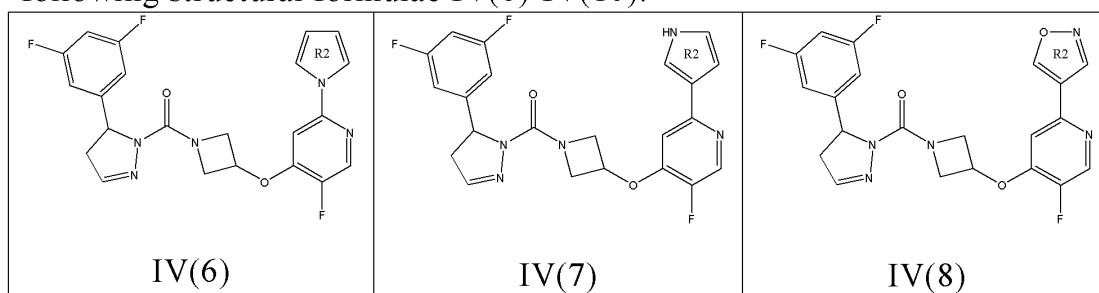
selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

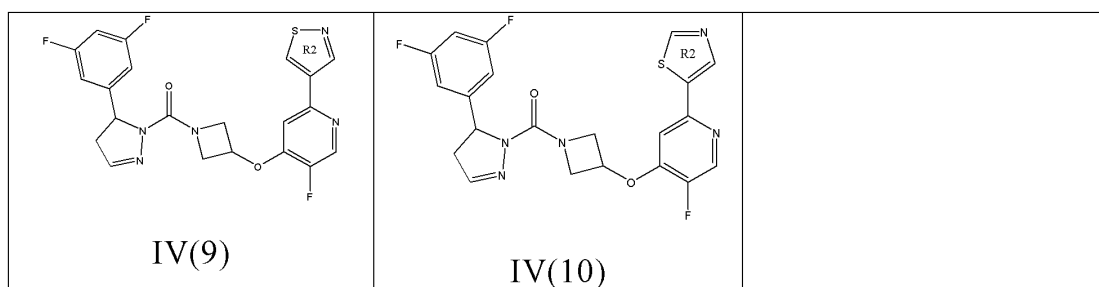
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has one of the
5 following structural formulae IV(1)-IV(5):



wherein R2 is a C5 aryl as set forth in structural formulae IV(1)-IV(5), substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

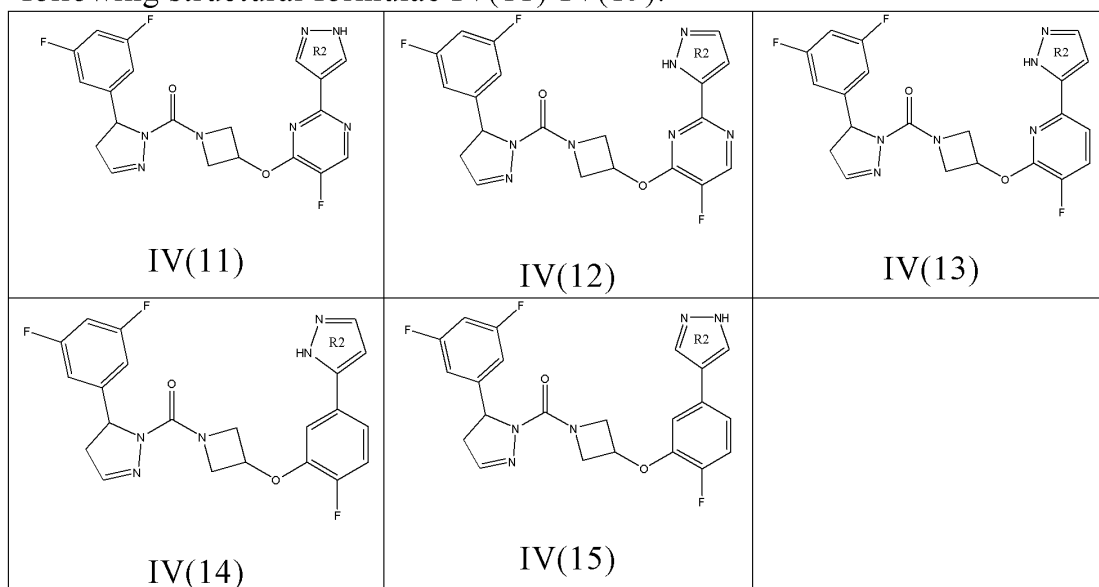
In one embodiment, the present disclosure provides a compound, a
10 salt, hydrate or stereoisomer thereof, wherein the compound has one of the following structural formulae IV(6)-IV(10):





wherein R2 is a C5 aryl as set forth in structural formulae IV(6)-IV(10), substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has one of the following structural formulae IV(11)-IV(15):



wherein R2 is a C5 aryl as set forth in structural formulae IV(11)-IV(15), substituted with 0-3 substituents selected from halide, optionally-substituted N, S or O, and optionally-substituted hydrocarbyl.

In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein R2 is substituted with 0-3 R^a, wherein R^a, for each occurrence, is independently selected from: halogen, cyano, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, -C(=O)(C₁-C₆ alkyl), -C(=O)(C₃-C₆ cycloalkyl),

-C(=O)(3- to 6-membered heterocyclyl), =O, -NO₂, -C(=O)OR^s, -C(=O)NR^pR^q, -NR^pR^q, -NR^pC(=O)R^s, -NR^pC(=O)OR^s, -NR^pC(=O)NR^qR^r, -NR^pS(=O)_wR^s, -OR^s, -OC(=O)R^s, -OC(=O)OR^s, -OC(=O)NR^pR^q, -S(=O)_wR^s, and -S(=O)_wNR^pR^q; wherein

5 the C₁-C₆ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₂-C₆ alkenyl, and C₁-C₆ alkoxy of R^a, the C₁-C₆ alkyl of -C(=O)(C₁-C₆ alkyl), the C₃-C₆ cycloalkyl of -C(=O)(C₃-C₆ cycloalkyl), and the 3- to 6-membered heterocyclyl of -C(=O)(3- to 6-membered heterocyclyl) are each optionally substituted with 1 to 3 groups selected from halogen,
 10 cyano, =O, -C(=O)R^s, -C(=O)OR^s, -C(=O)NR^pR^q, -NR^pR^q, -NR^pC(=O)R^s, -NR^pC(=O)OR^s, -NR^pC(=O)NR^qR^r, -NR^pS(=O)_wR^s, -OR^s, -OC(=O)R^s, -OC(=O)OR^s, -OC(=O)NR^pR^q, -S(=O)_wR^s, -S(=O)_wNR^pR^q, C₃-C₆ cycloalkyl, and 3- to 6-membered heterocyclyl; wherein

R^p, R^q, R^r, and R^s, for each occurrence, are each independently
 15 selected from hydrogen, OH, NH₂, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and 3- to 6-membered heterocyclyl; wherein

the C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and 3- to 6-membered heterocyclyl of any one of R^p, R^q, R^r, and R^s are optionally substituted with 1 to 3 groups selected from halogen, cyano, -OH, C₁-C₆ alkyl, -O(C₁-C₆ alkyl), -
 20 C(=O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)(3- to 6-membered heterocyclyl), -C(=O)(C₃-C₆ cycloalkyl), C₃-C₆ cycloalkyl, phenyl, and 3- to 6-membered heterocyclyl; and wherein

w is an integer selected from 0, 1, and 2; and

all other variables not specifically defined herein are as defined in any
 25 one of the appropriate preceding embodiments.

In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein R₂ is substituted with 1-3 R^a, wherein R^a, for each occurrence, is independently selected from: halogen; cyano; 4- to 6-membered heterocyclyl optionally substituted with oxo; -
 30 C(=O)(C₁-C₆ alkyl); -C(=O)(C₃-C₆ cycloalkyl); -C(=O)(4- to 6-membered heterocyclyl); 3- to 4-membered cycloalkyl;

-C(=O)OR^s, wherein R^s is H or C₁-C₃ alkyl;

C₁-C₃ alkyl, optionally substituted with OH, NH₂, cyano, halogen, C₁-C₃ alkoxy, 3- to 4-membered cycloalkyl, 4- to 6-membered heterocyclyl, -C(=O)OH, -C(=O)(4- to 6-membered heterocyclyl), -C(=O)NH(CH₂)₂OH, or -C(=O)NH₂;

-C(=O)NR^pR^q, wherein R^p and R^q each are independently selected from H, OH, CN, 4- to 6-membered heterocyclyl, C₁-C₃ alkyl optionally substituted with OH, and 3- to 4-membered cycloalkyl optionally substituted with OH;

-NR^pR^q, wherein R^p and R^q each are independently selected from H, OH, -C(=O)CH₃, and C₁-C₃ alkyl optionally substituted with OH, 3- to 4-membered cycloalkyl, or 6-membered heterocyclyl;

-NR^pC(=O)NR^qR^r, wherein R^p, R^q and R^r each are independently selected from H and C₁-C₃ alkyl;

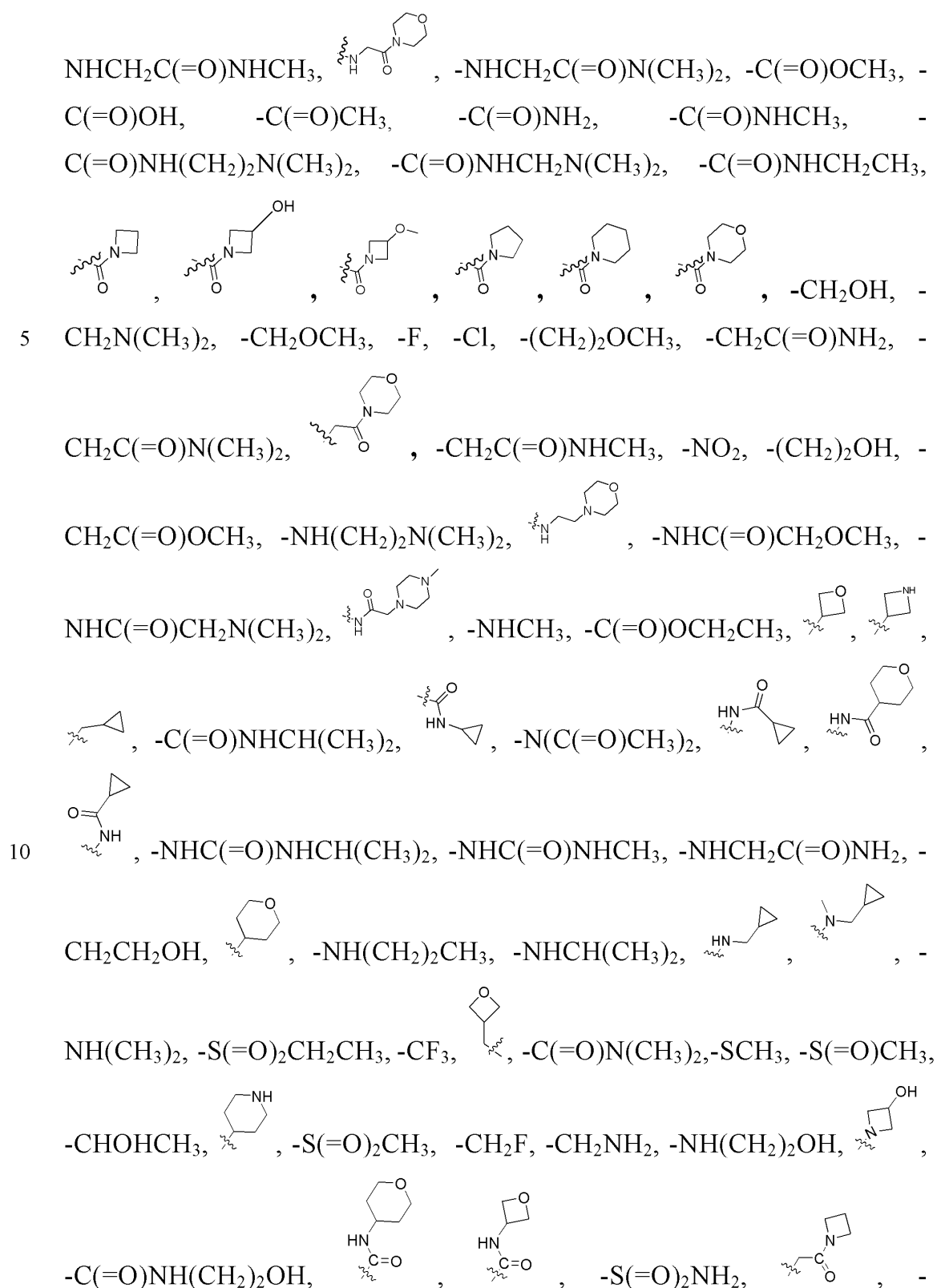
-NR^pC(=O)R^s, wherein R^p is selected from H and C₁-C₃ alkyl, and R^s is selected from C₁-C₃ alkyl and 3- to 4-membered cycloalkyl;

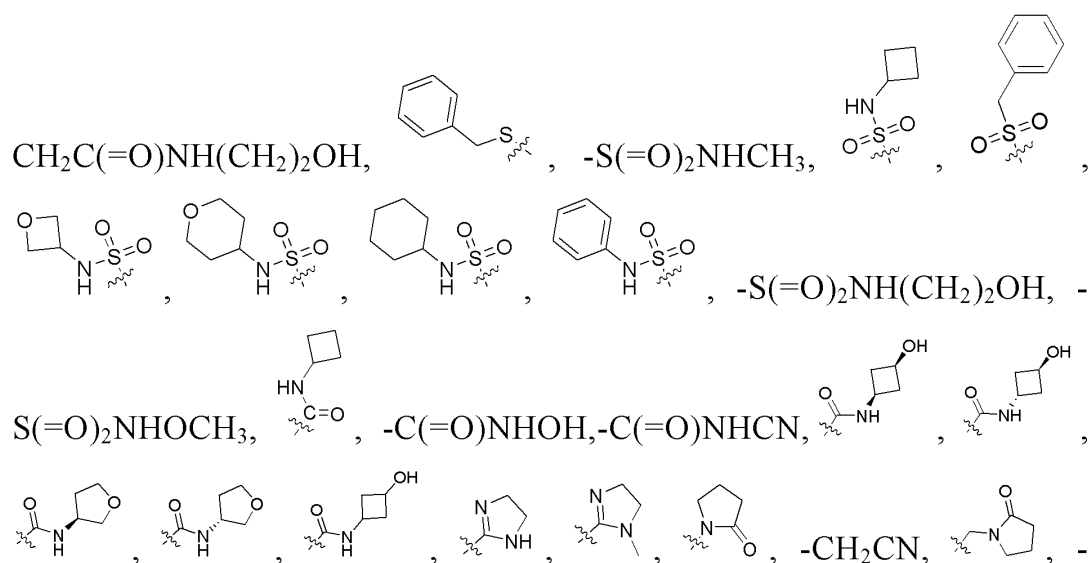
-S(=O)_wR^s, wherein R^s is selected from C₁-C₃ alkyl optionally substituted with phenyl or NH₂, and wherein w is 0 or 2; and

-S(=O)_wNR^pR^q, wherein R^p and R^q each are independently selected from H, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocyclyl, and C₁-C₃ alkyl optionally substituted with OH, C₁-C₃ alkoxy or phenyl, and wherein w is 2; and

all other variables not specifically defined herein are as defined in any one of the appropriate preceding embodiments.

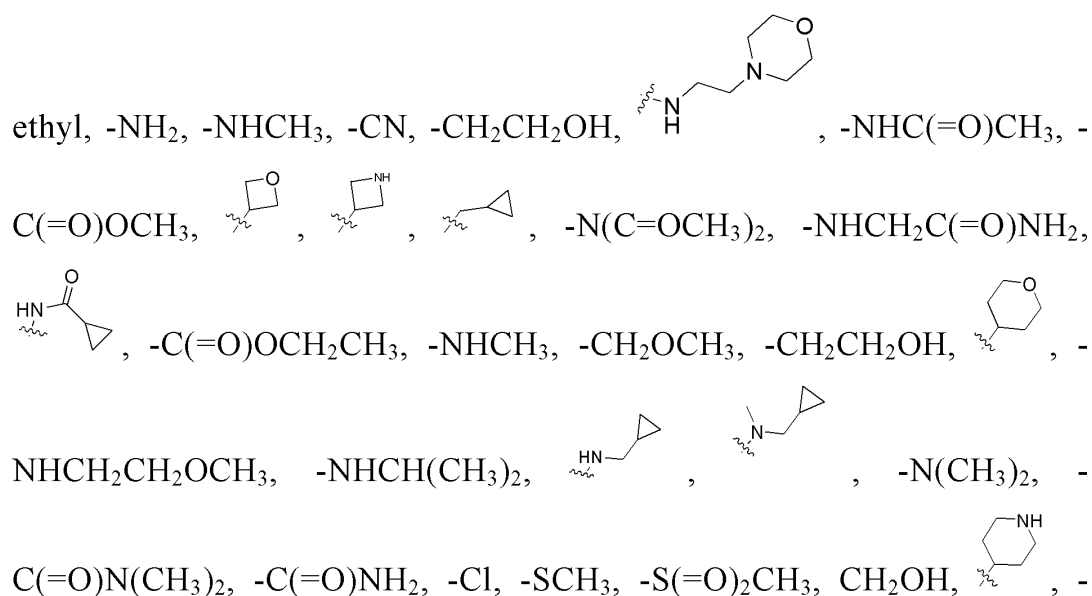
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein R₂ is substituted with 1-3 R^a, wherein R^a, for each occurrence, is independently selected from methyl, ethyl, -NH₂, -CN, -OCH₃, -O(CH₂)₂N(CH₃)₂, -NHCH₃, -O(CH₂)₂OCH₃, -N(CH₃)₂, -NH(CH₂)OCH₃, -NHC(=O)CH₃, -NHC(=O)CH₂CH₃, -NHC(=O)CH(CH₃)₂, -NHC(=O)CH₂CH(CH₃)₂, -NHCH₂C(=O)NHCH₃, -

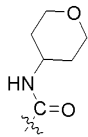
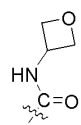
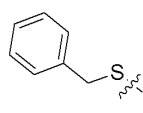
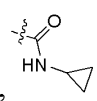
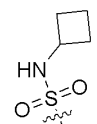
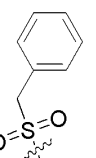
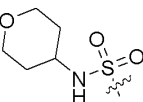
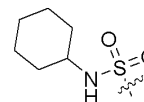
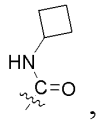
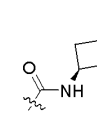
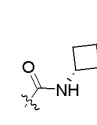
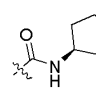
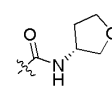
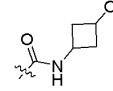


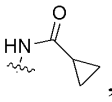
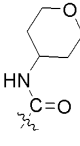
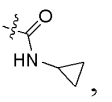
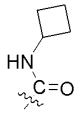


- 5 CH₂C(=O)OH, -C(CH₃)₂C(=O)OH, and -C(CH₃)₂C(=O)NH₂, and all other variables not specifically defined herein are as defined in any one of the appropriate preceding embodiments.

In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein R² is substituted with 1-3 R^a,
10 wherein R^a, for each occurrence, is independently selected from methyl,

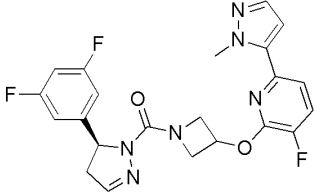
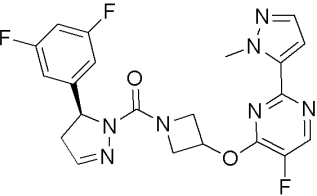
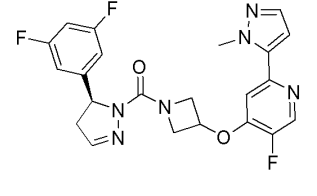
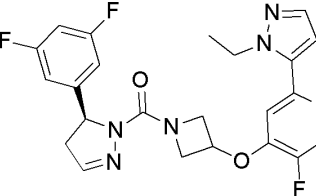
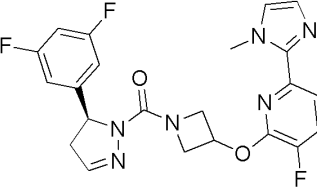
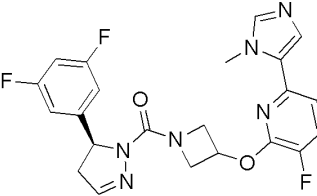
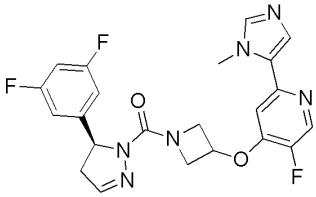
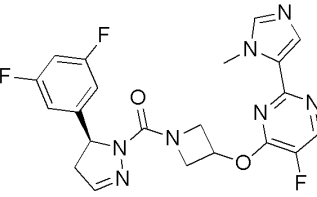
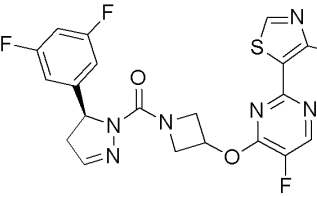
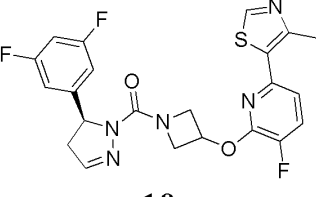
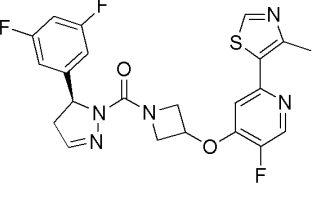
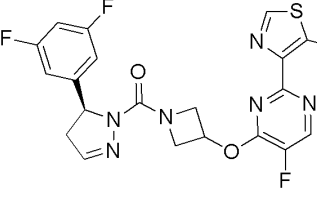
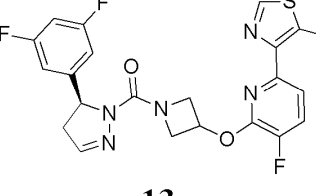
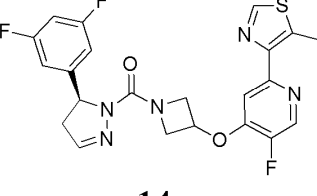
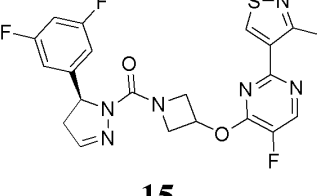


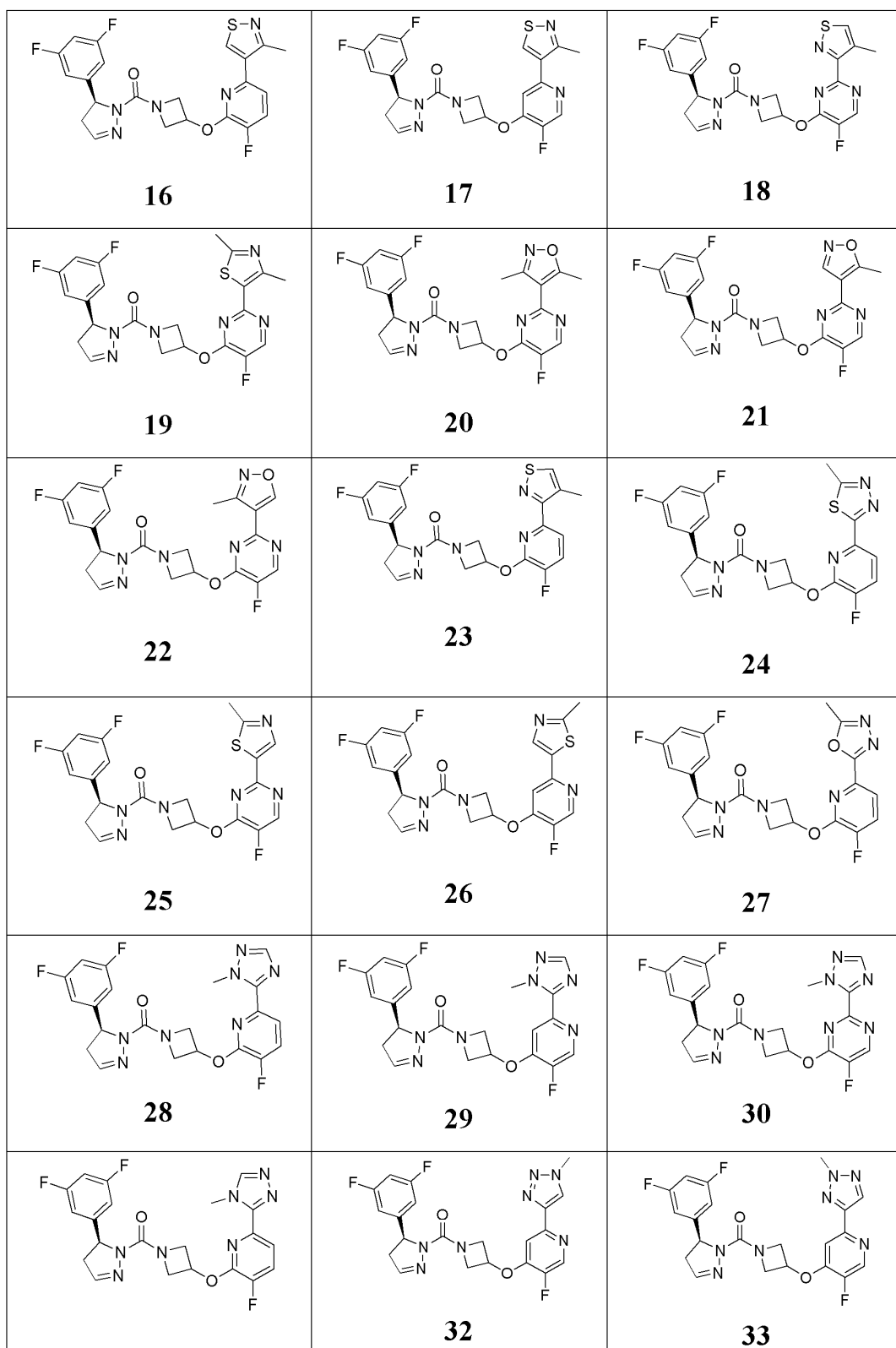
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 $S(=O)_2NH_2$, $-CH_2C(=O)NH_2$, ; $-C(=O)NHCH_2CH_3$, -
 $C(=O)OH$, , , , , , $-C(=O)NHCH_3$,
 $-S(=O)_2NHOCH_3$, , $-C(=O)NHOH$, , , ,
, , $-C(=O)NHCH_2CH_2OH$, and $-CH_2CN$, and all other
variables not specifically defined herein are as defined in any one of the
appropriate preceding embodiments.

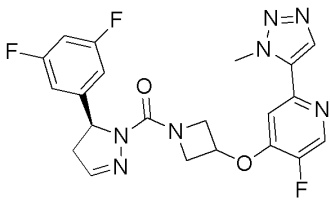
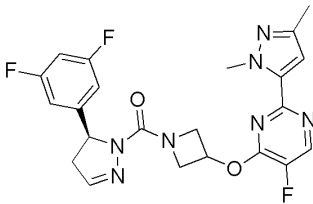
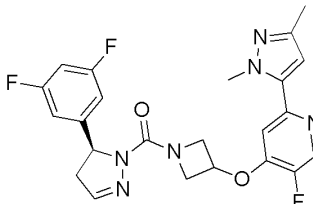
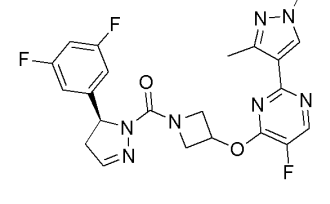
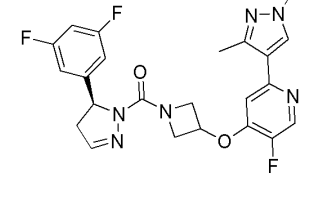
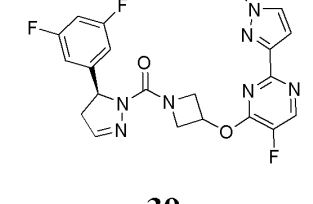
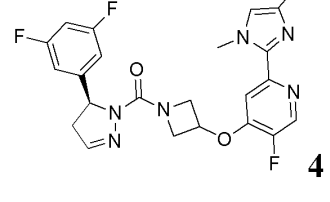
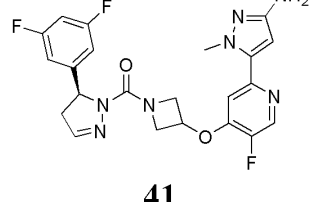
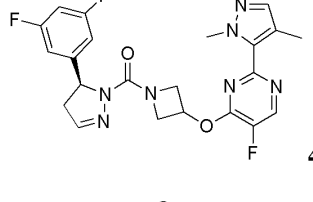
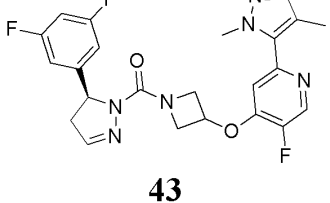
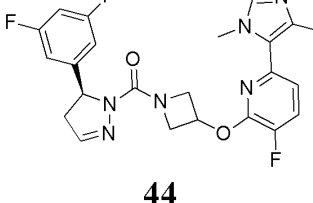
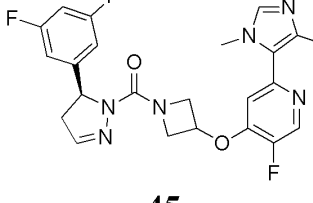
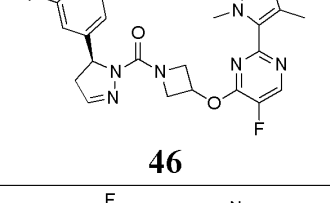
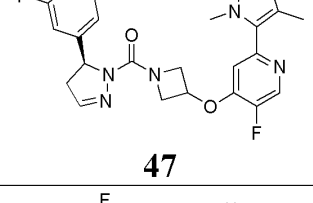
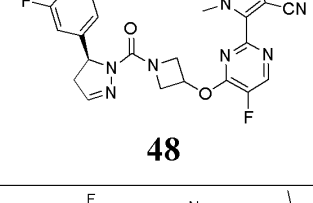
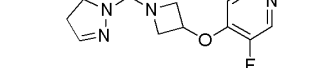
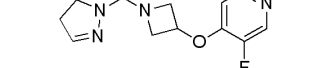
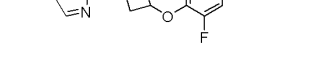
In one embodiment, the present disclosure provides a compound, a
 salt, hydrate or stereoisomer thereof, wherein R_2 is substituted with 1-3 R^a ,
 10 wherein R^a , for each occurrence, is independently selected from methyl,
 ethyl, $-NH_2$, $-C(=O)NH_2$, $-NHCH_3$, $-CN$, $-CH_2CN$, $-NHCH_2OH$, $-CH_2NH_2$,
 $-SCH_3$, $CONHCH_3$, $-SO_2CH_3$, $-CH_2OH$, $-Cl$, $-N(CH_3)_2$, $-NHCH(CH_3)_2$, -
 $NHCH_2CH_2OCH_3$, $-CH_2CH_2OH$, $-C(=O)OCH_2CH_3$, $-C(=O)OCH_3$, -
 $C(=O)OH$, $-S(=O)_2NH_2$, $-CH_2C(=O)NH_2$, $-C(=O)NHCH_2CH_2OH$, ,
, , , , , , , and , and all
 15 other variables not specifically defined herein are as defined in any one of
 the appropriate preceding embodiments.

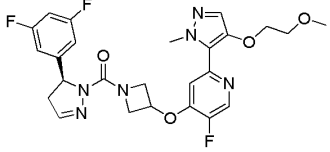
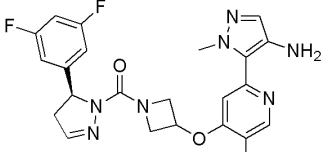
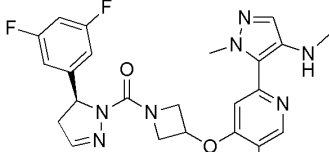
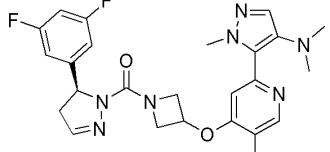
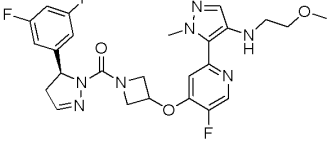
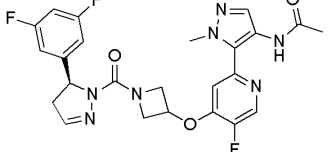
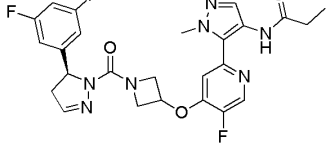
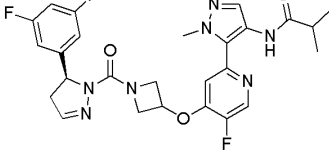
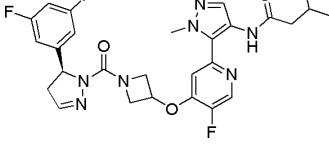
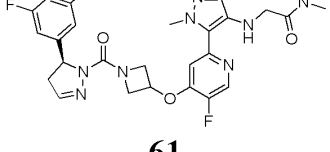
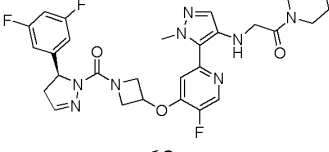
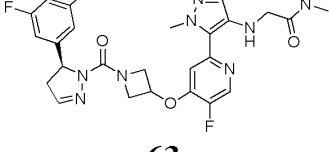
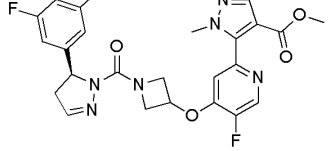
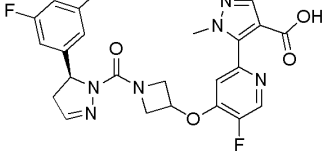
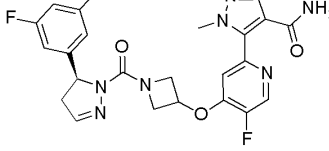
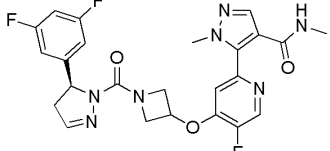
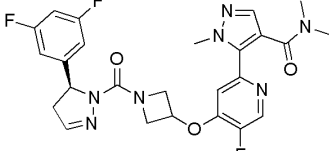
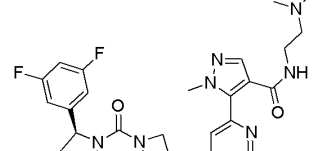
In one embodiment, the present disclosure provides a compound, a salt, hydrate or stereoisomer thereof, wherein the compound has one of structural formulae in Tables 1 and 3.

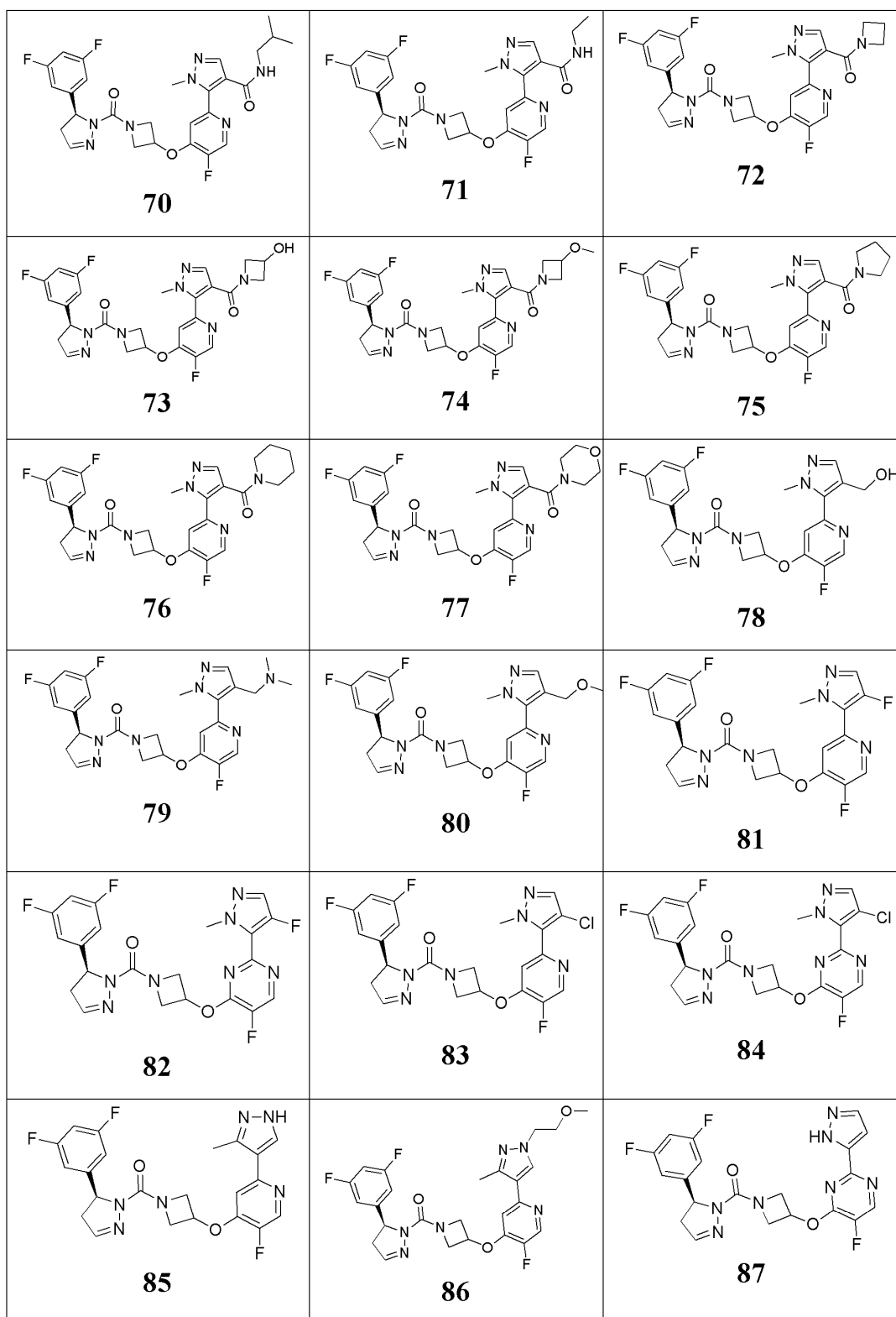
5 **Table 1: Active Compounds 1-116: Structures**

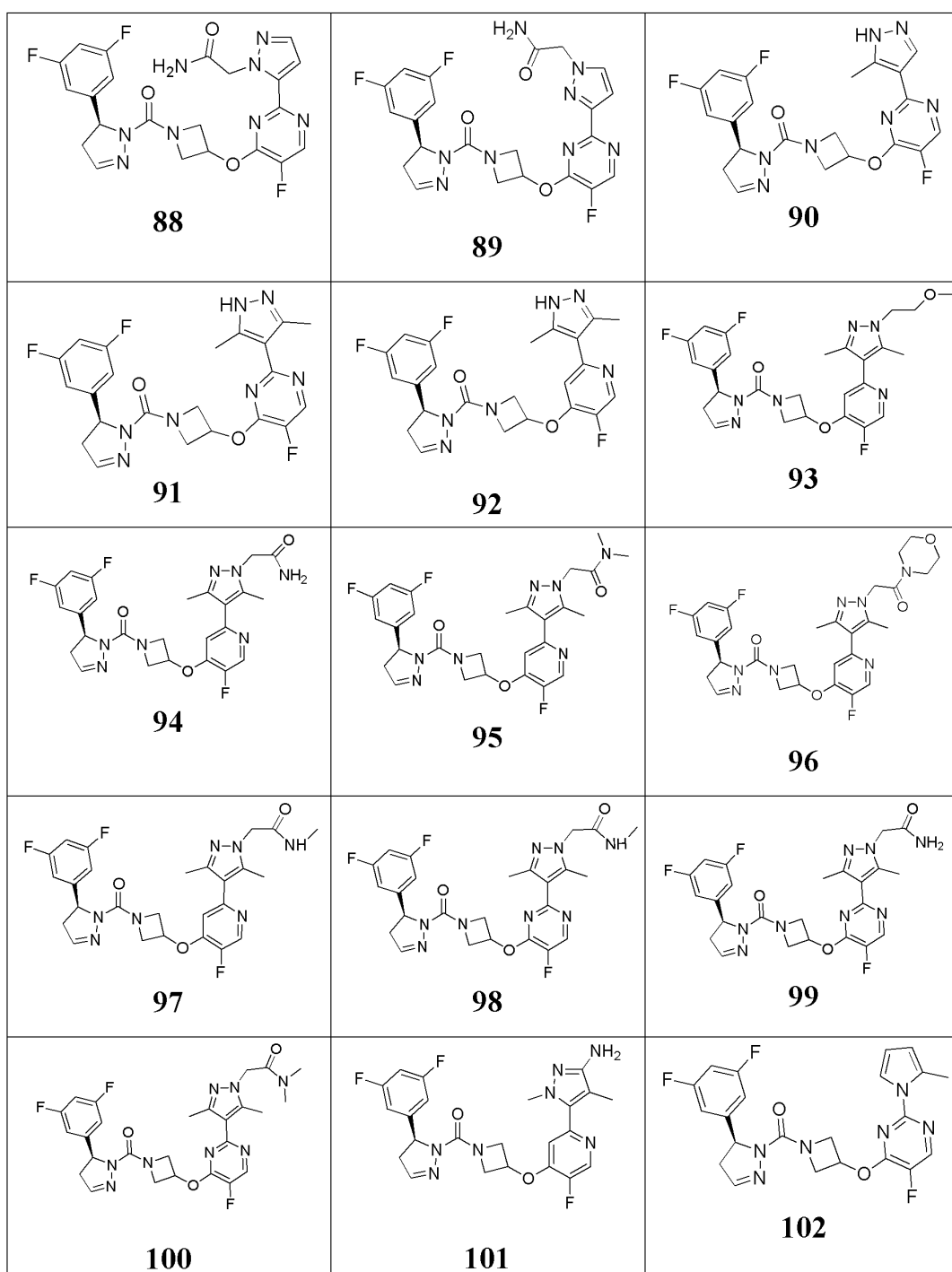
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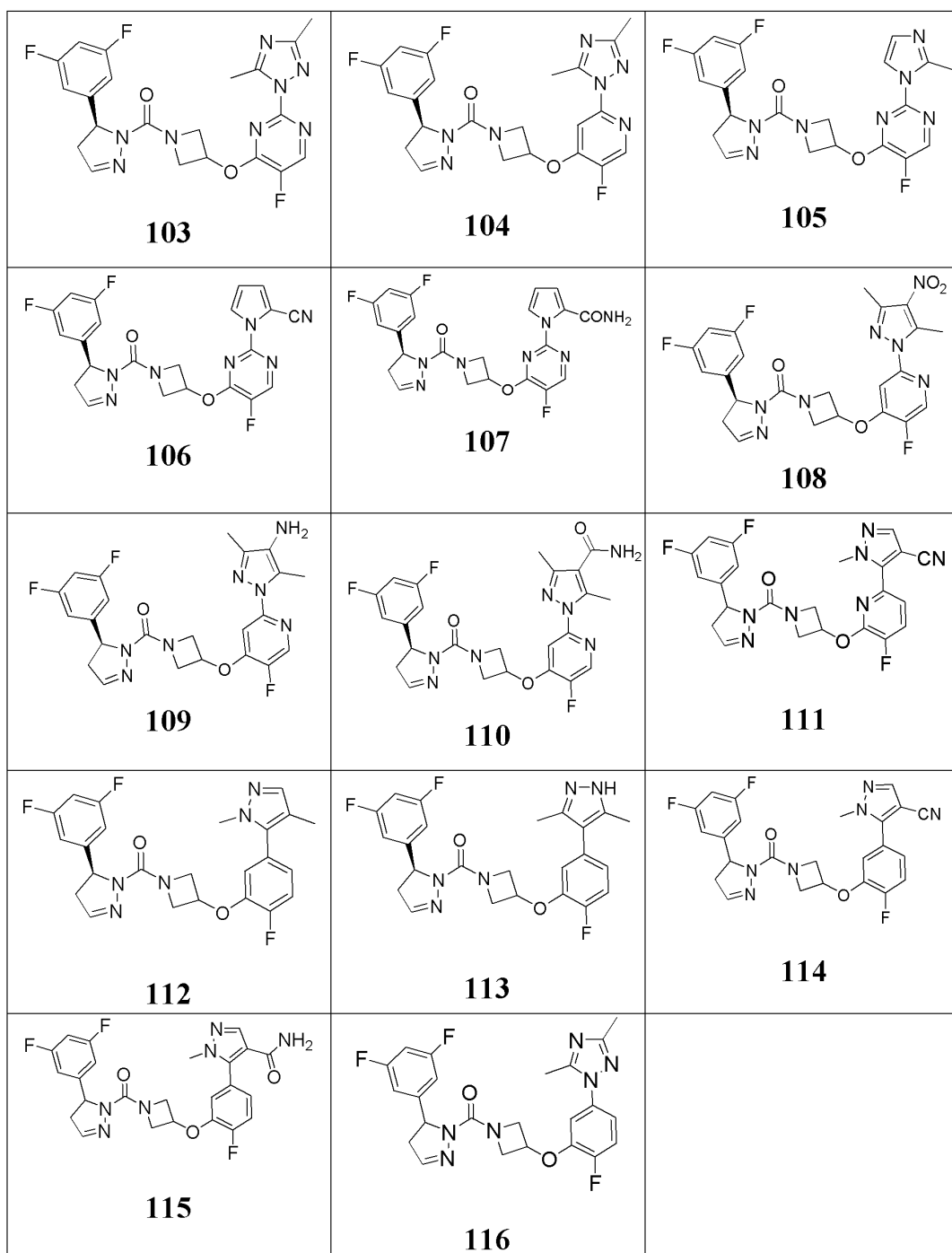


31  34	 35	 36
 37	 38	 39
 40	 41	 42
 43	 44	 45
 46	 47	 48
		

49  52	50  53	51  54
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 67	 68	 69



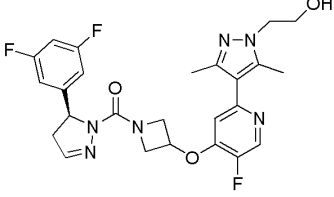
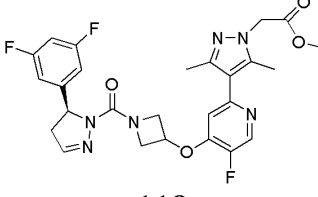
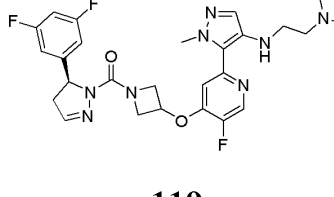
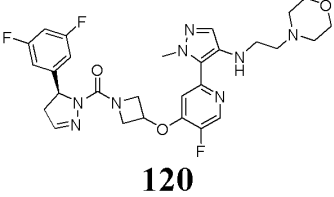
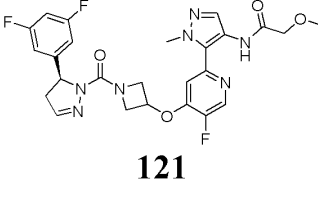
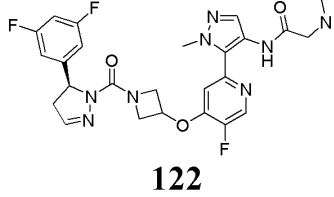
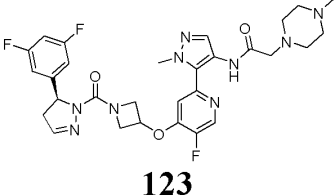
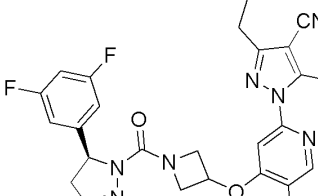
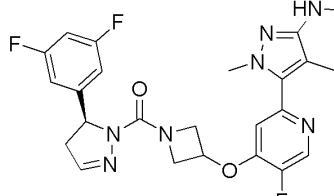
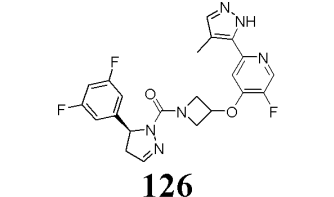
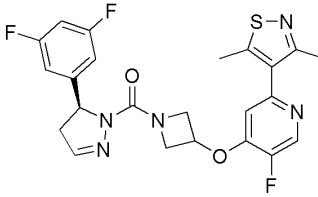
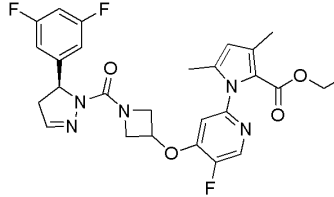
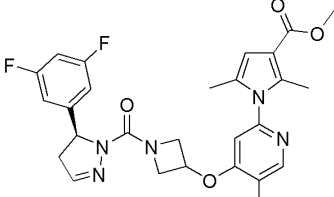
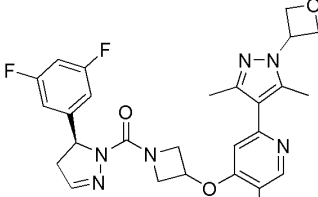
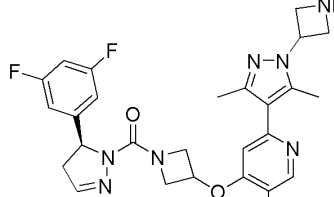
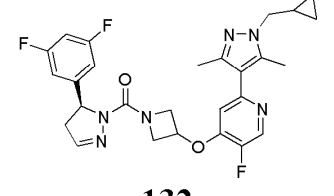
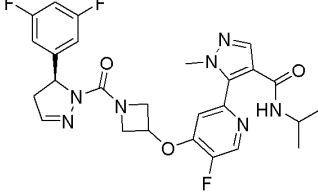
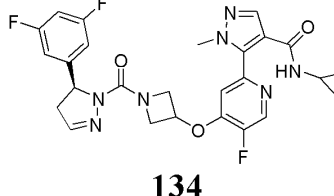


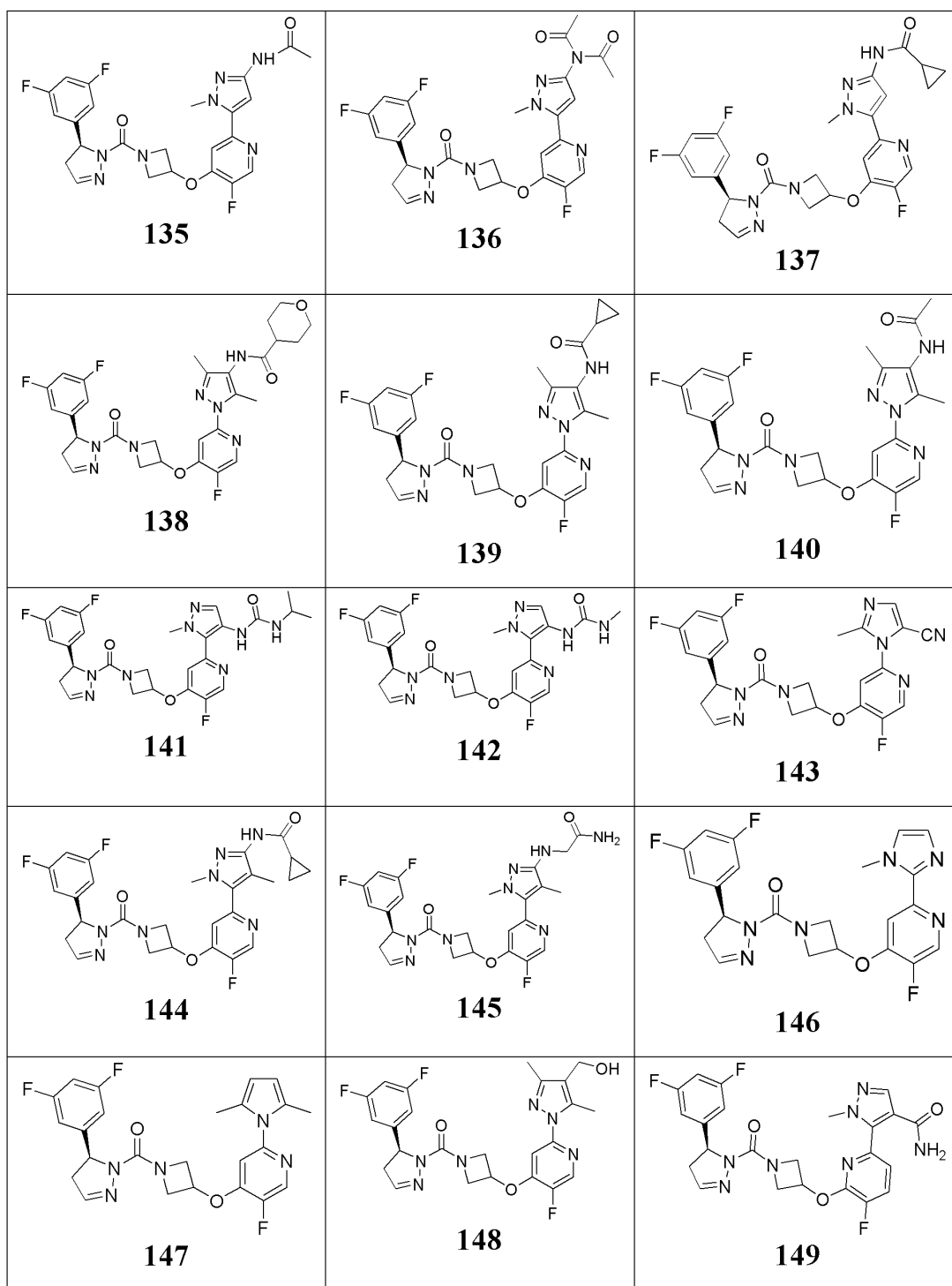
**Table 2 Cell activity (EC₅₀) of Compounds 1-116**

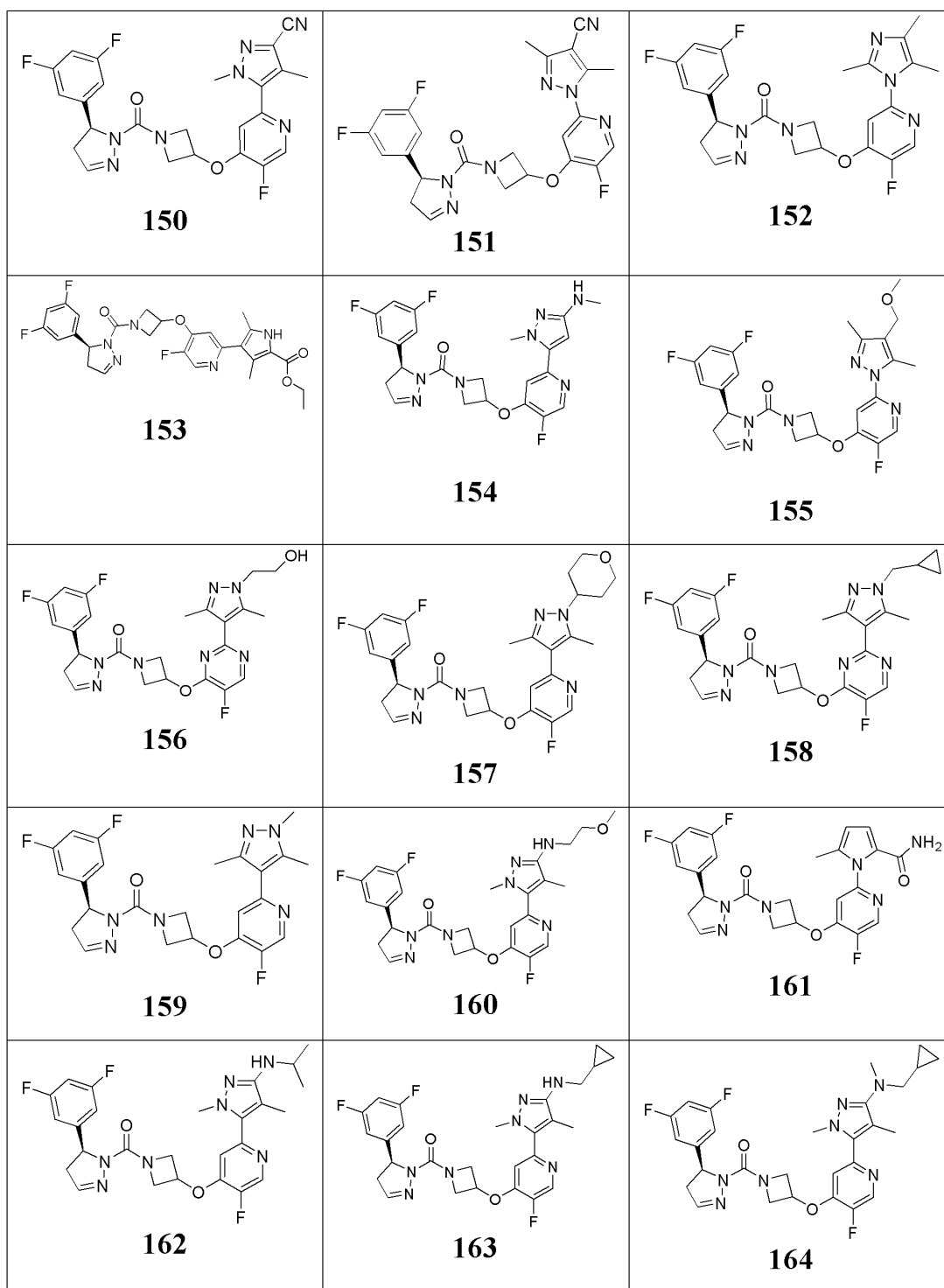
#	EC50	#	EC50	#	EC50	#	EC50
1	+++	30	+++	59	+++	88	++

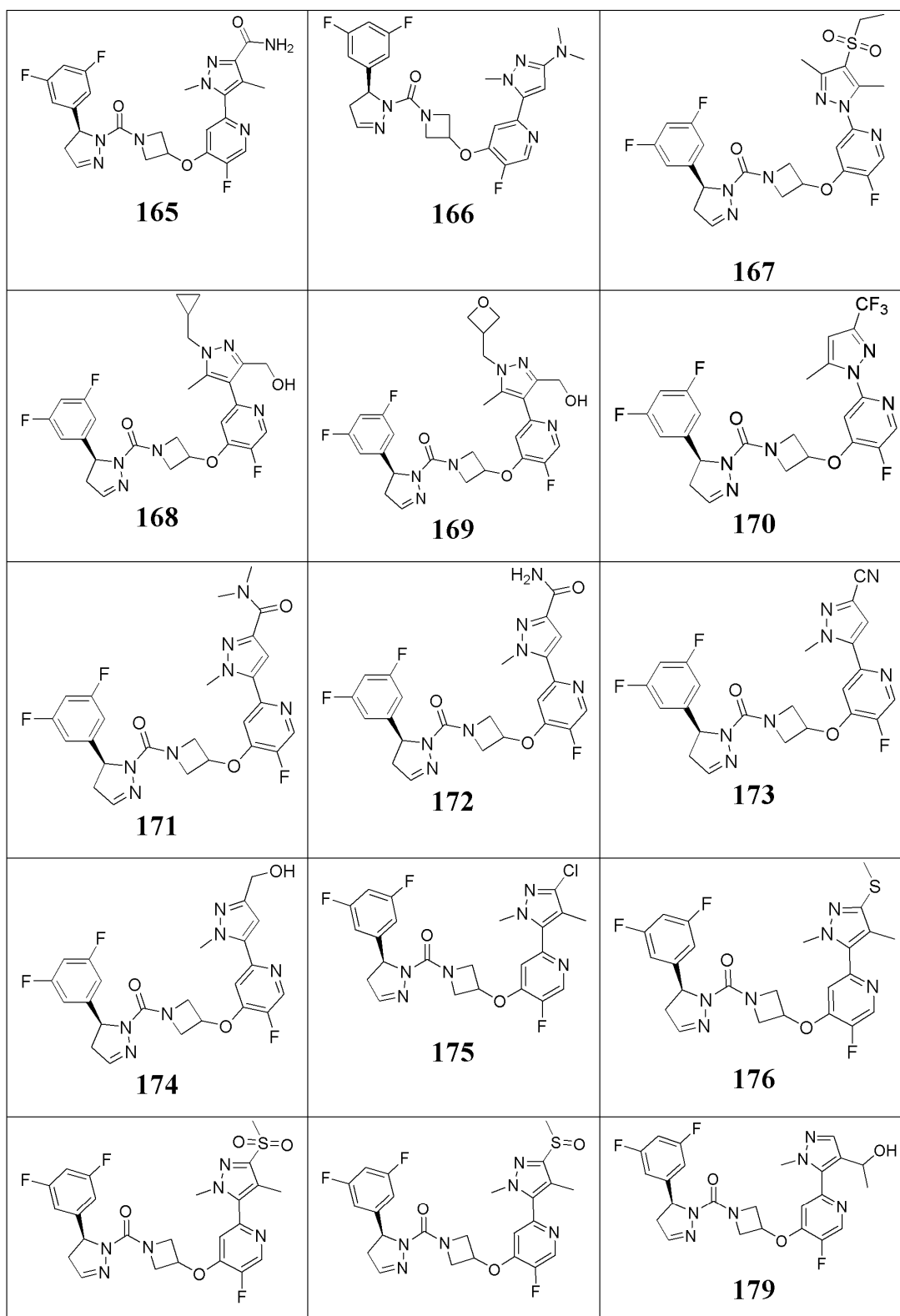
2	+++	31	+++	60	+++	89	++
3	+++	32	+++	61	+++	90	+++
4	+++	33	+++	62	+++	91	+++
5	+++	34	+++	63	+++	92	+++
6	+++	35	+++	64	+++	93	+++
7	+++	36	+++	65	+	94	+++
8	+++	37	+++	66	+++	95	+++
9	+++	38	+++	67	+++	96	+++
10	+++	39	++	68	+	97	+++
11	+++	40	+++	69	++	98	+++
12	+++	41	+++	70	+++	99	+++
13	+++	42	+++	71	+++	100	+++
14	+++	43	+++	72	++	101	+++
15	+++	44	+++	73	++	102	+++
16	+++	45	+++	74	++	103	+++
17	+++	46	+++	75	+	104	+++
18	+++	47	+++	76	+	105	+++
19	+++	48	+++	77	+	106	+++
20	+++	49	+++	78	+++	107	+++
21	+++	50	+++	79	+++	108	+++
22	+++	51	++	80	+++	109	+++
23	+++	52	+++	81	+++	110	+++
24	+++	53	+++	82	+++	111	+++
25	+++	54	+++	83	+++	112	+++
26	+++	55	+++	84	+++	113	+++
27	++	56	+++	85	+++	114	+++
28	+++	57	+++	86	+++	115	+++
29	+++	58	+++	87	+++	116	+++

Table 3: Active Compounds 117-281: Structures

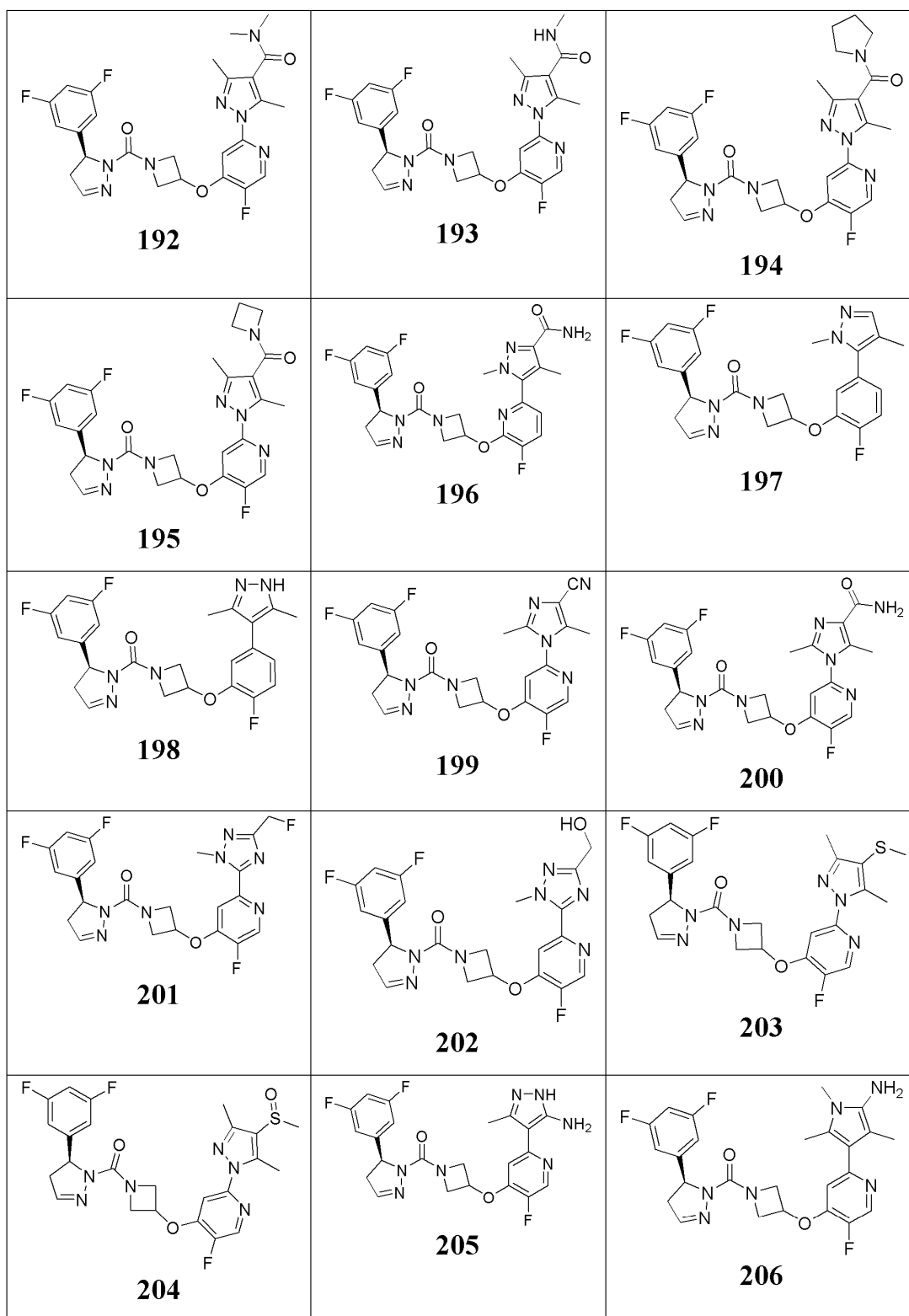
 117	 118	 119
 120	 121	 122
 123	 124	 125
 126	 127	 128
 129	 130	 131
 132	 133	 134

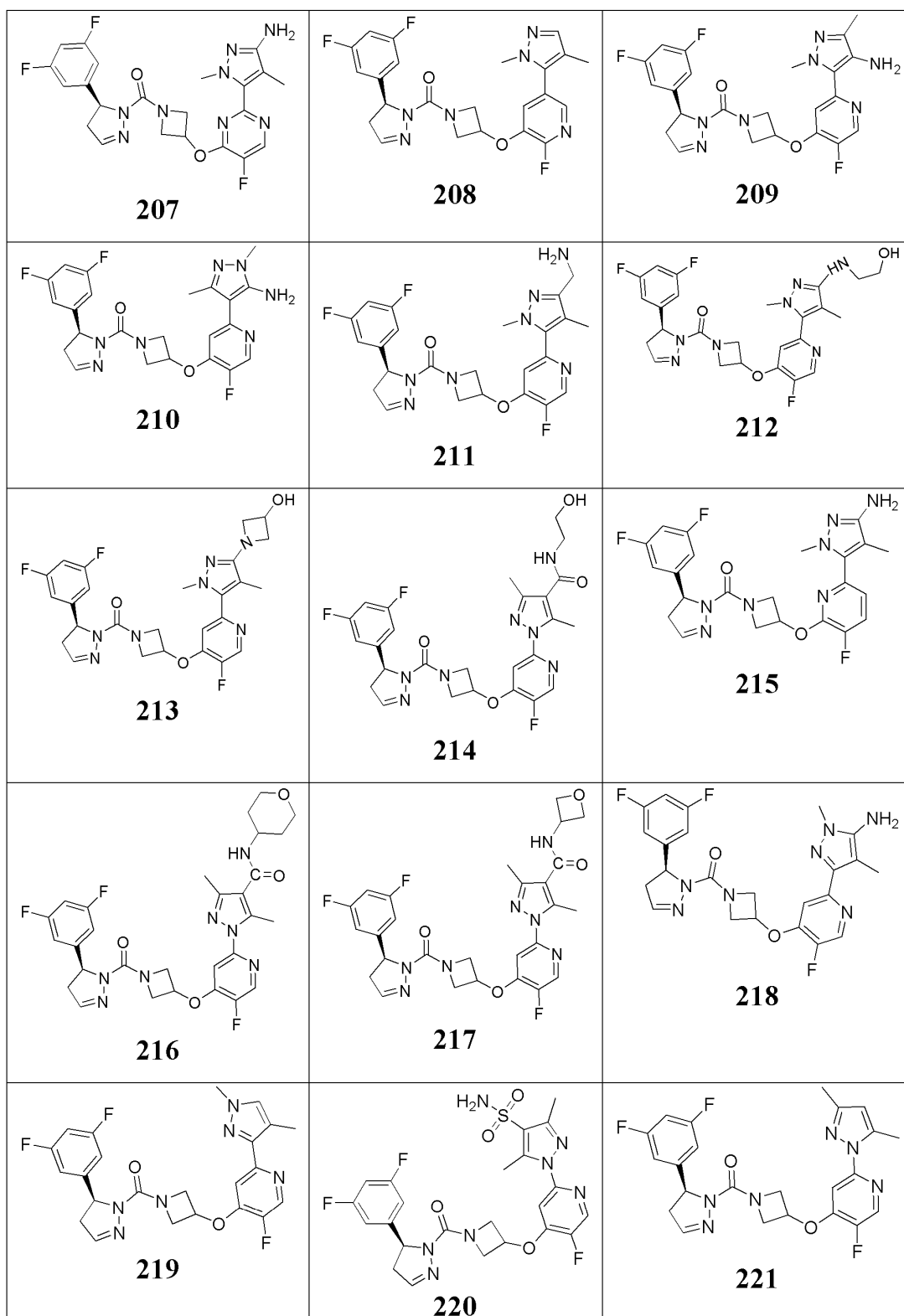


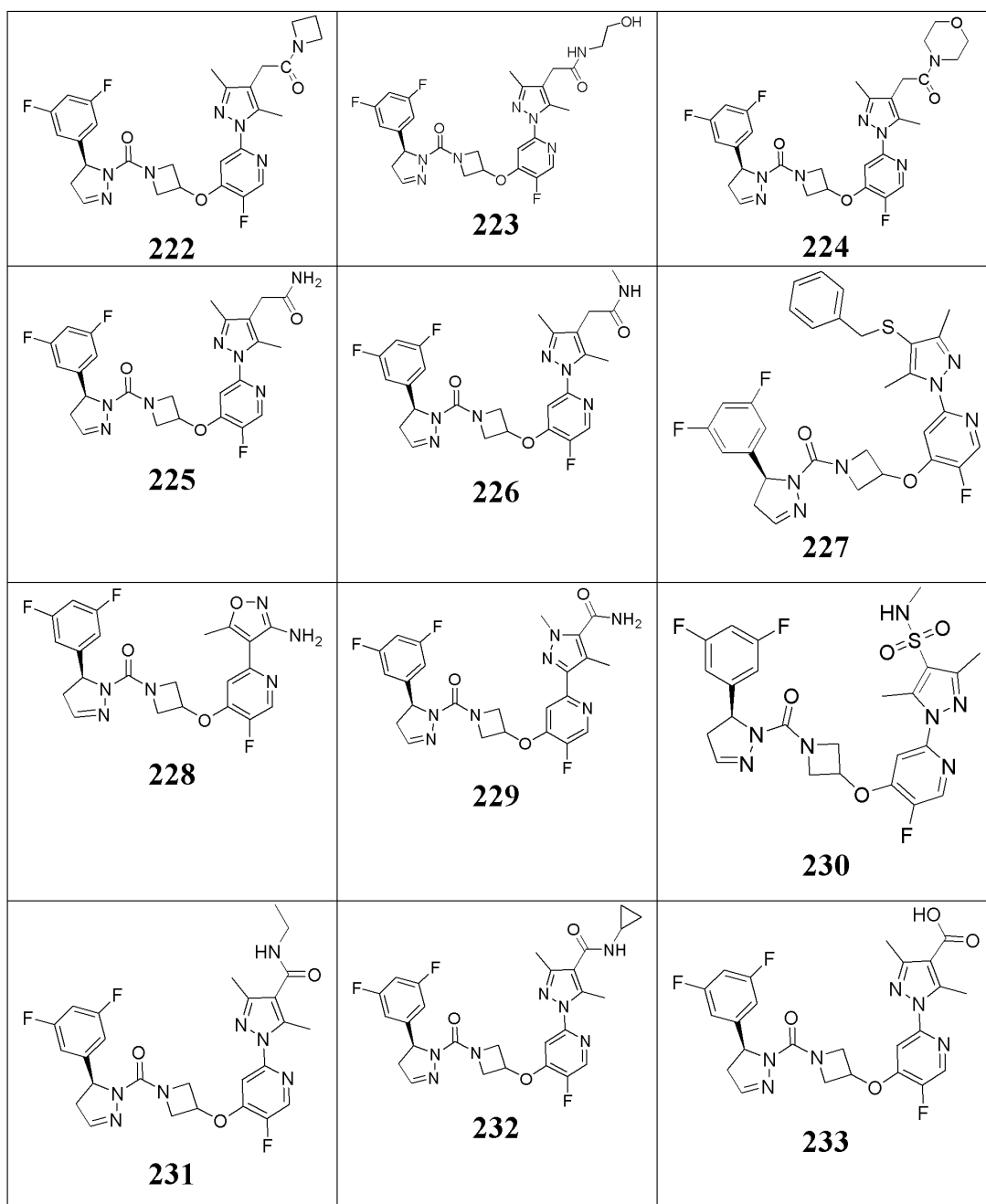


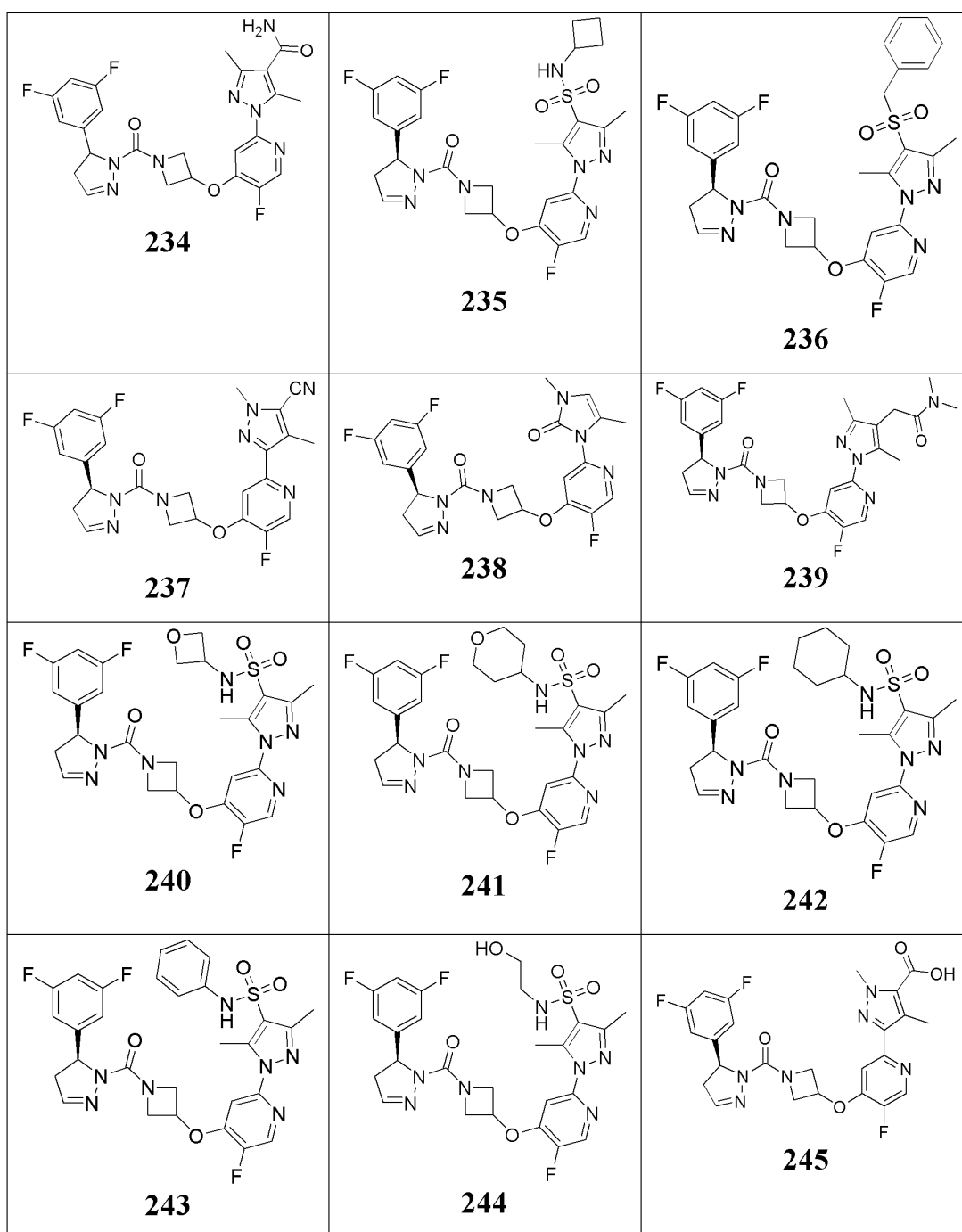


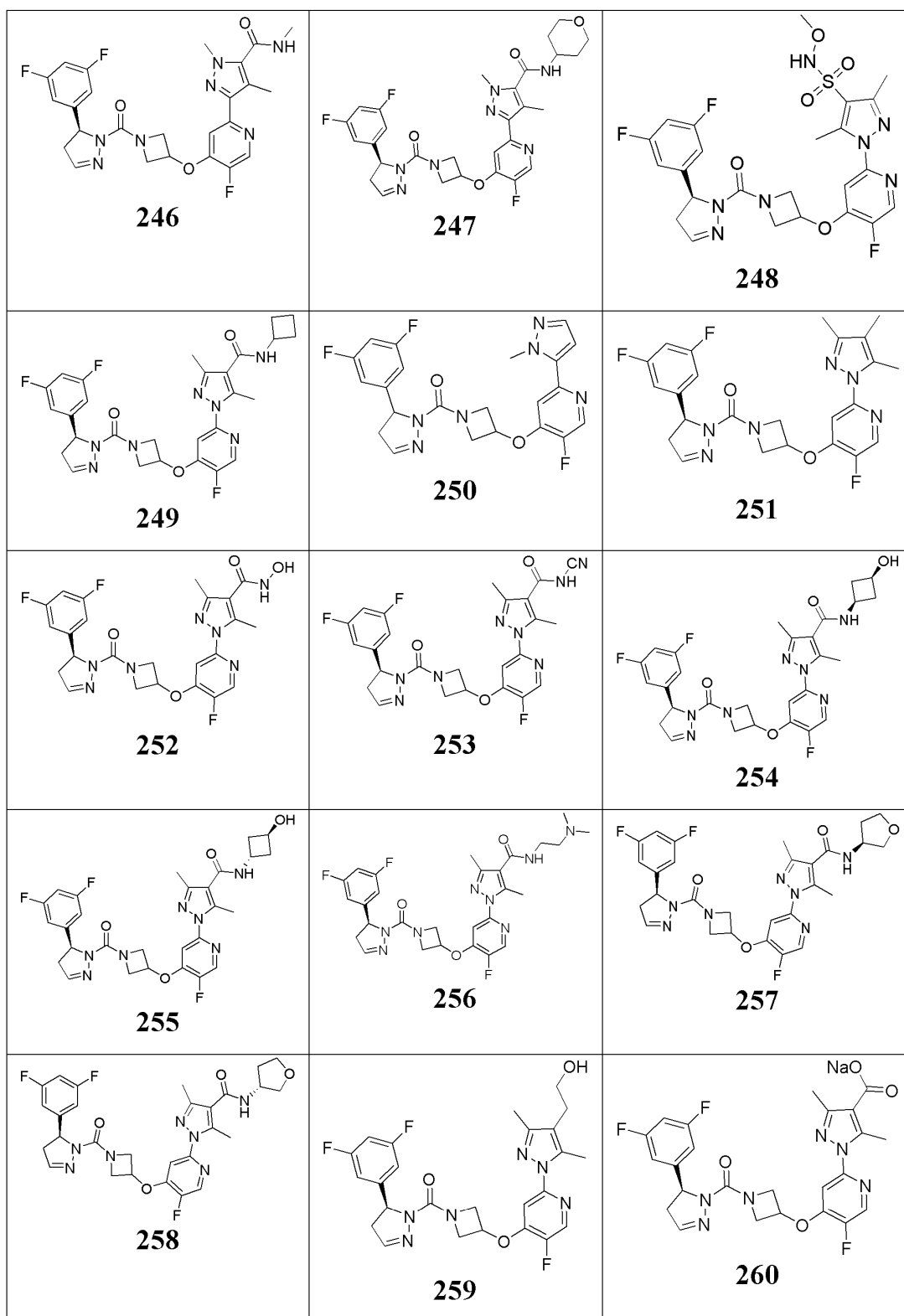
177 180	178 181	182
183	184	185
186	187	188
189	190	191

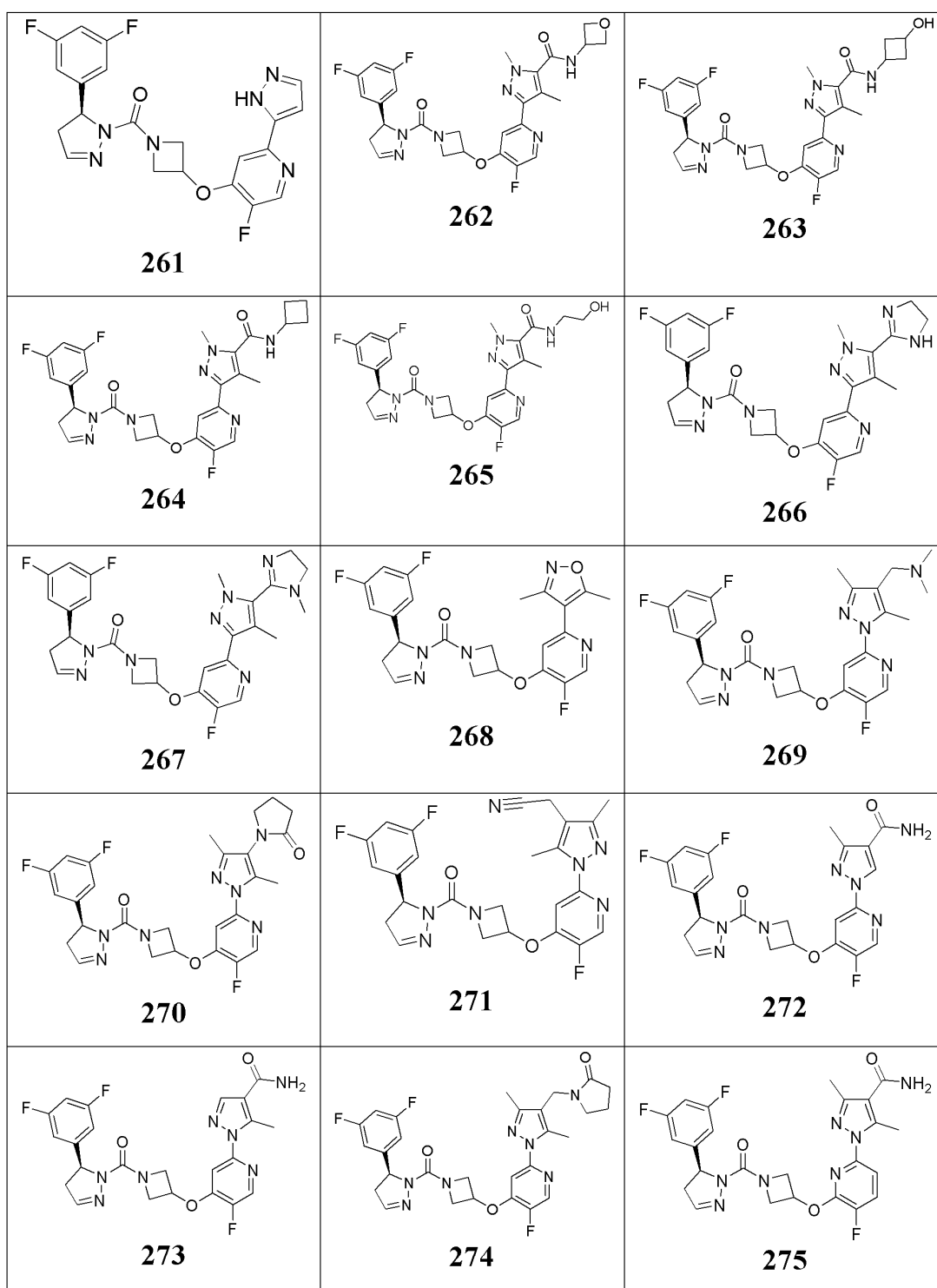












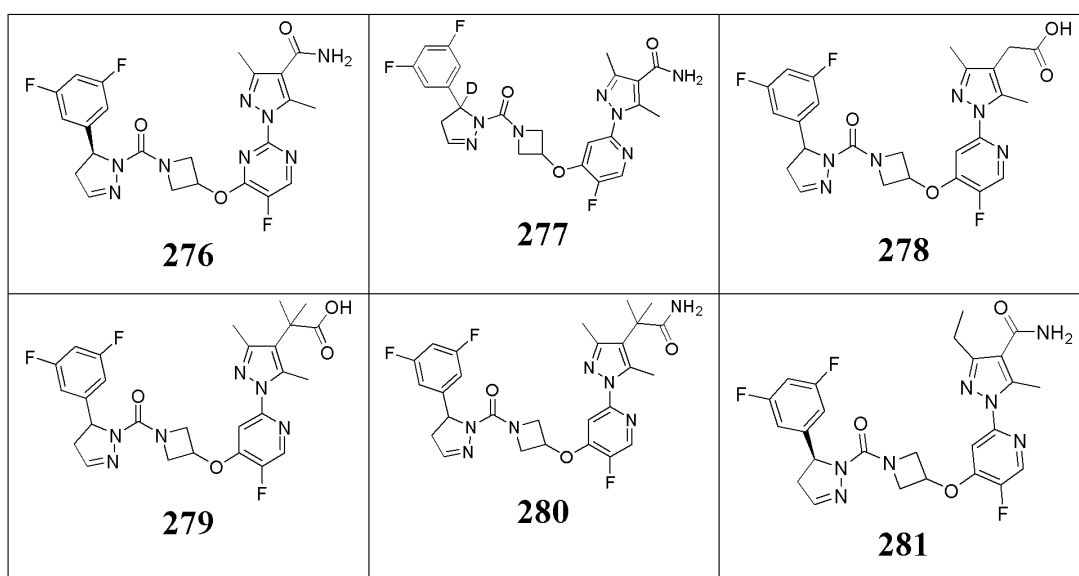


Table 4 Cell activity (EC₅₀) of Compounds 117-281

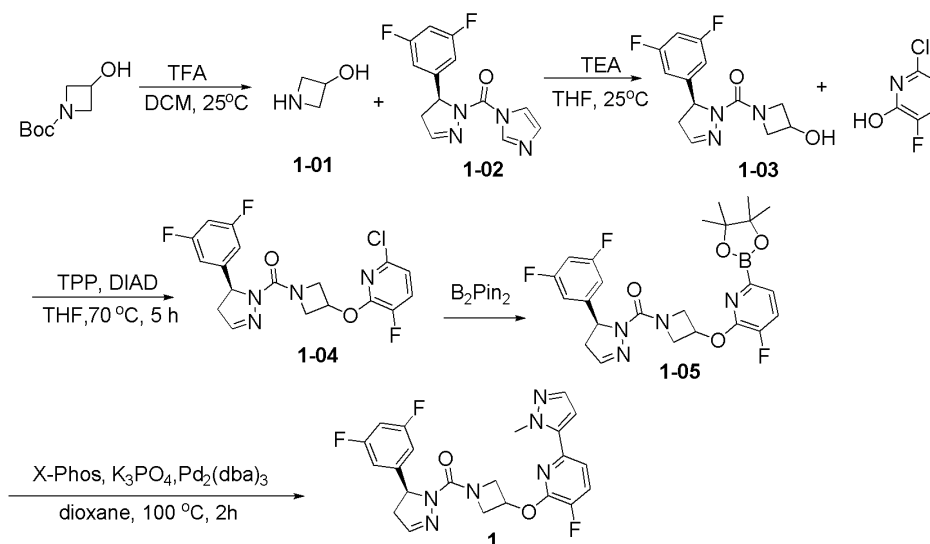
#	EC ₅₀	#	EC ₅₀	#	EC ₅₀	#	EC ₅₀
117	+++	118	+	119	++	120	+++
121	+++	122	+++	123	++	124	+++
125	+++	126	+++	127	+++	128	+++
129	+++	130	+++	131	+++	132	+++
133	+++	134	+++	135	+++	136	+++
137	+++	138	+++	139	+++	140	+++
141	+++	142	+++	143	+++	144	+++
145	+++	146	+++	147	+++	148	+++
149	+++	150	+++	151	+++	152	+++
153	+++	154	+++	155	+++	156	+++
157	+++	158	+++	159	+++	160	+++
161	+++	162	+++	163	+++	164	+++
165	+++	166	+++	167	+++	168	+++
169	+	170	+++	171	+++	172	+++
173	+++	174	+++	175	+++	176	+++
177	+++	178	+++	179	++	180	+++
181	+++	182	+++	183	+++	184	+++
185	+++	186	+++	187	+++	188	+++
189	+++	190	+++	191	+++	192	+++
193	+++	194	+++	195	+++	196	+++
197	+++	198	+++	199	+++	200	+++
201	+++	202	+++	203	+++	204	+++
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213	+++	214	+++	215	+++	216	+++
217	+++	218	+++	219	+++	220	+++
221	+++	222	+++	223	+++	224	+++
225	+++	226	+++	227	+++	228	+++

229	+++	230	+++	231	+++	232	+++
233	+++	234	+++	235	+++	236	+++
237	+++	238	++	239	+++	240	+++
241	+++	242	+++	243	+++	244	+++
245	+++	246	+++	247	+++	248	+++
249	+++	250	+++	251	+++	252	+++
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257	+++	258	+++	259	+++	260	+++
261	+++	262	+++	263	+++	264	+++
265	+++	266	+++	267	++	268	+++
269	+++	270	+++	271	+++	272	+++
273	+++	274	+++	275	+++	276	+++
277	+++	278	++	279	++	280	+++
281	+++						

EXAMPLES

Compound Preparation

5 (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (1)



Step 1: tert-butyl 3-hydroxyazetidine-1-carboxylate (1.5g, 8.66 mmol) was dissolved in 15mL of DCM, trifluoroacetic acid (1.5 ml, 13.1 mmol) was added, the mixture was stirred at r.t. for 30 min. Concentrated to give the desired product **1-01**, which was used for next step without further purification.

Step 2: **1-01** (633 mg, 8.66 mmol), **1-02** (2.39 g, 8.66 mmol) and TEA (1 mL) were dissolved in THF (15 mL) and stirred at 25°C for 6 h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the intermediate **1-03** (2.1 g, 87.5 %) MS (m/z): 282.3 [M+H]⁺.

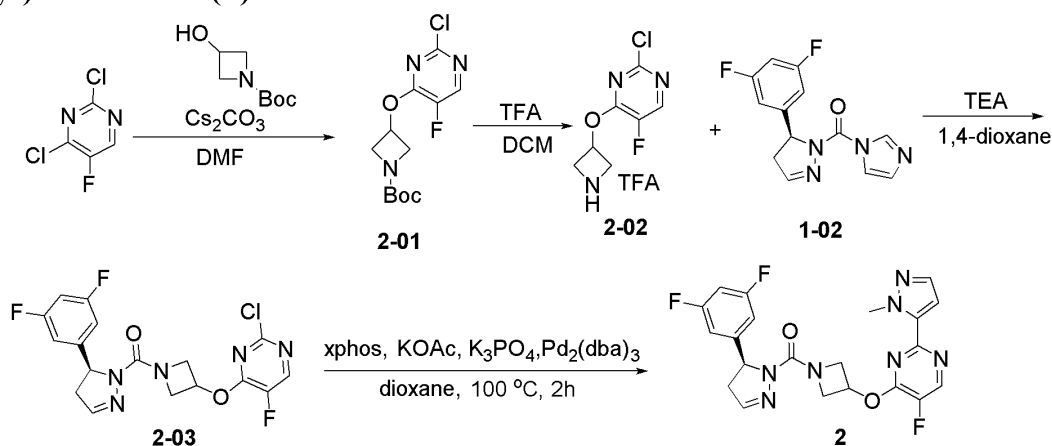
Step 3: 6-chloro-3-fluoropyridin-2-ol (200 mg, 1.36 mmol) was dissolved in 3 ml of dry THF. DEAD (328 mg ml, 1.63mmol), Compound **1-03** (400 mg, 1.423 mmol), PPh₃ (540 mg, 2.04 mmol) was added to the above solution at room temperature. The mixture was stirred for 12 hours at 25°C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give compound **1-04** (300 mg, 51%) as a white solid. Mass (m/z) 411.2 [M+H]⁺.

Step 4: **1-04** (200 mg, 0.49 mmol), x-phos (46.3 mg, 0.098 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (534 mg, 2 mmol) and KOAc (150mg, 1.5 mmol), Pd₂(dba)₃ (44.5mg, 0.098 mmol) were placed in dioxane (3 mL). The mixture was stirred for 2 h at 100°C under N₂, the mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the intermediate **1-05** as a white solid. Mass (m/z): 503.2 [M+H]⁺.

Step 5: **1-05** (100 mg, 0.24 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (101 mg, 0.48 mmol) X-Phos (11.42 mg, 0.028 mmol) and KOAc (70.56mg, 0.96 mmol), Pd₂(dba)₃ (21.9mg, 0.024 mmol), K₃PO₄ (5N, 1mL) were placed in dioxane (3 mL). The mixture was stirred 100°C for 2 h under N₂, the mixture was extracted with

EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **1** (20 mg, 20.3%) as a white solid. Mass (m/z) 457.2 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 0.0 Hz, 2H), 7.20 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.86 – 6.61 (m, 4H), 6.55 – 6.45 (m, 1H), 5.57 – 5.35 (m, 1H), 5.27 (dd, *J* = 12.3, 6.5 Hz, 1H), 4.70 – 4.45 (m, 2H), 4.31 (dd, *J* = 30.8, 9.7 Hz, 2H), 4.16 (s, 3H), 3.34 (dd, *J* = 18.6, 12.2 Hz, 1H), 2.69 (dd, *J* = 18.6, 6.4 Hz, 1H).

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-pyrazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (2)



Step 1. 2,4-dichloro-5-fluoropyrimidine (5g, 29.9mmol) was added to a solution of Cs₂CO₃ (19.5g, 59.9mmol) in DMF (100mL), and tert-butyl 3-hydroxyazetidine-1-carboxylate (5.7g, 32.9mmol) was added. The mixture was stirred at 100 °C for 2hrs. The reaction mixture was then extracted by EtOAc/H₂O (50mL/50mL) 3 times. The organic layer was combined, washed with brine, dried over Na₂SO₄, concentrated and further purified by silica gel column chromatography (PE/EA=5/1) to give tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate (**2-01**) 3.9g as a colorless oil (43%). Mass (m/z) 304.1 [M+H]⁺

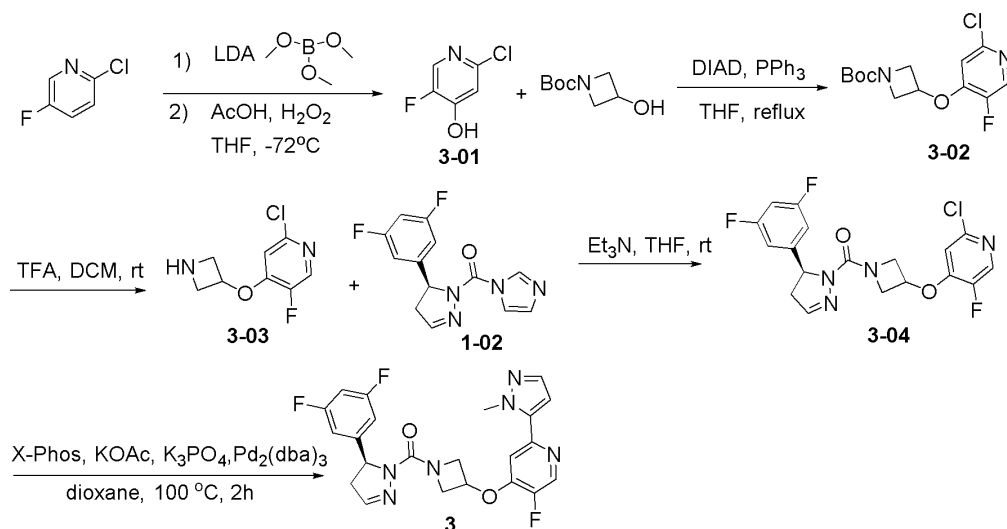
Step 2. TFA (5mL) was added to a solution of **2-01** (3.9g, 12.9mmol) in DCM (10mL). the reaction mixture was stirred at room temperature for

0.5hr. then the solvent was evaporated in vacuo to give 5.2g of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine as a colorless oil (**2-02**) (crude). Mass (m/z) 204.1 [M+H]⁺

Step 3. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (**1-02**) (3.23g, 11.7mmol) was added to a solution of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine (**2-02**) and TEA (3.55g, 35.1mmol) in 1,4-dioxane (30mL). The reaction mixture was stirred at room temperature overnight. Then the solvent was evaporated in vacuo. The oil residue was purified by silica gel column chromatography (PE/EA=1/1) to give 4.35g of (S)-(3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone as a yellow oil (**2-03**) (90%). Mass (ESI) *m/z* [M+H]⁺:412.1.

Step 4: The titled compound **2** was prepared in 59.2% yield from **2-03** according to the procedure outlined for compound **1**. Mass (m/z) 458.2 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.69 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.53 (tt, *J* = 6.6, 4.2 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.69 – 4.58 (m, 2H), 4.37 (dd, *J* = 10.7, 4.1 Hz, 1H), 4.30 (s, 4H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (3)



Step 1: Under a nitrogen atmosphere at -72 °C to a stirred solution of 2-chloro-5-fluoropyridine (25.0 g, 190 mmol) in tetrahydrofuran (250 mL) is added LDA (124 mL, 2M in tetrahydrofuran) dropwise over 30 min. The reaction mixture is stirred at -72 °C for 2 h. Afterwards a solution of trimethyl borate (39 g, 375 mmol) is added dropwise over 20 min. After addition, the reaction mixture is stirred at rt for another 2 h. The reaction mixture is cooled to 0 °C and acetic acid (32.5 mL) is added. The reaction mixture is stirred at 0 °C for 30 min. Hydrogen peroxide (58 mL, 30percent solution) is added dropwise at 0 °C. The reaction mixture is stirred at rt overnight. The reaction mixture is quenched with saturated aqueous Na₂S₂O₄. HCl (4M in dioxane) is added to the reaction mixture until the PH < 7. After extraction with EA (300 mL x 3), the combined organic phases are washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude is beaten with DCM and filtered. The mother liquor was recrystallized twice with DCM to afford 15.2 g of the intermediate **3-01** (yield: 54%) white solid.

Step 2: PPh₃ (1.43 g, 5.4 mmol) in 50 ml dry THF was added DIAD (1.1 g, 5.4 mmol) at rt under nitrogen protection. 5 min later, **3-01** (670 mg, 4.5 mmol) was added to the above solution at room temperature. The

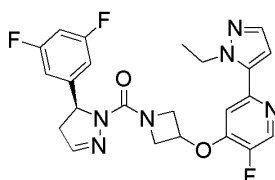
mixture was stirred for 30 min at rt. Then tert-butyl 3-hydroxyazetidine-1-carboxylate (944 mg, 5.4 mmol) was added. The mixture was heated to reflux for 3 h. The resulting solution was added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to afford of the intermediate **3-02** 1.3 g (yield: 95%) white solid.

Step 3 and 4: The intermediate **3-04** was prepared from **3-02** according to the procedure from for **2-03**.

Step 5: The title compound **3** was prepared from **3-04** according to the procedure from for **1**.

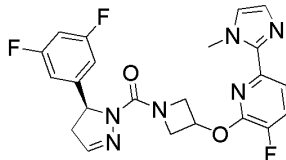
Mass (m/z) 457.2 [M+H]⁺ ¹H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 2.8 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 6.5 Hz, 1H), 6.80 (s, 1H), 6.78, 6.66 (m, 3H), 6.47 (d, *J* = 2.0 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.13– 5.04 (m, 1H), 4.67– 4.52 (m, 2H), 4.32 (dd, *J* = 29.1, 10.4 Hz, 2H), 4.17 (s, 3H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1-ethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (4)



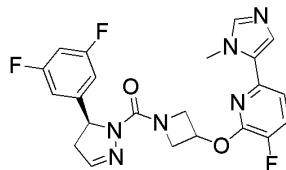
The titled compound **4** was prepared in a yield of 80.1% according to the procedure outlined for compound **3**. Mass (m/z) 471.2 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (dd, *J* = 2.8, 0.6 Hz, 1H), 7.51 (dd, *J* = 2.0, 0.6 Hz, 1H), 6.85 (d, *J* = 6.5 Hz, 1H), 6.80 – 6.66 (m, 4H), 6.44 (dd, *J* = 2.0, 0.6 Hz, 1H), 5.29 – 5.20 (m, 1H), 5.12-5.04 (m, 1H), 4.59 (q, *J* = 7.2 Hz, 4H), 4.39 – 4.15 (m, 2H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.7, 6.5, 1.7 Hz, 1H), 1.41 (t, *J* = 7.2, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(1-methyl-1H-imidazol-2-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (5)



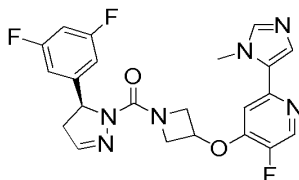
5 The titled compound **5** was prepared in a yield of 18.6% according to the procedure outlined for compound **1**. Mass (m/z) 457.2 $[M+H]^+$; 1H NMR (400 MHz, Chloroform- d) δ 7.98 (dd, $J = 8.1, 3.0$ Hz, 1H), 7.64 (td, $J = 8.8, 2.8$ Hz, 1H), 7.55 (s, 1H), 7.28 – 7.14 (d, 1H), 6.87 – 6.63 (m, 4H), 5.47-5.36 (m, 1H), 5.28 – 5.21 (m, 1H), 4.66-4.51 (m, 2H), 4.44 – 4.21 (m, 10 2H), 4.14 (s, 3H), 3.47 – 3.29 (m, 1H), 2.80 – 2.56 (m, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(1-methyl-1H-imidazol-5-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (6)



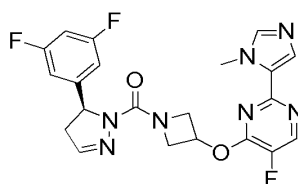
15 The titled compound **6** was prepared in a yield of 18.7% from **1-05** according to the procedure outlined for compound **1**. Mass (m/z) 457.3 $[M+H]^+$; 1H NMR (400 MHz, Chloroform- d) δ 7.41 – 6.70 (m, 4H), 6.70 – 5.98 (m, 4H), 4.89 (d, $J = 16.0$ Hz, 2H), 4.44-4.05 (m, 2H), 3.92 (d, $J = 37.8$ Hz, 2H), 3.54 (s, 3H), 3.11 – 2.85 (m, 1H), 2.43 – 2.18 (m, 1H).

20 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (7)**



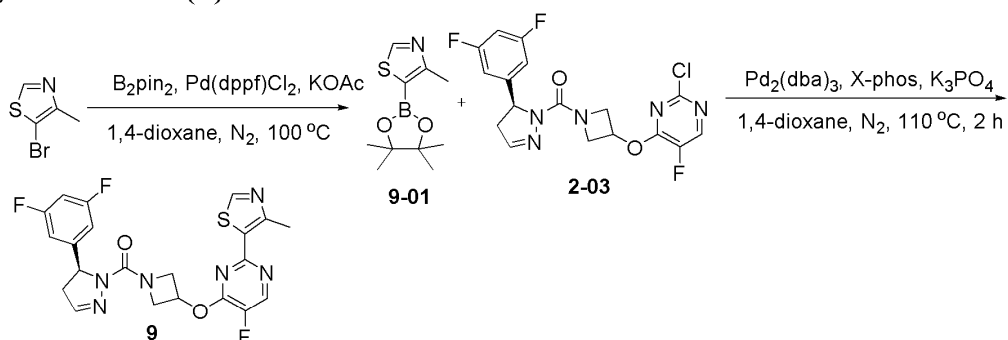
The titled compound **7** was prepared in a yield of 24.1% from **3-04** according to the procedure outlined for compound **3**. Mass (m/z): 457.2 [M+H]⁺, ¹H NMR (400 MHz, Chloroform-*d*) δ 8.36 (dd, *J* = 2.9, 1.0 Hz, 1H), 7.55 (s, 1H), 7.35 (s, 1H), 6.91 – 6.65 (m, 5H), 5.28 – 5.22 (m, 1H), 5.09 – 5.07 (m, 1H), 4.67 – 4.51 (s, 2H), 4.36 – 4.26 (dd, *J* = 27.7, 9.7 Hz, 2H), 3.95 (s, 3H), 3.43 – 3.29 (m, 1H), 2.78 – 2.65 (m, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-imidazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (8)



The titled compound **8** was prepared from **3-04** in a yield of 65.5% according to the procedure outlined for compound **2**. Mass (m/z) 458.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.43 (d, *J* = 2.2 Hz, 1H), 7.98 (s, 1H), 6.89 – 6.59 (m, 4H), 5.51 (s, 1H), 5.29 (dd, *J* = 12.3, 6.2 Hz, 1H), 4.64 (d, *J* = 25.7 Hz, 2H), 4.42 – 4.12 (m, 5H), 3.37 (dd, *J* = 18.7, 12.1 Hz, 1H), 2.72 (dd, *J* = 18.6, 6.4 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-methylthiazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (9)

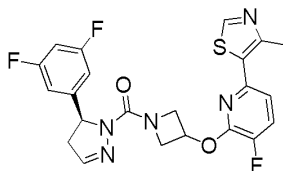


Step 1: 5-bromo-4-methylthiazole (89 mg, 0.5 mmol), B₂pin₂ (254 mg, 1.0 mmol), Pd(dppf)Cl₂ (36 mg, 0.05 mmol), KOAc (147 mg, 1.5 mmol)

in 1,4-dioxane (2 mL) under N₂ and the reaction mixture was stirred at 100 °C for 3 hours. Concentrated to give the intermediate **9-01**, which was used for next step without further purification. Mass (m/z): 226.2 [M+H]⁺.

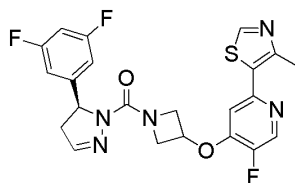
Step 2: Compound **2-03** (82 mg, 0.20 mmol), 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole **9-01** (90 mg, 0.40 mmol), Pd₂(dba)₃ (18 mg, 0.02 mmol), X-phos (19 mg, 0.04 mmol) was added to a solution of K₃PO₄ (5N, 0.2 mL, 1.0 mmol) in 1,4-dioxane (2 mL) under N₂ and the whole reaction mixture was stirred at 110 °C for 2 hours. After the mixture was concentrated and further purified by prep-HPLC to give the final compound **9** (9 mg, 9.5%) as a white solid. Mass (m/z) 475.2 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 8.40 (d, *J* = 2.3 Hz, 1H), 6.85 – 6.64 (m, 4H), 5.53 (s, 1H), 5.30 (d, *J* = 0.4 Hz, 1H), 4.66 (s, 2H), 4.46 – 4.25 (m, 2H), 3.37 (dd, *J* = 18.6, 11.5 Hz, 1H), 2.91 (s, 3H), 2.72 (dd, *J* = 18.4, 5.3 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(4-methylthiazol-5-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (10)



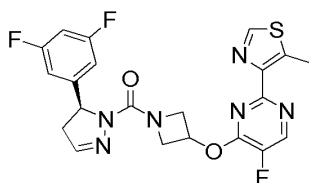
The titled compound **10** was prepared from **1-05** according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.67 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.48-7.34 (m, 1H), 7.20-7.07 (m, 1H), 6.84 – 6.56 (m, 4H), 5.50-5.35 (m, 1H), 5.30-5.20 (m, 1H), 4.77 – 4.48 (m, 2H), 4.43 – 4.17 (m, 2H), 3.44 – 3.16 (m, 1H), 2.68 (dd, *J* = 8.8, 4.2 Hz, 3H), 2.13 – 1.91 (m, 1H). Mass (m/z): 474.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-methylthiazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (11)



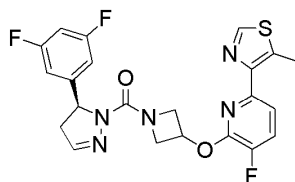
The titled compound **11** was prepared from **3-04** in 42.2% yield according to the procedure outlined for compound **3**. Mass (m/z) 474.2 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 8.43 (dd, *J* = 3.0, 1.7 Hz, 1H), 6.99 – 6.63 (m, 5H), 5.34 – 5.23 (m, 1H), 5.13 (s, 1H), 4.62 (s, 2H), 4.35 (dd, *J* = 35.1, 10.3 Hz, 2H), 3.38 (dd, *J* = 18.7, 12.1 Hz, 1H), 2.73 (s, 4H).

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(5-methylthiazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (12)



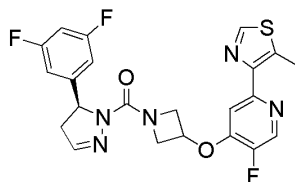
The titled compound **12** was prepared from **2-03** in 6.2% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.98 (s, 1H), 8.51 (s, 1H), 6.75 (dd, *J* = 23.2, 16.4 Hz, 4H), 5.76 (s, 1H), 5.37 – 5.24 (m, 1H), 4.65 (s, 2H), 4.41 – 4.23 (m, 2H), 3.39 – 3.32 (m, 1H), 2.89 (s, 3H), 2.70 (dd, *J* = 18.5, 6.3 Hz, 1H); Mass (m/z) 475.2 [M+H]⁺.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((3-fluoro-6-(5-methylthiazol-4-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (13)



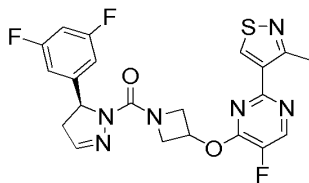
The titled compound **13** was prepared from **1-05** in 17.5% yield according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.78 (dd, *J* = 8.3, 3.1 Hz, 1H), 7.45 (dd, *J* = 9.8, 8.3 Hz, 1H), 6.83 – 6.66 (m, 4H), 5.52 (tt, *J* = 6.6, 4.2 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.59 (d, *J* = 8.2 Hz, 2H), 4.32 (dd, *J* = 38.5, 10.5 Hz, 2H), 3.35 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.84 (s, 3H), 2.69 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H). Mass (m/z) 474.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(5-methylthiazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (14)



The titled compound **14** was prepared from **3-04** in 30.3% yield according to the procedure outlined for compound **3**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 8.41 (d, *J* = 2.8 Hz, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 6.80 – 6.63 (m, 4H), 5.28 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.15 (td, *J* = 6.5, 3.3 Hz, 1H), 4.63 (s, 2H), 4.32 (dd, *J* = 27.0, 10.6 Hz, 2H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.86 (s, 3H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H). Mass (m/z) 474.2 [M+H]⁺.

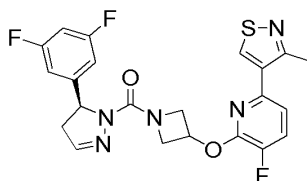
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-methylisothiazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (15)



The titled compound **15** was prepared from **2-03** in 19.2% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 8.43 (d, *J* = 2.4 Hz, 1H), 6.86 – 6.65 (m, 4H),

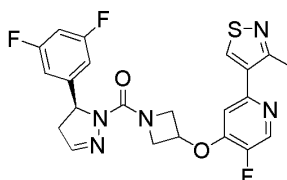
5.56 (s, 1H), 5.30 (dd, $J = 11.9, 6.3$ Hz, 1H), 4.66 (s, 2H), 4.46 – 4.25 (m, 2H), 3.40 – 3.29 (m, 1H), 2.85 (s, 3H), 2.72 (dd, $J = 18.7, 5.8$ Hz, 1H). Mass (m/z) 475.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(3-methylisothiazol-4-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (16)



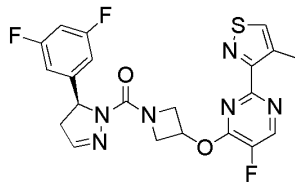
The titled compound **16** was prepared from **1-05** in 39.6% yield according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.32 (q, $J = 0.9$ Hz, 1H), 7.77 (dd, $J = 8.2, 3.2$ Hz, 1H), 7.47 (dd, $J = 9.8, 8.2$ Hz, 1H), 6.80 – 6.64 (m, 4H), 5.51 (tt, $J = 6.6, 4.1$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.59 (d, $J = 9.0$ Hz, 2H), 4.31 (dd, $J = 36.4, 10.0$ Hz, 2H), 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.5, 6.6, 1.7$ Hz, 1H), 2.60 (d, $J = 0.9$ Hz, 3H). Mass (m/z) 474.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-methylisothiazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (17)



The titled compound **17** was prepared from **3-04** in 30.3% yield according to the procedure outlined for compound **3**. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 8.44 (d, $J = 3.0$ Hz, 1H), 6.90 – 6.52 (m, 5H), 5.28 (dd, $J = 12.1, 6.4$ Hz, 1H), 5.10 (s, 1H), 4.60 (q, $J = 9.2, 8.8$ Hz, 2H), 4.33 (dd, $J = 24.1, 8.3$ Hz, 2H), 3.42 – 3.30 (m, 1H), 2.79 – 2.56 (m, 4H). Mass (m/z) 474.2 [M+H]⁺.

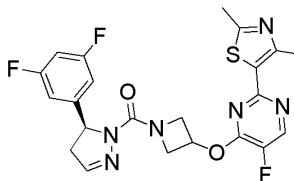
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-methylisothiazol-3-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (18)



5 The titled compound **18** was prepared from **2-03** in 0.6% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.42 (s, 1H), 6.83 (s, 1H), 6.77 – 6.51 (m, 3H), 5.65 (s, 1H), 5.32 (dt, *J* = 12.2, 5.7 Hz, 1H), 4.67 (s, 2H), 4.38 (d, *J* = 30.1 Hz, 2H), 3.38 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.81 – 2.66 (m, 1H), 2.62
10 (s, 3H).

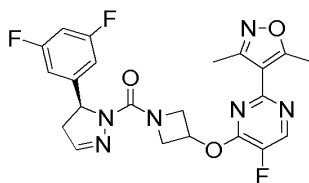
Mass (m/z) 475.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(2,4-dimethylthiazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (19)



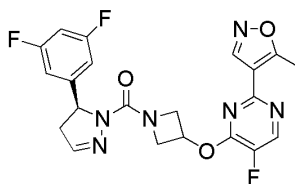
15 The titled compound **19** was prepared in 21.5% yield from **2-03** according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.35 (dd, *J* = 2.5, 0.4 Hz, 1H), 6.83 – 6.67 (m, 4H), 5.54 – 5.48 (m, 1H), 5.28 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.64 (q, *J* = 10.7 Hz, 2H),
20 4.41 – 4.24 (m, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.80 (s, 3H), 2.75 – 2.66 (m, 4H). Mass (m/z) 489.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethylisoxazol-4-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (20)



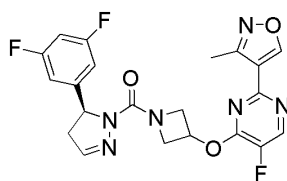
The titled compound **20** was prepared in 33.5% yield from **2-03** according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 2.5 Hz, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.70 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.53 (tt, *J* = 6.6, 4.0 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.62 (q, *J* = 11.3, 9.6 Hz, 2H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.29 (d, *J* = 10.1 Hz, 1H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.74 (s, 3H), 2.73 – 2.67 (m, 1H), 2.56 (s, 3H). Mass (m/z) 473.2 [M+H]⁺.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(5-methylisoxazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (21)



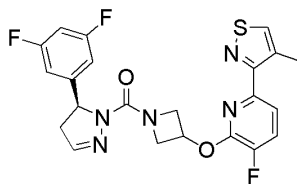
The titled compound **21** was prepared from **2-03** in 9.8% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.37 (d, *J* = 2.4 Hz, 1H), 6.83 – 6.66 (m, 4H), 5.56 – 5.49 (m, 1H), 5.28 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.65 (d, *J* = 18.1 Hz, 2H), 4.33 (dd, *J* = 33.0, 10.9 Hz, 2H), 3.36 (ddd, *J* = 18.5, 12.3, 1.6 Hz, 1H), 2.81 (s, 3H), 2.71 (ddd, *J* = 18.5, 6.4, 1.7 Hz, 1H). Mass (m/z) 459.2 [M+H]⁺.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(3-methylisoxazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (22)



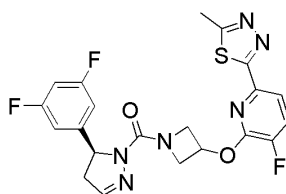
The titled compound **22** was prepared from **2-03** in 14.2% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-d) δ 8.95 (s, 1H), 8.37 (dd, J = 2.4, 0.8 Hz, 1H), 6.82 – 6.65 (m, 4H), 5.52 (qd, J = 6.6, 4.1 Hz, 1H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 4.63 (d, J = 18.1 Hz, 2H), 4.33 (dd, J = 33.3, 10.8 Hz, 2H), 3.36 (dd, J = 18.6, 12.2 Hz, 1H), 2.71 (dd, J = 18.8, 6.5 Hz, 1H), 2.63 (s, 3H). Mass (m/z) 459.2 [M+H]⁺.

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(4-methylisothiazol-3-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (23)



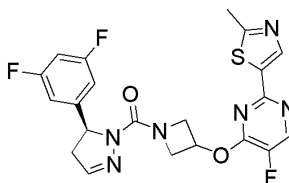
The titled compound **23** was prepared from **1-05** in 42.2% yield according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, Chloroform-d) δ 8.74 (d, J = 0.6 Hz, 1H), 7.43 (dd, J = 9.7, 8.1 Hz, 1H), 7.13 (dd, J = 8.1, 2.8 Hz, 1H), 6.81 – 6.64 (m, 4H), 5.47 (tt, J = 6.6, 4.2 Hz, 1H), 5.28 (dd, J = 12.2, 6.5 Hz, 1H), 4.60 (dd, J = 17.7, 10.9 Hz, 2H), 4.38 – 4.23 (m, 2H), 3.34 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.76 – 2.63 (m, 4H). Mass (m/z) 474.2 [M+H]⁺.

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-(5-methyl-1,3,4-thiadiazol-2-yl)pyridin-2-yl)oxy)azetidin-1-yl)methanone (24)



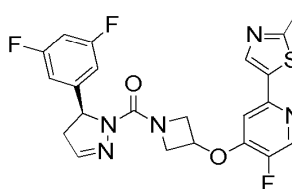
The titled compound **24** was prepared from **1-05** in 4.7% yield according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94 (dd, $J = 8.2, 3.1$ Hz, 1H), 7.51 (dd, $J = 9.4, 8.2$ Hz, 1H), 6.80 – 6.66 (m, 4H), 5.43 (ddd, $J = 11.2, 6.7, 4.4$ Hz, 1H), 5.32 – 5.22 (m, 1H), 4.64 (d, $J = 10.3$ Hz, 2H), 4.43 – 4.11 (m, 2H), 3.46 – 3.20 (m, 1H), 2.81 (s, 3H), 2.75 – 2.60 (m, 1H). Mass (m/z) 475.1 $[\text{M}+\text{H}]^+$

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-methylthiazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (25)



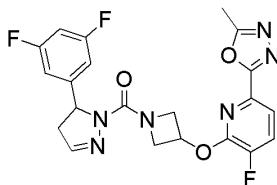
The titled compound **25** was prepared in 23.2% yield from **2-03** according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, $J = 2.5$ Hz, 1H), 8.28 (s, 1H), 6.80 – 6.66 (m, 4H), 5.52 (tt, $J = 6.7, 4.3$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.65 (dt, $J = 18.3, 8.4$ Hz, 2H), 4.32 (ddd, $J = 32.0, 10.7, 4.4$ Hz, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.76 (s, 3H), 2.70 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H). Mass (m/z) 475.2 $[\text{M}+\text{H}]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-methylthiazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (26)



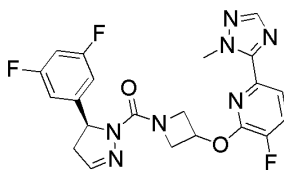
The titled compound **26** was prepared from **3-04** in 17.1% yield according to the procedure outlined for compound **3**. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.33 (d, $J = 3.0$ Hz, 1H), 7.92 (s, 1H), 6.89 (d, $J = 6.4$ Hz, 1H), 6.85 – 6.61 (m, 4H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.12 (ddd, $J =$
 5 10.6, 6.5, 4.0 Hz, 1H), 4.62 (q, $J = 9.3, 8.8$ Hz, 2H), 4.32 (ddd, $J = 24.0,$
 10.5, 4.0 Hz, 2H), 3.41 – 3.30 (m, 1H), 2.79 – 2.63 (m, 4H). Mass (m/z) 474.2 $[\text{M}+\text{H}]^+$.

(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-
 6-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)oxy)azetidin-1-
 10 yl)methanone (**27**)



The titled compound **27** was prepared from **1-05** in 4.5% yield according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, $J = 8.2, 3.0$ Hz, 1H), 7.55 – 7.48 (m, 1H), 6.81 –
 15 6.64 (m, 4H), 5.61-5.49 (m, 3.3 Hz, 1H), 5.29 (dd, $J = 12.3, 6.5$ Hz, 1H),
 476-4.54 (m, 2H), 4.37 – 4.23 (m, 2H), 3.42 – 3.28 (m, 1H), 2.73 – 2.66
 (m, 1H), 2.64 (s, 3H). Mass (m/z) 459.2 $[\text{M}+\text{H}]^+$

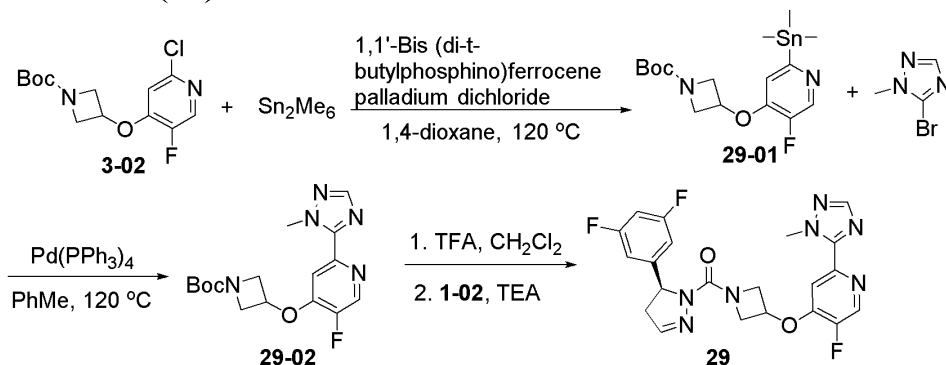
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-
 fluoro-6-(1-methyl-1H-1,2,4-triazol-5-yl)pyridin-2-yl)oxy)azetidin-1-
 20 yl)methanone (**28**)



The titled compound **28** was prepared from **1-05** in 23.5% yield according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.84 (m, 2H), 7.53 (dd, $J = 9.5, 8.2$ Hz, 1H), 6.81 –
 25 6.64 (m, 4H), 5.51 – 5.43 (m, 1H), 5.29 – 5.22 (m, 1H), 4.64 – 4.54 (d, $J =$

9.7 Hz, 2H), 4.44 – 4.30 (m, 2H), 4.29(s, 3H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H). Mass (m/z) 458.2 $[M+H]^+$

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-1,2,4-triazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (29)



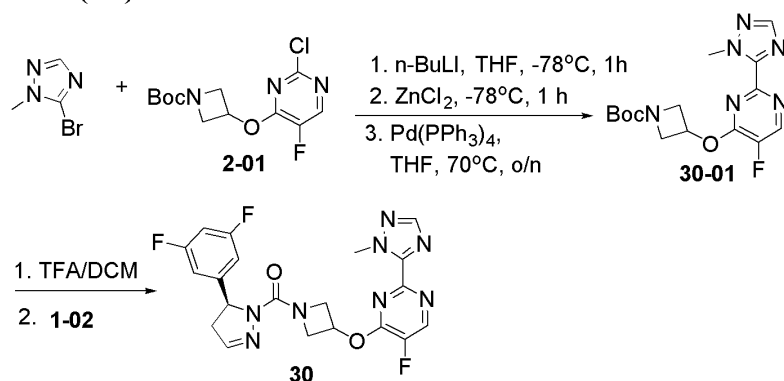
Step 1: compound **3-02** (1.04 g, 3.44 mmol), Sn_2Me_6 (1.7 g, 1.5 mmol), 1,1'-Bis (di-t-butylphosphino)ferrocene palladium dichloride (112 mg, 0.17 mmol) in 1,4-dioxane (15 mL) under N_2 and the whole reaction mixture was stirred at 120 °C for 3 hours. The black suspension was filtered through a plug of Celite and washed with EA (100 mL). Concentrated to give **29-01** (1.47 g, 99.3%) as a brown oil.

Step 2: **29-01** (320 mg, 0.74 mmol), 5-bromo-1-methyl-1H-1,2,4-triazole (61 mg, 0.38 mmol), $\text{Pd}(\text{PPh}_3)_4$ (58 mg, 0.05 mmol) in PhMe (5 mL) under N_2 and the whole reaction mixture was stirred at 120 °C for 15 hours. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give **29-02** (110 mg) as a yellow solid.

Step 3: The titled compound **29** was prepared from **29-02** in 19.4% yield according to the procedure outlined for compound **2-03**. Mass (m/z): 458.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.44 (d, $J = 2.5$ Hz, 1H), 7.95 (s, 1H), 7.72 (d, $J = 6.5$ Hz, 1H), 6.78 (d, $J = 1.6$ Hz, 1H), 6.77 – 6.73 (m, 2H), 6.69 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H),

5.19 (s, 1H), 4.67 (s, 2H), 4.35 (s, 3H), 4.29 (d, $J = 13.5$ Hz, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-1,2,4-triazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (30)

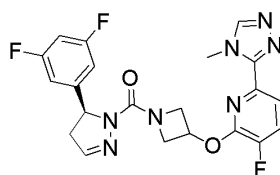


Step 1: To a solution of 5-bromo-1-methyl-1H-1,2,4-triazole (81 mg, 0.5 mmol) in THF (5 mL) was added n-BuLi (1.6 M, 0.38 mL, 0.6 mmol) under Ar at -78°C . The reaction was stirred at -78°C for 1 h. Then ZnCl_2 (1M in THF, 0.6 mL, 0.6 mmol) was added to the reaction and stirred at -78°C for another 0.5 h. The reaction mixture was allowed to warm to rt over 1 h at which time **2-01** (152 mg, 0.5 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (115 mg, 0.1 mmol) in THF was added. The reaction mixture was stirred at 70°C for 16 h. The reaction mixture was cooled to rt and diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed under vacuum and the crude product **30-01** was used to next step directly.

Step 2: To a solution of **30-01** (98 mg, 0.28 mmol) in DCM (5 mL) was added TFA (2 mL). The reaction was stirred at rt for 1 h. The solvent was removed under vacuum. To the resulting residue in THF (5 mL) was added TEA (3 mL) and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone **1-02** (76 mg, 0.28 mmol). The reaction mixture was stirred at rt for 1 h. The reaction was cooled to rt and concentrated. The crude product was purified by Pre-TLC to give required

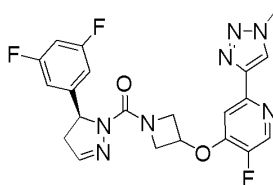
product **30** (27 mg, 20.9%) as a white solid. Mass (m/z): 459.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.01 (s, 1H), 6.84 – 6.65 (m, 4H), 5.69 (s, 1H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.66 (s, 2H), 4.32 (s, 5H), 3.45 – 3.22 (m, 2H), 2.70 (dd, *J* = 18.5, 6.0 Hz, 1H).

5 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-methyl-4H-1,2,4-triazol-3-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (31)**



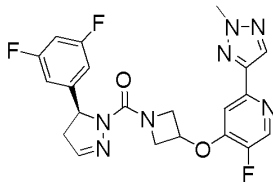
The titled compound **31** was prepared from **1-05** according to the
 10 procedure outlined for compound **1**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.86 (m, 2H), 7.55 (dd, *J* = 9.5, 8.2 Hz, 1H), 6.85 – 6.65 (m, 4H), 5.53 – 5.42 (m, 1H), 5.31 – 5.25 (m, 1H), 4.63 – 4.54 (d, *J* = 9.7 Hz, 2H), 4.46 – 4.33 (m, 2H), 4.29 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.72 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H). Mass (m/z) 458.2 [M+H]⁺

15 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-1,2,3-triazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (32)**



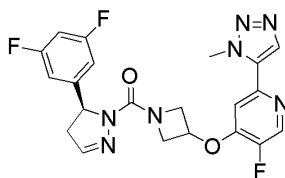
The titled compound **32** was prepared from **29-01** in a yield of 42.9%
 20 according to the procedure outlined for compound **29**. Mass (m/z): 458.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 2.9 Hz, 1H), 8.20 (s, 1H), 7.30 (d, *J* = 6.7 Hz, 1H), 6.82 (t, *J* = 1.7 Hz, 1H), 6.80 – 6.68 (m, 3H), 5.36 – 5.26 (m, 1H), 5.19 (dt, *J* = 6.5, 2.7 Hz, 1H), 4.68 (d, *J* = 7.8 Hz, 2H), 4.36 (dd, *J* = 32.6, 9.5 Hz, 2H), 4.27 (s, 3H), 3.39 (ddd, *J* =
 25 18.6, 12.2, 1.7 Hz, 1H), 2.74 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-methyl-2H-1,2,3-triazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (33)



5 The titled compound **33** was prepared from **29-01** in a yield of 38.2% according to the procedure outlined for compound **29**. Mass (m/z): 458.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.67 (d, $J = 3.8$ Hz, 1H), 8.56 (s, 1H), 7.74 (d, $J = 7.0$ Hz, 1H), 6.89 – 6.81 (m, 1H), 6.79 – 6.65 (m, 3H), 5.35 – 5.24 (m, 2H), 4.73 (s, 2H), 4.38 (dd, $J = 19.7, 10.8$ Hz, 2H),
10 4.22 (s, 3H), 3.38 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.73 (ddd, $J = 18.6, 6.2, 1.7$ Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (34)



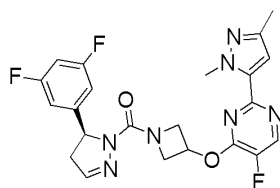
15

The titled compound **34** was prepared in 26.2% yield as white solid from 1-methyl-1H-1,2,3-triazole and **3-02** according to the procedure outlined for compound **30**. Mass (m/z): 458.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.46 (d, $J = 2.8$ Hz, 1H), 8.02 (s, 1H), 6.98 (d, $J = 6.3$ Hz, 1H), 6.80 (d, $J = 1.7$ Hz, 1H), 6.78 – 6.66 (m, 3H), 5.28 (dd, $J = 12.1, 6.3$ Hz, 1H), 5.16 (s, 1H), 4.64 (s, 2H), 4.37 (s, 3H), 4.35 – 4.23 (m, 2H), 3.46 – 3.30 (m, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.6$ Hz, 1H).

20

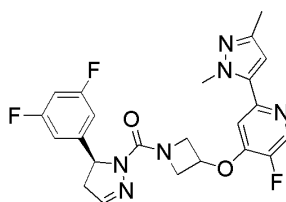
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,3-dimethyl-1H-pyrazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (35)

25



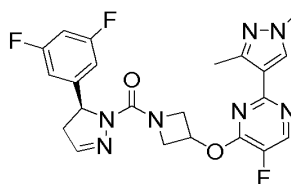
The titled compound **35** was prepared in 63.6% yield from **2-03** according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, $J = 2.4$ Hz, 1H), 6.81 – 6.66 (m, 5H), 5.52 (tt, $J = 6.7, 4.2$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.69 – 4.55 (m, 2H), 4.44 – 4.31 (m, 1H), 4.28 (s, 4H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.34 (s, 3H). Mass (m/z) 472.3 $[\text{M}+\text{H}]^+$.

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,3-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (36)



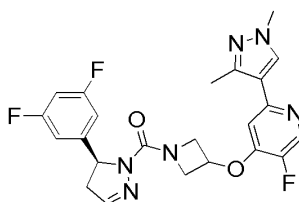
The titled compound **36** was prepared from **3-04** according to the procedure outlined for compound **3**. Mass (m/z): 471.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.43-8.40 (m, 1H), 6.86 – 6.65 (m, 5H), 6.28 – 6.22 (m, 1H), 5.32 – 5.24 (m, 1H), 5.12-5.04 (m, 1H), 4.67-4.54 (m, 2H), 4.41 – 4.32 (m, 1H), 4.31-4.23 (m, 1H), 4.11 – 4.06 (m, 3H), 3.42-3.31 (m, 1H), 2.77-2.67 (m, 1H), 2.33 – 2.27 (m, 3H).

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (37)



The titled compound **37** was prepared from **2-03** in 15.9% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 2.7 Hz, 1H), 7.96 (s, 1H), 6.86 – 6.61 (m, 4H), 5.60 – 5.45 (m, 1H), 5.28 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.70 – 4.54 (m, 2H), 4.33 (dd, *J* = 36.9, 10.4 Hz, 2H), 3.89 (s, 3H), 3.36 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.77 – 2.65 (m, 1H), 2.58 (s, 3H). Mass (m/z) 472.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (38)

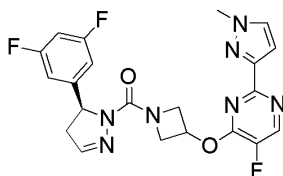


10

The titled compound **38** was prepared from **3-04** in a yield of 32% according to the procedure outlined for compound **3**. Mass (m/z): 471.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.35-8.32 (m, 1H), 7.74 (s, 1H), 6.82 – 6.65 (m, 5H), 5.27 (dd, *J* = 12.3, 6.4 Hz, 1H), 5.11-5.04 (m, 1H), 4.65-4.52 (m, 2H), 4.41-4.33 (m, 1H), 4.32-4.23 (m, 1H), 3.87 (s, 3H), 3.42 – 3.31 (m, 1H), 2.76 – 2.66 (m, 1H), 2.47 (s, 3H).

15

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-pyrazol-3-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (39)

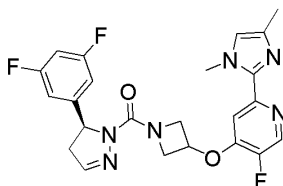


20

The titled compound **39** was prepared in 47.4% yield from **3-04** according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 2.5 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.71 (m, 2H), 6.69 (ddd, *J*

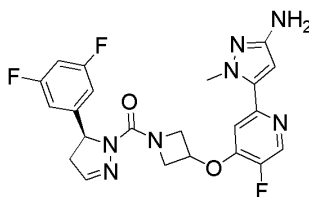
= 8.9, 6.5, 2.3 Hz, 1H), 5.61 (tt, $J = 6.7, 4.3$ Hz, 1H), 5.29 (dd, $J = 12.2, 6.4$ Hz, 1H), 4.66 (t, $J = 10.0$ Hz, 2H), 4.37 (d, $J = 9.9$ Hz, 1H), 4.33 – 4.26 (m, 1H), 4.01 (s, 3H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.4, 1.8$ Hz, 1H). Mass (m/z) 458.2 [M+H]⁺.

- 5 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-imidazol-2-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (40)**



- The titled compound **40** was prepared from **3-04** according to the
 10 procedure outlined for compound **3**. Mass (m/z): 471.3[M+H]⁺. ¹H NMR
 (400 MHz, Chloroform-*d*) δ 8.31 (d, $J = 2.7$ Hz, 1H), 7.57-7.49 (m, 1H),
 6.81 – 6.73 (m, 3H), 6.72 – 6.65 (m, 2H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H),
 5.21-5.15 (m, 1H), 4.70-4.57 (m, 2H), 4.36-4.22 (m, 2H), 4.01 (s, 3H),
 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.5, 1.7$ Hz,
 15 1H), 2.26 (s, 3H).

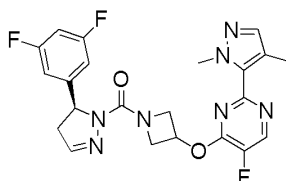
- (S)-(3-((2-(3-amino-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (41)**



- 20 The titled compound **41** was prepared from **29-01** and 5-bromo-1-methyl-1H-pyrazol-3-amine according to the procedure outlined for compound **29**. Mass (m/z): 472.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, $J = 2.9$ Hz, 1H), 6.84 – 6.65 (m, 5H), 5.82 (s, 1H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.12 – 5.02 (m, 1H), 4.66-4.51 (m, 2H),

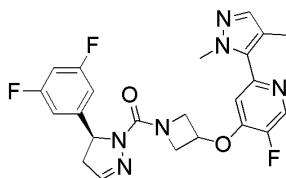
4.40-4.22 (m, 2H), 3.97 (s, 3H), 3.36 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (42)



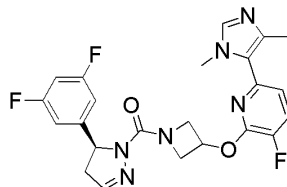
The titled compound **42** was prepared in 9.8% yield according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform- d) δ 8.47 (d, $J = 2.4$ Hz, 1H), 7.40 (s, 1H), 6.81 – 6.67 (m, 4H), 5.56 – 5.50 (m, 1H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 4.63 (d, $J = 17.2$ Hz, 2H), 4.33 (dd, $J = 33.8, 10.8$ Hz, 2H), 4.21 (s, 3H), 3.36 (ddd, $J = 18.7, 12.1, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.33 (s, 3H). Mass (m/z) 472.3 $[\text{M}+\text{H}]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (43)



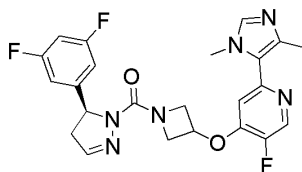
The titled compound **43** was prepared from **3-02** according to the procedure outlined for compound **3**. Mass (m/z): 471.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.52 – 8.47 (m, 1H), 7.36 (s, 1H), 6.83 – 6.65 (m, 5H), 5.27 (dd, $J = 12.2, 6.5$ Hz, 1H), 5.10-5.03 (m, 1H), 4.66 – 4.52 (m, 2H), 4.44-4.33 (m, 1H), 4.33-4.24 (m, 1H), 3.96 (s, 3H), 3.43 – 3.30 (m, 1H), 2.76-2.67 (m, 1H), 2.12 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-(1,4-dimethyl-1H-imidazol-5-yl)-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)methanone (44)



5 The titled compound **44** was prepared from **1-05** in a yield of 16.5% according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 7.94 (t, J = 8.6 Hz, 1H), 7.47 – 7.35 (m, 1H), 7.22 – 6.99 (m, 4H), 5.80-5.72 (m, 1H), 5.67 – 5.61 (m, 1H), 5.01 – 4.88 (m, 2H), 4.69 (dd, J = 25.3, 10.4 Hz, 2H), 4.28 (s, 3H), 3.74 (dd, J = 18.4,
10 12.4 Hz, 1H), 3.08 (dd, J = 18.6, 6.4 Hz, 1H), 2.84 (s, 3H). Mass (m/z) 471.2 $[\text{M}+\text{H}]^+$

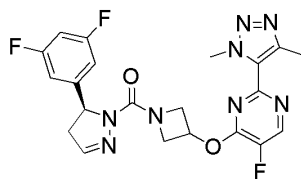
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-imidazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (45)



15

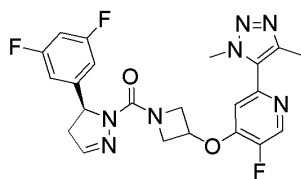
The titled compound **45** was prepared from **3-04** according to the procedure outlined for compound **3**. LC-Mass (m/z): 471.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, J = 3.0 Hz, 1H), 7.50-7.42 (m, 1H), 6.82 – 6.66 (m, 5H), 5.27 (dd, J = 12.2, 6.4 Hz, 1H), 5.10-5.03 (m, 1H), 4.65-4.51 (s, 2H), 4.41-4.24 (m, 2H), 3.77 (s, 3H), 3.36 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.35 (s, 3H).
20

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (46)



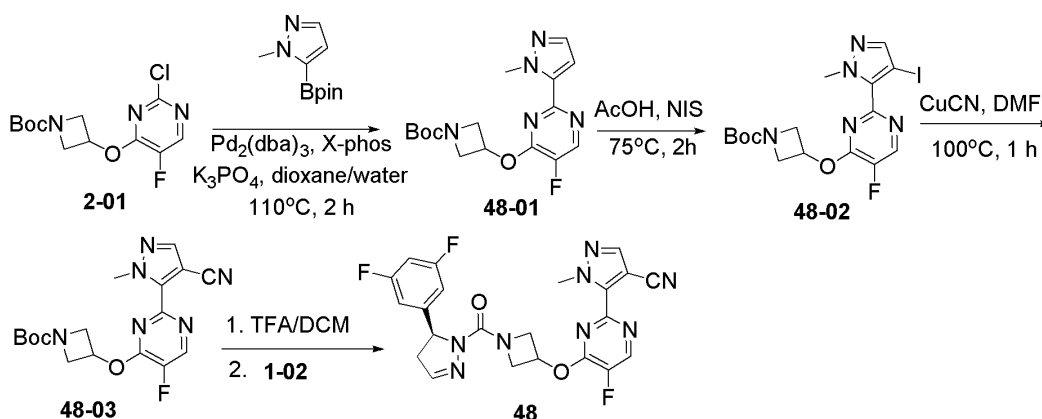
The titled compound **46** was prepared in 45.1% yield as white solid from **2-01** and 1,4-dimethyl-1H-1,2,3-triazole according to the procedure outlined for compound **30**. Mass (m/z): 473.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.3 Hz, 1H), 6.84 – 6.60 (m, 4H), 5.54 (tt, *J* = 6.6, 4.0 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.62 (dt, *J* = 16.6, 9.0 Hz, 2H), 4.37 (s, 4H), 4.29 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.64 (s, 3H).

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((1,4-dimethyl-1H-1,2,3-triazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (47)



The titled compound **47** was prepared in 30.8% yield as white solid from **3-02** and 1,4-dimethyl-1H-1,2,3-triazole according to the procedure outlined for compound **30**. Mass (m/z): 472.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 2.9 Hz, 1H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.79 – 6.66 (m, 4H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 5.09 (s, 1H), 4.60 (s, 2H), 4.37 (d, *J* = 10.3 Hz, 1H), 4.29 (d, *J* = 10.0 Hz, 1H), 4.18 (s, 3H), 3.37 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.76 – 2.67 (m, 1H), 2.45 (s, 3H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-1-methyl-1H-pyrazole-4-carbonitrile (48)



Step 1: A mixture of Compound **2-01** (1 g, 3.3 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (820 mg, 3.96 mmol), Pd₂(dba)₃ (310 mg, 0.33 mmol), X-Phos (320 mg, 0.66 mmol) and K₃PO₄ (3.5 g, 16.5 mmol) in dioxane (10 mL) and water (3 mL) was stirred under Ar at 110°C for 2 h. The reaction mixture was cooled to rt and diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **48-01** was used to next step directly.

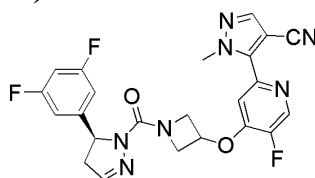
Step 2: To a solution of **48-01** (1.3 g, 3.7 mmol) in AcOH (20 mL) was added NIS (1 g, 4.5 mmol). The reaction was stirred at 75°C for 2 h. The reaction was quenched with water and extracted with EA. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated to give the crude product **48-02** which was used for next step directly.

Step 3: A mixture of Compound **48-02** (480 mg, 1.26 mmol) and CuCN (340 mg, 3.78 mmol) in DMF (10 mL) was stirred at 100°C for 1 h. The reaction mixture was cooled to rt and diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **48-03** was used to next step directly.

Step 4: To a solution of tert-butyl 3-((2-(4-cyano-1-methyl-1H-pyrazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate **48-03** (200 mg, 0.53 mmol) in DCM (5 mL) was added TFA (2 mL). The reaction was stirred at rt for 1 h. The solvent was removed under vacuum.

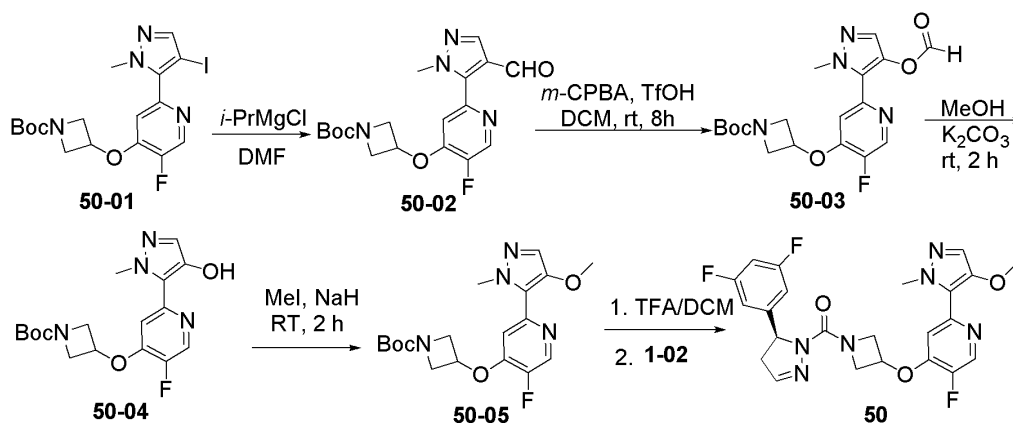
5 To the resulting residue in THF (5 mL) was added TEA (3 mL) and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (133 mg, 0.48 mmol), the reaction mixture was stirred at rt for 1 h. The reaction was cooled to rt and concentrated. The crude product was purified by Pre-TLC to give required product **48** (50 mg, 21.4%) as a white solid. MS (m/z): 483.3 [M+H]⁺. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 2.3 Hz, 1H), 7.85 (s, 1H), 6.80 – 6.73 (m, 3H), 6.69 (tt, *J* = 8.8, 2.2 Hz, 1H), 5.76 (tt, *J* = 6.7, 3.6 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.73 (s, 2H), 4.34 (s, 3H), 4.32 – 4.20 (m, 2H), 3.35 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.5, 6.4, 1.7 Hz, 1H).

15 **(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carbonitrile (49)**



The title compound **49** was prepared in a yield of 62% (200 mg, 0.42mmol) as a white solid from **3-02** according to the procedure for **48**. Mass (m/z): 482.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 2.7 Hz, 1H), 7.82 (s, 1H), 7.30 (d, *J* = 6.4 Hz, 1H), 6.81 – 6.73 (m, 3H), 6.69 (tt, *J* = 8.9, 2.4 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.16-5.09 (m, 1H), 4.74-4.60 (m, 2H), 4.40 – 4.26 (m, 2H), 4.19 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H).

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-methoxy-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (50)



Step 1: To a solution of **50-01** (1 g, 2.1 mmol) in THF (5 mL) was added *i*-PrMgCl (2 M, 5.2 mL, 10.5 mmol) at 0°C. The reaction was stirred at 0°C for 1 h then DMF (3 mL) was added. The reaction was stirred at RT for 2 h. The reaction was quenched with saturated NH₄Cl and extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **50-02** was used to next step directly.

Step 2: A mixture of **50-02** (800 mg, 2.1 mmol), TfOH (32 mg, 0.21 mmol) and *m*-CPBA (732 mg, 4.2 mmol) in DCM (20 mL) was stirred at RT for 6 h. The reaction mixture diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **50-03** was used to next step directly.

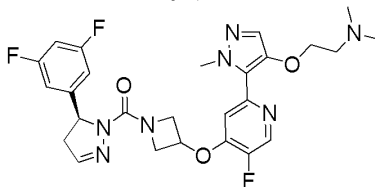
Step 3: A mixture of **50-03** (300 mg, 0.83 mmol) and K₂CO₃ (344 mg, 3.5 mmol) in MeOH (20 mL) was stirred at RT for 2 h. The reaction mixture filtered and concentrated to give the crude product **50-04** was used to next step directly.

Step 4: To a solution of **50-04** (80 mg, 0.22 mmol) in THF (5 mL) was added NaH (17 mg, 0.43 mmol) at 0°C. The reaction was stirred at rt for 1 h then MeI (63 mg, 0.43 mmol) was added. The reaction was stirred at RT for 2 h. The reaction was quenched with saturated NH₄Cl and extracted with EA. The combined organic extracts were washed with brine

and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **50-05** was used to next step directly.

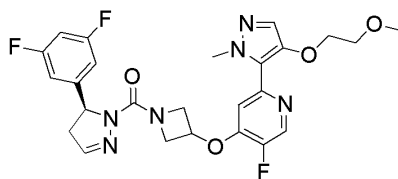
Step 5: To a solution of **50-05** (40 mg, 0.1 mmol) in DCM (5 mL) was added TFA (2 mL). The reaction was stirred at rt for 1 h. The solvent was removed under vacuum. To the resulting residue in THF (5 mL) was added TEA (3 mL) and **1-02** (26 mg, 0.09 mmol). The reaction mixture was stirred at rt for 1 h. The reaction was cooled to rt and concentrated. The crude product was purified by Pre-TLC to give required product **50** (14 mg, 27.4%) as a white solid. Mass (m/z): 487.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 2.9 Hz, 1H), 7.30 (s, 1H), 7.27-7.25 (m, 1H), 6.82 – 6.79 (m, 1H), 6.78 – 6.66 (m, 3H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.08 (ddd, *J* = 10.5, 6.5, 4.1 Hz, 1H), 4.60 (d, *J* = 7.9 Hz, 2H), 4.33 (dd, *J* = 37.0, 10.8 Hz, 2H), 4.17 (s, 3H), 3.87 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-(2-(dimethylamino)ethoxy)-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (51)



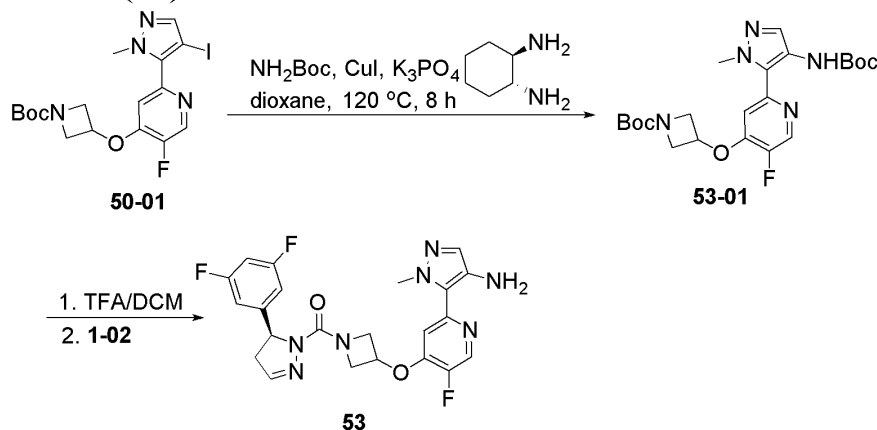
The titled compound **51** was prepared in 17.6% yield as white solid from **50-04** and 2-bromo-N,N-dimethylethan-1-amine according to the procedure outlined for compound **50**. Mass (m/z): 544.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 2.8 Hz, 1H), 7.28 (s, 1H), 7.04 (d, *J* = 6.5 Hz, 1H), 6.84 (s, 1H), 6.73 – 6.58 (m, 3H), 5.19 (dd, *J* = 11.6, 6.1 Hz, 2H), 4.57 (s, 2H), 4.46 (s, 2H), 4.21 (s, 2H), 3.99 (s, 3H), 3.40 – 3.26 (m, 3H), 2.78 (s, 6H), 2.66 (dd, *J* = 18.5, 6.0 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(2-methoxyethoxy)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (52)



The titled compound **52** was prepared in 11.1% yield as white solid from **50-04** and 1-bromo-2-methoxyethane according to the procedure outlined for compound **50**. Mass (m/z): 531.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.41 (s, 1H), 7.43 (d, J = 6.3 Hz, 1H), 7.35 (s, 1H), 6.80 (s, 1H), 6.77 – 6.66 (m, 3H), 5.35 – 5.25 (m, 1H), 5.10 (s, 1H), 4.64 (s, 2H), 4.33 (d, J = 26.2 Hz, 2H), 4.23 – 4.13 (m, 5H), 3.73 (s, 2H), 3.40 (s, 3H), 3.38 – 3.32 (m, 1H), 2.71 (dd, J = 18.5, 5.7 Hz, 1H).

(S)-3-((2-(4-amino-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (53**)**

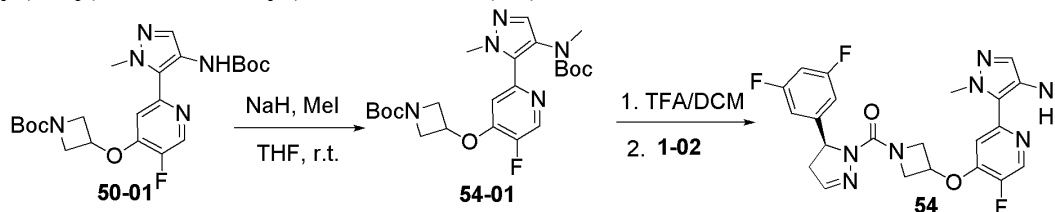


Step 1: A mixture of tert-butyl 3-((5-fluoro-2-(4-iodo-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidine-1-carboxylate **50-01** (500 mg, 1.05 mmol), (1R,2R)-cyclohexane-1,2-diamine (240 mg, 2.1 mmol), NH_2Boc (182 mg, 1.58 mmol), CuI (19 mg, 0.105 mmol) and K_3PO_4 (445 mg, 2.1 mmol) in dioxane (10 mL) was stirred under Ar at 120 °C for 8 h. The reaction mixture was cooled to rt and diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed

with brine and dried over Na_2SO_4 . The solvent was removed under vacuum and the crude product **53-01** was used to next step directly.

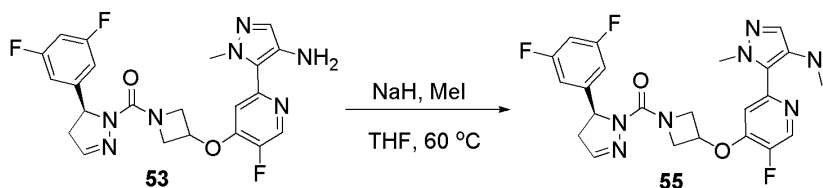
Step 2: The titled compound **53** was prepared in 57.3% yield as white solid from **53-01** according to the procedure outlined for compound **50** from **50-05**. Mass (m/z): 472.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.45 (d, $J = 2.8$ Hz, 1H), 7.27 (s, 1H), 7.06 (d, $J = 6.4$ Hz, 1H), 6.79 (s, 1H), 6.69 (t, $J = 6.9$ Hz, 3H), 5.14 (s, 2H), 4.72 (d, $J = 8.0$ Hz, 1H), 4.63 (s, 1H), 4.38 (s, 1H), 4.25 (s, 1H), 3.99 (s, 3H), 3.34 (dd, $J = 18.6, 12.0$ Hz, 1H), 2.67 (dd, $J = 18.4, 6.4$ Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-4-(methylamino)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (54)



The titled compound **54** was prepared in 42.6% yield as white solid from **50-01** and Iodomethane according to the procedure outlined for compound **50**. Mass (m/z): 486.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.43 (d, $J = 3.0$ Hz, 1H), 7.25 (s, 1H), 6.65 (d, $J = 6.5$ Hz, 1H), 6.82 – 6.79 (m, 1H), 6.77 – 6.65 (m, 3H), 5.26 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.15 – 5.05 (m, 1H), 4.62 (t, $J = 8.7$ Hz, 2H), 4.32 (dd, $J = 35.5, 9.6$ Hz, 2H), 4.00 (s, 3H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.83 (s, 3H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-(dimethylamino)-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (55)



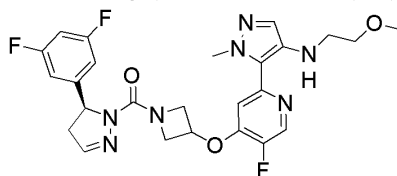
To a solution of **53** (64 mg, 0.14 mmol) in THF (5 mL) was added NaH (11 mg, 0.27 mmol) at 0 °C. The reaction was stirred at rt for 1 h then MeI (77 mg, 0.54 mmol) was added. The reaction was stirred at rt for 16 h.

5 The reaction was quenched with saturated NH₄Cl and extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum. The crude product was purified by Pre-TLC to give required product **55** (20 mg, 29.5%) as a white solid. Mass (m/z): 500.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ

10 8.43 (s, 1H), 7.62 (s, 1H), 6.79 (s, 1H), 6.77 – 6.66 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.07 (s, 1H), 4.61 (s, 2H), 4.43 – 4.22 (m, 2H), 4.05 (s, 3H), 3.46 – 3.30 (m, 1H), 2.70 (dd, *J* = 18.6, 6.4 Hz, 1H), 1.31 – 1.18 (m, 6H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-((2-methoxyethyl)amino)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (**56**)

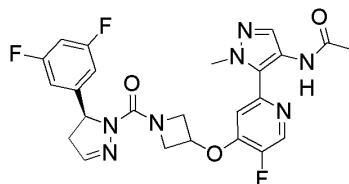
15



The titled compound **56** was prepared in 41.6% yield as white solid from **53-01** and 1-bromo-2-methoxyethane according to the procedure outlined for compound **50-04** to **50**. Mass (m/z): 530.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.6 Hz, 1H), 7.75 (s, 1H), 7.07 (d, *J* = 6.1 Hz, 1H), 6.82 (s, 1H), 6.78 – 6.65 (m, 4H), 5.29 (dd, *J* = 12.1, 6.0 Hz, 1H), 5.20 (s, 1H), 4.63 (s, 2H), 4.42 – 4.26 (m, 2H), 4.08 (s, 3H), 3.64 (s, 2H), 3.42 (s, 2H), 3.40 – 3.36 (m, 1H), 3.34 (s, 3H), 2.72 (dd, *J* = 18.7,

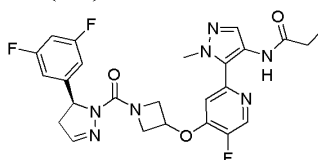
25 5.9 Hz, 1H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)acetamide (57)



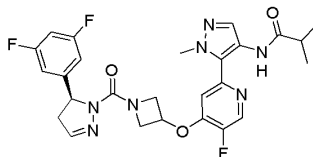
5 The titled compound **57** was prepared in 28.2% yield as white solid from **50-01** and Acetamide according to the procedure outlined for compound **53**. Mass (m/z): 514.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 8.48 (s, 1H), 8.11 (s, 1H), 6.87 (d, *J* = 6.3 Hz, 1H), 6.79 (s, 1H), 6.77 – 6.65 (m, 3H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H),
 10 5.08 (s, 1H), 4.60 (s, 2H), 4.32 (dd, *J* = 31.1, 9.6 Hz, 2H), 4.01 (s, 3H), 3.36 (dd, *J* = 18.6, 11.9 Hz, 1H), 2.71 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.14 (s, 3H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)propionamide (58)



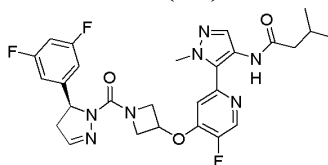
The titled compound **58** was prepared in 39.9% yield as white solid from **50-01** according to the procedure outlined for compound **53**. Mass (m/z): 528.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.23 (s, 1H),
 20 8.48 (d, *J* = 3.0 Hz, 1H), 8.21 (s, 1H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.82 – 6.78 (m, 1H), 6.78 – 6.62 (m, 3H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.09 (d, *J* = 3.7 Hz, 1H), 4.62 (d, *J* = 15.9 Hz, 2H), 4.33 (dd, *J* = 31.3, 9.8 Hz, 2H), 4.04 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.72 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.40 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 4H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)isobutyramide (59)



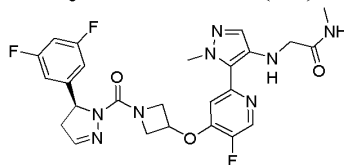
5 The titled compound **59** was prepared in 42.2% yield as white solid from **50-01** according to the procedure outlined for compound **53**. Mass (m/z): 542.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.49 (s, 1H), 8.48 (d, *J* = 3.0 Hz, 1H), 8.25 (s, 1H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.79 – 6.65 (m, 3H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.18 – 5.07 (m, 1H), 4.70 – 4.53 (m, 2H), 4.33 (dd, *J* = 33.2, 9.7 Hz, 2H), 4.05 (s, 3H), 3.37 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.72 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.55 (p, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-3-methylbutanamide (60)



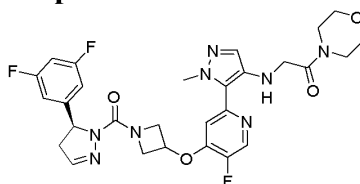
The titled compound **60** was prepared in 26.4% yield as white solid from **50-01** according to the procedure outlined for compound **53**. Mass (m/z): 556.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.49 (d, *J* = 3.0 Hz, 1H), 8.22 (s, 1H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.82 – 6.78 (m, 1H), 6.78 – 6.65 (m, 3H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.10 (s, 1H), 4.60 (s, 2H), 4.33 (dd, *J* = 31.4, 10.4 Hz, 2H), 4.04 (s, 3H), 3.37 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.72 (ddd, *J* = 18.7, 6.4, 1.7 Hz, 1H), 2.25 – 2.16 (m, 3H), 0.99 (d, *J* = 6.3 Hz, 7H).

(S)-2-((5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)amino)-N-methylacetamide (61)



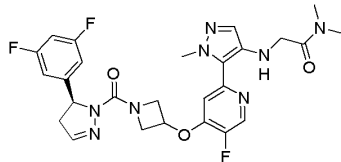
5 The titled compound **61** was prepared in 20.4% yield as white solid from **53-01** and 2-bromo-N-methylacetamide according to the procedure outlined for compound **50-04** to **50**. Mass (m/z): 543.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.52 (d, *J* = 2.8 Hz, 1H), 7.67 (s, 1H), 6.98 (d, *J* = 6.6 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.78 – 6.66 (m, 4H), 5.28 (dd, *J* = 12.1, 6.2 Hz, 1H), 5.02 (s, 1H), 4.56 (d, *J* = 32.7 Hz, 2H), 4.32 (dd, *J* = 23.3, 10.4 Hz, 2H), 4.08 (d, *J* = 3.7 Hz, 3H), 4.01 – 3.93 (m, 2H), 3.42 – 3.30 (m, 1H), 2.95 (d, *J* = 5.0 Hz, 3H), 2.74 – 2.66 (m, 1H).

(S)-2-((5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)amino)-1-morpholinoethan-1-one (62)



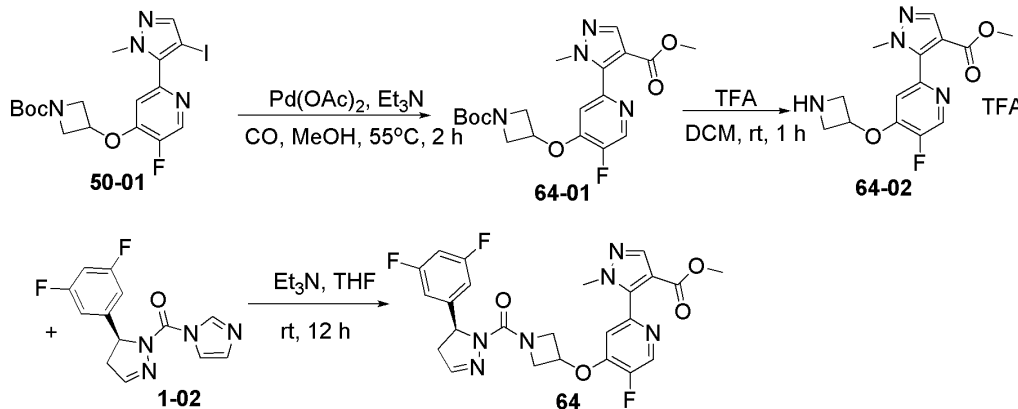
The titled compound **62** was prepared in 10.7% yield as white solid from **53-01** according to the procedure outlined for compound **50-04** to **50**. Mass (m/z): 599.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 2.9 Hz, 1H), 8.23 (s, 1H), 7.66 (s, 1H), 7.37 (d, *J* = 6.9 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.76 – 6.66 (m, 3H), 5.27 (ddd, *J* = 12.4, 6.5, 3.2 Hz, 1H), 5.11 (td, *J* = 6.6, 3.4 Hz, 1H), 4.59 (s, 2H), 4.35 – 4.22 (m, 2H), 4.15 (s, 3H), 3.81 (t, *J* = 4.9 Hz, 2H), 3.73 (dq, *J* = 4.9, 3.0, 2.6 Hz, 4H), 3.69 – 3.59 (m, 4H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-2-((5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)amino)-N,N-dimethylacetamide (63)



5 The titled compound **63** was prepared in 1.7% yield as white solid from **53-01** according to the procedure outlined for compound **50-04** to **50**. Mass (m/z): 557.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.9 Hz, 1H), 8.26 (d, *J* = 7.5 Hz, 0H), 7.52 (s, 1H), 6.82 – 6.66 (m, 4H), 5.35 (s, 1H), 5.27 (s, 1H), 5.11 (s, 1H), 4.60 (s, 2H), 4.31 (s, 2H), 4.12 (d, *J* = 43.2 Hz, 3H), 3.50 (s, 1H), 3.21 (d, *J* = 6.7 Hz, 1H), 3.10 – 2.99 (m, 3H), 2.71 (s, 1H), 2.28 – 2.15 (m, 1H), 2.02 (d, *J* = 10.1 Hz, 2H).

methyl (S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carboxylate (64)



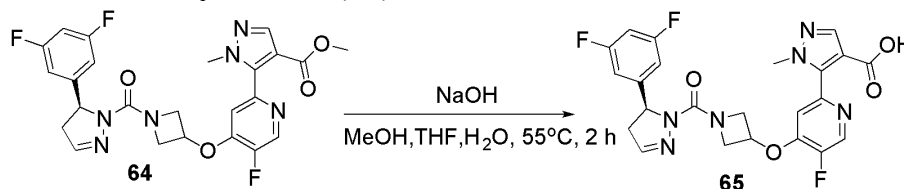
15

Step 1: Compound **50-01** (3.7g, crude) was dissolved in 40 ml CH₃OH. Pd(OAc)₂ (0.35 g, 1.56mmol), Et₃N (2.37 g, 23.4mmol) were added to the above solution at room temperature. The reaction was degassed with CO and stirred for 2 h at 55 °C. The resulting solution was
20 filtered and concentrated in vacuum. The crude product was purified by

silica gel chromatography to afford 2.6 g yellow solid. (Two-step yield: 70%) Mass (m/z): 407.3 [M+H]⁺.

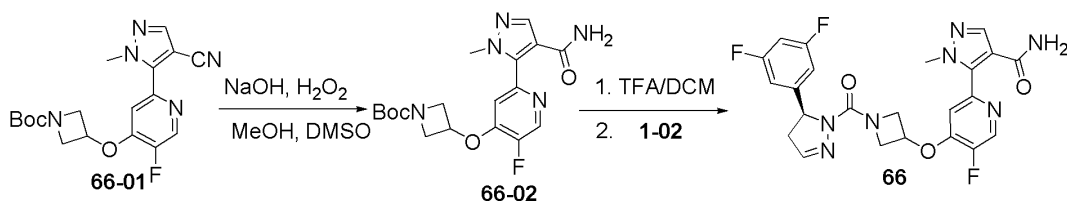
Step 2-3: The titled compound **64** was prepared in 66% yield from **64-01** according to the procedure outlined for compound **50-05** to **50**. Mass (m/z): 515.3[M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.8 Hz, 1H), 7.95 (s, 1H), 7.20 (d, *J* = 6.7 Hz, 1H), 6.80 – 6.73 (m, 3H), 6.69 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.13-5.05 (m, 1H), 4.66-4.54 (m, 2H), 4.42-4.24 (m, 2H), 3.65 (s, 3H), 3.77 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carboxylic acid (65)



Compound **64** (540 mg, 1.05mmol) was dissolved in 20 ml CH₃OH and 10 ml THF. Then NaOH (1M, 4.2 ml, 4.2mmol) was added at room temperature. The mixture was stirred for 2 h at 55 °C. The PH of the resulting solution was adjusted to 4-5. Then added H₂O and extracted with EA. The organic layers were concentrated under vacuum. The crude product was purified by silica gel chromatography to give the desired compound **65** (250 mg, yield: 48%) as a light yellow solid. Mass (m/z): 501.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.8 Hz, 1H), 8.03 (s, 1H), 7.10 (d, *J* = 6.5 Hz, 1H), 6.82 – 6.65 (m, 4H), 5.27 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.08-5.00 (m, 1H), 4.66-4.52 (m, 2H), 4.43 – 4.22 (m, 2H), 3.95 (s, 3H), 3.41-3.28 (m, 1H), 2.75 – 2.65 (m, 1H).

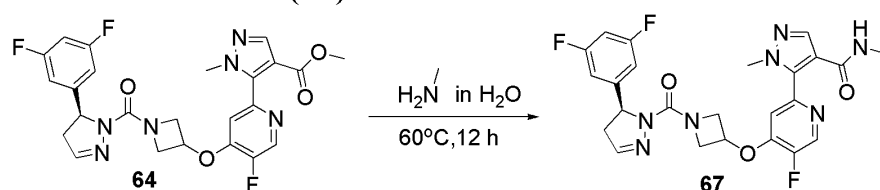
(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (66)



Step 1: To a solution of **66-01** (200 mg, 0.54 mmol) in MeOH (5 mL) and DMSO (5 mL) was added 15% NaOH (3 mL) and 3% H₂O₂ (5 mL). The reaction was stirred at rt for 1 h. The reaction mixture was diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product **66-02** was used to next step directly.

Step 2: The titled compound **66** was prepared in 31.2% yield as white solid from Compound **66-02** according to the procedure outlined for compound **50-05** to **50**. Mass (m/z): 500.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.90 (s, 1H), 7.04 (s, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.69 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.30 (dd, *J* = 12.2, 6.3 Hz, 1H), 5.05 (s, 1H), 4.61 (s, 2H), 4.34 (d, *J* = 35.3 Hz, 2H), 3.65 (s, 3H), 3.43 – 3.30 (m, 1H), 2.71 (ddd, *J* = 18.7, 6.4, 1.6 Hz, 1H).

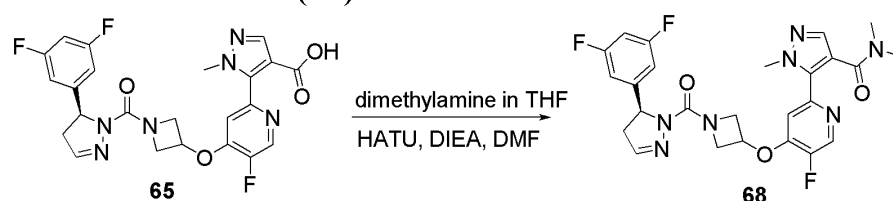
(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,1-dimethyl-1H-pyrazole-4-carboxamide (67)



Compound **64** (60 mg, 0.12mmol) in aqueous solution of methylamine was stirred at 60 ° C for 12 h. The resulting solution was added EA and washed by brine, dried over MgSO₄, concentrated in vacuum. The crude product was purified by Prep-HPLC to afford 20 mg (yield: 33%) white solid. Mass (m/z): 514.3[M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ

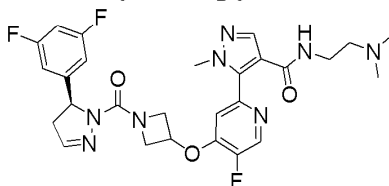
8.52-8.48 (m, 1H), 7.84 (s, 1H), 7.25-7.21 (m, 1H), 6.80 (s, 1H), 6.78 – 6.61 (m, 3H), 5.28 (dd, $J = 12.1, 6.3$ Hz, 1H), 5.20-5.08 (m, 1H), 4.71-4.55 (m, 2H), 4.42-4.24 (m, 2H), 3.93 (s, 3H), 3.42 – 3.31 (m, 1H), 2.88 (d, $J = 3.9$ Hz, 3H), 2.76 – 2.66 (m, 1H).

5 **(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,N,1-trimethyl-1H-pyrazole-4-carboxamide (68)**



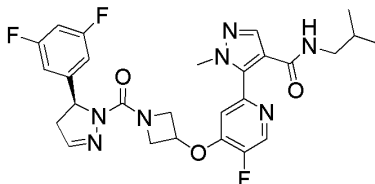
Compound **65** (50 mg, 0.1mmol) was dissolved in 10 ml DMF. HATU
 10 (57 mg, 0.15mmol), DIEA (39 mg, 0.3mmol) were added to the above solution at room temperature. The reaction was stirred for 15 min at rt. Then dimethylamine in THF was added. The reaction was stirred for 1 hour at rt. The resulting solution was added H₂O and extracted by EA. The combined organic layers were washed by brine, dried over MgSO₄,
 15 concentrated in vacuum. The crude product was purified by silica gel chromatography to afford 18.6 mg (yield: 35%) white solid. Mass (m/z): 528.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, $J = 2.8$ Hz, 1H), 7.54 (s, 1H), 7.35 (d, $J = 6.7$ Hz, 1H), 6.79 – 6.65 (m, 4H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.09-4.99 (m, 1H), 4.75 – 4.57 (m, 2H), 4.26 (t, $J =$
 20 11.5 Hz, 2H), 4.04 (s, 3H), 3.35 (ddd, $J = 18.6, 12.1, 1.7$ Hz, 1H), 3.04 (s, 3H), 2.84 (s, 3H), 2.69 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(2-(dimethylamino)ethyl)-1-methyl-1H-pyrazole-4-carboxamide (69)



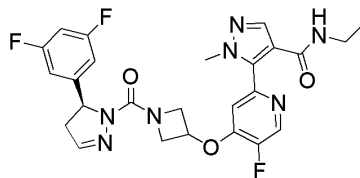
The title compound **69** was prepared in a yield of 46% (26 mg, 0.05mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 571.4 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 2.9 Hz, 1H), 7.92-7.83 (m, 2H), 6.84-6.81 (m, 1H), 6.78 – 6.66 (m, 3H), 5.26 (dd, *J* = 12.1, 6.2 Hz, 1H), 5.14-5.07 (m, 1H), 4.69-4.59 (m, 2H), 4.43-4.23 (m, 2H), 3.86 (s, 3H), 3.78-3.63 (m, 2H), 3.37 (ddd, *J* = 18.6, 12.1, 1.6 Hz, 1H), 3.27 (s, 2H), 2.89 (s, 6H), 2.71 (ddd, *J* = 18.6, 6.2, 1.8 Hz, 1H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-isobutyl-1-methyl-1H-pyrazole-4-carboxamide (70)



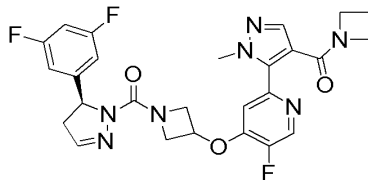
The title compound **70** was prepared in a yield of 27% (15.2 mg, 0.03mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 556.4 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.83 (s, 1H), 7.19 (d, *J* = 6.6 Hz, 1H), 6.81 – 6.64 (m, 4H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.15-5.07 (m, 1H), 4.69-4.52 (m, 2H), 4.39-4.22 (m, 2H), 3.90 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 3.21 – 3.09 (m, 2H), 2.70 (ddd, *J* = 18.6, 6.4, 1.8 Hz, 1H), 1.79 – 1.73 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 6H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-ethyl-1-methyl-1H-pyrazole-4-carboxamide (71)



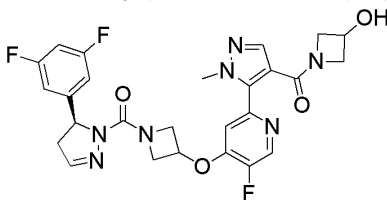
The title compound **71** was prepared in a yield of 29% (15.2 mg, 0.03mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 528.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.80 (s, 1H), 6.82 – 6.63 (m, 4H), 6.55-6.48 (m, 1H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.15-5.07 (m, 1H), 4.68-4.53 (m, 2H), 4.38-4.22 (m, 2H), 3.91 (s, 3H), 3.43 – 3.27 (m, 3H), 2.69 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 1.14 (t, *J* = 7.2 Hz, 3H).

(S)-azetidin-1-yl(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)methanone (72)



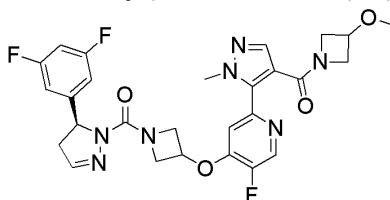
The title compound **72** was prepared in a yield of 21% (11.5 mg, 0.02mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 540.3[M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.8 Hz, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 6.79 – 6.64 (m, 4H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.16-5.08 (m, 1H), 4.70-4.56 (m, 2H), 4.37-4.22 (m, 2H), 4.15 – 4.05 (m, 4H), 3.97 (s, 3H), 3.34 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.68 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.32-2.19 (m, 2H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(3-hydroxyazetidine-1-carbonyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (73)



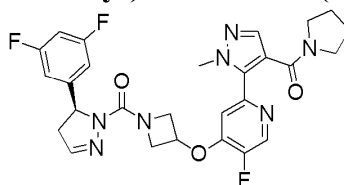
The title compound **73** was prepared in a yield of 59% (33 mg, 0.06mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 556.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.6 Hz, 1H), 7.60 (s, 1H), 7.37 (d, *J* = 6.6 Hz, 1H), 6.81 – 6.64 (m, 4H), 5.25 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.10 (s, 1H), 4.68-4.48 (m, 3H), 4.38 – 4.16 (m, 4H), 3.96 (s, 3H), 3.92-3.76 (m, 2H), 3.34 (ddd, *J* = 18.5, 12.2, 1.8 Hz, 1H), 2.68 (ddd, *J* = 18.6, 6.3, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(3-methoxyazetidine-1-carbonyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (74)



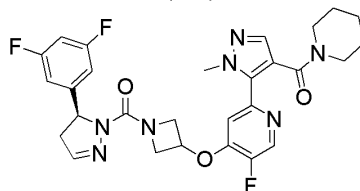
The title compound **74** was prepared in a yield of 81% (46 mg, 0.08mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 570.3[M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.8 Hz, 1H), 7.63 (s, 1H), 7.48 (d, *J* = 6.7 Hz, 1H), 6.81 – 6.64 (m, 4H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 5.14 (s, 1H), 4.70-4.55 (m, 2H), 4.38-4.12 (m, 5H), 3.99 (s, 3H), 3.97 – 3.91 (m, 2H), 3.35 (ddd, *J* = 18.6, 12.3, 1.6 Hz, 1H), 3.26 (s, 3H), 2.69 (ddd, *J* = 18.5, 6.5, 1.6 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-4-(pyrrolidine-1-carbonyl)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (75)



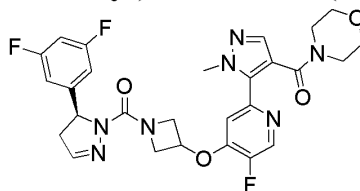
The title compound **75** was prepared in a yield of 78% (43 mg, 0.08mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 554.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.7 Hz, 1H), 7.61 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 6.78 – 6.64 (m, 4H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.11-5.02 (m, 1H), 4.72-4.55 (m, 2H), 4.25 (t, *J* = 12.9 Hz, 2H), 4.01 (s, 3H), 3.54 (t, *J* = 6.9 Hz, 2H), 3.34 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 3.25 (t, *J* = 6.5 Hz, 2H), 2.68 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.92 – 1.74 (m, 4H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-4-(piperidine-1-carbonyl)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (76)



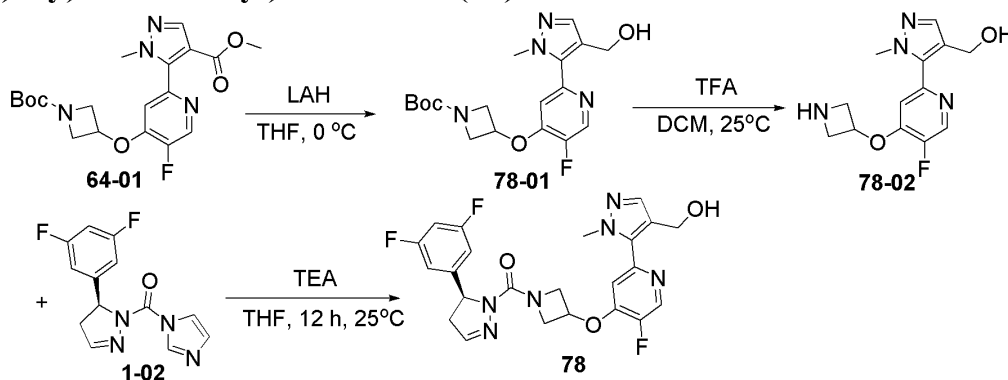
The title compound **76** was prepared in a yield of 75% (43 mg, 0.08mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 568.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 2.8 Hz, 1H), 7.52 (s, 1H), 7.32 (d, *J* = 6.7 Hz, 1H), 6.78 – 6.66 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.06-4.97 (m, 1H), 4.74-4.57 (m, 2H), 4.26 (t, *J* = 12.1 Hz, 2H), 4.05 (s, 3H), 3.65 (s, 2H), 3.35 (ddd, *J* = 18.6, 12.2, 1.6 Hz, 1H), 3.20 (s, 2H), 2.69 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.62-1.50 (m, 4H), 1.32-1.20 (m, 2H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-4-(morpholine-4-carbonyl)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (77)



The title compound **77** was prepared in a yield of 36% (20.3 mg, 0.04mmol) as a white solid from Compound **65** (50mg, 0.1mmol) according to the procedure for Compound **68**. Mass (m/z): 570.3 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.8 Hz, 1H), 7.53 (s, 1H), 7.32 (d, *J* = 6.6 Hz, 1H), 6.79 – 6.65 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.04 (s, 1H), 4.72-4.57 (m, 2H), 4.27 (t, *J* = 13.5 Hz, 2H), 4.03 (s, 3H), 3.83 – 3.20 (m, 9H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

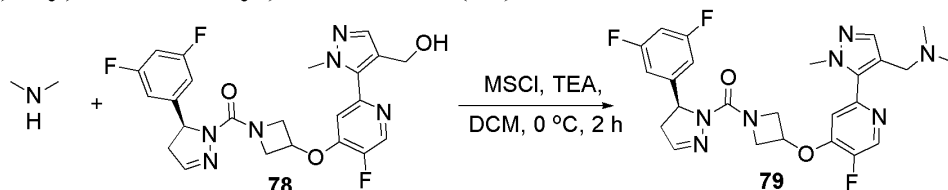
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(hydroxymethyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (**78**)



Step 1: **64-01** (2 g, 4.92 mmol) was dissolved in 20 ml of dry THF, AlLiH₄ (1M, 5 mL) was added to the above solution at 0 °C, the mixture was stirred for 10 min at 0 °C. water was added and extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated to dryness to give the intermediate **78-01**. MS (m/z): 379.2 [M+H]⁺.

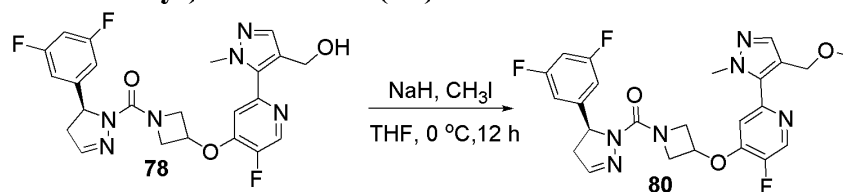
Step 2-3: The title compound **78** was prepared in a yield of 42.9% (55 mg) as a white solid from Compound **78-01** (100 mg, 0.27 mmol) according to the procedure for Compound **50-05** to **50**. Mass (m/z): 469.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 2.9 Hz, 1H), 7.54 (s, 1H), 7.25 (d, *J* = 6.7 Hz, 1H), 6.84 – 6.64 (m, 4H), 5.35 – 5.23 (m, 1H), 5.12 (ddd, *J* = 10.3, 6.5, 3.9 Hz, 1H), 4.70-4.60 (m, 2H), 4.48 (s, 2H), 4.35 (dd, *J* = 32.1, 10.3 Hz, 2H), 4.08 (s, 3H), 3.38 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.73 (ddd, *J* = 18.6, 6.4, 1.8 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-((dimethylamino)methyl)-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (79)



Compound **78** (54 mg, 0.11 mmol) was dissolved in 10 ml of dry DCM, TEA (0.1 mL) was added to the above solution at 0 °C, the mixture was stirred for 30 min at 0 °C. Then Dimethylamine (5 mg, 0.11 mmol) was added, the mixture was stirred for 1.5 h, water was added and extracted with EA, Purification by silica gel chromatography to give the titled compound **79** (21 mg, 46.2%) as a white solid. Mass (m/z): 514.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.69 (s, 1H), 6.90 (d, *J* = 6.3 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 6.80 – 6.69 (m, 3H), 5.30 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.25 – 5.17 (m, 1H), 4.70 – 4.57 (m, 2H), 4.43 – 4.26 (m, 2H), 4.20 (s, 2H), 3.96 (s, 3H), 3.45 – 3.40 (m, 1H), 2.78 (s, 6H), 2.74 – 2.70 (m, 1H).

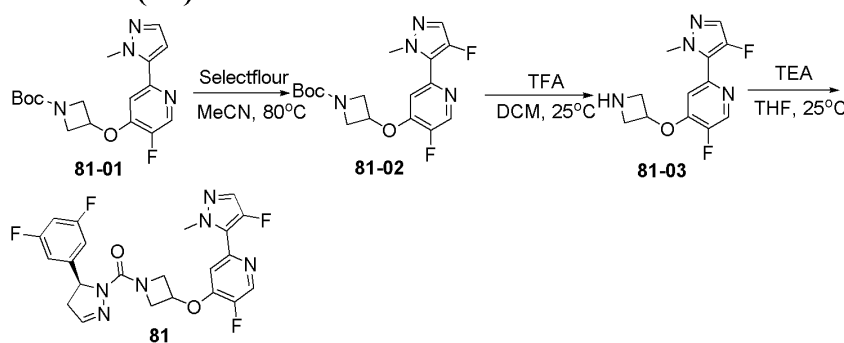
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(methoxymethyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (80)



Compound **78** (80 mg, 0.16 mmol) was dissolved in 10 ml of dry THF, NaH (1M, 5 mL) was added to the above solution at 0 °C, the mixture was stirred for 30 min at 0 °C. Then CH₃I (1g, 6.78 mmol) was added, the mixture was stirred for 10 min water was added and extracted with EA, Purification by silica gel chromatography to give the titled compound **80**

(50 mg, 60%) as a white solid. Mass (m/z): 501.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.9 Hz, 1H), 7.53 (s, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 6.83 – 6.64 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.03 (ddd, *J* = 10.2, 6.4, 3.9 Hz, 1H), 4.69 – 4.53 (m, 2H), 4.41 – 4.27 (m, 2H), 4.27 (s, 2H), 4.07 (s, 3H), 3.40 (s, 3H), 3.38 – 3.30 (m, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-fluoro-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (81)



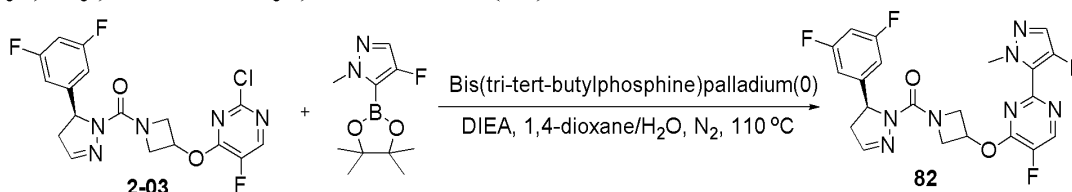
10

Step 1: **81-01** (1.1g, 3.16 mmol) was dissolved in 15ml of dry MeCN, Selectfluor (1.18g, 3.16mmol) was added to the above solution at 0 °C, the mixture was stirred for 3 h at 80 °C. Water was added and extracted with EA, Purification by silica gel chromatography to give the compound **81-02** (320mg, 27.6%). Mass (m/z): 367.2 [M+H]⁺.

Step 2-3: The title compound **81** was prepared in a yield of 26.9% from Compound **81-02** according to the procedure for Compound **50-05** to **50**. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 4.4 Hz, 1H), 6.99 (d, *J* = 6.6 Hz, 1H), 6.83 – 6.65 (m, 4H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.10 (ddd, *J* = 10.4, 6.5, 4.0 Hz, 1H), 4.68-4.53 (m, 2H), 4.32 (ddd, *J* = 24.3, 10.7, 4.0 Hz, 2H), 4.16 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H). Mass (m/z): 475.1 [M+H]⁺

20

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-fluoro-1-methyl-1H-pyrazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (82)

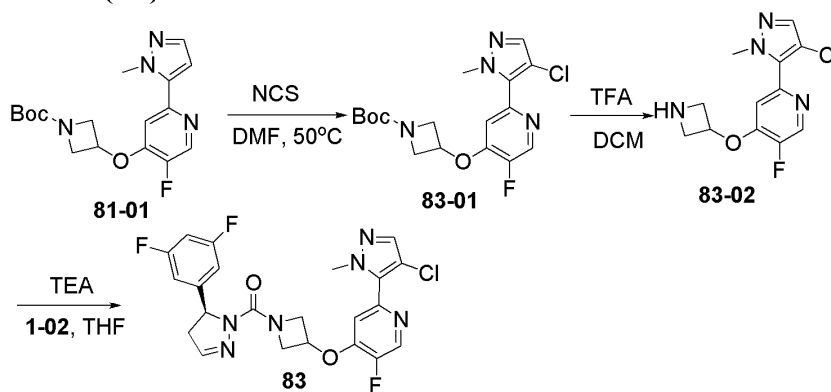


5

Compound **2-03** (82 mg, 0.2 mmol), 4-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (90 mg, 0.4 mmol), Bis(tri-tert-butylphosphine)palladium(0) (21 mg, 0.04 mmol), DIEA (155 mg, 1.2 mmol) in 1,4-dioxane (2 mL) and H₂O (0.2 mL) under N₂ and the whole reaction mixture was stirred at 100 °C for 2 hours. After the mixture was concentrated and further purified by prep-HPLC to give the title compound **82** (25 mg, 26.3%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 7.51 – 7.33 (m, 1H), 6.74 (t, *J* = 18.9 Hz, 4H), 5.52 (s, 1H), 5.29 (s, 1H), 4.63 (s, 2H), 4.24 (d, *J* = 31.7 Hz, 5H), 3.35 (t, *J* = 15.4 Hz, 1H), 2.70 (d, *J* = 18.4 Hz, 1H). Mass (*m/z*) 476.2 [M+H]⁺.

15

(S)-(3-((2-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (83)

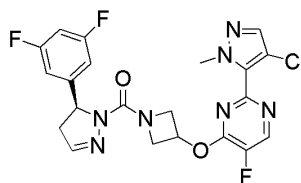


20

Step 1: 81-01 (600 mg, 1.72 mmol) was dissolved in 10 ml of dry DMF, NCS (230 mg, 1.72 mmol) was added to the above solution at 0 °C, the mixture was stirred for 12 h at 50 °C. water was added and extracted with EA, Purification by silica gel chromatography to give the intermediate **83-01** (360mg, 54%). Mass (m/z): 383.1 [M+H]⁺.

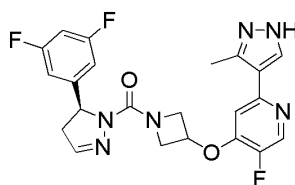
Step 2-3: The title compound **83** was prepared in a yield of 26.6% from Compound **83-01** according to the procedure for Compound **50-05** to **50**. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (d, *J* = 3.1 Hz, 1H), 7.67 (s, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.09 (tt, *J* = 9.3, 2.3 Hz, 1H), 7.01 (s, 1H), 6.92 – 6.86 (m, 2H), 5.31 – 5.17 (m, 2H), 4.60 – 4.45 (m, 2H), 4.14 – 4.00 (m, *J* = 10.7 Hz, 2H), 3.90 (s, 3H), 3.43 – 3.35 (m, 1H), 2.68 – 2.58 (m, 1H). Mass (m/z) 491.1 [M+H]⁺.

(S)-(3-((2-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (84)



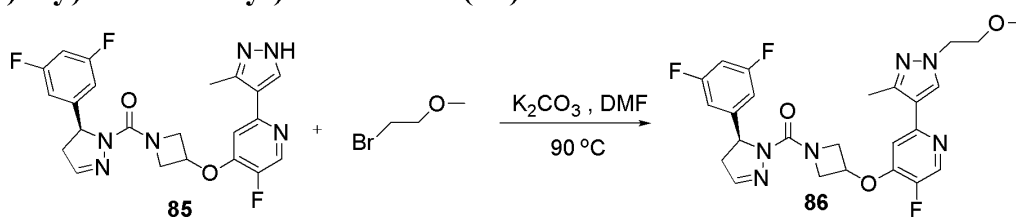
The titled compound **84** was prepared from **2-03** in 15.2% yield according to the procedure outlined for compound **2**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.47 (m, 1H), 7.55 – 7.48 (m, 1H), 6.82 – 6.66 (m, 4H), 5.63 – 5.55 (m, 1H), 5.28 (dd, *J* = 12.1, 6.3 Hz, 1H), 4.65 (s, 2H), 4.33 (dd, *J* = 27.2, 8.7 Hz, 2H), 4.18 (s, 3H), 3.36 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.70 (dd, *J* = 18.6, 6.3 Hz, 1H). Mass (m/z) 492.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (85)



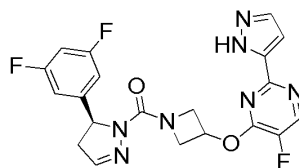
The titled compound **85** was prepared from **3-04** in 28.0% yield according to the procedure outlined for compound **3**. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.36 (d, $J = 3.0$ Hz, 1H), 7.86 (s, 1H), 6.87 – 6.63 (m, 5H), 5.28 (dd, $J = 12.1, 6.4$ Hz, 1H), 5.10 (q, $J = 5.3, 4.0$ Hz, 1H), 4.60 (q, $J = 8.7, 8.2$ Hz, 2H), 4.40 – 4.25 (m, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.77 – 2.67 (m, 1H), 2.65 (d, $J = 11.5$ Hz, 3H). Mass (m/z) 457.3 $[\text{M}+\text{H}]^+$.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(1-(2-methoxyethyl)-3-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (86)



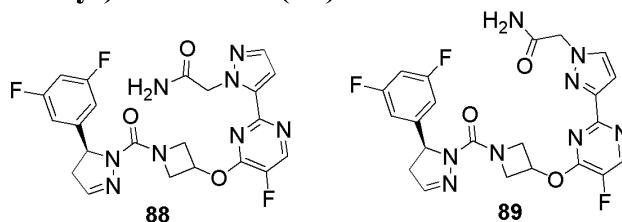
Compound **85** (70 mg, 0.15 mmol), 1-bromo-2-methoxyethane (107 mg, 0.75 mmol), K_2CO_3 (207 mg, 1.50 mmol) were placed in DMF (3 mL). The mixture was stirred 90 °C for overnight. Concentrated. Purification by prep-HPLC to give the titled compound **86** (19 mg, 24.1%) as a white solid. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.35 (t, $J = 3.1$ Hz, 1H), 7.77 (d, $J = 29.8$ Hz, 1H), 6.84 – 6.64 (m, 5H), 5.27 (dd, $J = 12.2, 6.5$ Hz, 1H), 5.08 (dq, $J = 6.5, 3.4$ Hz, 1H), 4.59 (q, $J = 8.1$ Hz, 2H), 4.40 – 4.20 (m, 4H), 3.76 (q, $J = 5.2$ Hz, 2H), 3.42 – 3.29 (m, 4H), 2.71 (ddd, $J = 18.6, 6.6, 1.7$ Hz, 1H), 2.53 (d, $J = 29.8$ Hz, 3H). Mass (m/z) 515.3 $[\text{M}+\text{H}]^+$.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(1H-pyrazol-5-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (87)



The titled compound **87** was prepared from **2-03** in a yield of 13.0% according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.87 – 6.56 (m, 4H), 5.57 (tt, J = 6.7, 4.3 Hz, 1H), 5.29 (dd, J = 12.2, 6.5 Hz, 1H), 4.66 (m, 2H), 4.34 (ddd, J = 32.8, 10.7, 4.3 Hz, 2H), 3.36 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H). Mass (m/z) 444.2 [$\text{M}+\text{H}$] $^+$,

(S)-2-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-1H-pyrazol-1-yl)acetamide (**88**) and (S)-2-(3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-1H-pyrazol-1-yl)acetamide (**89**)

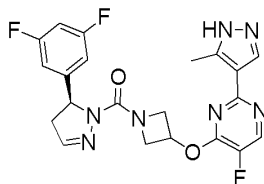


The titled compound **88** and **89** was prepared in a yield of 2.9% (1.1 mg) and 10.1% (3.8 mg) according to the procedure outlined for compound **86**. **88**: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, J = 2.3 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 1.8 Hz, 1H), 6.78 – 6.67 (m, 3H), 6.03 (s, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 5.48 (s, 2H), 5.30 (dd, J = 12.0, 6.3 Hz, 1H), 4.69 (s, 2H), 4.33 (dd, J = 23.8, 10.6 Hz, 2H), 3.40 – 3.33 (m, 1H), 2.75 – 2.70 (m, 1H). Mass (m/z) 501.3 [$\text{M}+\text{H}$] $^+$. **89**: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.57 (s, 1H), 6.96 (s, 1H), 6.81 – 6.67 (m, 4H), 6.23 (s, 1H), 5.60 (ddd, J = 11.8, 7.2, 4.9 Hz, 2H), 5.29 (dd, J = 12.2, 6.5 Hz, 1H), 4.92 (s, 2H), 4.68 (d, J = 17.7 Hz,

2H), 4.35 (dd, $J = 35.2, 10.7$ Hz, 2H), 3.36 (ddd, $J = 18.5, 12.2, 1.6$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

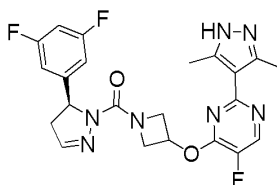
Mass (m/z) 501.3 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(5-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (90)



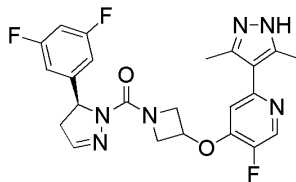
The titled compound **90** was prepared from **2-03** in a yield of 27% (30 mg) according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform- d) δ 8.32 (d, $J = 2.6$ Hz, 1H), 8.13 (s, 1H), 6.79 (t, $J = 1.7$ Hz, 1H), 6.77 – 6.57 (m, 3H), 5.58-5.49 (m, 1H), 5.33–5.25 (m, 1H), 4.66 (d, $J = 16.6$ Hz, 2H), 4.33 (dd, $J = 34.3, 10.5$ Hz, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.64 (s, 3H). Mass (m/z) 458.2 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (91)



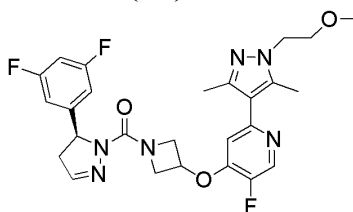
The titled compound **91** was prepared from **2-03** in a yield of 34.6% according to the procedure outlined for compound **2**. ^1H NMR (400 MHz, Chloroform- d) δ 8.37 (d, $J = 2.6$ Hz, 1H), 6.78 (t, $J = 1.7$ Hz, 1H), 6.77 – 6.61 (m, 3H), 5.58-5.50 (m, 1H), 5.30 – 5.25 (m, 1H), 4.61 (q, $J = 10.1, 8.8$ Hz, 2H), 4.32 (dd, $J = 35.8, 10.3$ Hz, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.61 (s, 6H). Mass (m/z) 472.3 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (92)



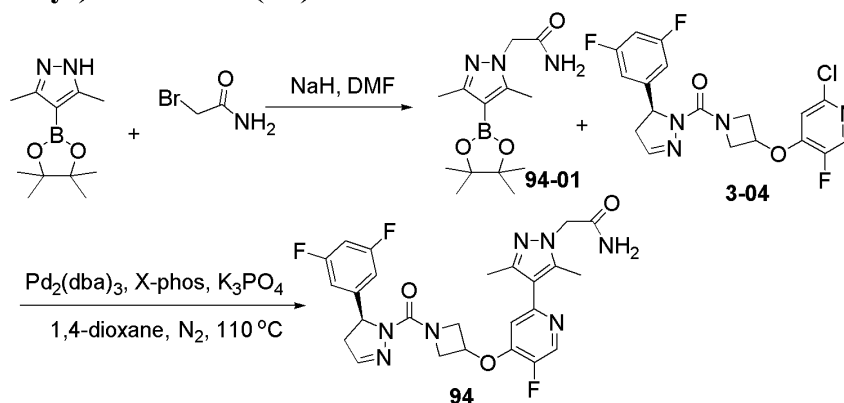
5 The titled compound **92** was prepared from **3-04** in 31.9% yield according to the procedure outlined for compound **3**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, $J = 3.1$ Hz, 1H), 6.83 – 6.67 (m, 4H), 6.62 (d, $J = 6.6$ Hz, 1H), 5.27 (dd, $J = 12.2, 6.5$ Hz, 1H), 5.09 – 5.01 (m, 1H), 4.58 (d, $J = 8.2$ Hz, 2H), 4.33 (dd, $J = 36.9, 10.3$ Hz, 2H), 3.36 (ddd, $J = 18.6, 12.2,$
10 1.7 Hz, 1H), 2.71 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.41 (s, 6H). Mass (m/z) 471.2 $[\text{M}+\text{H}]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-(2-methoxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (93)



15 The titled compound **93** was prepared in 29.6% yield from **92** according to the procedure outlined for compound **86**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (d, $J = 3.0$ Hz, 1H), 7.12 (tt, $J = 9.3, 2.4$ Hz, 1H), 7.03 (d, $J = 1.7$ Hz, 1H), 6.93 (qd, $J = 6.6, 3.3$ Hz, 2H), 6.84 (d, $J = 6.8$ Hz, 1H),
20 5.31 – 5.20 (m, 2H), 4.54 (s, 2H), 4.16 (t, $J = 5.4$ Hz, 2H), 4.09 (s, 2H), 3.65 (t, $J = 5.4$ Hz, 2H), 3.44 – 3.37 (m, 1H), 3.23 (s, 3H), 2.65 (ddd, $J = 18.7, 6.7, 1.8$ Hz, 1H), 2.35 (s, 3H), 2.24 (s, 3H). Mass (m/z) 529.4 $[\text{M}+\text{H}]^+$.

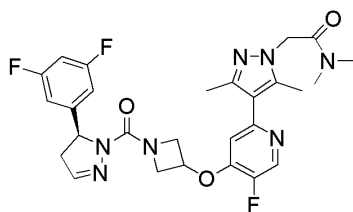
(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)acetamide (94)



Step 1: 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (222 mg, 1.0 mmol), 2-bromoacetamide (276 mg, 2.0 mmol), NaH (60%, 120 mg, 3.0 mmol) were placed in DMF (5 mL). The mixture was stirred 25 °C for 45 min, and then the reaction liquid was poured into water. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by prep-HPLC to give the intermediate compound **94-01** (215 mg, 77.0%) as a white solid.

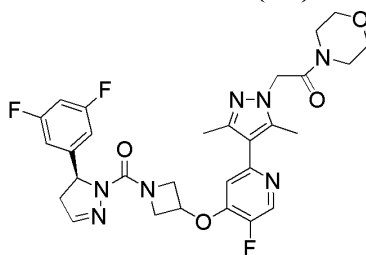
Step 2: The titled compound **94** was prepared in 36.5% yield (73 mg) according to the procedure outlined for compound **3**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 3.0 Hz, 1H), 6.83 – 6.65 (m, 4H), 6.59 (d, *J* = 6.5 Hz, 1H), 6.09 (s, 1H), 5.60 (s, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.05 (td, *J* = 6.5, 3.3 Hz, 1H), 4.72 (s, 2H), 4.56 (d, *J* = 14.8 Hz, 2H), 4.33 (dd, *J* = 34.3, 10.6 Hz, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 6H). Mass (*m/z*) 528.3 [M+H]⁺.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)-N,N-dimethylacetamide (95)



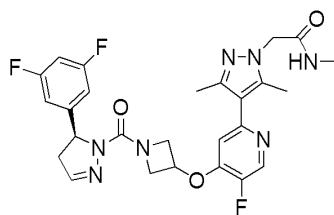
The titled compound **95** was prepared from compound **92** in 45.6% yield according to the procedure outlined for compound **86**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.79 – 6.66 (m, 4H), 5.28 (dd, J = 12.1, 6.3 Hz, 1H), 5.12 (s, 1H), 5.03 (s, 2H), 4.64 (s, 2H), 4.36 (dd, J = 27.1, 10.5 Hz, 2H), 3.38 (dd, J = 18.6, 12.1 Hz, 1H), 3.12 (s, 3H), 3.01 (s, 3H), 2.77 – 2.68 (m, 1H), 2.31 (s, 6H). Mass (m/z) 556.4 $[\text{M}+\text{H}]^+$.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)-1-morpholinoethan-1-one (96)



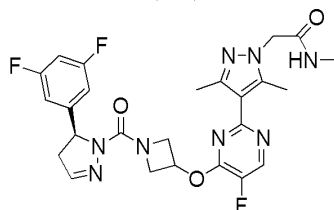
The titled compound **96** was prepared from compound **92** in 35.8% yield according to the procedure outlined for compound **86**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, J = 3.0 Hz, 1H), 6.82 – 6.58 (m, 5H), 5.27 (dd, J = 12.2, 6.4 Hz, 1H), 5.04 (s, 1H), 4.91 (s, 2H), 4.58 (s, 2H), 4.32 (dd, J = 29.2, 9.5 Hz, 2H), 3.71 (d, J = 4.6 Hz, 4H), 3.62 (dd, J = 12.8, 4.9 Hz, 4H), 3.36 (ddd, J = 18.6, 12.2, 1.6 Hz, 1H), 2.71 (ddd, J = 18.7, 6.5, 1.7 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H). Mass (m/z) 598.4 $[\text{M}+\text{H}]^+$.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)-N-methylacetamide (97)



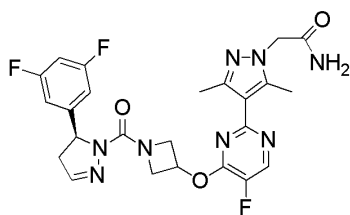
The titled compound **97** was prepared from compound **92** in 26.3% yield (30 mg) according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, J = 3.8 Hz, 1H), 6.85 (d, J = 1.7 Hz, 1H), 6.82 – 6.66 (m, 4H), 6.48 (d, J = 5.1 Hz, 1H), 5.30 (dd, J = 12.1, 6.3 Hz, 1H), 5.19 (tt, J = 6.5, 3.8 Hz, 1H), 4.82 (s, 2H), 4.66 (s, 2H), 4.39 (dd, J = 30.1, 10.5 Hz, 2H), 3.40 (ddd, J = 18.7, 12.1, 1.7 Hz, 1H), 2.83 (d, J = 4.7 Hz, 3H), 2.76 (ddd, J = 18.7, 6.3, 1.8 Hz, 1H), 2.32 (d, J = 8.6 Hz, 6H). Mass (m/z) 542.3 [M+H]⁺.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)-N-methylacetamide (98)



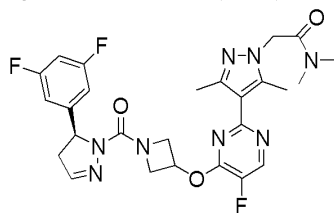
The titled compound **98** was prepared from compound **91** in 6.1% yield according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, J = 2.5 Hz, 1H), 6.77 – 6.59 (m, 4H), 6.08 (s, 1H), 5.45 (td, J = 6.5, 3.2 Hz, 1H), 5.21 (dd, J = 12.2, 6.4 Hz, 1H), 4.70 (s, 2H), 4.55 (s, 2H), 4.26 (dd, J = 31.8, 10.4 Hz, 2H), 3.36 – 3.22 (m, 1H), 2.74 (d, J = 4.8 Hz, 3H), 2.64 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.51 (d, J = 20.5 Hz, 6H). Mass (m/z) 543.3 [M+H]⁺.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)acetamide (99)



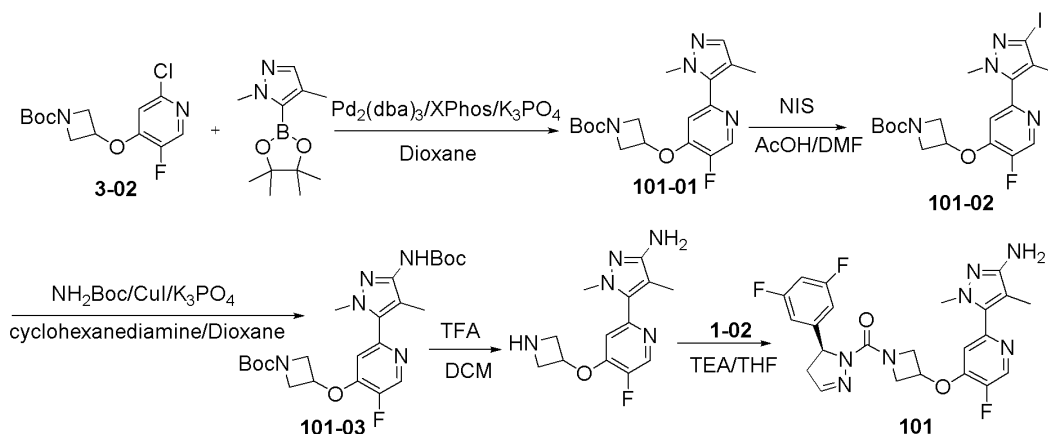
The titled compound **99** was prepared from compound **91** in 22.5% yield according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (dd, $J = 2.6, 1.1$ Hz, 1H), 6.87 – 6.68 (m, 4H), 6.35 (s, 1H), 5.81 (s, 1H), 5.55 (s, 1H), 5.31 (dd, $J = 12.2, 6.3$ Hz, 1H), 4.86 (s, 2H), 4.65 (s, 2H), 4.37 (d, $J = 32.3$ Hz, 2H), 3.39 (dd, $J = 18.7, 12.2$ Hz, 1H), 2.74 (dd, $J = 18.8, 6.3$ Hz, 1H), 2.62 (dt, $J = 33.5, 2.0$ Hz, 6H). Mass (m/z) 529.3 [M+H]⁺.

(S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)-N,N-dimethylacetamide (100)



The titled compound **100** was prepared from compound **91** in 8.5% yield according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, $J = 2.6$ Hz, 1H), 6.73 – 6.65 (m, 3H), 6.61 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.44 (td, $J = 6.6, 3.4$ Hz, 1H), 5.19 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.86 (s, 2H), 4.52 (d, $J = 8.9$ Hz, 2H), 4.23 (dd, $J = 30.7, 10.8$ Hz, 2H), 3.27 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 3.03 (s, 3H), 2.91 (s, 3H), 2.62 (ddd, $J = 18.5, 6.5, 1.7$ Hz, 1H), 2.48 (d, $J = 21.3$ Hz, 6H). Mass (m/z) 557.4 [M+H]⁺.

(S)-3-((2-(3-amino-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (101)



Step 1: Compound **3-02** (2.0 g, 6.62 mmol), 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.2 g, 9.93 mmol), $\text{Pd}_2(\text{dba})_3$ (605 mg, 0.66 mmol), XPhos (314 mg, 0.66 mmol) and 5N K_3PO_4 (4 mL, 19.9 mmol) were dissolved in dioxane (30 mL) under $\text{N}_2(\text{g})$ atmosphere. The mixture was stirred at 100°C for 15 hours. Concentrated and purified by flash chromatography (PE/EA=1/1) to give yellow oil 1.1 g. Yield: 45.8%

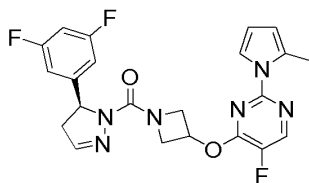
Step 2: The intermediate **101-01** (800 mg, 2.21 mmol) was dissolved in AcOH (5 mL) and DMF (2 mL). Then NIS (994 mg, 4.42 mmol) was added. The mixture was stirred at 80°C for 4 hours. EA (50 mL) was added. H_2O (20 mL) and NaHCO_3 (20 mL) washed. Then purified by flash chromatography (PE/EA=1/1) to give 300 mg of **101-02** as brown oil. Yield: 27.8%

Step 3: **101-02** (360 mg, 0.74 mmol), tert-butyl carbamate (173 mg, 1.48 mmol), CuI (141 mg, 0.74 mmol), Cyclohexanediamine (253 mg, 2.22 mmol) and K_3PO_4 (471 mg, 22.2 mmol) were dissolved in dioxane (15 mL) under $\text{N}_2(\text{g})$ atmosphere. The mixture was stirred at 100°C for 15 hours. Concentrated and purified by TLC-chromatography (DCM/MeOH=30/1) to give 70 mg of **101-03** as yellow solid. Yield: 18.6%.

Step 4-5: The titled compound **101** was prepared from compound **101-03** (20 mg, 0.04 mmol) according to the procedure outlined for compound **50-05** to **50**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, J =

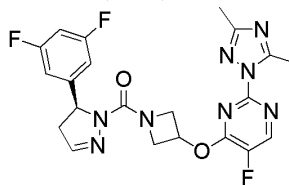
2.9 Hz, 1H), 6.84 – 6.79 (m, 1H), 6.78 – 6.56 (m, 4H), 5.27 (dd, $J = 12.2$, 6.4 Hz, 1H), 5.11 – 5.01 (m, 1H), 4.61 (d, $J = 16.4$ Hz, 2H), 4.32 (dd, $J = 31.4$, 10.7 Hz, 2H), 3.78 (s, 3H), 3.36 (ddd, $J = 18.7$, 12.2, 1.7 Hz, 1H), 2.71 (ddd, $J = 18.6$, 6.5, 1.8 Hz, 1H), 1.95 (s, 3H). Mass (m/z) 486.2 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-methyl-1H-pyrrol-1-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (102)



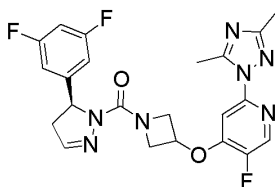
Compound **2-03** (60 mg, 0.144 mmol), 2-methyl-1H-pyrrole (24 mg, 0.29 mmol), NaOtBu (18 mg, 0.18 mmol), Pd₂(dba)₃ (12 mg, 0.012 mmol) and X-Phos (6 mg, 0.012 mmol) were added to DMF (3 mL) under N₂ atmosphere. The mixture was stirred at 90°C overnight. The mixture was concentrated and purified by TLC (PE/EA = 2/1) to give white solid 17 mg, yield: 21.9%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, $J = 2.2$ Hz, 1H), 7.55 (dd, $J = 3.3$, 1.9 Hz, 1H), 6.82 – 6.73 (m, 3H), 6.73–6.66 (m, 1H), 6.16 (t, $J = 3.3$ Hz, 1H), 6.03–5.99 (m, 1H), 5.53–5.46 (m, 1H), 5.28 (dd, $J = 12.2$, 6.5 Hz, 1H), 4.69–4.56 (m, 2H), 4.41–4.23 (m, 2H), 3.35 (ddd, $J = 18.6$, 12.2, 1.7 Hz, 1H), 2.70 (ddd, $J = 18.6$, 6.5, 1.7 Hz, 1H), 2.59 (s, 3H). Mass (m/z) 457.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)methanone (103)



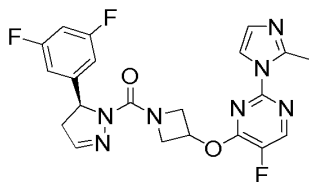
The titled compound **103** was prepared from **2-03** in 1.0 % yield according to the procedure outlined for compound **102**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 6.82 (t, *J* = 2.0 Hz, 1H), 6.77 – 6.56 (m, 4H), 5.62-5.52 (m, 1H), 5.29 (dd, *J* = 12.2, 6.2 Hz, 1H), 4.72-4.57 (m, 2H), 4.36 (dd, *J* = 27.7, 11.0 Hz, 2H), 3.38 (ddd, *J* = 18.6, 12.1, 1.7 Hz, 1H), 2.91 (s, 3H), 2.73 (ddd, *J* = 18.6, 6.1, 1.7 Hz, 3H), 2.57-2.41 (m, 3H). Mass (m/z) 473.3[M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (**104**)



The titled compound **104** was prepared from **3-04** in 48.1% yield according to the procedure outlined for compound **102**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 6.1 Hz, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.58 (m, 3H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.19-5.10 (m, 1H), 4.71-4.59 (m, 2H), 4.32 (dd, *J* = 31.3, 10.0 Hz, 2H), 3.36 (ddd, *J* = 18.7, 12.2, 1.8 Hz, 1H), 2.84 (s, 3H), 2.71 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.43 (s, 3H). Mass (m/z) 472.2 [M+H]⁺.

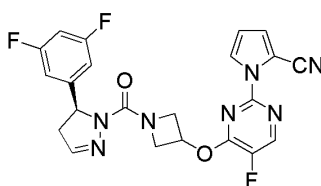
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-methyl-1H-imidazol-1-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (**105**)



The titled compound **105** was prepared from **2-03** in 18.2% yield according to the procedure outlined for compound **102**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 1.7 Hz, 1H), 7.89 (s, 1H), 7.37 (s, 1H),

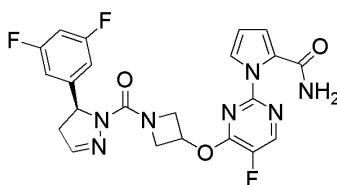
6.83 – 6.78 (m, 1H), 6.78 – 6.62 (m, 3H), 5.55-5.49 (m, 1H), 5.27 (dd, $J = 12.1, 6.4$ Hz, 1H), 4.66 (dd, $J = 19.8, 11.1$ Hz, 2H), 4.35 (dd, $J = 22.3, 10.7$ Hz, 2H), 3.37 (ddd, $J = 18.6, 12.1, 1.7$ Hz, 1H), 3.08 (s, 3H), 2.72 (ddd, $J = 18.6, 6.3, 1.7$ Hz, 1H). Mass (m/z) 458.2 $[M+H]^+$.

5 **(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-1H-pyrrole-2-carbonitrile (106)**



The titled compound **106** was prepared from **2-03** in 29.8% yield according to the procedure outlined for compound **102**. ^1H NMR (400 MHz, Chloroform- d) δ 8.32 (d, $J = 2.1$ Hz, 1H), 7.88 (dd, $J = 3.1, 1.7$ Hz, 1H), 7.06 (dd, $J = 3.7, 1.7$ Hz, 1H), 6.86 – 6.73 (m, 3H), 6.72-6.65 (m, 1H), 6.36 (dd, $J = 3.7, 3.2$ Hz, 1H), 5.77-5.70 (m, 1H), 5.28 (dd, $J = 12.2, 6.3$ Hz, 1H), 4.82-4.67 (m, 2H), 4.30 (t, $J = 13.0$ Hz, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.3, 1.7$ Hz, 1H). Mass (m/z) 468.3 $[M+H]^+$.

15 **(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-1H-pyrrole-2-carboxamide (107)**

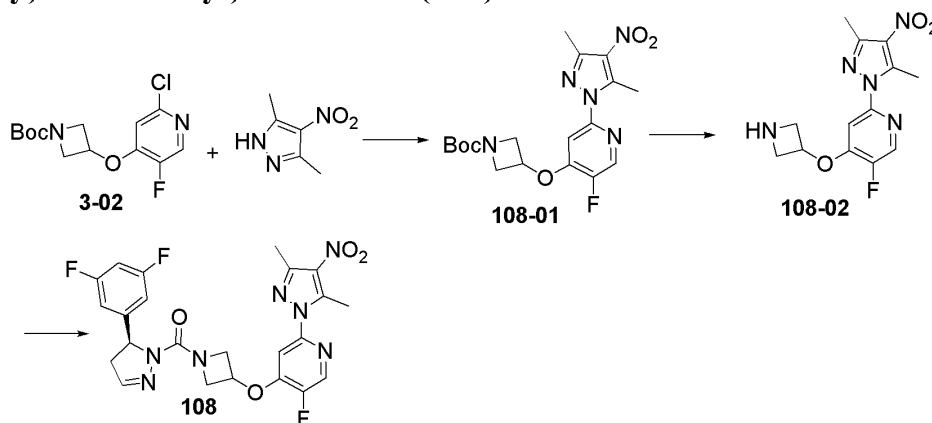


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The titled compound **107** was prepared from compound **106** in 10.3% yield according to the procedure outlined for compound **66-02**. ^1H NMR (400 MHz, Chloroform- d) δ 8.31 (s, 1H), 7.55 (s, 1H), 6.91 – 6.62 (m, 5H), 6.27 (t, $J = 3.3$ Hz, 1H), 5.50-5.49 (m, 1H), 5.33-5.23 (m, 1H), 4.70-4.56

(m, 2H), 4.42-4.25 (m, 2H), 3.44 – 3.29 (m, 1H), 2.76-2.65 (m, 1H). Mass (m/z) 486.2 [M+H]⁺.

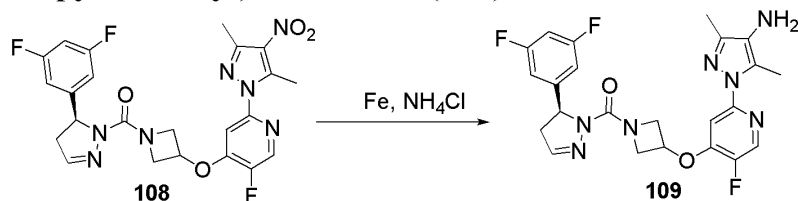
(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (108)



Step 1: To a mixture of tert-butyl 3-((2-chloro-5-fluoropyridin-4-yl)oxy)azetidine-1-carboxylate **3-02** (300 mg, 0.99 mmol), 3,5-dimethyl-4-nitro-1H-pyrazole (280 mg, 1.98 mmol) and (1S,2S)-cyclohexane-1,2-diamine (338 mg, 2.97 mmol) were added anhydrous DMF (4.0 mL). This mixture was purged with argon for 5 minutes and copper(I) iodide (56 mg, 0.297 mmol) and K₃PO₄ (629 mg, 2.97 mmol) were added. The reaction mixture was heated at 140°C. for 24 hours and then purification by column chromatography to give compound **108-01** as yellow oil. (yield:28.3%, 210 mg).

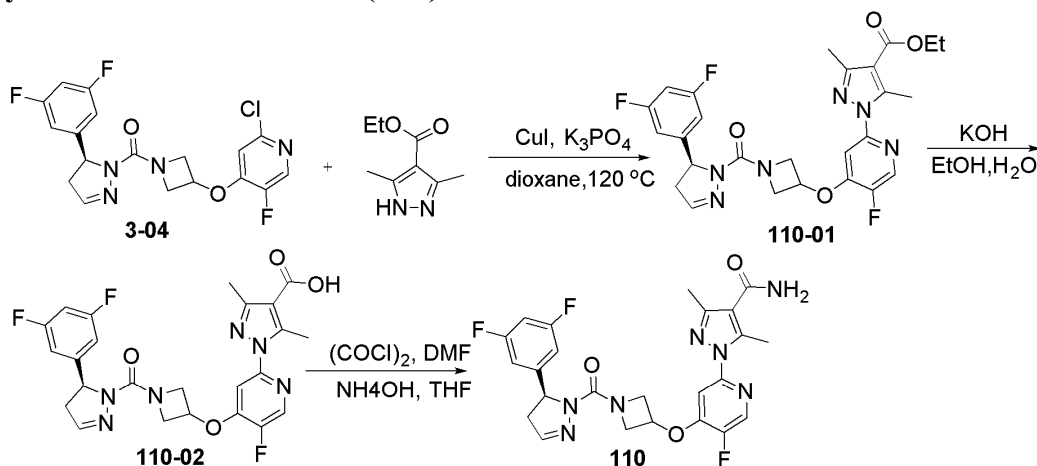
Step 2-3: The titled compound **108** was prepared from compound **108-01** according to the procedure outlined for compound **50-05** to **50**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 6.1 Hz, 1H), 6.85 – 6.78 (m, 1H), 6.78 – 6.58 (m, 3H), 5.34 – 5.22 (m, 1H), 5.19-5.12 (m, 1H), 4.71-4.57 (m, 2H), 4.33 (dd, *J* = 33.7, 10.0 Hz, 2H), 3.37 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.97 (s, 3H), 2.71 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.58 (s, 3H). Mass (m/z) 516.2 [M+H]⁺.

(S)-3-((2-(4-amino-3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (109)



Compound **108** (45 mg, 0.087 mmol), Fe (24 mg, 0.44 mmol) and NH₄Cl (24 mg, 0.44 mmol) were dissolved in EtOH (2 mL) and H₂O (2 mL). The mixture was stirred at 80 °C for 2 hrs. The mixture was reduced pressure and purified by prep-TLC to give the title compound **109** as white solid. 42 mg, yield: 89.4%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 2.5 Hz, 1H), 7.17 (d, *J* = 6.2 Hz, 1H), 6.78 (t, *J* = 1.7 Hz, 1H), 6.77 – 6.41 (m, 3H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.19 – 5.05 (m, 1H), 4.69–4.56 (m, 2H), 4.31 (dd, *J* = 31.0, 10.4 Hz, 2H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.52 (s, 3H), 2.25 (s, 3H). Mass (*m/z*) 486.2[M+H]⁺.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (110)

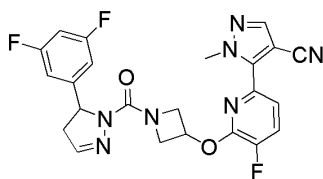


Step 1: **3-04** (2 g, 4.87 mmol), ethyl 3,5-dimethyl-1H-pyrazole-4-carboxylate (900 mg, 5.36 mmol), CuI (4.3 g, 9.74 mmol) and K₃PO₄ (3.1 g, 14.61 mmol), (1S, 2S)-N¹, N²-dimethylcyclohexane-1,2-diamine (1.38 g, 9.74 mmol) were placed in dioxane (50 mL). The mixture was stirred for 12 h at 120 °C under N₂. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the intermediate compound **110-01** (800 mg, 30.2%) as a white solid. Mass (m/z): 453.2 [M+H]⁺.

Step 2: Compound **110-01** (700 mg, 1.55 mmol), and KOH (200 mg, 3.57 mmol) were placed in EtOH (3 mL) and H₂O (3 mL). The mixture was stirred for 12 h at 55 °C, then adjust pH to 7, extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the compound **110-02 (compound 233)** (520 mg, 65%) as a white solid. Mass (m/z): 515.2 [M+H]⁺.

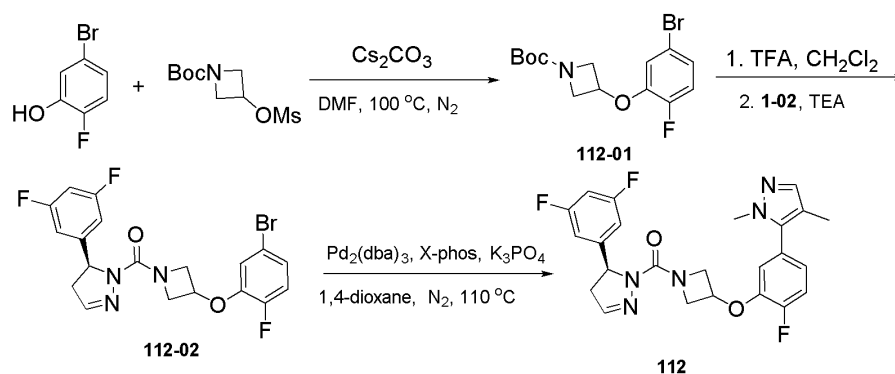
Step 3: **110-02** (250 mg, 0.48 mmol), DMF (0.01 mL) were placed in THF (5 mL). Then Oxalyl chloride (0.2 mL) was added to the mixture. The mixture was stirred for 30 min at 25 °C, then NH₄OH (10 mL, 30%), stirred 30 min at 25 °C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **110** (18 mg, 24.2%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.10 (d, *J* = 6.1 Hz, 1H), 6.75 – 6.59 (m, 4H), 5.56 (s, 2H), 5.21 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.11–5.05 (m, 1H), 4.64 – 4.47 (m, 2H), 4.25 (dd, *J* = 33.0, 10.6 Hz, 2H), 3.29 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.75 (s, 3H), δ 2.64 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.41 (s, 3H). Mass (m/z): 515.2 [M+H]⁺.

5-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carbonitrile (111)



The titled compound **111** was prepared in 11.1% yield from **1-05** according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.77 (m, 1H), 7.60 – 7.43 (m, 2H), 6.80-6.62 (m, 4H), 5.49-5.39 (m, 1H), 5.32 – 5.21 (m, 1H), 4.67-4.49 (m, 2H), 4.4.-4.20 (m, 2H), 4.08 (s, 3H), 3.40-3.27(m, 1H), 2.75-2.61 (m, 1H). Mass (m/z) 482.2[M+H]⁺

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(5-(1,4-dimethyl-1H-pyrazol-5-yl)-2-fluorophenoxy)azetidin-1-yl)methanone
(112)

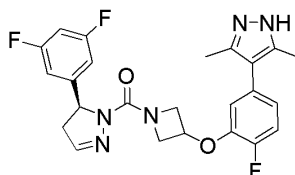


Step 1: 5-bromo-2-fluorophenol (0.96 g, 5.0 mmol), 6-tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (1.3 g, 5.25 mmol), Cs_2CO_3 (2.4 g, 7.5 mmol) were placed in DMF (20 mL). The mixture was stirred 100 °C for 2 hours, water was added and extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated to dryness to give the intermediate **112-01** (1.4 g, 82.5%) as a white solid. Mass (m/z): 290.1 [M-56+H]⁺.

Step 2: The intermediate compound **112-02** was prepared in 86.1% yield from **112-01** according to the procedure outlined for compound **50-5** to **50**. Mass (m/z): 246.0 [M+H]⁺.

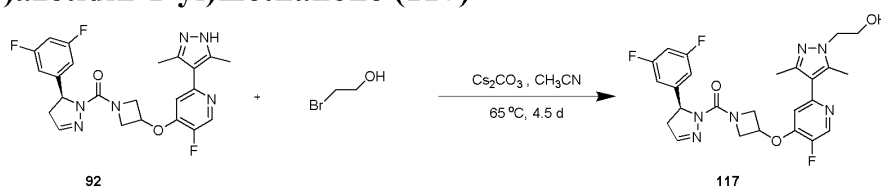
Step 3: The titled compound **112** was prepared in 41.5% yield from **112-02** according to the procedure outlined for compound **3**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 (s, 1H), 7.21 (dd, *J* = 11.0, 8.3 Hz, 1H), 6.89 (ddd, *J* = 8.3, 4.3, 2.0 Hz, 1H), 6.80 – 6.73 (m, 3H), 6.69 (tt, *J* = 8.9, 2.4 Hz, 1H), 6.62 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.97 (td, *J* = 6.3, 3.2 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 2H), 4.30 (dd, *J* = 26.0, 9.8 Hz, 2H), 3.74 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.8 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.98 (s, 3H). Mass (m/z): 470.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-fluorophenoxy)azetidin-1-yl)methanone (113)



The titled compound **113** was prepared in 35.1% yield from **112-02** according to the procedure outlined for compound **3**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 (dd, *J* = 11.2, 8.4 Hz, 1H), 6.85 – 6.64 (m, 5H), 6.58 (dd, *J* = 8.0, 2.1 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.97 (td, *J* = 6.4, 3.2 Hz, 1H), 4.60 – 4.47 (m, 2H), 4.31 (dd, *J* = 31.5, 10.1 Hz, 2H), 3.38 – 3.29 (m, 1H), 2.69 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.26 (s, 6H). Mass (m/z): 470.3 [M+H]⁺.

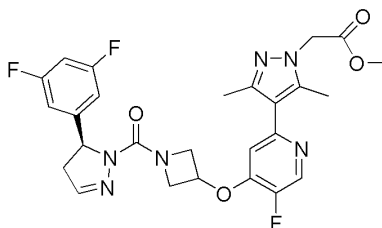
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (117)



Compound **92** (99 mg, 0.21 mmol), 2-bromoethan-1-ol (250 mg, 0.42 mmol), Cs₂CO₃ (342 mg, 1.05 mmol) were placed in CH₃CN (5 mL). The

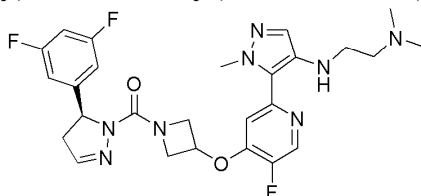
mixture was stirred at 65 °C for 4.5 d, and then the reaction liquid was poured into water. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by prep-HPLC to give the titled compound **117** (29 mg, 26.8%) as a white solid. Mass (m/z) 515.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 3.8 Hz, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.79 – 6.63 (m, 4H), 5.28 (dd, *J* = 12.1, 6.2 Hz, 1H), 5.16 (s, 1H), 4.76 – 4.55 (m, 2H), 4.50 – 4.20 (m, 4H), 3.99 (d, *J* = 8.7 Hz, 2H), 3.38 (ddd, *J* = 18.7, 12.1, 1.6 Hz, 1H), 2.73 (ddd, *J* = 18.7, 6.3, 1.8 Hz, 1H), 2.33 (dd, *J* = 22.7, 9.5 Hz, 6H).

methyl (S)-2-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-1-yl)acetate (118)



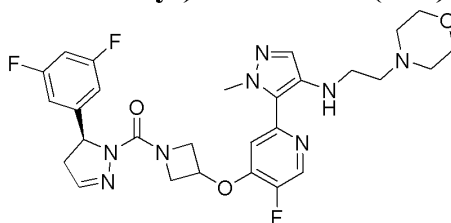
The titled compound **118** was prepared in 34.6% yield from compound **92** according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 3.2 Hz, 1H), 7.01 – 6.64 (m, 5H), 5.16 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H), 4.81 (d, *J* = 7.8 Hz, 1H), 4.46 (t, *J* = 7.8 Hz, 2H), 4.20 (d, *J* = 9.1 Hz, 2H), 3.80 (s, 3H), 3.04 (dd, *J* = 16.8, 6.1 Hz, 1H), 2.91 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.32 (d, *J* = 4.6 Hz, 6H). Mass (m/z) 543.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-((2-(dimethylamino)ethyl)amino)-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (119)



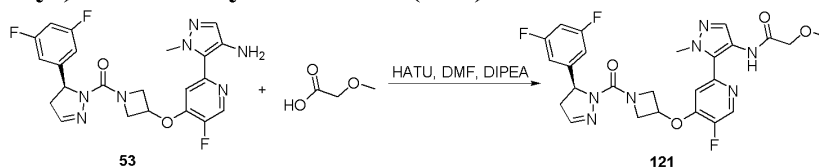
The titled compound **119** was prepared in 16.8% yield from compound **53** according to the procedure outlined for compound **50**. Mass (m/z) 543.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 2.9 Hz, 1H), 7.24 (s, 1H), 7.10 (d, *J* = 6.5 Hz, 1H), 6.79 (s, 1H), 6.76 – 6.65 (m, 3H), 5.51 (s, 1H), 5.25 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.63 (s, 2H), 4.35 – 4.21 (m, 2H), 3.97 (s, 3H), 3.52 (d, *J* = 5.6 Hz, 2H), 3.34 (dd, *J* = 18.6, 12.3 Hz, 1H), 3.26 (s, 2H), 2.84 (s, 6H), 2.71 – 2.65 (m, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-4-((2-morpholinoethyl)amino)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (**120**)



The titled compound **120** was prepared in 19.8% yield from compound **53** according to the procedure outlined for compound **50**. Mass (m/z) 585.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.9 Hz, 1H), 7.20 (s, 1H), 6.95 (d, *J* = 6.5 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.78 – 6.66 (m, 3H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.10 (s, 1H), 4.60 (s, 2H), 4.32 (dd, *J* = 33.6, 10.4 Hz, 2H), 4.00 (s, 3H), 3.70 (s, 4H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 3.17 (s, 2H), 2.76 – 2.62 (m, 3H), 2.52 (s, 4H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-methoxyacetamide (**121**)

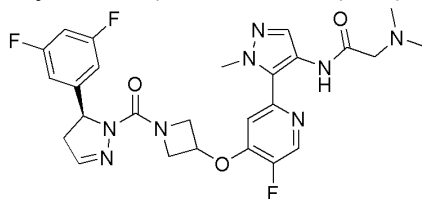


Compound **53** (200 mg, 0.42 mmol), 2-methoxyacetic acid (76 mg, 0.84 mmol), DIPEA (110 mg, 0.84 mmol), HATU (160 mg, 0.42 mmol)

were dissolved in DMF (5 mL) and stirred at 25 °C for 10 mins. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by prep-HPLC gave the titled compound **121** (54 mg, 23.5%) as a white solid. Mass (m/z) 544.1 [M+H]⁺.

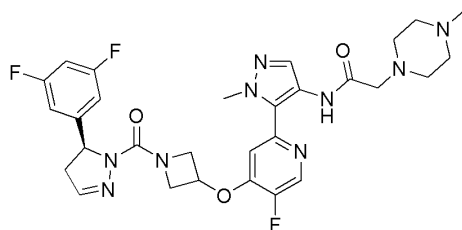
¹H NMR (400 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 8.51 (d, *J* = 2.8 Hz, 1H), 8.20 (s, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.82 (d, *J* = 1.7 Hz, 1H), 6.79 – 6.69 (m, 3H), 5.30 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.10 (td, *J* = 6.5, 3.3 Hz, 1H), 4.70 – 4.55 (m, 2H), 4.35 (dd, *J* = 30.2, 10.3 Hz, 2H), 4.07 (s, 3H), 4.05 (s, 2H), 3.51 (s, 3H), 3.39 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.74 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(dimethylamino)acetamide (122)



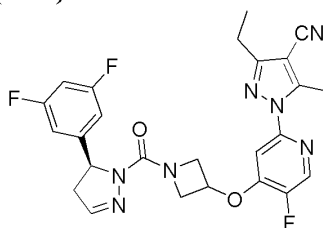
The titled compound **122** was prepared in 25.8% yield from compound **53** according to the procedure outlined for compound **121**. Mass (m/z) 557.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.27 (s, 1H), 8.49 (d, *J* = 2.9 Hz, 1H), 8.01 (s, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.81 (d, *J* = 1.7 Hz, 1H), 6.78 – 6.66 (m, 3H), 5.30 – 5.23 (m, 1H), 5.17 (s, 1H), 4.59 (s, 2H), 4.32 (dd, *J* = 31.6, 10.5 Hz, 2H), 3.98 (s, 5H), 3.46 – 3.29 (m, 1H), 2.97 (s, 6H), 2.70 (ddd, *J* = 18.5, 6.3, 1.7 Hz, 1H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-methylpiperazin-1-yl)acetamide (123)



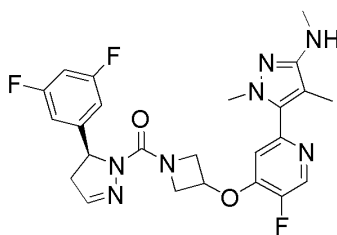
The titled compound **123** was prepared in 24.3% yield from compound **53** according to the procedure outlined for compound **121**. Mass (m/z) 612.3 [M+H⁺]. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 8.46 (d, *J* = 2.9 Hz, 1H), 8.13 (s, 1H), 6.92 (d, *J* = 6.4 Hz, 1H), 6.88 – 6.81 (m, 1H), 6.79 – 6.65 (m, 3H), 5.27 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.12 (q, *J* = 6.0, 4.9 Hz, 1H), 4.62 (d, *J* = 9.9 Hz, 2H), 4.33 (dd, *J* = 29.8, 10.6 Hz, 2H), 4.02 (s, 3H), 3.58 (s, 2H), 3.43 – 3.32 (m, 3H), 3.04 (s, 6H), 2.86 (s, 3H), 2.73 (ddd, *J* = 18.7, 6.3, 1.8 Hz, 1H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3-ethyl-5-methyl-1H-pyrazole-4-carbonitrile (124)



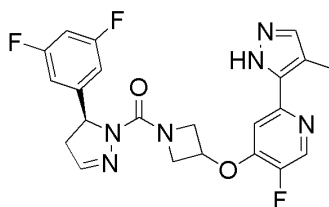
The titled compound **124** was prepared in a yield of 23.1% according to the procedure outlined for compound **110**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 2.3 Hz, 1H), 7.23 (s, 1H), 6.81 – 6.65 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.14 (dt, *J* = 6.4, 2.7 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 2H), 4.31 (dd, *J* = 36.7, 10.6 Hz, 2H), 3.35 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.80 – 2.67 (m, 6H), 1.33 (t, *J* = 7.6 Hz, 3H). Mass (m/z) 510.1 [M+H]⁺.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-3-((2-(1,4-dimethyl-3-(methylamino)-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (125)



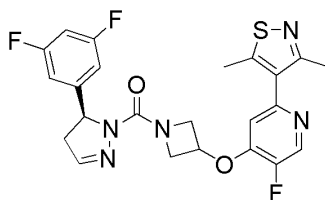
The titled compound **125** was prepared from compound **101-03** according to the procedure outlined for compound **56**. Mass (m/z) 500.2 [M+H]⁺.

- 5 **(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((5-fluoro-2-(4-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (126)**



- The titled compound **126** was prepared from **29-01** in a yield of 1.2% according to the procedure outlined for compound **29**. Mass (m/z) 456.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (d, *J* = 2.8 Hz, 1H), 7.56 (s, 1H), 7.33 (d, *J* = 6.8 Hz, 1H), 7.17 – 7.08 (m, 1H), 7.03 (d, *J* = 1.6 Hz, 1H), 6.97 – 6.90 (m, 2H), 5.30 – 5.21 (m, 2H), 4.59 – 4.51 (m, 2H), 4.15 – 4.05 (m, 2H), 3.41 – 3.35 (m, 1H), 2.70 – 2.65 – 2.56 (m, 1H), 2.31 (s, 3H).

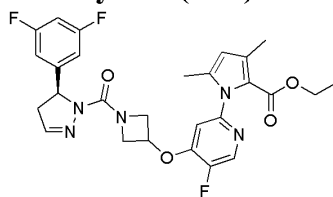
- 15 **(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((2-(3,5-dimethylisothiazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (127)**



- The titled compound **127** was prepared from **29-01** in a yield of 4.7% according to the procedure outlined for compound **29**. Mass (m/z) 488.3

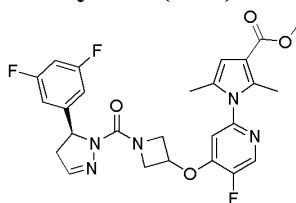
[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 3.1 Hz, 1H), 6.81 (d, *J* = 1.7 Hz, 1H), 6.79 – 6.66 (m, 3H), 6.62 (d, *J* = 6.5 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.08 (s, 1H), 4.59 (s, 2H), 4.34 (dd, *J* = 27.8, 10.3 Hz, 2H), 3.37 (dd, *J* = 18.7, 12.2 Hz, 1H), 2.72 (dd, *J* = 18.7, 6.3 Hz, 2H), 2.47 (s, 3H), 2.41 (s, 3H).

Ethyl (S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (128)



The titled compound **128** was prepared from compound **3-04** in a yield of 12.0% according to the procedure outlined for compound **108**. Mass (m/z) 542.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 2.7 Hz, 1H), 6.75 – 6.56 (m, 4H), 6.44 (d, *J* = 6.0 Hz, 1H), 5.84 (s, 1H), 5.20 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.93 (td, *J* = 6.4, 3.3 Hz, 1H), 4.47 (s, 2H), 4.22 (dd, *J* = 25.3, 10.2 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.29 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.73 – 2.39 (m, 2H), 2.28 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

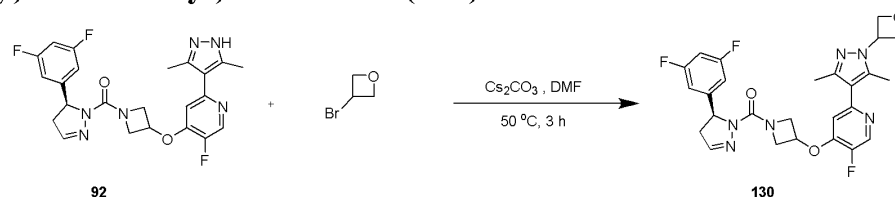
methyl (S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (129)



The titled compound **129** was prepared from compound **3-04** in a yield of 11.5% according to the procedure outlined for compound **108**. Mass (m/z) 528.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 2.7

Hz, 1H), 6.78 – 6.51 (m, 4H), 6.45 (d, $J = 6.0$ Hz, 1H), 6.27 (d, $J = 1.1$ Hz, 1H), 5.20 (ddd, $J = 12.2, 6.5, 3.0$ Hz, 1H), 5.00 – 4.84 (m, 1H), 4.59 – 4.40 (m, 2H), 4.33 – 4.13 (m, 2H), 3.74 (s, 3H), 3.30 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 – 2.58 (m, 1H), 2.28 (s, 3H), 1.97 (d, $J = 1.0$ Hz, 3H).

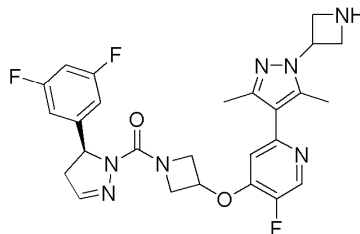
5 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1-(oxetan-3-yl)-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (130)**



Compound 92 (94 mg, 0.2 mmol), 3-bromooxetane (55 mg, 0.4 mmol), Cs_2CO_3 (261 mg, 0.8 mmol) were placed in DMF (4 mL). The mixture was stirred 50 °C for 3 hours, and then the reaction liquid was poured into water. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by prep-HPLC to give the titled compound **130** (20 mg, 19.0%) as a white solid.

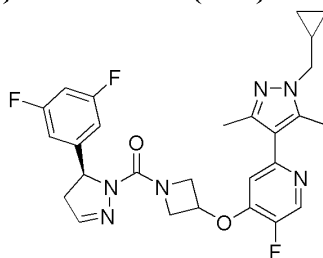
15 ^1H NMR (400 MHz, Chloroform- d) δ 8.43 (d, $J = 3.1$ Hz, 1H), 6.82 – 6.65 (m, 4H), 6.59 (d, $J = 6.6$ Hz, 1H), 5.40 (p, $J = 7.1$ Hz, 1H), 5.25 (dt, $J = 22.5, 6.4$ Hz, 3H), 5.05 (s, 1H), 4.97 (dd, $J = 7.6, 6.4$ Hz, 2H), 4.58 (s, 2H), 4.33 (dd, $J = 35.0, 10.4$ Hz, 2H), 3.36 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.5, 1.8$ Hz, 1H), 2.35 (d, $J = 13.0$ Hz, 6H). Mass (m/z) 527.3 $[\text{M}+\text{H}]^+$.

20 **(S)-(3-((2-(1-(azetidin-3-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (131)**



The titled compound **131** was prepared from compound **92** in a yield of 57.1% according to the procedure outlined for compound **130**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 3.2 Hz, 1H), 6.85 – 6.58 (m, 5H), 5.41 – 5.22 (m, 2H), 5.09 (tt, *J* = 6.6, 3.8 Hz, 1H), 4.74 – 4.21 (m, 8H), 3.36 (ddd, *J* = 18.7, 12.1, 1.6 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.40 – 2.21 (m, 6H). Mass (m/z) 526.3 [M+H]⁺.

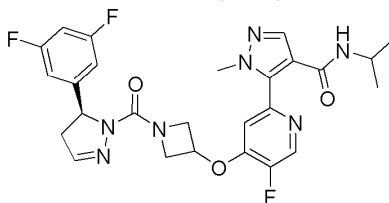
(S)-(3-((2-(1-(cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (132)



10

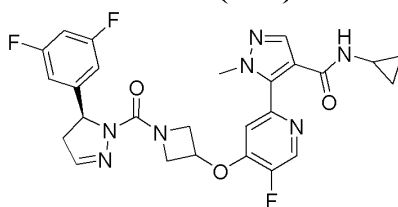
The titled compound **132** was prepared from compound **92** in a yield of 29.5% according to the procedure outlined for compound **130**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 3.0 Hz, 1H), 6.83 – 6.65 (m, 4H), 6.59 (d, *J* = 6.6 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.04 (td, *J* = 6.5, 3.3 Hz, 1H), 4.59 (t, *J* = 9.4 Hz, 2H), 4.32 (dd, *J* = 35.0, 10.2 Hz, 2H), 3.92 (d, *J* = 6.8 Hz, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.36 (d, *J* = 26.0 Hz, 6H), 1.26 (dddt, *J* = 8.1, 6.4, 3.2, 1.6 Hz, 1H), 0.63 – 0.53 (m, 2H), 0.38 (dt, *J* = 6.2, 4.8 Hz, 2H). Mass (m/z) 525.3 [M+H]⁺.

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-isopropyl-1-methyl-1H-pyrazole-4-carboxamide (133)



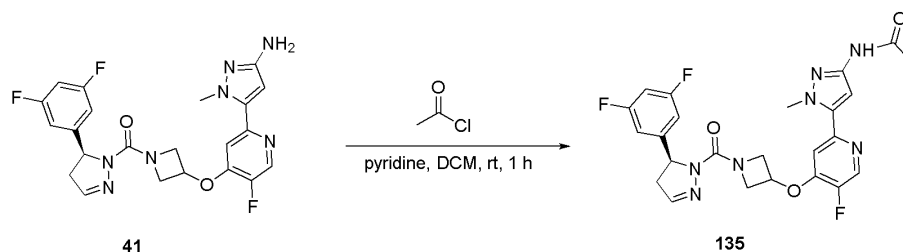
The titled compound **133** was prepared from compound **65** in a yield of 68% according to the procedure outlined for compound **68**. Mass (m/z) 542.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.79 (s, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 6.80 – 6.64 (m, 4H), 6.38 (d, *J* = 7.7 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.15-5.07 (m, 1H), 4.69-4.54 (m, 2H), 4.38-4.24 (m, 2H), 4.17 – 4.04 (m, 1H), 3.91 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.8 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 6H).

(S)-N-cyclopropyl-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (134)



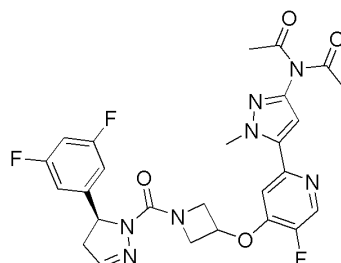
The titled compound **134** was prepared from compound **65** in a yield of 69 % according to the procedure outlined for compound **68**. Mass (m/z) 540.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.78 (s, 1H), 7.24 (d, *J* = 6.7 Hz, 1H), 6.88 – 6.61 (m, 4H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.70-4.53 (m, 2H), 4.41 – 4.25 (m, 2H), 3.90 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.77 (dq, *J* = 7.2, 3.5 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 0.84 – 0.74 (m, 2H), 0.57 – 0.44 (m, 2H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-3-yl)acetamide (135)



Compound **41** (57 mg, 0.12 mmol), acetyl chloride and pyridine were placed in DCM (5 mL). The mixture was stirred at room temperature for 1 h. Added H₂O and DCM, the combined organic layers were washed by saturated NaHCO₃ solution and 1N HCl solution. Concentrated in vacuo and purification by silica gel plate to give the titled compound **135** (5 mg, 8%) as a white solid. Mass (m/z) 514.3[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 2.7 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.82 – 6.65 (m, 4H), 5.28 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.12-5.04 (m, 1H), 4.66-4.53 (m, 2H), 4.37-4.23 (m, 2H), 4.06 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.17 (s, 3H).

(S)-N-acetyl-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-3-yl)acetamide (136)

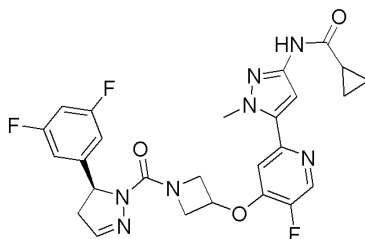


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The title compound **136** was prepared in a yield of 10% as a white solid from compound **41** according to the procedure outlined for compound **135**. Mass (m/z) 556.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.8 Hz, 1H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.64 (m, 3H), 6.39 (s, 1H), 5.27 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.10-5.02 (m, 1H), 4.68-4.52 (m, 2H), 4.40 – 4.23 (m, 2H), 4.16

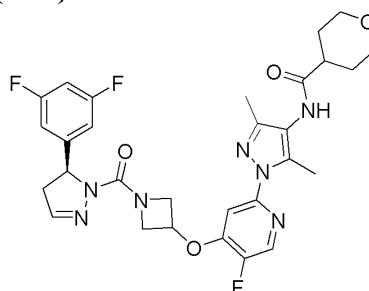
(s, 3H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.7, 6.5, 1.8$ Hz, 1H), 2.36 (s, 6H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-3-yl)cyclopropanecarboxamide (137)



The title compound **137** was prepared in a yield of 14% as a white solid from compound **41** according to the procedure outlined for compound **135**. Mass (m/z) 540.3 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.40 (d, $J = 2.7$ Hz, 1H), 8.26 (s, 1H), 6.93 (s, 1H), 6.88 (d, $J = 6.4$ Hz, 1H), 6.82 – 6.65 (m, 4H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.08-4.98 (m, 1H), 4.71 – 4.52 (m, 2H), 4.35-4.21 (m, 2H), 4.07 (s, 3H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.8$ Hz, 1H), 1.57-1.47(m, 1H), 1.14 – 1.06 (m, 2H), 0.91-0.83 (m, 2H).

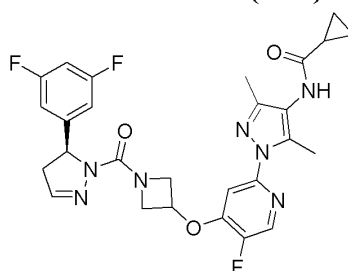
(S)-N-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide (138)



The title compound **138** was prepared in a yield of 19.5% as a white solid from compound **109** according to the procedure outlined for compound **135**. Mass (m/z) 598.4 $[M+H]^+$. 1H NMR (400 MHz,

Chloroform-*d*) δ 8.14 (d, $J = 2.4$ Hz, 1H), 7.20 (d, $J = 6.2$ Hz, 1H), 6.80 (d, $J = 1.7$ Hz, 1H), 6.78 – 6.74 (m, 2H), 6.73 – 6.67 (m, 1H), 5.32 – 5.25 (m, 1H), 5.14 (d, $J = 6.3$ Hz, 1H), 4.69 – 4.52 (m, 2H), 4.41 – 4.22 (m, 4H), 4.09 (dd, $J = 11.0, 7.4$ Hz, 2H), 3.49 (td, $J = 11.3, 3.2$ Hz, 2H), 3.44 – 3.27 (m, 2H), 2.76 – 2.66 (m, 1H), 2.64 – 2.52 (m, 1H), 2.46 (s, 3H), 2.18 (s, 3H), 2.08 – 1.84 (m, 4H).

(S)-N-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopropanecarboxamide (139)

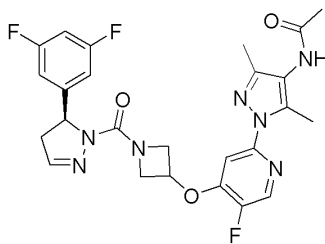


10

The title compound **139** was prepared in a yield of 30% as a white solid from compound **109** according to the procedure outlined for compound **135**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.18 (dd, $J = 10.3, 2.4$ Hz, 1H), 7.21 (d, $J = 6.2$ Hz, 1H), 6.82 (d, $J = 1.8$ Hz, 1H), 6.80 – 6.76 (m, 2H), 6.73 – 6.68 (m, 1H), 5.34 – 5.26 (m, 1H), 5.22 – 5.3 (m, 1H), 4.70 – 4.60 (m, 2H), 4.34 (d, $J = 28.2$ Hz, 2H), 3.37 (dd, $J = 18.8, 12.3$ Hz, 1H), 2.78 – 2.69 (m, 1H), 2.51 (s, 3H), 2.23 (s, 3H), 1.37 – 1.34 (m, 2H), 1.10 (ddd, $J = 10.0, 5.9, 3.6$ Hz, 2H), 0.89 (dq, $J = 7.2, 4.0$ Hz, 2H), 0.81 – 0.75 (m, 1H). Mass (m/z) 554.3 $[\text{M}+\text{H}]^+$.

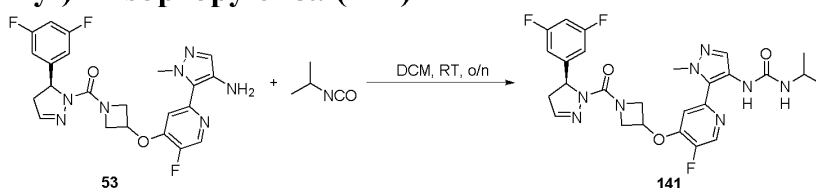
(S)-N-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)acetamide (140)

20



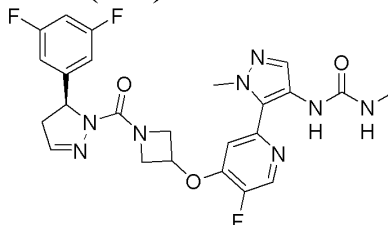
The title compound **140** was prepared in a yield of 19.8% as a white solid from compound **109** according to the procedure outlined for compound **135**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, $J = 2.4$ Hz, 1H), 7.19 (d, $J = 6.2$ Hz, 1H), 6.79 (d, $J = 1.6$ Hz, 1H), 6.75 (dt, $J = 6.4$, 2.1 Hz, 2H), 6.71 – 6.66 (m, 1H), 5.27 (ddd, $J = 12.1$, 6.4, 3.2 Hz, 1H), 5.20 – 5.09 (m, 1H), 4.71 – 4.53 (s, 2H), 4.40 – 4.24 (m, 2H), 3.42 – 3.30 (m, 1H), 2.74 – 2.65 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H). Mass (m/z) 528.3 $[\text{M}+\text{H}]^+$.

(S)-1-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-3-isopropylurea (141)



A mixture of compound **53** (50 mg, 0.11 mmol) and 2-isocyanatopropane (18 mg, 0.22 mmol) in DCM (5 mL) reacted under N_2 and the whole reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated. The crude product was purified by Pre-TLC to give required product **141** (27 mg, 45.7%) as a white solid. Mass (m/z) 557.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, $J = 2.9$ Hz, 1H), 7.68 (s, 1H), 7.05 (d, $J = 6.5$ Hz, 1H), 6.79 (d, $J = 1.7$ Hz, 1H), 6.76 – 6.66 (m, 3H), 5.26 (dd, $J = 12.2$, 6.4 Hz, 1H), 5.15 (s, 1H), 4.62 (s, 2H), 4.30 (dd, $J = 21.6$, 10.7 Hz, 2H), 4.05 (s, 3H), 3.93 – 3.84 (m, 1H), 3.36 (ddd, $J = 18.7$, 12.2, 1.7 Hz, 1H), 2.70 (ddd, $J = 18.6$, 6.4, 1.7 Hz, 1H), 1.09 (d, $J = 6.5$ Hz, 6H).

(S)-1-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazol-4-yl)-3-methylurea (142)

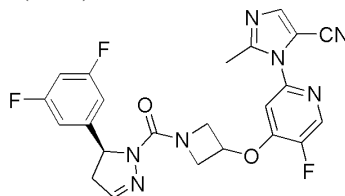


5 The title compound **142** was prepared in a yield of 37.5% as a white solid from compound **53** according to the procedure outlined for compound **141**. Mass (m/z) 529.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.44 (d, $J = 2.8$ Hz, 1H), 7.68 (s, 1H), 6.97 (d, $J = 6.6$ Hz, 1H), 6.79 (d, $J = 1.6$ Hz, 1H), 6.77 – 6.64 (m, 3H), 5.26 (dd, $J = 12.1$, 6.4

10 Hz, 1H), 5.07 (s, 1H), 4.73 (s, 1H), 4.59 (s, 2H), 4.28 (dd, $J = 21.1$, 10.4 Hz, 2H), 4.05 (s, 3H), 3.35 (dd, $J = 18.6$, 12.2 Hz, 1H), 2.78 (s, 3H), 2.75 – 2.64 (m, 1H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-2-methyl-1H-imidazole-5-carbonitrile (143).

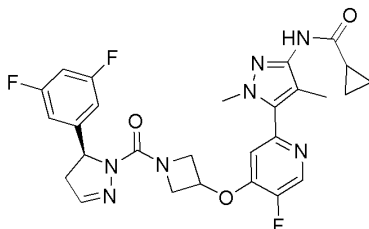
15



The title compound **143** was prepared in a yield of 8.6% as a white solid from compound **3-04** according to the procedure outlined for compound **110**. Mass (m/z) 482.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ

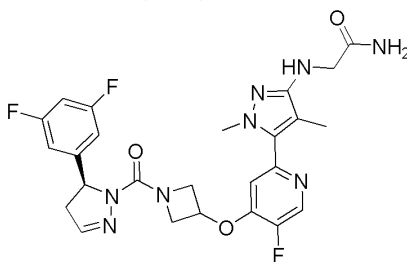
20 8.34 (d, $J = 2.6$ Hz, 1H), 7.72 (s, 1H), 6.88 – 6.48 (m, 5H), 5.27 (dd, $J = 12.2$, 6.4 Hz, 1H), 5.10 (d, $J = 3.8$ Hz, 1H), 4.62 (dd, $J = 18.8$, 10.9 Hz, 2H), 4.33 (dd, $J = 27.3$, 10.3 Hz, 2H), 3.37 (ddd, $J = 18.7$, 12.2, 1.7 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.54 (s, 3H).

(S)-N-(5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazol-3-yl)cyclopropanecarboxamide (144)



5 The title compound **144** was prepared in a yield of 12.5% as a brown solid from compound **101** according to the procedure outlined for compound **135**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.8 Hz, 1H), 6.89 – 6.52 (m, 5H), 5.26 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.09-4.97 (m, 1H), 4.66 – 4.48 (m, 2H), 4.41 – 4.24 (m, 2H), 3.90 (s, 3H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 3.18-3.08 (m, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.00 (s, 3H), 1.38 (t, *J* = 7.3 Hz, 2H), 1.13 – 1.06 (m, 2H). Mass (*m/z*) 554.3 [*M*+*H*]⁺.

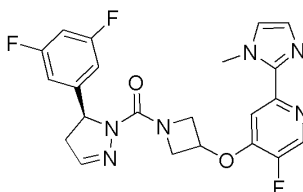
15 **(S)-2-((5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazol-3-yl)amino)acetamide (145)**



The title compound **145** was prepared in a yield of 82.1% as a white solid from compound **101** according to the procedure outlined for compound **56**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 – 8.44 (m, 1H), 6.80 (t, *J* = 1.5 Hz, 1H), 6.78 – 6.53 (m, 4H), 5.26 (dd, *J* = 12.1, 6.4 Hz, 1H), 5.13 – 4.99 (m, 1H), 4.59 (s, 2H), 4.39 – 4.25 (m, 2H), 4.14 – 4.01 (m,

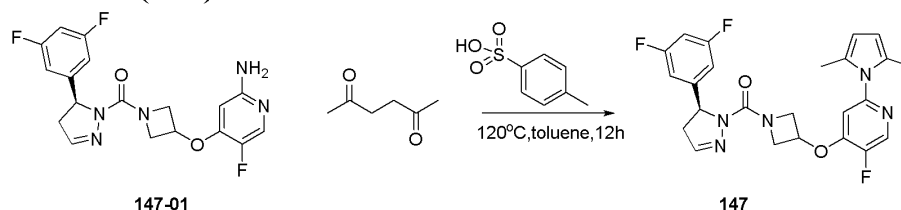
2H), 3.92 – 3.73 (m, 3H), 3.36 (dd, $J = 18.6, 12.2$ Hz, 1H), 2.71 (ddd, $J = 18.7, 6.5, 1.7$ Hz, 1H), 2.05 – 1.90 (m, 3H). Mass (m/z) 543.3 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-imidazol-2-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (146)



The title compound **146** was prepared in a yield of 34.5% as a white solid from compound **3-02** according to the procedure outlined for compound **30**. Mass (m/z) 457.3 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.33 (d, $J = 2.7$ Hz, 1H), 7.59 (d, $J = 6.8$ Hz, 1H), 7.09 (d, $J = 1.1$ Hz, 1H), 6.96 (s, 1H), 6.82 – 6.60 (m, 4H), 5.32 – 5.25 (m, 1H), 5.21 – 5.10 (m, 1H), 4.65 (s, 2H), 4.29 (t, $J = 12.3$ Hz, 2H), 4.08 (s, 3H), 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.68 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H).

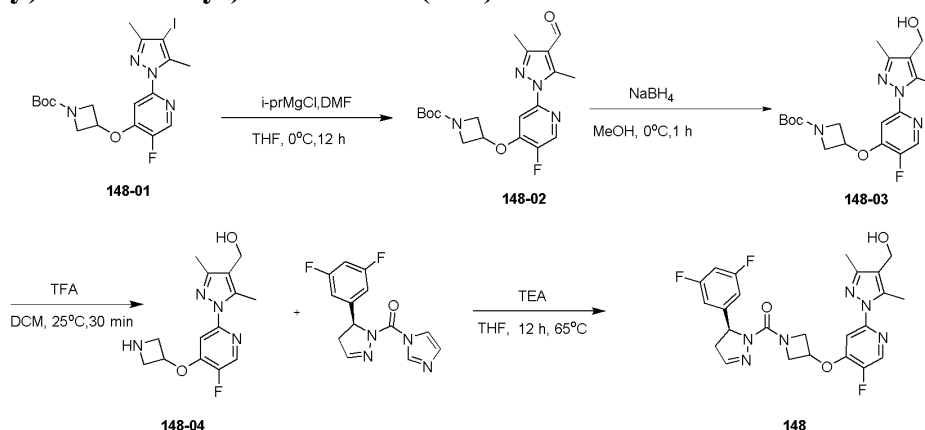
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (147)



Compound **147-01** (100 mg, 0.25 mmol) was dissolved in 3 mL of toluene, hexane-2,5-dione (115 mg, 1 mmol) and 4-methylbenzenesulfonic acid (20mg, 0.025 mmol) and the mixture was stirred at 120°C for 12 h. Concentrated and purification by prep-HPLC to give the titled compound **147** (50 mg, 48.2%) as a white solid. ^1H NMR (400 MHz, Chloroform- d) δ 8.37 (d, $J = 2.7$ Hz, 1H), 6.82 (t, $J = 1.7$ Hz, 1H), 6.78 (dd, $J = 4.8, 3.3$ Hz,

2H), 6.76 – 6.69 (m, 1H), 6.54 (d, $J = 6.0$ Hz, 1H), 5.91 (s, 2H), 5.29 (dd, $J = 12.2, 6.5$ Hz, 1H), 5.03 (td, $J = 6.4, 3.2$ Hz, 1H), 4.66 – 4.53 (m, 2H), 4.33 (dd, $J = 23.3, 10.4$ Hz, 2H), 3.39 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.74 (ddd, $J = 18.7, 6.5, 1.8$ Hz, 1H), 2.13 (s, 6H). Mass (m/z) 470.3
 5 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(hydroxymethyl)-3,5-dimethyl-1H-pyrazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (148)

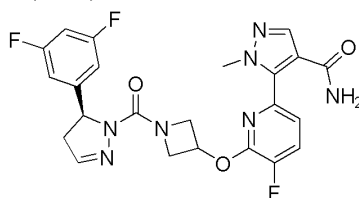


10 **Step 1:** Compound **148-01** (500mg, 1.02 mmol) were dissolved in THF (10 mL), *i*-PrMgCl (250 ul, 2M, 2.52 mmol) was added at 0°C, stirred at 0°C for 1 h. DMF(1 mL) was added and the reaction mixture was stirred at rt for 12 h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel
 15 chromatography to give the compound **148-02** (96 mg, 25.1%). MS (m/z) 391.2 $[M+H]^+$.

Step 2: Compound **148-02** (96 mg, 0.25 mmol), were dissolved in MeOH (2 mL) and NaBH₄ (20 mg, 0.51 mmol) was added, stirred at 0°C for 1 h. The mixture was extracted with EA, washed with brine, dried
 20 (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the compound **148-03** (76 mg, 79.1%). MS (m/z) 393.3 $[M+H]^+$.

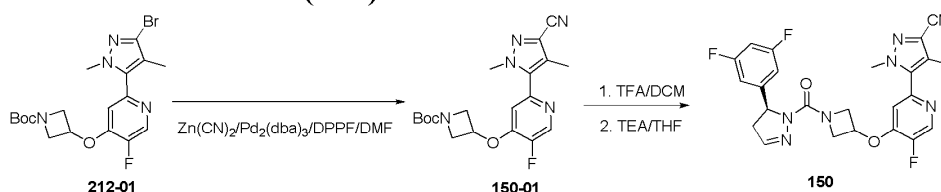
The title compound **148** was prepared in a yield of 10.2% as a white solid from compound **148-03** according to the procedure outlined for compound **1-03**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 6.2, 2.6 Hz, 1H), 6.80 – 6.66 (m, 4H), 5.27 (dd, J = 12.2, 6.4 Hz, 1H), 5.21 – 5.12 (m, 1H), 4.670 – 4.56 (m, 2H), 4.54 (m, 2H), 4.31 (dd, J = 30.7, 10.2 Hz, 3H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.76 – 2.67 (m, 1H), 2.61 (s, 3H), 2.34 (s, 3H). Mass (m/z) 501.2 [M+H]⁺.

(S)-5-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (149)



The title compound **149** was prepared in a yield of 82% as a pale green solid from compound **111** according to the procedure outlined for compound **66**. Mass (m/z) 500.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.54-7.48 (m, 1H), 7.30 (dd, J = 8.1, 3.0 Hz, 1H), 6.81 – 6.72 (m, 3H), 6.71-6.64 (m, 1H), 5.44 – 5.34 (m, 1H), 5.26 (dd, J = 12.2, 6.5 Hz, 1H), 4.67 – 4.47 (m, 2H), 4.38 – 4.20 (m, 2H), 3.84 (s, 3H), 3.34 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-3-carbonitrile (150)



5

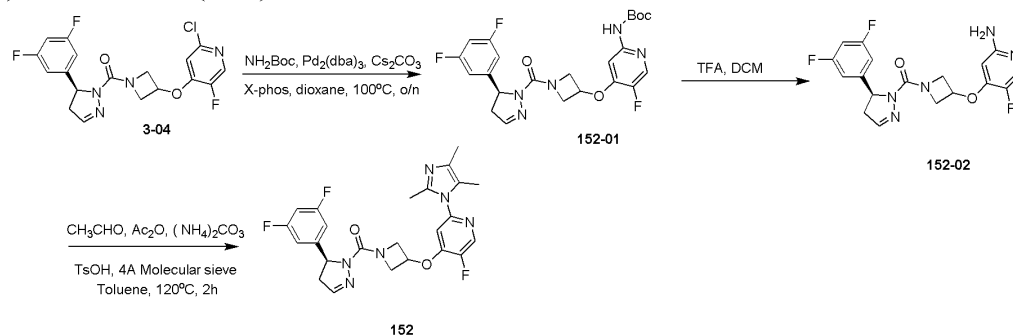
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15



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(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2,4,5-trimethyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (152).



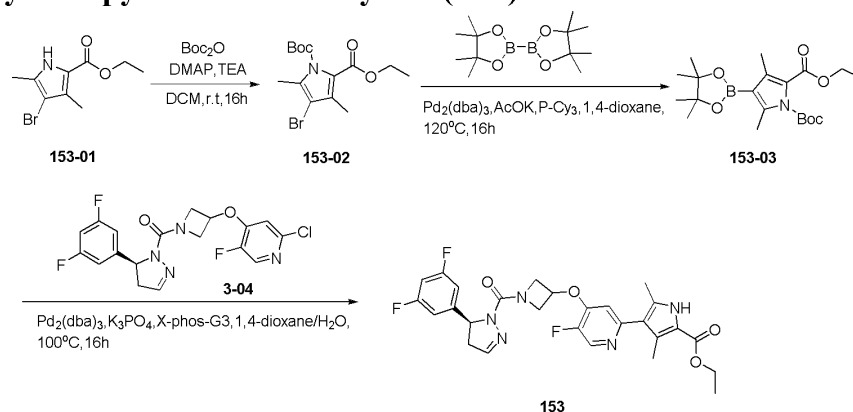
- Step 1:** Compound **3-04** (960 mg, 2.3 mmol), NH_2Boc (1.08 g, 9.37 mmol), $\text{Pd}_2(\text{dba})_3$ (214 mg, 0.23 mmol), Cs_2CO_3 (2.3 g, 7.02 mmol) and X-phos (111 mg, 0.23 mmol) were placed in dioxane (10 mL). The mixture was stirred 100°C for overnight under N_2 , the mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo.
- Purification by column chromatography on silica gel eluting with (PE: EA = 1:2) to give the titled compound **152-01** (500 mg, 43%). Mass (m/z) 492.4 $[\text{M}+\text{H}]^+$;

- Step 2:** Compound **152-01** (1.3 g, 2.60 mmol) was dissolved in 15 mL of DCM, trifluoroacetic acid (1.5 ml, 13.1 mmol) was added, the mixture was stirred at room temperature for 30 min. Concentrated to give the desired product **152-02**, which was used for next step without further purification. Mass (m/z) 392.4 $[\text{M}+\text{H}]^+$.

- Step 3:** Compound **152-02** (50 mg, 0.13 mmol), CH_3CHO (5.6 mg, 0.13 mmol), Ac_2O (50 mg, 0.13 mmol) and p-toluenesulfonic acid (2 mg, 0.012 mmol) (bound with 4A Molecular sieve) in Toluene. The mixture was stirred 120°C for 2 h under N_2 and concentrated. Purification by prep-HPLC to give the titled compound **152** (10 mg, 16%). Mass (m/z) 485.4 $[\text{M}+\text{H}]^+$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.66 (d, $J = 2.8$ Hz, 1H), 7.44 (d, $J = 6.2$ Hz, 1H), 7.10 (t, $J = 9.4$ Hz, 1H), 7.02 (s, 1H), 6.94 – 6.68 (m,

2H), 5.36 – 5.13 (m, 2H), 4.54 (s, 1H), 4.09 (d, $J = 7.0$ Hz, 2H), 3.42 – 3.29 (m, 1H), 2.65 (dd, $J = 18.6, 6.3$ Hz, 1H), 2.45 (s, 6H), 1.99 (s, 3H).

Ethyl (S)-4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (153)



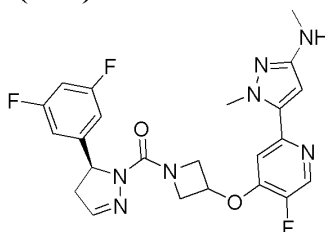
Step 1: Compound **153-01** (3 g, 12.195 mmol), Boc₂O (3.19 g, 14.616 mmol), DMAP (0.297 g, 2.43 mmol) and TEA (1 ml) were dissolved in 30 mL DCM. Let it stir at room temperature for 16h. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 10/1) to give compound **153-02** (4.2 g, 99.5%) as colorless oil. Mass (m/z) 347.3 [M+H]⁺.

Step 2: Compound **153-02** (212 mg, 0.613 mmol), Pd₂(dba)₃ (56 mg, 0.061 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (466.8 mg, 1.838 mmol), AcOK (172.4 mg, 1.838 mmol) and P-Cy₃ (34.3 mg, 0.123 mmol) were mixed in 4 mL 1,4-dioxane. Let it stir at 120°C for 16h under N₂. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 5/1) to give compound **153-03** (110 mg, 45.7%) as light-yellow oil. Mass (m/z) 394.3 [M+H]⁺.

Step 3: Compound **3-04** (100 mg, 0.244 mmol), compound **153-03** (110 mg, 0.28 mmol), X-Phos-G₃ (20.6 mg, 0.024 mmol), Pd₂(dba)₃ (22.3mg, 0.023 mmol), K₃PO₄ (517 mg, 2.439 mmol) were placed in 5 mL 1,4-dioxane/H₂O(v/v =4/1). The mixture was stirred at 100 °C for 16 h

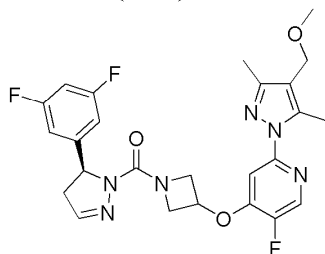
under N₂. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 1/2) to give 8 mg white solid, Yield: 5.24%. Mass (m/z) 542.4 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.78 (brs, 1H), 8.42 (d, *J* = 3.2 Hz, 1H), 6.79 (t, *J* = 1.2 Hz, 1H), 6.77 – 6.73 (m, 2H), 6.72 – 6.66 (m, 1H), 6.56 (d, *J* = 6.8 Hz, 1H), 5.27 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.63-4.51 (m, 2H), 4.40 – 4.23 (m, 4H), 3.36 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.71 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).

(S)-3-fluoro-5-(1-(3-((5-fluoro-2-(1-methyl-3-(methylanino)-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile (154)



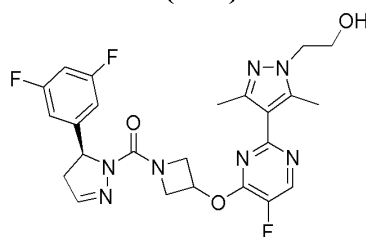
The title compound **154** was prepared in a yield of 8% as a white solid from compound **41** according to the procedure outlined for compound **56**. Mass (m/z) 486.3[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.8 Hz, 1H), 6.94 (d, *J* = 6.3 Hz, 1H), 6.83-6.80 (m, 1H), 6.78 – 6.67 (m, 3H), 5.74 (s, 1H), 5.29 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.18-5.09 (m, 1H), 4.62 (s, 3H), 4.33 (dd, *J* = 32.4, 10.5 Hz, 3H), 4.05 (s, 3H), 3.44 – 3.31 (m, 1H), 2.91 (s, 3H), 2.73 (ddd, *J* = 18.7, 6.3, 1.8 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(methoxymethyl)-3,5-dimethyl-1H-pyrazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (155)



The title compound **155** was prepared in a yield of 40% as a white solid from compound **148** according to the procedure outlined for compound **50**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 6.94 (s, 1H), 6.62 – 6.37 (m, 4H), 5.05 – 4.87 (m, 2H), 4.50 – 4.23 (m, 2H), 4.10 – 3.88 (m, 4H), 3.20 – 3.10 (m, 1H), 3.10–3.01 (m, 3H), 2.85 (s, 3H), 2.44 (d, J = 18.9 Hz, 1H), 2.31 (m, 3H). Mass (m/z) 515.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (156)

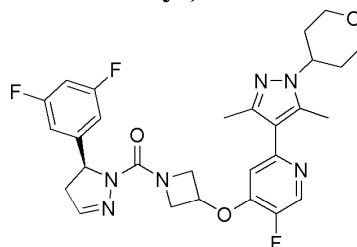


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The title compound **156** was prepared in a yield of 8.7% as a white solid from compound **91** according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, J = 2.6 Hz, 1H), 6.76 – 6.58 (m, 4H), 5.50 – 5.41 (m, 1H), 5.21 (dd, J = 12.2, 6.4 Hz, 1H), 4.54 (s, 2H), 4.25 (dd, J = 34.6, 10.7 Hz, 2H), 4.12 (t, J = 4.8 Hz, 2H), 3.96 (t, J = 4.8 Hz, 2H), 3.34 – 3.22 (m, 1H), 2.63 (ddd, J = 18.7, 6.5, 1.7 Hz, 1H), 2.55 (s, 3H), 2.47 (s, 3H). Mass (m/z) 516.3 [M+H]⁺.

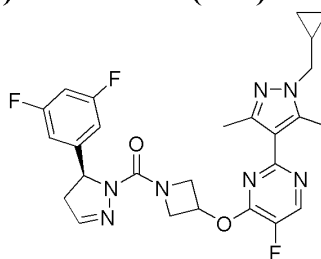
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (157)

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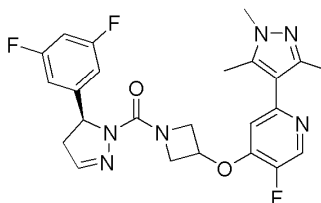
The title compound **157** was prepared in a yield of 21.6% as a white solid from compound **92** according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.80 – 6.64 (m, 4H), 5.28 (dd, *J* = 12.1, 6.3 Hz, 1H), 5.15 (s, 1H), 4.64 (s, 2H), 4.37 (dd, *J* = 34.8, 10.1 Hz, 2H), 4.28 – 4.19 (m, 1H), 4.14 (dd, *J* = 11.7, 4.3 Hz, 2H), 3.54 (t, *J* = 11.9 Hz, 2H), 3.45 – 3.33 (m, 1H), 2.79 – 2.69 (m, 1H), 2.34 (d, *J* = 30.9 Hz, 8H), 1.85 (d, *J* = 12.9 Hz, 2H). Mass (*m/z*) 555.4 [M+H]⁺.

(S)-(3-((2-(1-(cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (158)



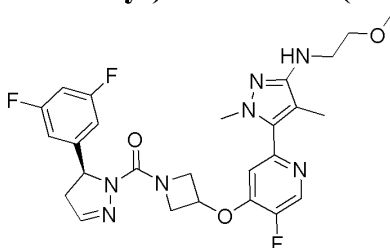
The title compound **158** was prepared in a yield of 24.7% as a white solid from compound **91** according to the procedure outlined for compound **86**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 2.6 Hz, 1H), 6.83 – 6.65 (m, 4H), 5.53 (s, 1H), 5.29 (s, 1H), 4.61 (s, 2H), 4.33 (d, *J* = 27.3 Hz, 2H), 3.98 (d, *J* = 6.8 Hz, 2H), 3.35 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.77 – 2.49 (m, 7H), 1.26 (s, 1H), 0.58 (dd, *J* = 7.7, 5.2 Hz, 2H), 0.41 (t, *J* = 5.0 Hz, 2H). Mass (*m/z*) 526.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (159)



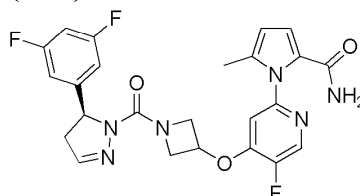
The title compound **159** was prepared in a yield of 30.5% as a white solid from compound **3-04** according to the procedure outlined for compound **3**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, J = 3.1 Hz, 1H), 6.81 – 6.65 (m, 4H), 6.57 (d, J = 6.6 Hz, 1H), 5.27 (dd, J = 12.2, 6.5 Hz, 1H), 5.04 (ddd, J = 7.8, 6.4, 3.9 Hz, 1H), 4.58 (t, J = 10.0 Hz, 2H), 4.32 (dd, J = 35.2, 10.2 Hz, 2H), 3.76 (s, 3H), 3.36 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.35 (d, J = 22.7 Hz, 6H). Mass (m/z) 485.3 $[\text{M}+\text{H}]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-((2-methoxyethyl)amino)-1,4-dimethyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (160)



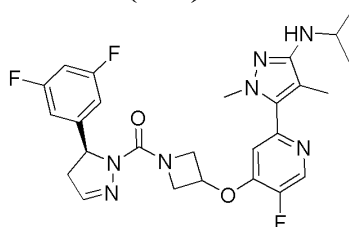
The title compound **160** was prepared in a yield of 36.8% as a white solid from compound **101-03** according to the procedure outlined for compound **56**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (d, J = 2.9 Hz, 1H), 6.91 – 6.60 (m, 5H), 5.28 (dd, J = 12.1, 6.3 Hz, 1H), 5.13-5.05 (m, 1H), 4.71-4.54 (m, 2H), 4.33 (dd, J = 23.8, 10.5 Hz, 2H), 3.80 (s, 3H), 3.62 (t, J = 4.6 Hz, 2H), 3.55 (t, J = 4.7 Hz, 2H), 3.40 (s, 3H), 3.39 – 3.31 (m, 1H), 2.72 (dd, J = 18.6, 6.2 Hz, 1H), 1.95 (s, 3H). Mass (m/z) 544.4 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-5-methyl-1H-pyrrole-2-carboxamide (161)



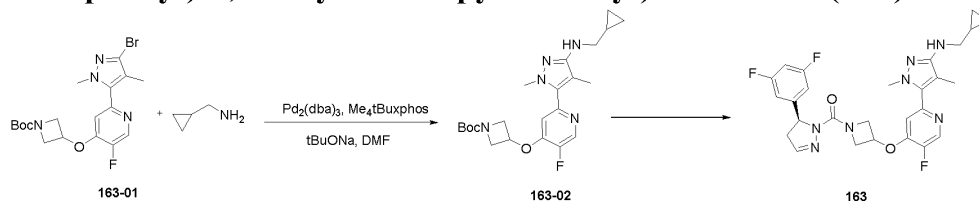
The titled compound **161** was prepared in 19.2% yield according to the procedure outlined for compound **66-02**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, $J = 2.7$ Hz, 1H), 6.79 (d, $J = 1.7$ Hz, 1H), 6.77-6.65 (m, 3H), 6.10 (d, $J = 2.8$ Hz, 1H), 6.04 (d, $J = 4.0$ Hz, 1H), 5.75 (s, 1H), 5.33 – 5.21 (m, 1H), 5.08-5.00 (m, 1H), 4.62-4.49 (m, 2H), 4.42 – 4.19 (m, 2H), 3.41-3.30 (m, 1H), 2.77 – 2.63 (m, 1H), 2.08 (s, 3H). Mass (m/z) 499.3 $[\text{M}+\text{H}]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(isopropylamino)-1,4-dimethyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (**162**)



The title compound **162** was prepared in a yield of 42.8% as a white solid from compound **101-03** according to the procedure outlined for compound **56**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.52 (d, $J = 2.8$ Hz, 1H), 6.81 (t, $J = 1.6$ Hz, 1H), 6.78 – 6.55 (m, 4H), 5.28 (dd, $J = 12.1, 6.3$ Hz, 1H), 5.14-5.02 (m, 1H), 4.71-4.52 (m, 2H), 4.32 (dd, $J = 21.1, 10.1$ Hz, 2H), 3.92 – 3.84 (m, 1H), 3.82 (s, 3H), 3.44 – 3.28 (m, 1H), 2.76-2.67 (m, 1H), 1.99 (s, 3H), 1.43 – 1.18 (m, 6H). Mass (m/z) 528.4 $[\text{M}+\text{H}]^+$.

(S)-(3-((2-(3-((cyclopropylmethyl)amino)-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (**163**)

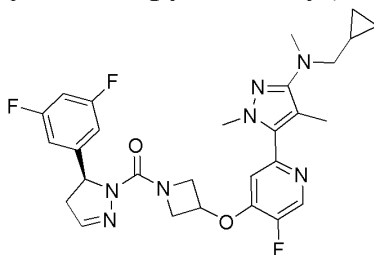


Step 1: Compound **163-01** (150 mg, 0.34 mmol), cyclopropylmethanamine (48.4 mg, 0.68 mmol), $\text{Pd}_2(\text{dba})_3$ (27 mg, 0.03

mmol), Me₄tBuPhos (16 mg, 0.03 mmol) and NaOtBu (65 mg, 0.68 mmol) were dissolved in DMF (3 mL). The mixture was stirred at 90 °C for 2 hrs under N₂ atmosphere. Concentrated and purified by prep-TLC to give compound **163-02** (70 mg, 42.2%) as yellow oil.

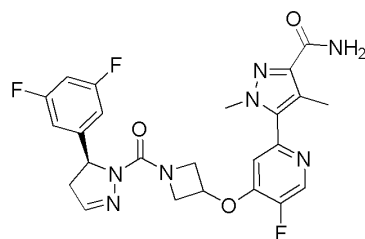
5 The title compound **163** was prepared in a yield of 42.1% as a white solid from compound **163-02** according to the procedure outlined for compound **1-03**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.9 Hz, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.57 (m, 4H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.09-5.01 (m, 1H), 4.67-4.51 (m, 2H), 4.32 (dd, *J* = 31.8, 10.5 Hz, 2H), 3.77 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 3.13 (d, *J* = 7.0 Hz, 2H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.95 (s, 3H), 1.18-1.09 (m, 1H), 0.58 – 0.49 (m, 2H), 0.29 – 0.20 (m, 2H). Mass (m/z) 539.2 [M+H]⁺.

(S)-(3-((2-(3-((cyclopropylmethyl)(methyl)amino)-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (**164**)



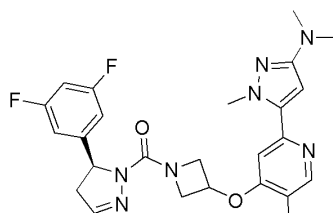
The title compound **164** was prepared in a yield of 16.7% as a white solid from compound **163** according to the procedure outlined for compound **56**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 2.7 Hz, 1H), 6.82 (s, 1H), 6.69 (d, *J* = 25.6 Hz, 4H), 5.30 (s, 1H), 5.07 (s, 1H), 4.63 (d, *J* = 25.8 Hz, 2H), 4.33 (s, 2H), 3.89 (s, 3H), 3.39 (d, *J* = 7.1 Hz, 2H), 3.36 – 3.29 (m, 1H), 3.26 (s, 2H), 2.73 (s, 1H), 2.19 (s, 3H), 1.05 (s, 1H), 0.62 (d, *J* = 7.9 Hz, 2H), 0.35 (s, 2H). Mass (m/z) 554.4 [M+H]⁺.

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-3-carboxamide (**165**)



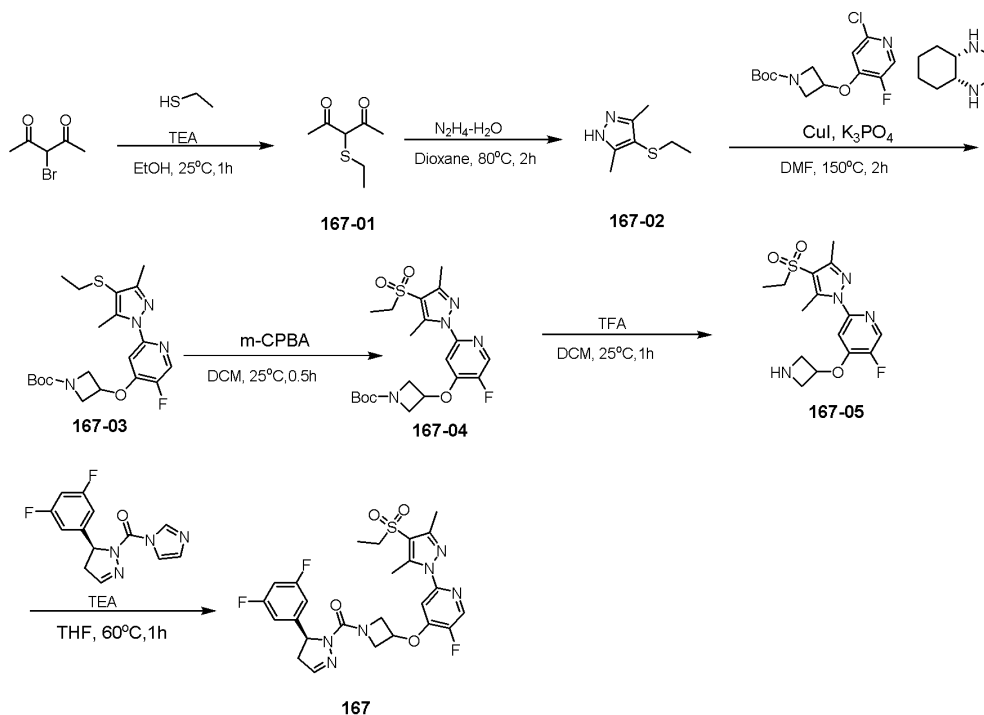
The title compound **165** was prepared in a yield of 96.1% as a white solid from compound **150** according to the procedure outlined for compound **66**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, J = 2.9 Hz, 1H), 6.87-6.78 (m, 2H), 6.78 – 6.55 (m, 4H), 5.46 (s, 1H), 5.27 (dd, J = 12.2, 6.4 Hz, 1H), 5.11-5.04 (m, 1H), 4.60 (dd, J = 19.7, 10.9 Hz, 2H), 4.33 (dd, J = 25.1, 10.3 Hz, 2H), 3.95 (s, 3H), 3.36 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, J = 18.6, 6.4, 1.7 Hz, 1H), 2.37 (s, 3H). Mass (m/z) 514.2 $[\text{M}+\text{H}]^+$.

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3-(dimethylamino)-1-methyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (166)



The title compound **166** was prepared in a yield of 48% as a white solid from compound **41** according to the procedure outlined for compound **56**. Mass (m/z) 500.3 $[\text{M}+\text{H}]^+$. ^1H NMR (301 MHz, Chloroform-*d*) δ 8.46-8.39 (m, 1H), 6.90 – 6.62 (m, 5H), 5.95 (s, 1H), 5.28 (dd, J = 12.3, 6.4 Hz, 1H), 5.15-5.04 (m, 1H), 4.69-4.53 (m, 2H), 4.41-4.22 (m, 2H), 4.04 (s, 3H), 3.45-3.29 (m, 1H), 2.98 (s, 6H), 2.79 – 2.64 (m, 1H).

(S)-((5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-(ethylsulfonyl)-3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (167)



Step 1: 3-bromopentane-2,4-dione (1.0g, 5.65 mmol), ethanethiol (700 mg, 11.29 mmol), TEA (1.1g, 1.89 mmol) in EtOH (10 mL) under N₂ and the whole reaction mixture was stirred at 25°C for 1 hour. The mixture was concentrated in vacuo to give compound **167-01** (1.5 g) as a yellow oil and used into next step reaction without purification. MS (m/z) 161.2 [M+H]⁺.

Step 2: Compound **167-01** (1.5g, crude), N₂H₄·H₂O (5 mL) were in dioxane (10 mL) under N₂ and the whole reaction mixture was stirred at 80°C for 2 hours. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give compound **167-02** (100 mg) as a yellow oil. MS (m/z) 157.2 [M+H]⁺.

Step 3: Compound **167-02** (100 mg, 0.64 mmol), tert-butyl 3-((2-chloro-5-fluoropyridin-4-yl)oxy)azetidine-1-carboxylate (386 mg, 1.27 mmol), (1R,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (273 mg, 1.92 mmol), CuI (365 mg, 1.92 mmol) and K₃PO₄ (407 mg, 1.92 mmol) were

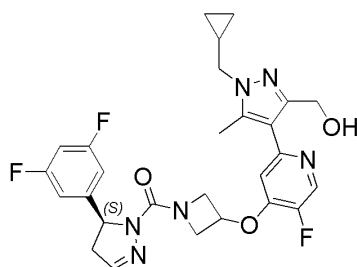
in DMF (10 mL) under N₂ and the whole reaction mixture was stirred at 150 °C for 2 hours. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give compound **167-03** (200 mg) as a yellow oil. MS (m/z) 423.5 [M+H]⁺.

Step 4: Compound **167-03** (200 mg, 0.47 mmol), m-CPBA (200 mg, 1.16 mmol) were in DCM (10 mL) under N₂ and the whole reaction mixture was stirred at 25 °C for 0.5 hours. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give compound **167-04** (300 mg, crude) as a yellow oil and used into next step reaction without purification. MS (m/z) 455.5 [M+H]⁺.

Step 5: Compound **167-04** (300 mg, crude), TFA (2 mL) were dissolved in DCM (5 mL) and stirred at 25 °C for 1 h. The mixture was concentrated in vacuo to give compound **167-05** (400 mg, crude) as a yellow oil and used into next step reaction without purification. MS (m/z): 355.4 [M+H]⁺.

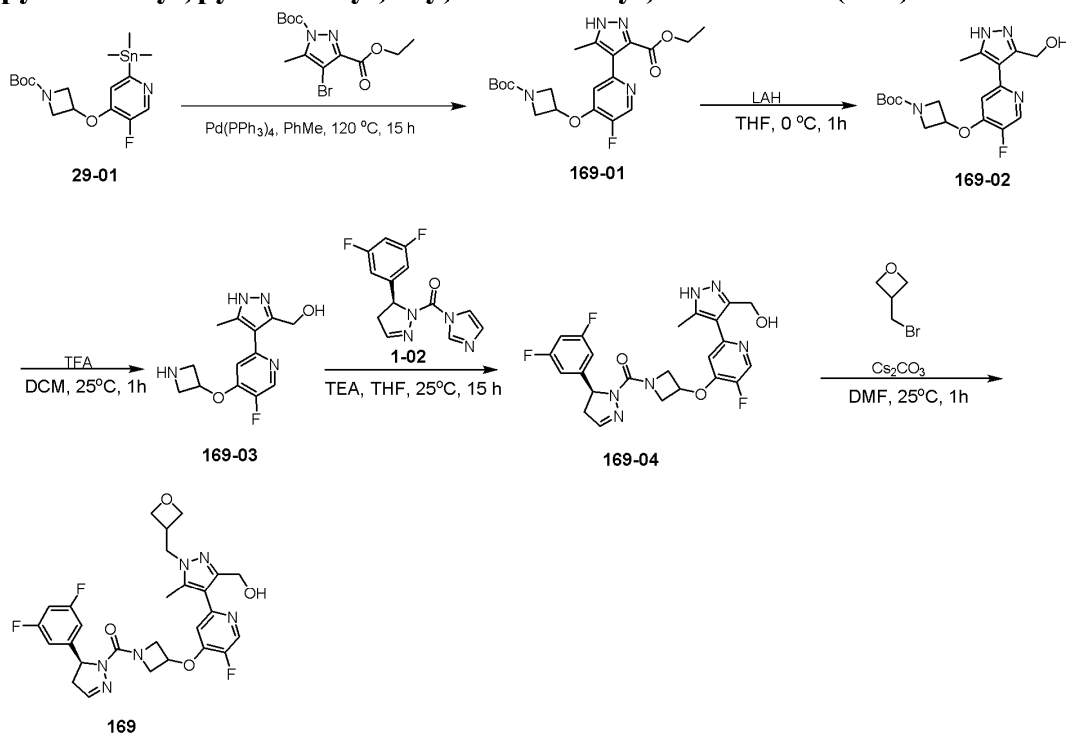
Step 6: Compound **167-05** (400 mg, crude), (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (80 mg, 0.28 mmol) and TEA (3 mL) were in THF (5 mL) under N₂ and the whole reaction mixture was stirred at 60 °C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give compound **167** (2.0 mg, 1.2%) as a grey solid. Mass (m/z): 563.5 [M+H]⁺.

(S)-(3-((2-(1-(cyclopropylmethyl)-3-(hydroxymethyl)-5-methyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (168)



The titled compound **168** was prepared from **169-04** in a yield of 2.0% according to the procedure outlined for compound **169**. Mass (m/z): 541.5 $[M+H]^+$. 1H NMR (300 MHz, $DMSO-d_6$) δ 8.50 (d, $J = 3.2$ Hz, 1H), 7.32 (d, $J = 7.2$ Hz, 1H), 7.10 (tt, $J = 9.6, 2.4$ Hz, 1H), 7.02 (d, $J = 1.6$ Hz, 1H), 6.96 – 6.86 (m, 2H), 5.23 (m, 2H), 4.59 – 4.50 (m, 2H), 4.48 – 4.41 (m, 2H), 4.11 – 4.05 (m, 2H), 3.94 (d, $J = 6.8$ Hz, 2H), 3.39 (dd, $J = 18.8, 12.0$ Hz, 1H), 2.74 – 2.54 (m, 1H), 2.47 (s, 3H), 1.30 – 1.23 (m, 1H), 0.56 – 0.45 (m, 2H), 0.42 – 0.32 (m, 2H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(hydroxymethyl)-5-methyl-1-(oxetan-3-ylmethyl)-1H-pyrazol-4-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (169)



Step 1: Compound **29-01** (7.0g, crude), 1-(tert-butyl) 3-ethyl 4-bromo-5-methyl-1H-pyrazole-1,3-dicarboxylate (5.0g, 15.06 mmol), Pd(PPh₃)₄ (1.70 g, 1.47 mmol) in PhMe (50 mL) under N₂ and the whole reaction mixture was stirred at 120 °C for 15 hours. The mixture was
5 extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **169-01** (1.0 g) as a yellow solid. MS (m/z): 421.4 [M+H]⁺.

Step 2: **169-01** (600 mg, 1.42 mmol), LAH (7.0 mL, 1 mol/L, 5.00 mmol), in THF (5 mL) under N₂ and the whole reaction mixture was
10 stirred at 0 °C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **169-02** (300 mg) as a yellow oil. MS (m/z): 379.4 [M+H]⁺.

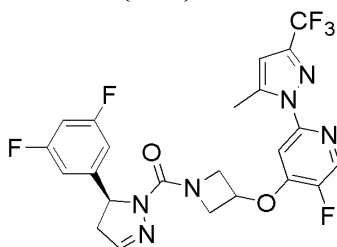
Step 3: **169-02** (300 mg, 0.79 mmol), TFA (3 mL), in DCM (6 mL)
15 under N₂ and the whole reaction mixture was stirred at 25 °C for 1 hour. The mixture was concentrated in vacuo and used into next step reaction without purification. MS (m/z): 279.4 [M+H]⁺.

Step 4: **169-03** (500 mg, crude), **1-02** (400 mg, 1.45 mmol) and TEA (1 mL) in THF (5 mL) under N₂ and the whole reaction mixture was stirred
20 at 25 °C for 15 hours. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **169-04** (200 mg) as a yellow oil. MS (m/z): 487.4 [M+H]⁺.

Step 5: **169-04** (70 mg, 0.14 mmol), Cs₂CO₃ (100 mg, 0.30 mmol) and
25 3-(bromomethyl)oxetane (50 mg, 0.33 mmol) were dissolved in DMF (5 mL) and stirred at 25 °C for 1 h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the **169** (1.7 mg, 2.0%) as a yellow oil. MS (m/z): 557.5 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 3.2 Hz, 1H), 7.16 – 7.07 (m, 2H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.94 – 6.87 (m, 2H), 5.75 (s, 1H), 5.29 – 5.20 (m, 2H), 4.77 (s, 2H), 4.73 – 4.31 (m,
30

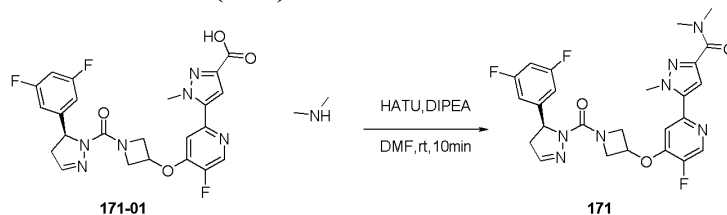
6H), 4.15 – 4.05 (m, 2H), 3.63 (d, $J = 5.6$ Hz, 2H), 3.49 – 3.33 (m, 2H), 2.74 – 2.60 (m, 1H), 2.56 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (170)



The titled compound **170** was prepared from **3-04** in a yield of 4.0% according to the procedure outlined for compound **102**. Mass (m/z): 525.4 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.51 (d, $J = 2.8$ Hz, 1H), 7.30 (d, $J = 6.0$ Hz, 1H), 7.10 (tt, $J = 9.6, 2.4$ Hz, 1H), 7.02 (d, $J = 1.6$ Hz, 1H), 6.96 – 6.86 (m, 2H), 6.81 (s, 1H), 5.35 (dd, $J = 6.4, 3.2$ Hz, 1H), 5.24 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.55 – 4.50 (m, 2H), 4.12 – 4.07 (m, 2H), 3.48 – 3.35 (m, 1H), 2.74 – 2.57 (m, 1H), 2.54 (d, $J = 0.8$ Hz, 3H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,N,1-trimethyl-1H-pyrazole-3-carboxamide (171)

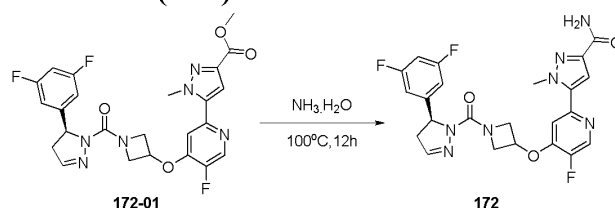


Compound **171-01** was prepared in a yield of 34.0% according to the procedure outlined for compound **2**.

Compound **171-01** (100 mg, 0.2 mmol), dimethylamine (16 mg, 0.40 mmol), DIPEA (100 mg), HATU (188 mg, 0.5 mmol) were dissolved in DMF (5 mL) and stirred at 25°C for 10 mins. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo.

Purification by prep-HPLC to give the titled compound **171** (20 mg, 19.0 %) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 2.7 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.86 – 6.68 (m, 4H), 5.30 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.13-5.05 (m, 1H), 4.72-4.54 (m, 3H), 4.46-4.25(m,2H), 4.21 (s, 3H), 3.43 (s, 3H), 3.41 – 3.32 (m, 1H), 3.15 (s, 3H), 2.73 (dd, *J* = 18.7, 6.5 Hz, 1H). Mass (m/z) 528.3 (M+H⁺).

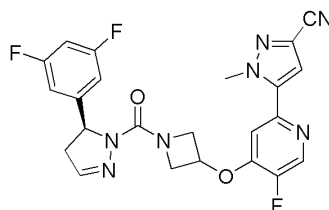
(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-3-carboxamide (172)



10

Compound **172-01** (200 mg, 0.4 mmol), NH₃ in MeOH (2 mL) stirred at 100°C for 12h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by prep-HPLC to give the titled compound **172** (34 mg, 16.9%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 2.7 Hz, 1H), 6.98 (s, 1H), 6.84 – 6.62 (m, 5H), 5.21 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.05 – 4.05 (m, 1H), 4.63 – 4.43 (m, 2H), 4.29 – 4.20 (m, 2H), 4.14 (s, 3H), 3.30 (dd, *J* = 18.6, 12.2 Hz, 1H), 2.65 (dd, *J* = 18.7, 6.3 Hz, 1H). Mass (m/z) 500.2 [M+H]⁺.

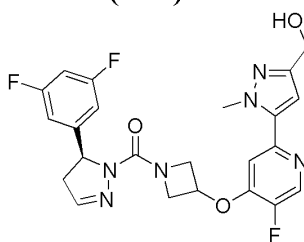
(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1-methyl-1H-pyrazole-3-carbonitrile (173)



The titled compound **173** was prepared from **3-04** in a yield of 16.2% according to the procedure outlined for compound **3**. ¹H NMR (400 MHz,

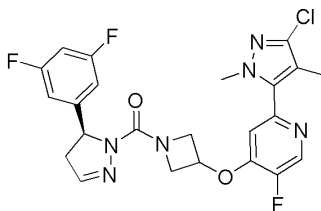
Chloroform-*d*) δ 8.46 (d, J = 2.8 Hz, 1H), 6.94 – 6.66 (m, 6H), 5.29 (dd, J = 12.0, 6.2 Hz, 1H), 5.11 (s, 1H), 4.68 – 4.56 (m, 2H), 4.32 (dd, J = 26.8, 10.6 Hz, 2H), 4.21 (d, J = 3.6 Hz, 3H), 3.45 – 3.33 (m, 1H), 2.72 (dd, J = 18.6, 6.4 Hz, 1H). Mass (m/z) 482.7 [M+H]⁺.

- 5 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (174)**



- The titled compound **174** was prepared from **3-04** in a yield of 10.2% according to the procedure outlined for compound **3**. ¹H NMR (301 MHz, Chloroform-*d*) δ 8.46 (d, J = 2.7 Hz, 1H), 6.99 – 6.47 (m, 6H), 5.28 (dd, J = 12.1, 6.3 Hz, 1H), 5.16-5.02 (m, 1H), 4.70-4.50 (m, 2H), 4.62 (s, 2H), 4.44 – 4.25 (m, 2H), 4.19 (s, 3H), 3.37 (dd, J = 18.8, 12.2 Hz, 1H), 2.72 (dd, J = 18.2, 6.3 Hz, 1H). Mass (m/z) 487.2 [M+H]⁺.

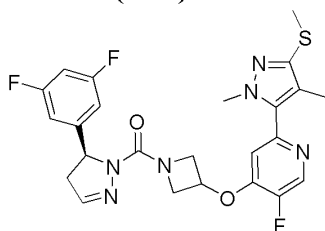
- 15 **(S)-(3-((2-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (175)**



- The titled compound **175** was prepared from **3-02** in a yield of 47.2% according to the procedure outlined for compound **101-02**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, J = 2.9 Hz, 1H), 6.80 (t, J = 1.7 Hz, 1H), 6.78 – 6.57 (m, 4H), 5.26 (dd, J = 12.1, 6.4 Hz, 1H), 5.06 (td, J = 6.4, 3.2 Hz, 1H), 4.58 (dt, J = 16.3, 8.6 Hz, 2H), 4.41 – 4.22 (m, 2H), 3.89 (s, 3H),

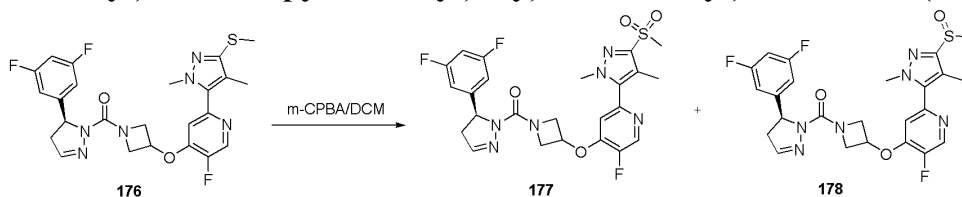
3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.8$ Hz, 1H), 2.05 (s, 3H). Mass (m/z): 505.2[M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-3-(methylthio)-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (176)



The titled compound **176** was prepared according to the procedure outlined for compound **163**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.52 (d, $J = 3.0$ Hz, 1H), 6.82 (d, $J = 1.7$ Hz, 1H), 6.79 – 6.64 (m, 4H), 5.31 – 5.25 (m, 1H), 5.07 (d, $J = 3.6$ Hz, 1H), 4.60 (s, 2H), 4.34 (dd, $J = 29.7, 10.6$ Hz, 2H), 3.92 (s, 3H), 3.43 – 3.31 (m, 1H), 2.76 – 2.70 (m, 1H), 2.47 (s, 3H), 2.08 (s, 3H). Mass (m/z): 517.2[M+H]⁺.

(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-3-(methylsulfonyl)-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (177) and **(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-3-(methylsulfinyl)-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (178)**



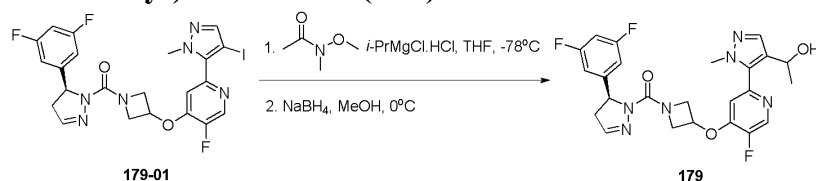
Compound **176** (20 mg, 0.04 mmol) and m-CPBA (3.3 mg, 0.02 mmol) were dissolved in DCM (2 mL). The mixture was stirred at r.t. for 90 min. Concentrated and purified by prep-TLC to give compound **177** (10 mg) and compound **178** (0.7 mg) as white solid.

compound **177**: ¹H NMR (301 MHz, Chloroform-*d*) δ 8.53 (d, $J = 3.0$ Hz, 1H), 8.07 (s, 1H), 7.97 (d, $J = 7.7$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H),

6.85 – 6.64 (m, 3H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.13-5.03 (m, 1H), 4.70-5.51 (m, 2H), 4.40 – 4.19 (m, 2H), 3.98 (s, 3H), 3.37 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 3.21 (s, 3H), 2.72 (ddd, $J = 18.8, 6.6, 1.8$ Hz, 1H), 2.32 (s, 3H). Mass (m/z): 548.3[M+H]⁺

5 compound **178**: Mass (m/z): 533.3[M+H]⁺

((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(1-hydroxyethyl)-1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (179)



10 To a solution of compound **179-01** (100 mg, 0.17 mmol) in THF (2 mL) was added isopropylmagnesium chloride lithium chloride complex solution (0.15 mL, 0.20 mmol) at 0 °C. The reaction mixture was stirred for 30 min before cooling to -78 °C and addition of N-methoxy-N-methylacetamide (53 mg, 0.51 mmol). The solution was stirred at -78 °C

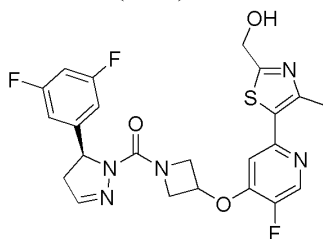
15 for 1 h before removing the cold bath and warming to ambient temperature. The solution was diluted with EtOAc and quenched via the addition of 1N HCl. The layers were separated and the aqueous was extracted with EtOAc. The combined organics layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was taken up in MeOH and

20 cooled to 0 °C before addition of NaBH₄ (19 mg, 0.51 mmol). The reaction was stirred while warming to ambient temperature and quenched when LCMS showed disappearance of starting material. This solution was then diluted with 1N HCl and EtOAc. The layers were separated and the aqueous was extracted with EtOAc. The combined organic layer was

25 washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by Pre-HPLC to give required product **179** (6 mg, 7%) as a white solid. Mass (m/z) 501.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, $J = 2.7$ Hz, 1H), 7.58 (s, 1H), 6.88 (d, $J = 6.3$ Hz,

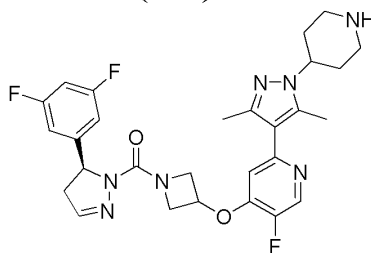
1H), 6.76 – 6.68 (m, 3H), 6.51 (s, 1H), 5.31 (d, $J = 5.2$ Hz, 1H), 5.19 – 5.04 (m, 1H), 4.63 (s, 2H), 4.45 – 4.26 (m, 2H), 4.19 (s, 3H), 3.98 (dt, $J = 27.4, 6.0$ Hz, 1H), 3.02 – 2.93 (m, 3H), 1.29 (dd, $J = 6.2, 4.2$ Hz, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(2-(hydroxymethyl)-4-methylthiazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (180)



The titled compound **180** was prepared from **3-04** in a yield of 28 % according to the procedure outlined for compound **2**. Mass (m/z) 504.2
 10 $[M+H]^+$. 1H NMR (300 MHz, Chloroform- d) δ 8.39 (d, $J = 2.8$ Hz, 1H), 7.01 – 6.55 (m, 5H), 5.27 (dd, $J = 12.1, 6.1$ Hz, 1H), 5.10 (s, 1H), 4.93 (s, 2H), 4.61 (s, 2H), 4.34 (d, $J = 27.3$ Hz, 2H), 3.37 (dd, $J = 18.4, 11.8$ Hz, 1H), 2.74 (d, $J = 5.9$ Hz, 1H), 2.66 (d, $J = 9.9$ Hz, 3H).

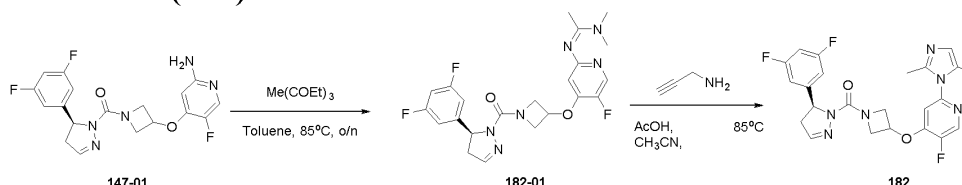
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1-(piperidin-4-yl)-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (181)



The titled compound **181** was prepared from **92** in a yield of 23.6% according to the procedure outlined for compound **86**. 1H NMR (400 MHz, Chloroform- d) δ 9.69 (s, 1H), 9.14 (s, 1H), 8.65 (s, 1H), 6.86 – 6.64 (m, 4H), 5.28 (dd, $J = 12.1, 6.3$ Hz, 1H), 5.14 (s, 1H), 4.98 (s, 1H), 4.63 (s, 2H), 4.37 (d, $J = 31.5$ Hz, 3H), 3.72 (s, 2H), 3.38 (dd, $J = 18.6, 12.2$ Hz,

1H), 3.21 (s, 2H), 2.73 (dd, $J = 18.7, 6.3$ Hz, 1H), 2.30 (d, $J = 31.0$ Hz, 8H). Mass (m/z) 554.4[M+H]⁺.

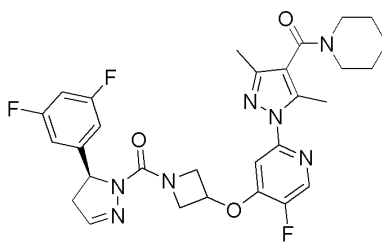
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(2,5-dimethyl-1H-imidazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (182).



Step 1: Compound **147-01** (100 mg, 0.26 mmol) and N,N-dimethylacetamide dimethylacetal (170 mg, 1.28 mmol) mixed in toluene, and the reaction mixture was heated to 85°C while stirring and was kept at this temperature overnight. The mixture was cooled to room temperature to give the desired product **182-01** in 90% purity. Mass (m/z) 461.4 [M+H]⁺.

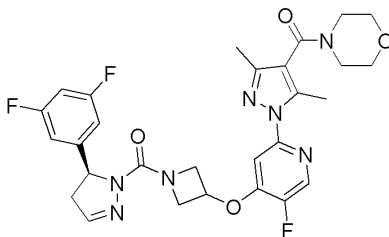
Step 2: Compound **182-01** (50 mg, 5.4 mmol) in 50 ml dry MeCN was added prop-2-yn-1-amine (8 mg, 0.15 mmol) and AcOH (20 mg, 0.33 mmol) to 0°C. The mixture reaction was stirred at 80°C for overnight and was cooled to room temperature. After the mixture was concentrated and further purified by prep-HPLC to give the final compound **182** (20 mg, 40%) as a white solid. Mass (m/z) 470.2 [M+H]⁺; ¹H NMR (301 MHz, CDCl₃) δ 8.41 (d, $J = 2.0$ Hz, 1H), 7.07 (d, $J = 19.1$ Hz, 2H), 6.85 – 6.58 (m, 4H), 5.34 – 5.02 (m, 2H), 4.64 (s, 2H), 4.30 (s, 2H), 3.35 (dd, $J = 18.4, 12.0$ Hz, 1H), 2.69 (dd, $J = 18.5, 5.3$ Hz, 1H), 2.53 (s, 3H), 2.07 (d, $J = 32.8$ Hz, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-(piperidine-1-carbonyl)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (183)



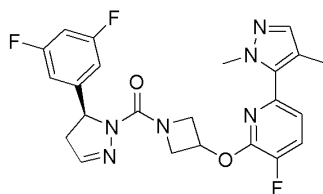
The titled compound **183** was prepared from **110-02** in a yield of 14.8 % according to the procedure outlined for compound **68**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.12 (s, 1H), 6.76 - 6.57 (dd, *J* = 23.8, 17.0 Hz, 4H), 5.21 (dd, *J* = 12.0, 6.3 Hz, 1H), 5.014-5.02 (m, 1H), 4.64-4.50 (m, 2H), 4.25 (dd, *J* = 29.1, 9.9 Hz, 2H), 3.75-3.54 (m, 2H), 3.39-3.20 (m, 3H), 2.64 (dd, *J* = 18.6, 6.2 Hz, 1H), 2.51 (s, 3H), 2.21 (s, 3H), 1.56 (s, 6H). Mass (m/z) 582.3 [M+H]⁺.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((2-(3,5-dimethyl-4-(morpholine-4-carbonyl)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (184)



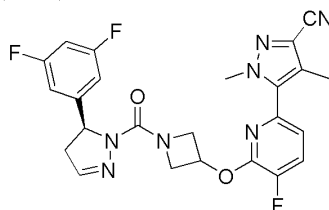
The titled compound **184** was prepared from **110-02** in a yield of 14.9% according to the procedure outlined for compound **68**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.22 (d, *J* = 6.1 Hz, 1H), 6.85 – 6.69 (m, 4H), 5.30 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.18 (s, 1H), 4.65 (s, 2H), 4.34 (dd, *J* = 31.0, 10.5 Hz, 2H), 3.62 (d, *J* = 94.6 Hz, 8H), 3.38 (dd, *J* = 18.5, 12.2 Hz, 1H), 2.73 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.61 (s, 3H), 2.32 (s, 3H). Mass (m/z) 584.3 [M+H]⁺.

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((6-(1,4-dimethyl-1H-pyrazol-5-yl)-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)methanone (185)



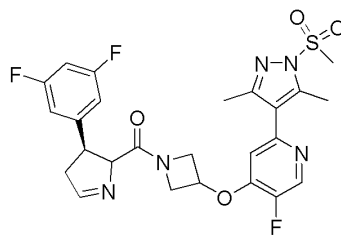
The titled compound **185** was prepared from **1-04** in a yield of 47% according to the procedure outlined for compound **2**. Mass (m/z): 471.3[M+H]⁺. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.52-7.42 (m, 1H), 7.37 (s, 1H), 7.01 (dd, *J* = 8.1, 2.9 Hz, 1H), 6.85 – 6.73 (m, 3H), 6.68 (tt, *J* = 8.8, 2.4 Hz, 1H), 5.49-5.36 (m, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.69-4.45 (m, 1H), 4.40-4.21 (m, 2H), 3.96 (s, 3H), 3.34 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.12 (s, 3H).

(S)-5-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-3-carbonitrile (186)



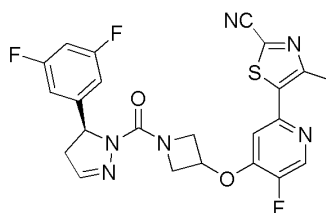
The titled compound **186** was prepared in a yield of 51% according to the procedure outlined for compound **150**. Mass (m/z): 496.3[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 9.4, 8.0 Hz, 1H), 7.02 (dd, *J* = 8.0, 2.8 Hz, 1H), 6.81 – 6.72 (m, 3H), 6.69 (tt, *J* = 8.8, 2.2 Hz, 1H), 5.44-5.35 (m, 1H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.68 – 4.49 (m, 2H), 4.38-4.21 (m, 2H), 3.99 (s, 3H), 3.42-3.29 (m, 1H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 2.23 (s, 3H).

(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1-(methylsulfonyl)-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (187)



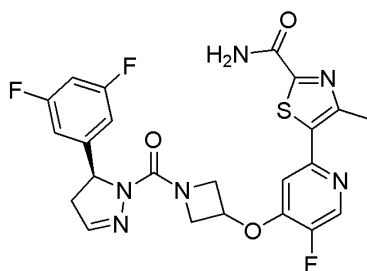
The titled compound **187** was prepared from compound **92** in a yield of 33.2% according to the procedure outlined for compound **86**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, J = 3.0 Hz, 1H), 6.80 (d, J = 1.7 Hz, 1H), 6.78 – 6.65 (m, 3H), 6.60 (d, J = 6.5 Hz, 1H), 5.27 (dd, J = 12.2, 6.4 Hz, 1H), 5.07 (tt, J = 6.7, 4.0 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.40 – 4.25 (m, 2H), 3.41 – 3.34 (m, 1H), 3.33 (s, 3H), 2.73 – 2.67 (m, 1H), 2.56 (s, 3H), 2.32 (s, 3H). Mass (m/z) 549.3 [$M+H$] $^+$.

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-4-methylthiazole-2-carbonitrile (188)



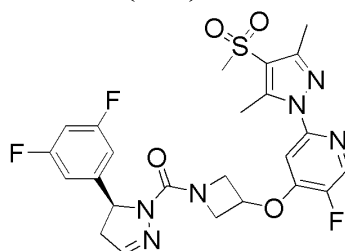
The titled compound **188** was prepared from compound **3-02** in a yield of 11% according to the procedure outlined for compound **48**. Mass (m/z) 499.1 [$M+H$] $^+$. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.42 (d, J = 2.9 Hz, 1H), 6.96 (d, J = 6.2 Hz, 1H), 6.88 – 6.63 (m, 4H), 5.28 (dd, J = 12.1, 6.4 Hz, 1H), 5.12 (s, 1H), 4.62 (d, J = 8.5 Hz, 2H), 4.35 (dd, J = 27.0, 10.6 Hz, 2H), 3.38 (dd, J = 18.7, 12.2 Hz, 1H), 2.77-2.68 (m, 4H).

(S)-5-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-4-methylthiazole-2-carboxamide (189)



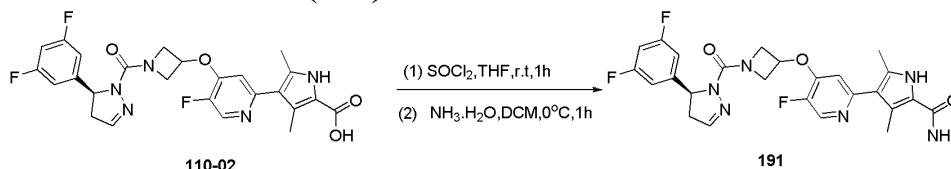
The titled compound **189** was prepared from compound **188** in a yield of 7.9% according to the procedure outlined for compound **66**. Mass (m/z) 517.2 $[M+H]^+$. 1H NMR (300 MHz, Chloroform- d) δ 8.43 (d, $J = 2.9$ Hz, 1H), 7.14 (s, 1H), 6.88 (d, $J = 6.3$ Hz, 1H), 6.84 – 6.64 (m, 4H), 5.77 (s, 1H), 5.28 (dd, $J = 12.1, 6.3$ Hz, 1H), 5.10 (s, 1H), 4.72 – 4.50 (m, 2H), 4.46 – 4.22 (m, 2H), 3.37 (dd, $J = 18.6, 12.1$ Hz, 1H), 2.79 – 2.69 (m, 1H), 2.66 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-(methylsulfonyl)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (190)



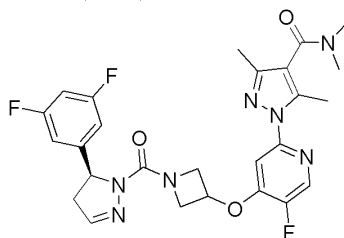
The titled compound **190** was prepared from compound **3-02** in a yield of 5.0% according to the procedure outlined for compound **167**. Mass (m/z): 549.5 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.16 (d, $J = 2.4$ Hz, 1H), 7.09 (d, $J = 6.0$ Hz, 1H), 6.73 (t, $J = 1.6$ Hz, 1H), 6.71 – 6.75 (m, 2H), 6.63 (tt, $J = 8.8, 2.4$ Hz, 1H), 5.21 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.08 (ddd, $J = 10.4, 6.4, 4.0$ Hz, 1H), 4.60 – 4.55 (m, 2H), 4.29 – 4.23 (m, 2H), 3.30 (ddd, $J = 18.4, 12.0, 1.6$ Hz, 1H), 3.01 (s, 3H), 2.78 (s, 3H), 2.64 (ddd, $J = 18.4, 6.4, 1.6$ Hz, 1H), 2.43 (s, 3H).

(S)-4-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrrole-2-carboxamide (191)



Compound **110-02** (50 mg, 0.097 mmol) was dissolved in 2 mL THF. 0.1 mL SOCl₂ was added. Let it stir at r.t for 1h. The solvent was evaporated to dryness. It was used for next step without further purification. The above residue was dissolved in 2 mL DCM. It was added dropwise to the solution of ammonia solution (0.5 ml) in 2 mL DCM at 0°C. Let it stir at 0°C for 30 min. The organic layer was separated and evaporated to dryness and purified by prep-TLC (PE/EA = 1/3) to give compound **191** (5 mg, 10%) as white solid. Mass (m/z) 513.4 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.85 (brs, 1H), 8.71 (s, 1H), 6.81 (s, 1H), 6.77-6.70 (m, 2H), 6.69-6.60 (m, 2H), 6.00 (brs, 2H), 5.27 (dd, *J* = 11.6, 6.4 Hz, 1H), 5.17-5.10 (m, 1H), 4.68-4.53 (m, 2H), 4.45-4.26 (m, 2H), 3.37 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.72 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H), 2.29 (s, 6H).

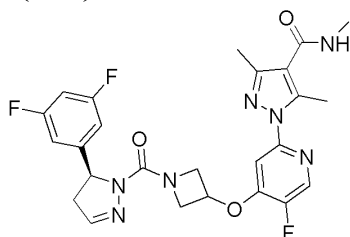
(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,N,3,5-tetramethyl-1H-pyrazole-4-carboxamide (192)



The titled compound **192** was prepared from compound **191** in a yield of 16.4% according to the procedure outlined for compound **68**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 2.5 Hz, 1H), 7.21 (d, *J* = 6.1 Hz,

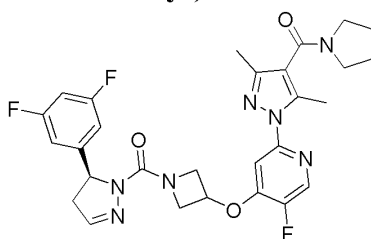
1H), 6.82 (t, $J = 1.7$ Hz, 1H), 6.78 (dt, $J = 6.5, 2.2$ Hz, 2H), 6.72 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.30 (dd, $J = 12.2, 6.5$ Hz, 1H), 5.17 (td, $J = 6.5, 3.2$ Hz, 1H), 4.71 – 4.58 (m, 2H), 4.34 (dd, $J = 30.3, 10.4$ Hz, 2H), 3.38 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 3.14 (s, 3H), 3.04 (s, 3H), 2.73 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.59 (s, 3H), 2.31 (s, 3H). Mass (m/z) 542.3 $[M+H]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,3,5-trimethyl-1H-pyrazole-4-carboxamide (193)



The titled compound **193** was prepared from compound **191** in a yield of 15.2% according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform- d) δ 8.22 (s, 1H), 7.20 (s, 1H), 6.82 – 6.67 (m, 4H), 5.61 (s, 1H), 5.30 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.19 (s, 1H), 4.65 (s, 2H), 4.35 (d, $J = 32.9$ Hz, 2H), 3.38 (dd, $J = 18.0, 12.4$ Hz, 1H), 3.02 (d, $J = 3.7$ Hz, 3H), 2.79 (s, 2H), 2.73 (dd, $J = 17.9, 6.5$ Hz, 1H), 2.47 (s, 3H). Mass (m/z) 528.3 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-(pyrrolidine-1-carbonyl)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (194)

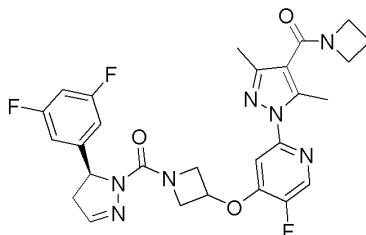


20

The titled compound **194** was prepared from compound **191** in a yield of 21.2 % according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform- d) δ 8.18 (s, 1H), 7.21 (s, 1H), 6.82 (s, 1H), 6.79 –

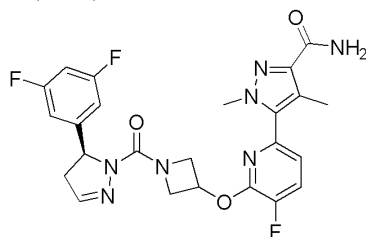
6.64 (m, 3H), 5.27 (s, 1H), 5.18 (s, 1H), 4.67 (s, 2H), 3.67 (s, 2H), 3.35 (d, $J = 18.6$ Hz, 3H), 2.78 – 2.67 (m, 2H), 2.57 (s, 4H), 2.32 (s, 3H), 1.97 (d, $J = 26.7$ Hz, 4H). Mass (m/z) 568.1 $[M+H]^+$.

(S)-azetidin-1-yl(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)methanone (195)



The titled compound **195** was prepared from compound **191** in a yield of 2.9% according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, $J = 2.4$ Hz, 1H), 7.13 (d, $J = 6.3$ Hz, 1H), 6.74 – 6.60 (m, 4H), 5.21 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.13 – 5.03 (m, 1H), 4.65 – 4.48 (m, 2H), 4.25 (dd, $J = 29.0, 10.2$ Hz, 2H), 3.60 (t, $J = 6.8$ Hz, 2H), 3.37 – 3.26 (m, 3H), 2.64 (dd, $J = 18.8, 6.5$ Hz, 2H), 2.51 (s, 3H), 2.24 (s, 3H), 1.97 – 1.84 (m, 2H). Mass (m/z) 554.3 $[M+H]^+$.

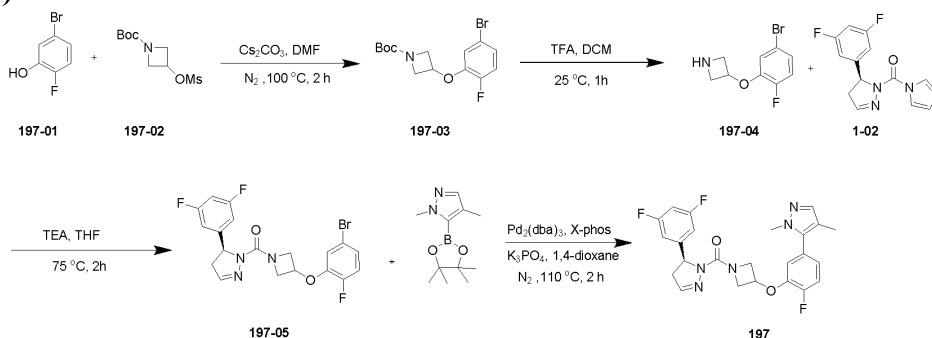
(S)-5-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-3-carboxamide (196)



The titled compound **196** was prepared from compound **186** in a yield of 46% according to the procedure outlined for compound **66**. Mass (m/z): 514.3 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.50 (dd, $J = 9.5, 8.0$ Hz, 1H), 7.02 (dd, $J = 8.0, 2.9$ Hz, 1H), 6.86 (s, 1H), 6.80 – 6.72 (m, 3H),

6.68 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.73 (s, 1H), 5.45-5.37 (m, 1H), 5.27 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.66-4.48 (m, 2H), 4.39-4.22 (m, 2H), 3.92 (s, 3H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.36 (s, 3H).

5 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(5-(1,4-dimethyl-1H-pyrazol-5-yl)-2-fluorophenoxy)azetidin-1-yl)methanone (197)**



Step 1: Compound **197-01** (955 mg, 5.0 mmol), compound **197-02** (1320 mg, 5.25 mmol), Cs_2CO_3 (2445 mg, 7.5 mmol), in DMF (20 mL) under N_2 and the whole reaction mixture was stirred at 100 °C for 2 hours. After the mixture was concentrated and further purification by silica gel chromatography to give compound **197-03** (1.43 g, 82.5%) as a white solid.

Mass (m/z) 290.1 $[\text{M}+\text{H}-56]^+$.

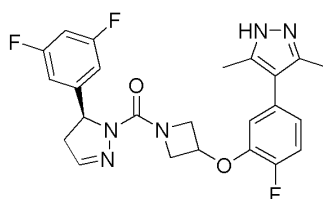
15 **Step 2:** Compound **197-03** (710 mg, 2.05 mmol) was dissolved in 10 mL of DCM, trifluoroacetic acid (2337 mg, 20.5 mmol) was added, the mixture was stirred at 25 °C for 1 hour. Concentrated to give the desired product compound **197-04**, which was used for next step without further purification.

20 **Step 3:** Compound **197-04**, compound **1-05** (510 mg, 1.845 mmol) and TEA (5 mL) were dissolved in THF (10 mL) and stirred at 75 °C for 2 h. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give compound **197-05** (720 mg, 86.1%) as a yellow solid. Mass (m/z) 454.0 $[\text{M}+\text{H}]^+$.

25

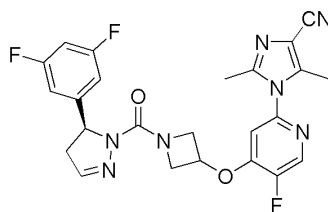
Step 4: Compound **197-05** (91 mg, 0.2 mmol), 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (54 mg, 0.24 mmol), Pd₂(dba)₃ (19 mg, 0.02 mmol), X-phos (19 mg, 0.04 mmol) was added to a solution of K₃PO₄ (5N, 0.2 mL, 1.0 mmol) in 1,4-dioxane (2 mL) under N₂ and the whole reaction mixture was stirred at 110°C for 2 hours. After the mixture was concentrated and further purification by prep-HPLC to give compound **197** (39 mg, 41.5 %) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 (s, 1H), 7.21 (dd, *J* = 11.0, 8.3 Hz, 1H), 6.89 (ddd, *J* = 8.3, 4.3, 2.0 Hz, 1H), 6.80 – 6.73 (m, 3H), 6.69 (tt, *J* = 8.9, 2.4 Hz, 1H), 6.62 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.97 (td, *J* = 6.3, 3.2 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 2H), 4.30 (dd, *J* = 26.0, 9.8 Hz, 2H), 3.74 (s, 3H), 3.35 (ddd, *J* = 18.6, 12.2, 1.8 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.98 (s, 3H). Mass (m/z) 470.3 [M+H]⁺.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-fluorophenoxy)azetidin-1-yl)methanone (198)



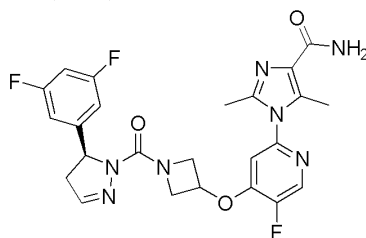
The titled compound **198** was prepared from compound **197-05** in a yield of 35.1 % according to the procedure outlined for compound **197**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 (dd, *J* = 11.2, 8.4 Hz, 1H), 6.85 – 6.64 (m, 5H), 6.58 (dd, *J* = 8.0, 2.1 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.97 (td, *J* = 6.4, 3.2 Hz, 1H), 4.60 – 4.47 (m, 2H), 4.31 (dd, *J* = 31.5, 10.1 Hz, 2H), 3.38 – 3.29 (m, 1H), 2.69 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.26 (s, 6H). Mass (m/z) 470.3 [M+H]⁺.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-2,5-dimethyl-1H-imidazole-4-carbonitrile (199).



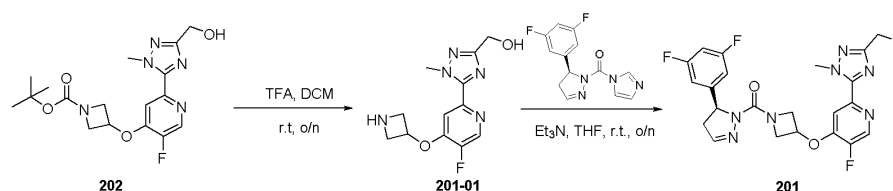
The titled compound **199** was prepared from compound **182** in a yield of 16% according to the procedure outlined for compound **150**. Mass (m/z) 496.4 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, $J = 2.6$ Hz, 1H), 6.75 (s, 1H), 6.71 – 6.53 (m, 4H), 5.20 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.04 (s, 1H), 4.56 (s, 2H), 4.31 – 4.15 (m, 2H), 3.30 (dd, $J = 18.7, 12.3$ Hz, 1H), 2.65 (dd, $J = 18.7, 6.4$ Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-2,5-dimethyl-1H-imidazole-4-carboxamide (200)



The titled compound **200** was prepared from compound **199** in a yield of 62% according to the procedure outlined for compound **66**. Mass (m/z) 514.4 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, $J = 2.7$ Hz, 1H), 6.92 (brs, 1H), 6.74 (t, $J = 1.6$ Hz, 1H), 6.70 – 6.58 (m, 3H), 6.47 (d, $J = 5.9$ Hz, 1H), 5.23 – 5.16 (m, 1H), 5.03 – 4.96 (m, 1H), 4.61 – 4.42 (m, 2H), 4.25 (dd, $J = 16.9, 10.6$ Hz, 2H), 3.30 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.65 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H), 2.35 (s, 3H), 2.18 (s, 3H).

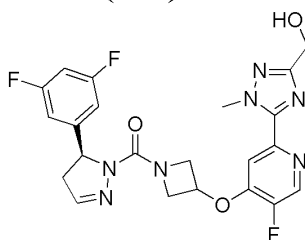
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(fluoromethyl)-1-methyl-1H-1,2,4-triazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (201)



Step 1: TFA (1 mL) was added to a solution of compound **202** (100 mg, 0.26 mmol) in DCM (3 mL). The reaction mixture was stirred at room temperature for 0.5hr. Then the solvent was evaporated in vacuo to give compound **201** as a colorless oil. Mass (m/z) 280.1 [M+H]⁺.

Step 2: Compound **201-01** was added to a solution of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (87 mg, 0.31 mmol) and TEA (80 mg, 0.79 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature overnight. Then the solvent was evaporated in vacuo. The oil residue was purified by prep-HPLC to give compound **201** (20 mg, 15%) as a white solid. Mass (m/z) 490.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 2.3 Hz, 1H), 7.57 (d, *J* = 6.7 Hz, 1H), 6.76 – 6.57 (m, 4H), 5.44 (s, 1H), 5.32 (s, 1H), 5.21 (dd, *J* = 12.2, 6.3 Hz, 1H), 5.10 (td, *J* = 6.4, 3.3 Hz, 1H), 4.60 (s, 2H), 4.27 (d, *J* = 0.7 Hz, 3H), 4.22 (d, *J* = 11.0 Hz, 2H), 3.29 (ddd, *J* = 18.6, 12.2, 1.6 Hz, 1H), 2.64 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (202)

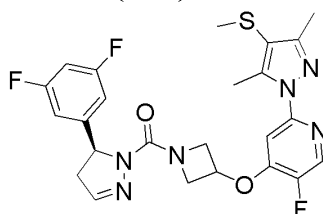


20

The titled compound **202** was prepared from compound **3-02** in a yield of 24.7% according to the procedure outlined for compound **30**. Mass (m/z) 488.1 [M+H]⁺. ¹H NMR (301 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 2.6 Hz, 1H), 7.59 (d, *J* = 6.7 Hz, 1H), 6.83 – 6.64 (m, 4H), 5.27 (dd, *J* = 12.2,

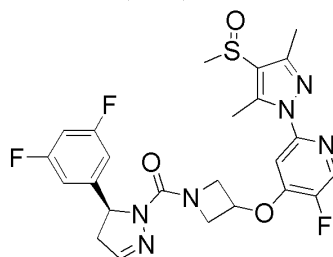
6.4 Hz, 1H), 5.16 (d, $J = 4.4$ Hz, 1H), 4.78 (s, 2H), 4.66 (s, 2H), 4.30 (s, 5H), 3.45 – 3.27 (m, 1H), 2.79 – 2.62 (m, 1H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-(methylthio)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (203)



The titled compound **203** was prepared from compound **3-02** in a yield of 32.0% according to the procedure outlined for compound **167**. Mass (m/z) 517.5 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.19 – 8.13 (m, 1H), 7.21 (d, $J = 6.0$ Hz, 1H), 6.79 (t, $J = 1.6$ Hz, 1H), 6.77 – 6.73 (m, 2H), 6.70 (tt, $J = 8.8, 2.4$ Hz, 1H), 5.28 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.15 (td, $J = 6.4, 3.2$ Hz, 1H), 4.68 – 4.57 (m, 2H), 4.39 – 4.24 (m, 2H), 3.36 (ddd, $J = 18.4, 12.0, 1.6$ Hz, 1H), 2.75 – 2.70 (m, 1H), 2.69 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H).

((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-4-(methylsulfinyl)-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (204)

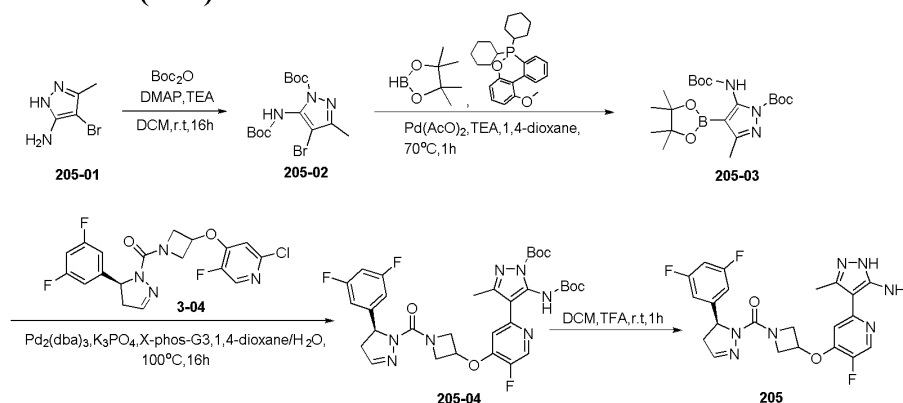


The titled compound **204** was prepared from compound **203** in a yield of 32.0% according to the procedure outlined for compound **167**. Mass (m/z) 533.5 $[M+H]^+$.

1H NMR (400 MHz, Chloroform- d) δ 8.19 (d, $J = 2.4$ Hz, 1H), 7.19 (d, $J = 6.0$ Hz, 1H), 6.80 (t, $J = 1.6$ Hz, 1H), 6.78 – 6.73 (m, 2H), 6.73 – 6.67

(m, 1H), 5.28 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.15 (ddd, $J = 10.4, 6.4, 4.0$ Hz, 1H), 4.70 – 4.57 (m, 2H), 4.41 – 4.24 (m, 2H), 3.41 – 3.31 (m, 1H), 2.93 (s, 3H), 2.75 (s, 3H), 2.73 – 2.65 (m, 1H), 2.52 (s, 3H).

(S)-((3-((2-(5-amino-3-methyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (205)



Step 1: Compound **205-01** (1 g, 5.68 mmol), Boc_2O (4.96 g, 22.75 mmol), DMAP (0.139 g, 1.14 mmol) and TEA (2 ml) were dissolved in 15 mL DCM. Let it stir at room temperature for 16h. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 3/1) to give compound **205-02** (430 mg, 20.1%) as a white solid. Mass (m/z) 377.3 $[\text{M}+\text{H}]^+$.

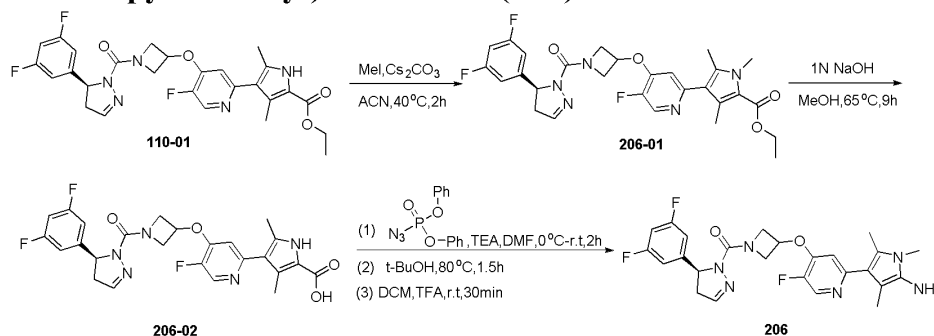
Step 2: Compound **205-02** (430 mg, 1.144 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphane (55.7 mg, 0.136 mmol), $\text{Pd}(\text{AcO})_2$ (15.2 mg, 0.068 mmol) were mixed in 8 mL 1,4-dioxane. TEA (411 mg, 4.07 mmol) was added. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (694 mg, 5.42 mmol) was added slowly to the reaction. Let it stir at 70°C for 1h. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 3.5/1) to give compound **205-03** (210 mg, 43.5%) as light-yellow oil. Mass (m/z) 424.3 $[\text{M}+\text{H}]^+$.

Step 3: Compound **205-03** (190 mg, 0.463 mmol), tert-butyl 5-((tert-butoxycarbonyl)amino)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (210 mg, 0.506 mmol), X-Phos-G₃ (39 mg, 0.043 mmol), Pd₂(dba)₃ (39 mg, 0.043 mmol), K₃PO₄ (982 mg, 4.63 mmol) were mixed in 8 mL 1,4-dioxane/H₂O (v/v = 4/1). The mixture was stirred at 100 °C for 16 h under N₂. The solvent was
 5 evaporated to dryness and purified by prep-TLC (PE/EA = 1/3) to give compound **205-04** (40 mg, 12.9%) as light-yellow solid. Mass (m/z) 673.4 [M+H]⁺.

Step 4: Compound **205-04** (40 mg, 0.06 mmol) was dissolved in 2 mL DCM, 2 mL DCM/TFA(1/1) was added. Let it stir at r.t for 1h. The solvent
 10 was evaporated to dryness and purified by prep-TLC (DCM/MeOH = 12/1) to give compound **205** (9.8 mg, 34.6%) as light-yellow oil. Mass (m/z) 473.4 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 2.8 Hz, 1H), 6.80 (t, *J* = 1.6 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.73 – 6.65 (m, 1H), 6.64 (d, *J* = 6.4 Hz, 1H), 5.27 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.11 – 5.01 (m, 1H), 4.65
 15 – 4.51 (m, 2H), 4.42 – 4.33 (m, 1H), 4.30 – 4.23 (m, 1H), 3.36 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.71 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H), 2.49 (s, 3H).

(S)-(3-((2-(5-amino-1,2,4-trimethyl-1H-pyrrol-3-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (206)



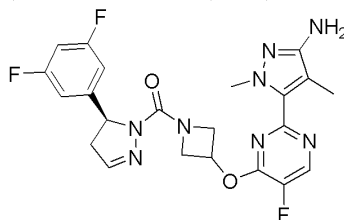
20

Step 1: Compound **110-01** (260 mg, 0.48 mmol) and Cs₂CO₃ (623.6 mg, 1.92 mmol) were mixed in 8 mL CAN. MeI (170.3 mg, 1.2 mmol) was added. Let it stir at 40 °C for 2h. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 1/3) to give compound **206-01** (190 mg, 71.2%) as light-yellow oil. Mass (m/z) 556.4 [M+H]⁺.
 25

Step 2: Compound **206-01** (190 mg, 0.34 mmol) was dissolved in 5 mL MeOH. 2 mL THF was added. 4 mL 1N NaOH was added. Let it stir at 65°C for 9h. The solvent was evaporated to dryness and acidified with 1N HCl to PH=6. It was extracted with EA (15 ml X 3). The organic layer was
5 evaporated to dryness and purified by column chromatography (PE/EA = 1/3) to give compound **206-02** (60 mg, 34.2%). Mass (m/z) 514.3 [M+H]⁺.

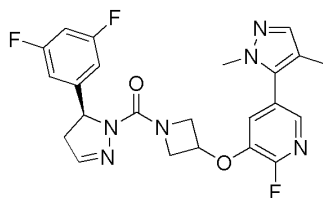
Step 3: Compound **206-02** (60 mg, 0.114 mmol) and TEA (11.5 mg, 0.114 mmol) were dissolved in 1 mL DMF. Diphenyl phosphorazidate (282.2 mg, 0.102 mmol) was added to the mixture at 0°C. Let it stir at r.t.
10 under dark for 2h. Then it was added to 2 mL t-BuOH solution. Let it stir at 80°C for 1.5h. The solvent was evaporated to dryness and water was added. It was extracted with EA (15 ml X 3). The organic layer was evaporated to dryness and purified by column chromatography (PE/EA = 1/3) to give 5 mg tert-butyl (S)-(4-(4-((1-(5-(3,5-difluorophenyl)-4,5-
15 dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,3,5-trimethyl-1H-pyrrol-2-yl)carbamate as light-yellow solid. Yield: 8.2%. Mass (m/z) 599.4 [M+H]⁺. The above residue was dissolved in 2 mL DCM. It was added dropwise to the solution of ammonia solution (0.5 ml) in 2 mL DCM at 0°C. Let it stir at 0°C for 30 min. The organic layer was
20 separated and evaporated to dryness and purified by prep-TLC (DCM/MeOH = 8/1) to give compound **206** (2 mg, 48%) as white solid. Mass (m/z) 499.4 [M+H]⁺.

**(S)-(3-((2-(3-amino-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-
25 dihydro-1H-pyrazol-1-yl)methanone (207)**



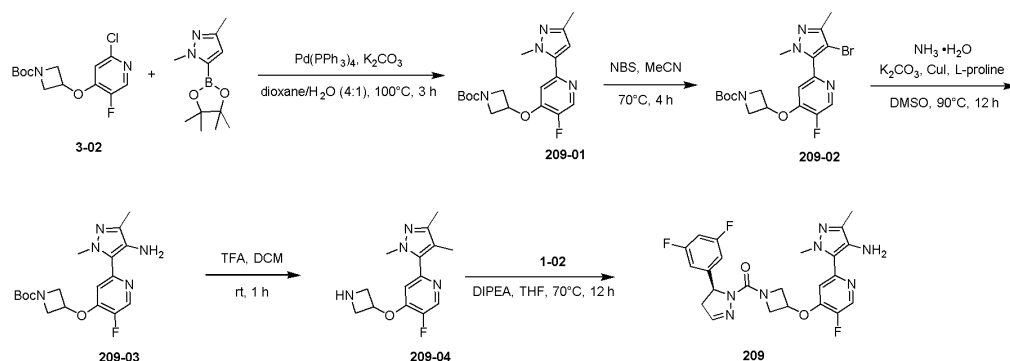
The titled compound **207** was prepared in a yield of 44% according to the procedure outlined for compound **1-03**. Mass (m/z) 487.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, *J* = 2.2 Hz, 1H), 6.78 – 6.56 (m, 4H), 5.69 (brs, 2H), 5.43 (ddd, *J* = 10.5, 6.6, 4.0 Hz, 1H), 5.21 (dd, *J* = 12.1, 6.3 Hz, 1H), 4.62 – 4.46 (m, 2H), 4.27 (dd, *J* = 28.6, 7.7 Hz, 2H), 3.98 (s, 3H), 3.30 (ddd, *J* = 18.6, 12.2, 1.5 Hz, 1H), 2.65 (ddd, *J* = 18.7, 6.3, 1.6 Hz, 1H), 2.09 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-(1,4-dimethyl-1H-pyrazol-5-yl)-2-fluoropyridin-3-yl)oxy)azetidin-1-yl)methanone (**208**)



The titled compound **208** was prepared in 26.1% yield according to the procedure outlined for compound **197**. ¹H NMR (301 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.44 (s, 1H), 6.97 (d, *J* = 9.3 Hz, 1H), 6.85 – 6.61 (m, 4H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 5.01 (s, 1H), 4.57 (d, *J* = 10.5 Hz, 2H), 4.32 (dt, *J* = 21.5, 6.6 Hz, 2H), 3.80 (s, 3H), 3.37 (ddd, *J* = 18.6, 12.1, 1.6 Hz, 1H), 2.71 (ddd, *J* = 18.7, 6.5, 1.7 Hz, 1H), 2.02 (s, 3H). Mass (m/z) 471.3 [M+H]⁺.

(S)-(3-((2-(4-amino-1,3-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (**209**)



Step 1: To a solution of compound **3-02** (1 g, 3.3 mmol) in dioxane/H₂O (4:1, 50 mL) was added 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (807 mg, 3.63 mmol), Pd(PPh₃)₄ (573 mg, 495.5 μmol) and K₂CO₃ (1.37 g, 9.91 mmol) under Ar. The reaction mixture was stirred at 100°C for 3 h. The crude mixture was purified by column chromatography on silica gel to give compound **209-01** (0.9 g, 75%) as a white solid. Mass (m/z) 363.3 [M+H]⁺.

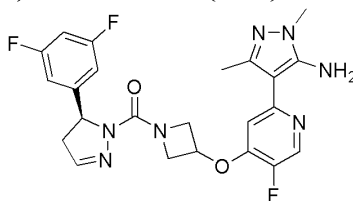
Step 2: To a solution of compound **209-01** (900 mg, 2.48 mmol) in MeCN (50 mL) was added NBS (884 mg, 4.97 mmol). The reaction mixture was stirred at 70°C for 4 h. The crude mixture was purified by column chromatography on silica gel to give compound **209-02** (1 g, 91%) as a white solid. Mass (m/z) 442.2 [M+H]⁺.

Step 3: To a solution of compound **209-02** (1 g, 2.27 mmol) in DMSO (20 mL) was added NH₃·H₂O (950 mg, 6.8 mmol), K₂CO₃ (375 mg, 2.72 mmol), CuI (648 mg, 3.4 mmol) and L-proline (392 mg, 3.4 mmol) under Ar. The reaction mixture was stirred at 90°C for 12 h. The crude mixture was purified by column chromatography on silica gel to give compound **209-03** (180 mg, 21%) as a light-yellow solid. Mass (m/z) 378.1 [M+H]⁺.

Step 4: To a solution of compound (120 mg, 317.95 μmol) in DCM (2 mL) was added TFA (2 mL). The reaction mixture was stirred at rt for 1 h. The solvent was concentrated under vacuum. The crude compound **209-04** was used to next step directly MS (m/z) 278.1 [M+H]⁺.

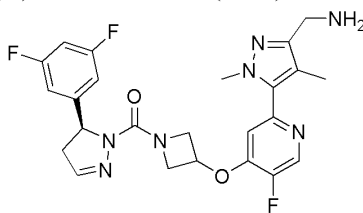
Step 5: To a solution of compound **209-04** (40 mg, 144.8 μmol) in THF (5 mL) was added compound **1-02** (44 mg, 159.3 μmol) and DIPEA (95 mg, 724 μmol). The reaction mixture was stirred at 70°C for 12 h. The crude mixture was purified by Pre-HPLC to give compound **209** (14 mg, 21%) as a white solid. Mass (m/z) 485.1 $[\text{M}+\text{H}]^+$.

(S)-(3-((2-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (210)



The titled compound **210** was prepared as white solid in 41.4% yield from compound **3-04** according to the procedure outlined for compound **3**. Mass (m/z) 486.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 2.8$ Hz, 1H), 6.80 (t, $J = 1.6$ Hz, 1H), 6.79 – 6.64 (m, 4H), 5.27 (dd, $J = 12.0$, 6.4 Hz, 1H), 5.11 – 5.01 (m, 1H), 4.65 – 4.51 (m, 2H), 4.42 – 4.33 (m, 1H), 4.30 – 4.23 (m, 1H), 3.80 (s, 3H), 3.36 (ddd, $J = 18.4$, 12.0, 1.6 Hz, 1H), 2.71 (ddd, $J = 18.4$, 6.4, 1.6 Hz, 1H), 2.54 (s, 3H).

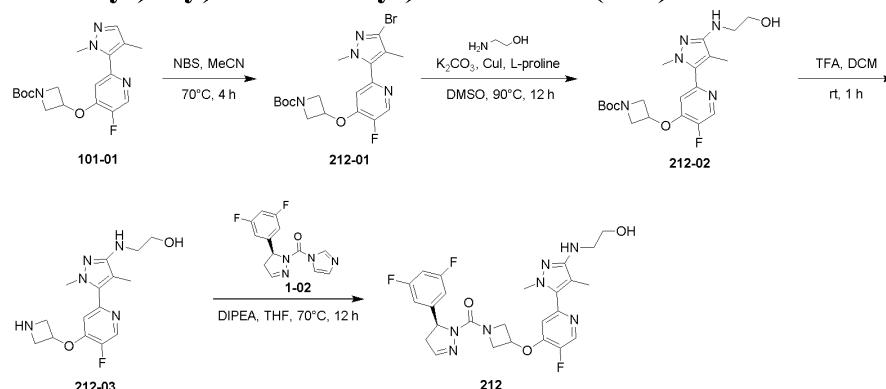
(S)-(3-((2-(3-(aminomethyl)-1,4-dimethyl-1H-pyrazol-5-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (211)



The title compound **211** was prepared in a yield of 16% (13 mg, 0.03mmol) as a white solid according to the procedure for compound **30**. Mass (m/z) 500.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.48 (d, $J = 2.9$ Hz, 1H), 6.81-6.78 (m, 1H), 6.78 – 6.65 (m, 4H), 5.26 (dd, $J = 12.2$,

6.4 Hz, 1H), 5.10-5.02 (m, 1H), 4.67-4.50 (m, 2H), 4.42-4.22 (m, 2H), 3.99-3.77 (m, 5H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H), 2.19-2.10 (m, 2H), 2.08 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-((2-hydroxyethyl)amino)-1,4-dimethyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (212)



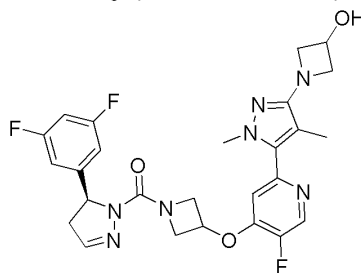
Step 1: To a solution of compound **101-01** (5 g, 13.8 mmol) in MeCN (50 mL) was added NBS (2.7 g, 15.2 mmol). The reaction mixture was stirred at 70 °C for 12 h. The crude mixture was purified by column chromatography on silica gel to give compound **212-01** (5.2 g, yield 85%) as a white solid. Mass (m/z) 441.1 $[M+H]^+$.

Step 2: To a solution of compound **212-01** (400 mg, 906.4 μ mol) in DMSO (10 mL) was added 2-aminoethan-1-ol (85 mg, 1.36 mmol), K_2CO_3 (375 mg, 2.72 mmol), CuI (180 mg, 906.4 μ mol) and L-proline (110 mg, 906.4 μ mol) under Ar. The reaction mixture was stirred at 90 °C for 12 h. The crude mixture was purified by column chromatography on silica gel to give compound **212-02** (100 mg, 26%) as a white solid. Mass (m/z) 422.1 $[M+H]^+$.

Step 3: To a solution of compound **212-02** (100 mg, 237.3 μ mol) in DCM (3 mL) was added TFA (3 mL). The reaction mixture was stirred at rt for 1 h. The solvent was concentrated under vacuum. The crude compound **212-03** was used to next step directly MS (m/z) 322.1 $[M+H]^+$.

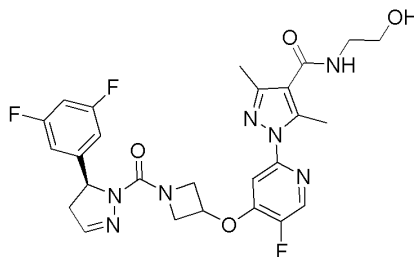
Step 4: To a solution of compound **212-03** (70 mg, 253.4 μmol) in THF (7 mL) was added compound **1-02** (82 mg, 253.4 μmol) and DIPEA (165 mg, 1.27 mmol). The reaction mixture was stirred at 70°C for 12 h. The crude mixture was purified by Pre-HPLC to give compound **212** (33 mg, 24%) as a white solid. MS (m/z) 530.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.66 (d, $J = 3.0$ Hz, 1H), 7.17-7.06 (m, 2H), 7.03 (d, $J = 1.7$ Hz, 1H), 6.96-6.85 (m, 2H), 5.33-5.19 (m, 2H), 4.61 (d, $J = 36.7$ Hz, 4H), 3.71 (s, 3H), 3.61 (t, $J = 5.8$ Hz, 2H), 3.40 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 3.27 (t, $J = 5.8$ Hz, 2H), 2.66 (ddd, $J = 18.7, 6.6, 1.8$ Hz, 1H), 1.94 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3-(3-hydroxyazetidin-1-yl)-1,4-dimethyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (213)



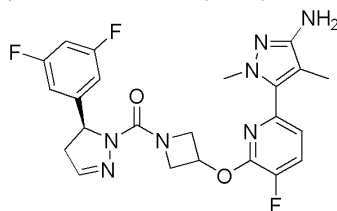
The titled compound **213** was prepared from compound **212-01** in a yield of 27.0% according to the procedure outlined for compound **212**. MS (m/z) 542.1 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (214)



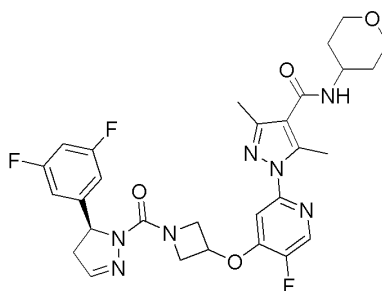
The titled compound **214** was prepared from compound **110-02** in a yield of 7.5% according to the procedure outlined for compound **68**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.7 Hz, 1H), 7.85 (t, *J* = 5.7 Hz, 1H), 7.32 (d, *J* = 6.3 Hz, 1H), 7.20 (tt, *J* = 9.4, 2.4 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.05 – 6.98 (m, 2H), 5.45 – 5.38 (m, 1H), 5.33 (dd, *J* = 12.2, 6.6 Hz, 1H), 4.80 (t, *J* = 5.4 Hz, 1H), 4.61 (s, 2H), 4.17 (s, 2H), 3.58 (q, *J* = 6.0 Hz, 2H), 3.53 – 3.44 (m, 1H), 3.40 – 3.35 (m, 2H), 2.78 – 2.69 (m, 1H), 2.67 (s, 3H), 2.39 (s, 3H). Mass (m/z) 558.4 [M+H]⁺.

(S)-(3-((6-(3-amino-1,4-dimethyl-1H-pyrazol-5-yl)-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (215)



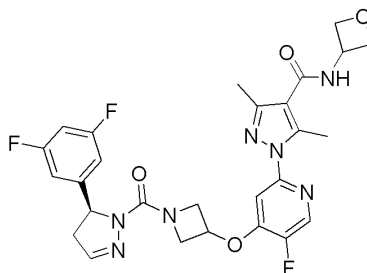
The title compound **215** was prepared in a yield of 47% (43 mg, 0.09 mmol) as a white solid according to the procedure for **207**. Mass (m/z) 486.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.55-7.48 (m, 1H), 7.07 – 7.01 (m, 1H), 6.81 – 6.73 (m, 3H), 6.72-6.65 (m, 1H), 5.43-5.34 (m, 1H), 5.27 (dd, *J* = 12.1, 6.5 Hz, 1H), 4.67-4.49 (m, 2H), 4.39-4.22 (m, 2H), 3.84 (s, 3H), 3.40-3.28 (m, 1H), 2.74-2.64 (m, 1H), 2.49-2.14 (m, 2H), 1.97 (s, 3H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide (216)



The titled compound **216** was prepared in 7.5% yield according to the procedure outlined for compound **214**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, $J = 2.4$ Hz, 1H), 7.16 (d, $J = 6.1$ Hz, 1H), 6.82 – 6.79 (m, 1H), 6.75 (dt, $J = 6.6, 2.1$ Hz, 2H), 6.70 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.50 (d, $J = 7.9$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.15 (td, $J = 6.4, 3.3$ Hz, 1H), 4.72 – 4.56 (m, 2H), 4.32 (dd, $J = 32.7, 9.4$ Hz, 2H), 4.20 (dp, $J = 11.5, 4.2, 3.7$ Hz, 1H), 4.00 (ddd, $J = 11.4, 5.4, 2.9$ Hz, 2H), 3.54 (td, $J = 11.7, 2.2$ Hz, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.03 (d, $J = 13.0$ Hz, 2H), 1.59 – 1.48 (m, 2H). Mass (m/z) 598.4 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-(oxetan-3-yl)-1H-pyrazole-4-carboxamide (217)



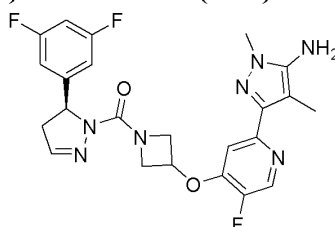
15

The titled compound **217** was prepared in 7.5% yield according to the procedure outlined for compound **214**. ^1H NMR (301 MHz, Chloroform-*d*) δ 8.20 (d, $J = 2.5$ Hz, 1H), 7.16 (d, $J = 6.1$ Hz, 1H), 6.85 – 6.62 (m, 4H), 6.09 (d, $J = 7.4$ Hz, 1H), 5.30 – 5.12 (m, 2H), 5.03 (t, $J = 7.0$ Hz, 2H), 4.61 (dt, $J = 13.0, 7.7$ Hz, 4H), 4.45 – 4.21 (m, 3H), 3.36 (ddd, $J = 18.6, 12.2,$

20

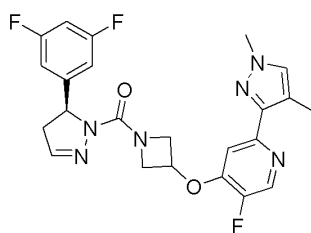
1.7 Hz, 1H), 2.78 (s, 3H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H), 2.47 (s, 3H). Mass (m/z) 570.4 $[M+H]^+$.

(S)-(3-((2-(5-amino-1,4-dimethyl-1H-pyrazol-3-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (218)



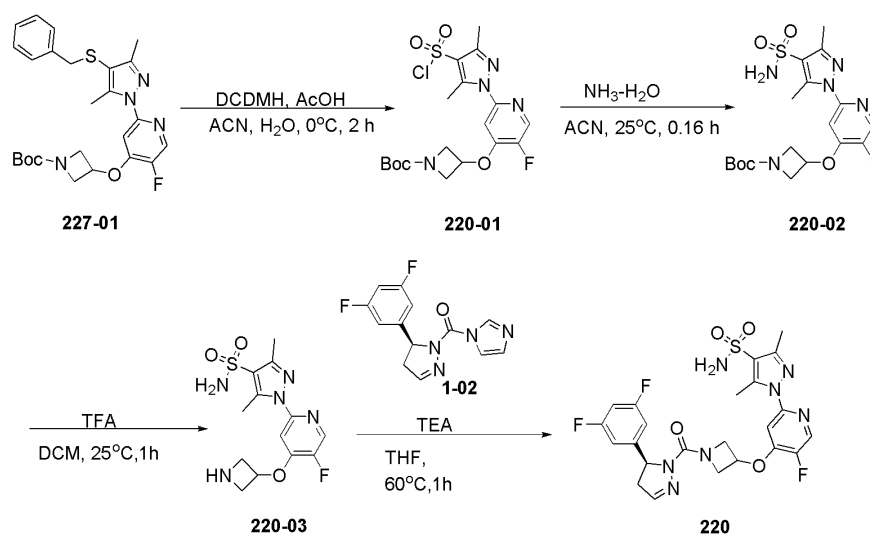
The titled compound **218** was prepared in a 9% yield according to the procedure outlined for compound **209**. Mass (m/z) 486.1 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-1H-pyrazol-3-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (219)



The titled compound **219** was prepared in a 37% yield from compound **3-02** according to the procedure outlined for compound **101-01**. Mass (m/z) 471.1 $[M+H]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (220)



Step 1: **227-01** (300 mg, 0.62 mmol), DCDMH (300 mg, 1.52 mmol), AcOH (1.4 mL), H₂O (0.6 mL) were in CAN (20 mL) under N₂ and the whole reaction mixture was stirred at 0°C for 2 hours. The mixture was concentrated in vacuo to give **220-01** (500 mg, crude) as a brown oil and used into next step reaction without purification. Mass (m/z) 461.4 [M+H]⁺.

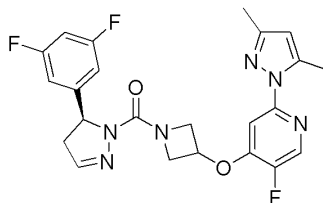
Step 2: **220-01** (500 mg, crude) and NH₃-H₂O (3 mL, 30w%) were in ACN (5 mL) under N₂ and the whole reaction mixture was stirred at 25°C for 0.16 hours. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **220-02** (150 mg, crude) as a yellow oil. Mass (m/z) 442.4 [M+H]⁺.

Step 3: **220-02** (150 mg, crude) and TFA (3 mL) were in DCM (5 mL) under N₂ and the whole reaction mixture was stirred at 25°C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give **220-03** (200 mg, crude) as a brown oil and used into next step reaction without purification. Mass (m/z) 342.4 [M+H]⁺.

Step 4: **220-03** (200 mg, crude), TEA (3 mL), **1-02** (50 mg, 0.18 mmol) were in THF (20 mL) under N₂ and the whole reaction mixture was

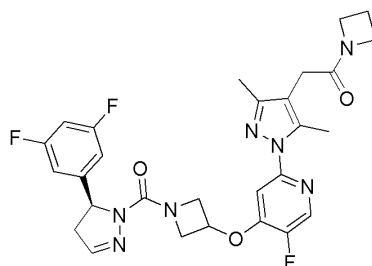
stirred at 60°C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography gave **220** (12.3 mg, 13.5%) as a light yellow solid. Mass (m/z) 550.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 2.4 Hz, 1H), 7.32 (s, 2H), 7.26 (d, *J* = 6.4 Hz, 1H), 7.12 (tt, *J* = 9.2, 2.4 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.98 – 6.88 (m, 2H), 5.32 (tt, *J* = 6.8, 3.6 Hz, 1H), 5.24 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.59 – 4.47 (m, 2H), 4.15 – 4.00 (m, 2H), 3.46 – 3.36 (m, 1H), 2.67 (dd, *J* = 6.4, 1.8 Hz, 1H), 2.63 (s, 3H), 2.38 (s, 3H).

- 10 (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (**221**)



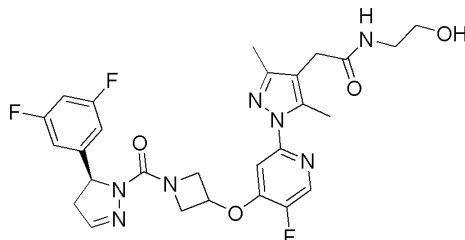
- 15 The titled compound **221** was prepared in 15.2% yield according to the procedure outlined for compound **110**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 6.2 Hz, 1H), 6.85 – 6.63 (m, 4H), 5.98 (s, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.20 – 5.13 (m, 1H), 4.71 – 4.56 (m, 2H), 4.41 – 4.24 (m, 2H), 3.36 (ddd, *J* = 18.6, 12.1, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.7, 6.5, 1.8 Hz, 1H), 2.59 (s, 3H), 2.28 (s, 20 3H). Mass (m/z) 471.3 [M+H]⁺.

(S)-1-(azetidin-1-yl)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)ethan-1-one (**222**)



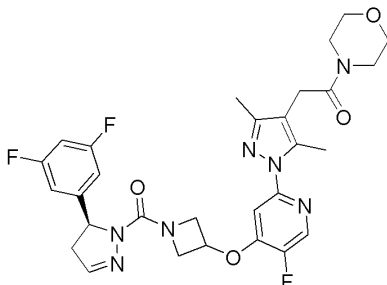
The titled compound **222** was prepared in 41.2% yield according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, $J = 2.5$ Hz, 1H), 7.19 (d, $J = 6.1$ Hz, 1H), 6.82 – 6.66 (m, 4H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.20 – 5.10 (m, 1H), 4.72– 4.57 (d, $J = 9.9$ Hz, 2H), 4.31 (dd, $J = 26.8, 9.9$ Hz, 2H), 4.16 (t, $J = 7.6$ Hz, 2H), 4.06 (t, $J = 7.8$ Hz, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 3.24 (s, 2H), 2.70 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H), 2.54 (s, 3H), 2.34 – 2.23 (m, 5H). Mass (m/z) 568.4 $[\text{M}+\text{H}]^+$.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-hydroxyethyl)acetamide (223)



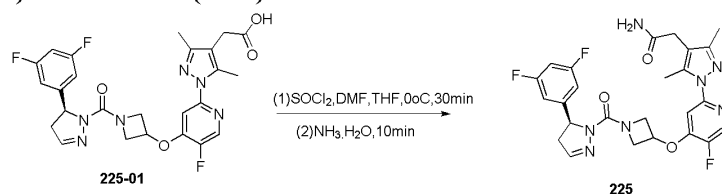
The titled compound **223** was prepared in 38.5% yield according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, $J = 2.3$ Hz, 1H), 7.21 (d, $J = 6.1$ Hz, 1H), 6.84 – 6.64 (m, 4H), 6.00 (s, 1H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.19– 5.11 (m, 1H), 4.671– 4.56 (m, 2H), 4.32 (dd, $J = 31.4, 10.4$ Hz, 2H), 3.68 (dd, $J = 5.5, 4.3$ Hz, 2H), 3.46 – 3.31 (m, 5H), 2.70 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.55 (s, 3H), 2.24 (s, 3H). Mass (m/z) 572.4 $[\text{M}+\text{H}]^+$.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-1-morpholinoethan-1-one (224)



5 The titled compound **224** was prepared in 42.8% yield according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, $J = 2.5$ Hz, 1H), 7.21 (d, $J = 6.2$ Hz, 1H), 6.82 – 6.65 (m, 4H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.16 (td, $J = 6.4, 3.2$ Hz, 1H), 4.70 – 4.57 (m, 2H), 4.31 (dd, $J = 28.1, 10.3$ Hz, 2H), 3.72 – 3.61 (m, 6H), 3.53 (t, $J =$
10 4.8 Hz, 2H), 3.45 (s, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H), 2.53 (s, 3H), 2.24 (s, 3H). Mass (m/z) 598.4 $[\text{M}+\text{H}]^+$.

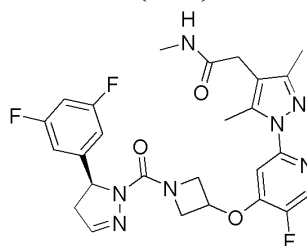
(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)acetamide (225)



Step 1: **225-01** (100 mg, 0.29 mmol) were dissolved in THF (1 mL) and DMF (1 drop), SOCl_2 (0.05 mL) was added to the above solution at 0°C , the mixture was stirred for 30 min, then the mixture was drop into
20 $\text{NH}_3\cdot\text{H}_2\text{O}$ (2 mL), the mixture was stirred for 10 min, quenched by ice-water. Concentrated and purification by prep-HPLC to give the titled compound **225** (41 mg, 41.2%) as a white solid. ^1H NMR (400 MHz,

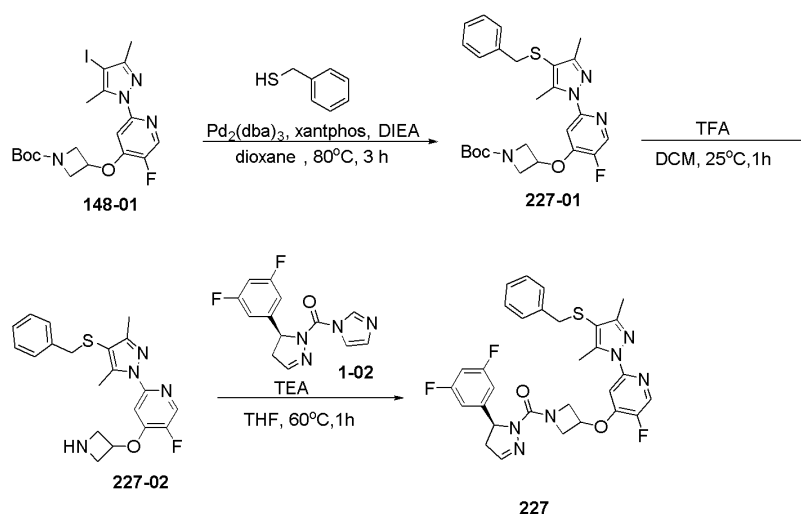
Chloroform-*d*) δ 8.17 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 6.2$ Hz, 1H), 6.81 – 6.67 (m, 4H), 5.54 (s, 1H), 5.36 (s, 1H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.16 (td, $J = 6.5, 3.3$ Hz, 1H), 4.70 – 4.56 (m, 2H), 4.32 (dd, $J = 31.0, 10.3$ Hz, 2H), 3.42 – 3.28 (m, 3H), 2.71 (ddd, $J = 18.6, 6.5, 1.8$ Hz, 1H), 2.57 (s, 3H), 2.27 (s, 3H). Mass (m/z) 528.3 [M+H]⁺.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylacetamide (226)



The titled compound **226** was prepared in 21.4% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 6.1$ Hz, 1H), 6.81 – 6.79 (m, 1H), 6.75 (dt, $J = 6.4, 2.1$ Hz, 2H), 6.70 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.56 (s, 1H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.21 – 5.12 (m, 1H), 4.70 – 4.57 (m, 2H), 4.32 (dd, $J = 30.7, 10.4$ Hz, 2H), 3.44 – 3.32 (m, 3H), 2.79 (d, $J = 4.6$ Hz, 3H), 2.71 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H), 2.54 (s, 3H), 2.24 (s, 3H). Mass (m/z) 542.3 [M+H]⁺.

(S)-3-((2-(4-(benzylthio)-3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (227)



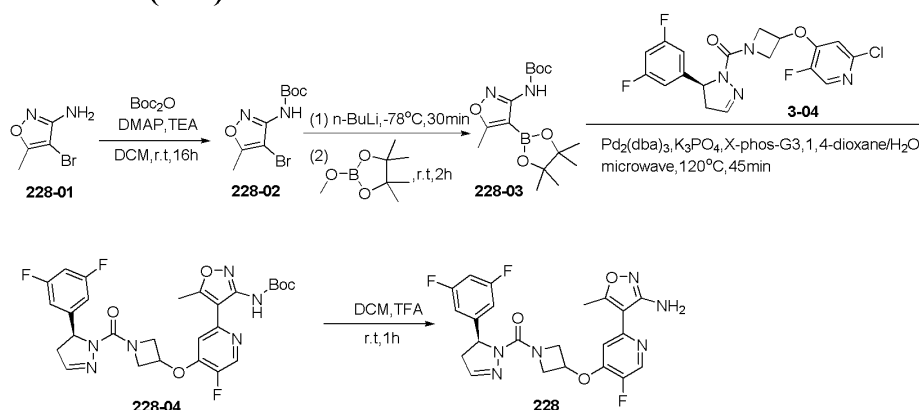
Step 1: Compound **148-01** (1.8g, 3.68 mmol), phenylmethanethiol (680 mg, 5.48 mmol), $\text{Pd}_2(\text{dba})_3$ (675 mg, 0.74 mmol), xantphos (852 mg, 1.47 mmol) and DIEA (951mg, 7.37 mmol) were in dioxane (30 mL) under N_2 and the whole reaction mixture was stirred at 80°C for 3 hours. The mixture was concentrated in vacuo. Purification by silica gel chromatography to give **227-01** (850 mg, 47.0%) as a brown oil. Mass (m/z) 485.6 $[\text{M}+\text{H}]^+$.

Step 2: **227-01** (80 mg, 0.16 mmol) and TFA (3 mL) were in DCM (5 mL) under N_2 and the whole reaction mixture was stirred at 25°C for 2 hours. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give **227-02** (150 mg, crude) as a yellow oil and used into next step reaction without purification. Mass (m/z) 385.5 $[\text{M}+\text{H}]^+$.

Step 3: **227-02** (150 mg, crude), TEA (1 mL), **1-02** (45 mg, 0.16 mmol) were in THF (5 mL) under N_2 and the whole reaction mixture was stirred at 60°C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give **227** (13.0 mg, 13.5%) as a white solid. Mass (m/z) 593.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.14 (d, $J = 2.4$ Hz, 1H), 7.24 – 7.18 (m, 4H), 7.06 (dt, $J = 6.4, 2.2$ Hz, 2H), 6.81 –

6.73 (m, 3H), 6.70 (tt, $J = 8.8, 2.4$ Hz, 1H), 5.28 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.15 (ddd, $J = 10.4, 6.4, 4.0$ Hz, 1H), 4.68 – 4.55 (m, 2H), 4.39 – 4.22 (m, 2H), 3.67 (s, 2H), 3.36 (ddd, $J = 18.4, 12.0, 1.6$ Hz, 1H), 2.70 (ddd, $J = 18.4, 6.4, 1.6$ Hz, 1H), 2.37 (s, 3H), 2.09 (s, 3H).

5 **(S)-(3-((2-(3-amino-5-methylisoxazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (228)**



Step 1: Compound **228-01** (1.77 g, 10 mmol), Boc_2O (2.616 g, 12 mmol), DMAP (0.122 g, 1 mmol) and TEA (0.4 ml) were dissolved in 20 mL DCM. Let it stir at room temperature for 16h. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 6/1) to give compound **228-02** (1.2 g, 43.3%) as white solid. Mass (m/z) 278.3 [$\text{M}+\text{H}$]⁺.

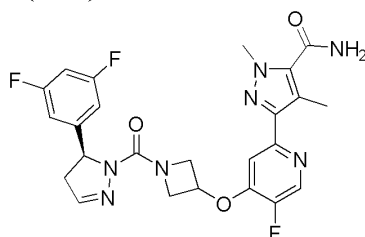
Step 2: Compound **228-02** (715 mg, 2.58 mmol) was dissolved in 15 mL of THF. $n\text{-BuLi}$ (2.42 mL, 3.87 mmol) was added slowly at -78°C . Let it stir at -78°C for 30 min. Then 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (960 mg, 5.16 mmol) was added. Let it stir at -78°C for 1h. Water was added to quench the reaction. The solvent was evaporated to dryness and used for next step without further purification.

Step 3: Compound **228-03** (250 mg, 0.61 mmol), tert-butyl (5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazol-3-yl)carbamate (750 mg, crude), X-Phos- G_3 (101.5 mg, 0.12 mmol), $\text{Pd}_2(\text{dba})_3$ (109.8 mg, 0.12 mmol), K_3PO_4 (1.272 g, 6.1 mmol) were mixed in 12 mL 1,4-

dioxane/H₂O(v/v =4/1). The mixture was stirred at 120 °C for 45min under microwave. The solvent was evaporated to dryness and purified by column chromatography (EA) to give compound **228-04** (80 mg, 22.9%) as brown oil. Mass (m/z) 573.4 [M+H]⁺.

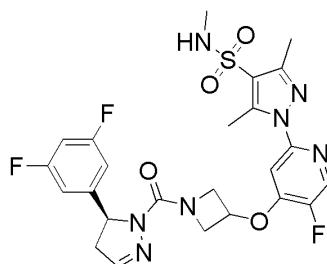
5 **Step 4:** Compound **228-04** (80 mg, 0.14 mmol) was dissolved in 3 mL of DCM. 2 mL of DCM/TFA (1/1) was added. Let it stir at r.t. for 1h. The solvent was evaporated to dryness and purified by prep-HPLC to give compound **228** (40 mg, 60.6%) as white solid. Mass (m/z) 473.4 [M+H]⁺.
1H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 6.81 (t, *J* = 1.2 Hz, 1H), 6.78 –
10 6.71 (m, 2H), 6.69 (m, 2H), 5.28 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.66 – 4.51 (m, 2H), 4.43-4.34 (m, 1H), 4.32 – 4.25 (m, 1H), 3.37 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.72 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H), 2.54 (s, 3H).

15 **(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-5-carboxamide (229)**



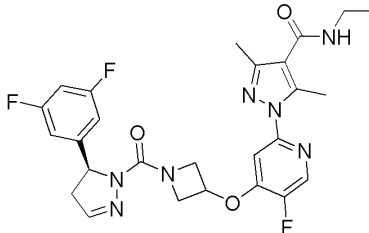
The titled compound **229** was prepared in 9% yield according to the procedure outlined for compound **66** as a white solid. MS (m/z) 514.1
20 [M+H]⁺.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,3,5-trimethyl-1H-pyrazole-4-sulfonamide (230)



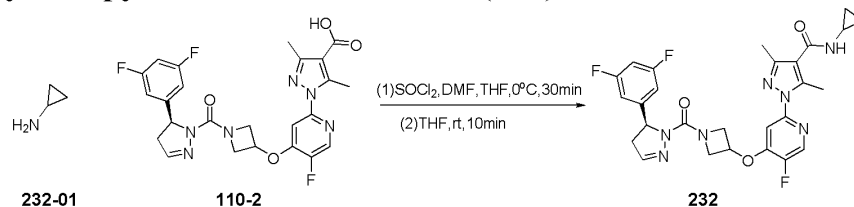
The titled compound **230** was prepared from **220-01** in a yield of 19.8% according to the procedure outlined for compound **220**. Mass (m/z) 564.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (d, *J* = 2.4 Hz, 1H), 7.36 (q, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 6.4 Hz, 1H), 7.12 (tt, *J* = 9.2, 2.4 Hz, 1H), 7.03 (t, *J* = 1.6 Hz, 1H), 6.96 – 6.87 (m, 2H), 5.32 (dq, *J* = 6.4, 3.6 Hz, 1H), 5.24 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.60 – 4.43 (m, 2H), 4.16 – 4.40 (m, 2H), 3.45 – 3.36 (m, 1H), 2.67 (dd, *J* = 6.4, 1.6 Hz, 1H), 2.63 (s, 3H), 2.44 (d, *J* = 5.2 Hz, 3H), 2.37 (s, 3H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-ethyl-3,5-dimethyl-1H-pyrazole-4-carboxamide (231)



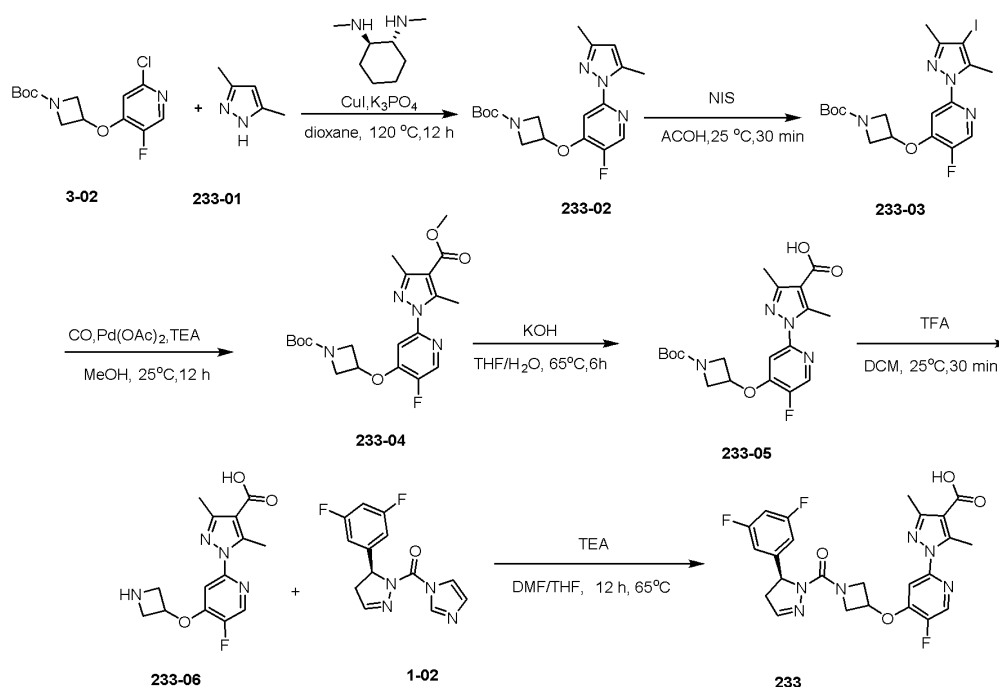
The titled compound **231** was prepared in 32.4% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 2.4 Hz, 1H), 7.34 (t, *J* = 1.5 Hz, 1H), 7.29–7.24 (m, 1H), 7.20 (dt, *J* = 9.2, 2.0 Hz, 1H), 7.16 (d, *J* = 6.1 Hz, 1H), 6.83 (t, *J* = 1.7 Hz, 1H), 5.56 (s, 1H), 5.31 (dd, *J* = 12.2, 6.7 Hz, 1H), 5.15 (td, *J* = 6.5, 3.4 Hz, 1H), 4.63 (s, 2H), 4.33 (d, *J* = 29.5 Hz, 2H), 3.55 – 3.36 (m, 3H), 2.76 (s, 3H), 2.70 (ddd, *J* = 18.6, 6.7, 1.7 Hz, 1H), 2.43 (s, 3H), 1.25 (t, *J* = 7.3 Hz, 3H). Mass (m/z) 542.3 [M+H]⁺.

(S)-N-cyclopropyl-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (232)



5 The titled compound **232** was prepared according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 2.5 Hz, 1H), 7.34 (t, *J* = 1.5 Hz, 1H), 7.3 – 7.23 (m, 1H), 7.2 – 7.19 (m, 1H), 7.15 (d, *J* = 6.1 Hz, 1H), 6.86– 6.78 (m, 1H), 5.73 (s, 1H), 5.31 (dd, *J* = 12.2, 6.7 Hz, 1H), 5.15 (td, *J* = 6.4, 3.3 Hz, 1H), 4.70 – 4.54 (m, 2H),
 10 4.33 (d, *J* = 31.4 Hz, 2H), 3.40 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.87 (dd, *J* = 7.2, 3.9 Hz, 1H), 2.75 (s, 3H), 2.75 – 2.63 (m, 1H), 2.41 (s, 3H), 0.89 (q, *J* = 6.3 Hz, 2H), 0.64 – 0.56 (m, 2H). Mass (*m/z*) 554.4 [*M*+*H*]⁺.

15 **(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxylic acid (233)**



Step 1: **3-02** (8.5 g, 28.15 mmol) and **233-01** (2.76 g, 42.23 mmol) were dissolved in 200 ml of dry dioxane, CuI (10.7 g, 56.3 mmol), K₃PO₄ (12 g, 56.3 mmol), and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (7.9 g, 56.3 mmol) was added to the above solution, the mixture was stirred for 12 h at 120 °C. Water was added and the reaction mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification of the concentrate by silica gel chromatography gave the compound **233-02** (6 g, 58.8%). Mass (m/z) 363.2 [M+H]⁺.

Step 2: **233-02** (6 g, 16.57 mmol) was dissolved in 60 mL of acetic acid, NIS (3.7g, 16.57 mmol) was added, and the mixture was stirred at r.t. for 30 min. Water was added and the reaction mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification of the concentrate by silica gel chromatography gave the compound **233-03** (3.85 g, 47.6%). Mass (m/z) 489.2 [M+H]⁺.

Step 3: **233-03** (3.8g, 7.89 mmol) and Pd(OAc)₂ (176 mg, 0.789 mmol) were dissolved in MeOH (150 mL), and the reaction mixture was stirred at 25 °C under CO (1atm) for 12 h. The mixture was extracted with EA,

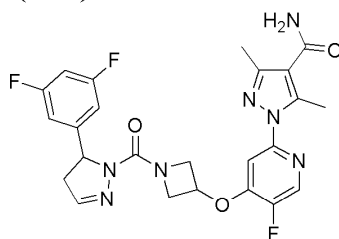
washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the compound **233-04** (2.9 g, crude). Mass (m/z) 388.1 $[\text{M}+\text{H}]^+$.

Step 4: 233-04 (1.2 g, 3.9 mmol) was dissolved in EtOH (10 mL), KOH (5mL, 2M) was added, and the reaction mixture was stirred at 65°C for 12h. Water was added and the reaction mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the concentrate by silica gel chromatography gave the compound **233-05** (800 mg, 69.6%).

Step 5: 233-05 (800 mg, 1.97 mmol) was dissolved in 10mL of DCM, trifluoroacetic acid (1mL) was added, and the mixture was stirred at r.t. for 30 min. The reaction mixture was concentrated to give the desired product **233-06**, which was used for next step without further purification.

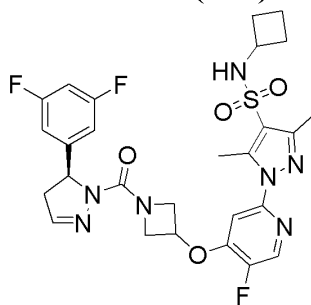
Step 6: 233-06 (crude), **1-02** (545 mg, 1.97mmol) and TEA (1 mL) were dissolved in THF (30 mL) and DMF (5 mL) and stirred at 65°C for 6 h. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the concentrate by silica gel chromatography gave the titled compound. ^1H NMR (400 MHz, Chloroform- d) δ 8.23 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 6.1$ Hz, 1H), 6.83 – 6.68 (m, 4H), 5.28 (dd, $J = 12.1, 6.5$ Hz, 1H), 5.16 (s, 1H), 4.64 (s, 2H), 4.33 (dd, $J = 31.2, 10.5$ Hz, 2H), 3.36 (dd, $J = 18.4, 12.0$ Hz, 1H), 2.88 (s, 3H), 2.71 (dd, $J = 18.7, 6.9$ Hz, 1H), 2.51 (s, 3H).

1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (234)



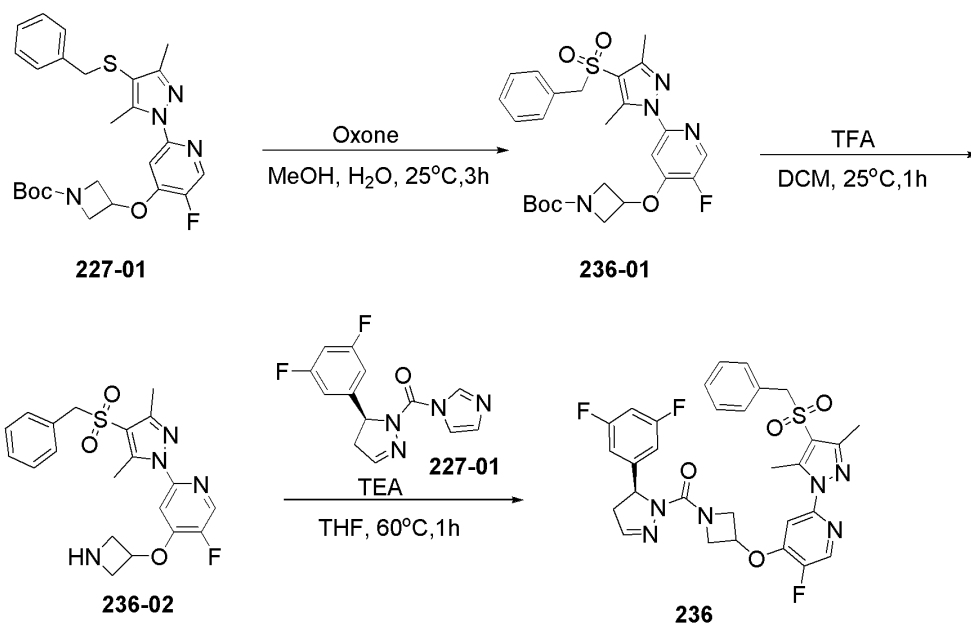
The titled compound **234** was prepared in a 63.2% yield according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 6.1$ Hz, 1H), 6.81 – 6.79 (m, 1H), 6.77 – 6.74 (m, 2H), 6.70 (ddd, $J = 8.8, 6.5, 2.3$ Hz, 1H),
 5 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.19 – 5.13 (m, 1H), 4.70 – 4.56 (m, 2H), 4.39 – 4.29 (m, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 2H), 2.88 (s, 3H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 2H), 2.51 (s, 3H). Mass (m/z) 514.3 $[\text{M}+\text{H}]^+$.

(S)-N-cyclobutyl-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (**235**)



The titled compound **235** was prepared from **220-01** in a yield of 3.4% according to the procedure outlined for compound **220**. Mass (m/z) 604.3
 15 $[\text{M}+\text{H}]^+$.

(S)-(3-((2-(4-(benzylsulfonyl)-3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (**236**)

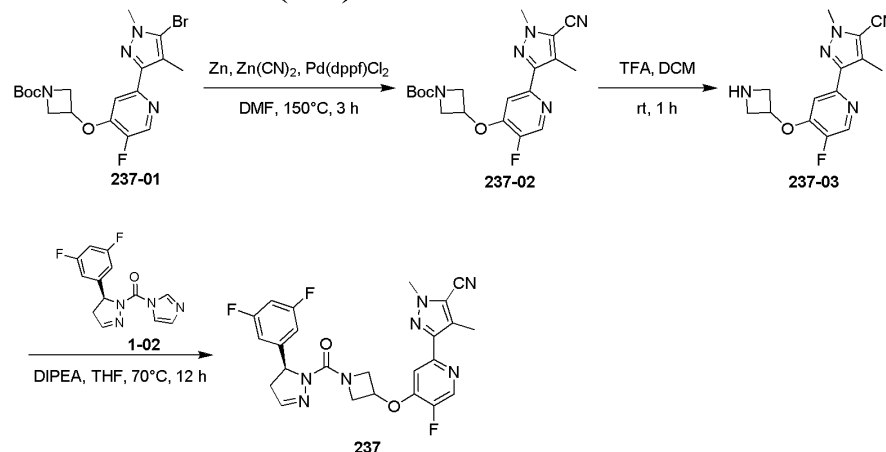


Step 1: **227-01** (100 mg, 0.20 mmol), Oxone (300 mg, 0.49 mmol) were in MeOH (5 mL) and H₂O (3 mL) under N₂ and the whole reaction mixture was stirred at 25°C for 3 hours. The mixture was concentrated in vacuo. Purification by silica gel chromatography to give **236-01** (70 mg, 66.0%) as a grey solid. Mass (m/z) 517.3 [M+H]⁺.

Step 2: **236-01** (70 mg, 0.14 mmol) and TFA (3 mL) were in DCM (5 mL) under N₂ and the whole reaction mixture was stirred at 25°C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give **236-02** (100 mg, crude) as a yellow oil and used into next step reaction without purification. Mass (m/z) 417.4 [M+H]⁺.

Step 3: **236-02** (100 mg, crude), TEA (1 mL), **1-02** (30 mg, 0.16 mmol) were in THF (5 mL) under N₂ and the whole reaction mixture was stirred at 60°C for 1 hour. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **236** (20.0 mg, 29.8%) as a white solid. Mass (m/z) 625.4 [M+H]⁺.

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-5-carbonitrile (237)



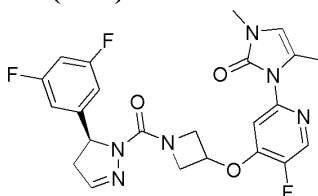
Step 1: To a solution of compound **237-01** (360 mg, 815.8 μmol) in DMF (4 mL) was added Zn (160 mg, 2.54 μmol), Zn(CN)₂ (192 mg, 1.63 mmol) and Pd(dppf)Cl₂ (60 mg, 81.6 μmol) under Ar. The reaction mixture was stirred at 150°C for 3 h. The crude mixture was purified by column chromatography on silica gel to give compound **237-02** (80 mg, 25%) as a white solid. Mass (m/z) 388.1 [M+H]⁺.

Step 2: To a solution of compound **237-02** (80 mg, 206.5 μmol) in DCM (3 mL) was added TFA (3 mL). The reaction mixture was stirred at rt for 1 h. The solvent was concentrated under vacuum. The crude compound **237-03** was used to next step directly Mass (m/z) 288.1 [M+H]⁺.

Step 3: To a solution of compound **237-03** (50 mg, 181 μmol) in THF (4 mL) was added compound **1-02** (52 mg, 181 μmol) and DIPEA (94 mg, 724.0 μmol). The reaction mixture was stirred at 70°C for 12 h. The crude mixture was purified by Pre-HPLC to give compound **237** (68 mg, 76%) as a white solid. Mass (m/z) 496.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J* = 2.8 Hz, 1H), 7.28-7.26 (m, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.77-6.67 (m, 2H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.13 (td, *J* = 6.4, 3.3 Hz, 1H),

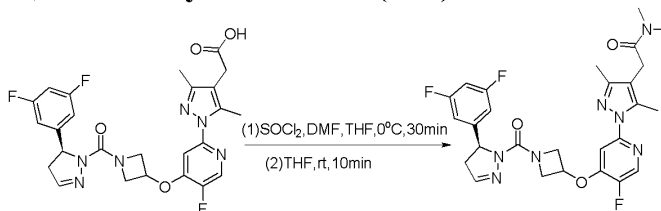
4.71-4.54 (m, 2H), 4.43-4.21 (m, 2H), 4.04 (s, 3H), 3.36 (ddd, $J = 18.6$, 12.2, 1.7 Hz, 1H), 2.71 (ddd, $J = 18.6$, 6.5, 1.8 Hz, 1H), 2.51 (s, 3H).

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1,3-dihydro-2H-imidazol-2-one (238)



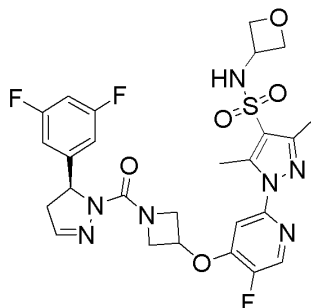
The titled compound **238** was prepared from compound **3-02** in a yield of 18.0% according to the procedure outlined for compound **167-03**. Mass (m/z) 487.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.22 (d, $J = 2.6$ Hz, 1H), 7.22 (d, $J = 6.2$ Hz, 1H), 6.82 – 6.65 (m, 4H), 6.04 (d, $J = 1.4$ Hz, 1H), 5.28 (dd, $J = 12.2$, 6.4 Hz, 1H), 5.11 (td, $J = 6.4$, 3.2 Hz, 1H), 4.62 (s, 2H), 4.31 (t, $J = 14.9$ Hz, 2H), 3.44 – 3.30 (m, 1H), 3.27 (s, 3H), 2.69 (ddd, $J = 18.6$, 6.4, 1.8 Hz, 1H), 2.20 (d, $J = 1.4$ Hz, 3H).

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-N,N-dimethylacetamide (239)



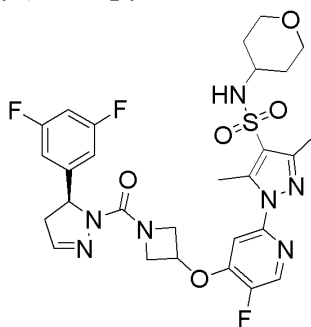
The titled compound **239** was prepared in 10.6% yield according to the procedure outlined for compound **225**. 1H NMR (400 MHz, Chloroform- d) δ 8.16 (s, 1H), 7.19 (d, $J = 6.1$ Hz, 1H), 6.80 (s, 1H), 6.77 – 6.73 (m, 2H), 6.73 – 6.66 (m, 1H), 5.28 (dd, $J = 12.1$, 6.4 Hz, 1H), 5.15 (s, 1H), 4.6 – 4.55 (s, 2H), 4.31 (dd, $J = 26.0$, 10.4 Hz, 2H), 3.46 (s, 2H), 3.36 (dd, $J = 18.4$, 12.3 Hz, 1H), 3.10 (s, 3H), 2.99 (s, 3H), 2.70 (dd, $J = 19.3$, 7.2 Hz, 1H), 2.51 (s, 3H), 2.24 (s, 3H). Mass (m/z) 556.4 $[M+H]^+$.

(S)-N-cyclobutyl-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (240)



5 The titled compound **240** was prepared from **220-01** in a yield of 14.3% according to the procedure outlined for compound **220**. Mass (m/z) 606.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.50 (d, $J = 2.4$ Hz, 1H), 8.47 (d, $J = 6.4$ Hz, 1H), 7.28 (d, $J = 6.0$ Hz, 1H), 7.12 (tt, $J = 9.2, 2.4$ Hz, 1H), 7.06 – 7.00 (m, 1H), 6.96 – 6.89 (m, 2H), 5.36 – 5.29 (m, 1H), 5.24
10 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.60 – 4.46 (m, 4H), 4.39 – 4.29 (m, 3H), 4.13 – 4.02 (m, 2H), 3.43 – 3.36 (m, 1H), 2.70 – 2.65 (m, 1H), 2.63 (s, 3H), 2.37 (s, 3H).

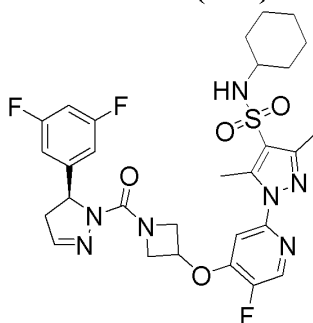
(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-sulfonamide (241)



The titled compound **241** was prepared from **220-01** in a yield of 19.0% according to the procedure outlined for compound **220**. Mass (m/z) 634.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 2.4$ Hz, 1H),

7.77 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 6.0$ Hz, 1H), 7.16 – 7.07 (m, 1H), 7.03 (d, $J = 1.6$ Hz, 1H), 6.96 – 6.89 (m, 2H), 5.36 – 5.30 (m, 1H), 5.24 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.61 – 4.40 (m, 2H), 4.19 – 3.97 (m, 2H), 3.75 (d, $J = 11.6$ Hz, 2H), 3.46 – 3.36 (m, 1H), 3.31 – 3.22 (m, 2H), 3.18 (d, $J = 6.4$ Hz, 1H), 2.66 (s, 3H), 2.65 – 2.61 (m, 1H), 2.38 (s, 3H), 1.57 (d, $J = 12.0$ Hz, 2H), 1.48 – 1.34 (m, 2H).

(S)-N-cyclohexyl-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (242)

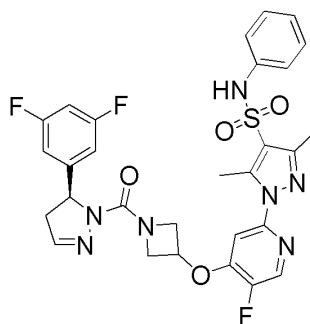


10

The titled compound **242** was prepared from **220-01** in a yield of 12.6% according to the procedure outlined for compound **220**. Mass (m/z) 632.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.48 (d, $J = 2.8$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 6.4$ Hz, 1H), 7.17 – 7.06 (m, 1H), 7.05 – 7.00 (m, 1H), 6.96 – 6.89 (m, 2H), 5.37 – 5.29 (m, 1H), 5.24 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.60 – 4.44 (m, 2H), 4.16 – 3.99 (m, 2H), 3.44 – 3.37 (m, 1H), 2.98 – 2.86 (m, 1H), 2.69 – 2.66 (m, 1H), 2.65 (s, 3H), 2.37 (s, 3H), 1.66 – 1.55 (m, 4H), 1.50 – 1.42 (m, 1H), 1.20 – 1.11 (m, 4H), 1.07 – 1.02 (m, 1H).

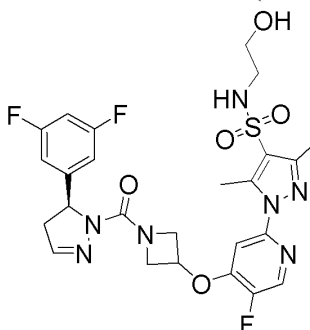
(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-phenyl-1H-pyrazole-4-sulfonamide (243)

20



The titled compound **243** was prepared from **220-01** in a yield of 16.1% according to the procedure outlined for compound **220**. Mass (m/z) 626.4 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.23 (brs, 1H), 8.45 (d, $J = 2.4$ Hz, 1H), 7.31 – 7.20 (m, 3H), 7.15 – 7.00 (m, 5H), 6.94 – 6.88 (m, 2H), 5.32 – 5.26 (m, 1H), 5.23 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.60 – 4.44 (m, 2H), 4.16 – 3.99 (m, 2H), 3.44 – 3.35 (m, 1H), 2.68 – 2.58 (m, 1H), 2.55 (s, 3H), 2.28 (s, 3H).

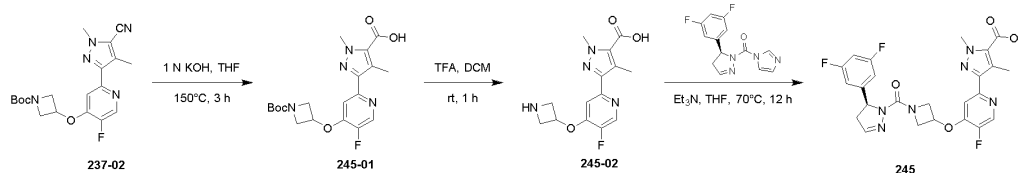
(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (244)



The titled compound **244** was prepared from **220-01** in a yield of 14.6% according to the procedure outlined for compound **220**. Mass (m/z) 594.3 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.49 (d, $J = 2.4$ Hz, 1H), 7.53 (t, $J = 6.0$ Hz, 1H), 7.29 (d, $J = 6.4$ Hz, 1H), 7.12 (tt, $J = 9.2, 2.4$ Hz, 1H), 7.06 – 7.00 (m, 1H), 6.97 – 6.89 (m, 2H), 5.32 (dd, $J = 6.4, 3.2$ Hz, 1H), 5.24 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.70 (t, $J = 5.6$ Hz, 1H), 4.61 – 4.45

(m, 2H), 4.14 – 4.00 (m, 2H), 3.46 – 3.36 (m, 3H), 2.83 (q, $J = 6.4$ Hz, 2H), 2.69 – 2.66 (m, 1H), 2.63 (s, 3H), 2.37 (s, 3H).

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-5-carboxylic acid (245)

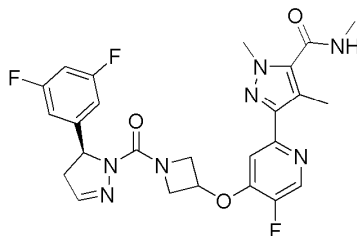


Step 1: To a solution of compound **237-02** (1.2 g, 3.1 mmol) in THF (20 mL) was added 1 N KOH (20 mL). The reaction mixture was stirred at 150°C for 3 h. The crude mixture was purified by column chromatography on silica gel to give compound **245-01** (400 mg, 32%) was obtained as a white solid. Mass (m/z) 407.1 $[M+H]^+$.

Step 2: To a solution of compound **245-01** (400 mg, 984.2 μ mol) in DCM (6 mL) was added TFA (6 mL). The reaction mixture was stirred at rt for 1 h. The solvent was concentrated under vacuum. The crude compound **245-02** was used to next step directly Mass (m/z) 307.1 $[M+H]^+$.

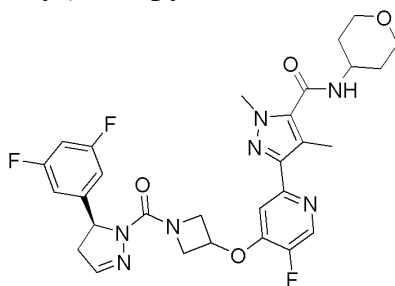
Step 3: To a solution of compound **245-02** (235 mg, 848.9 μ mol) in THF (5mL) was added compound **1-02** (260 mg, 848.9 μ mol) and Et_3N (430 mg, 4.24 mmol). The reaction mixture was stirred at 70°C for 12 h. The crude mixture was purified by Pre-HPLC to give compound **245** (220 mg, 50%) was obtained as a white solid Mass (m/z) 515.1 $[M+H]^+$.

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N,1,4-trimethyl-1H-pyrazole-5-carboxamide (246)



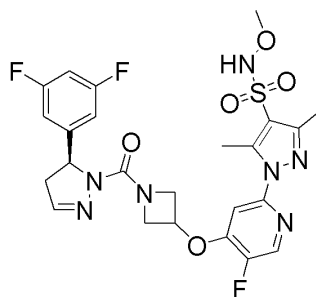
The titled compound **246** was prepared from **245** in a yield of 54% according to the procedure outlined for compound **68**. Mass (m/z) 528.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J* = 2.8 Hz, 1H), 7.28-7.26 (m, 1H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.77-6.67 (m, 2H), 5.24-5.19 (m, 2H), 4.59-4.51 (m, 2H), 4.20-4.05 (m, 2H), 3.90 (s, 3H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.82 (s, 3H), 2.35 (s, 3H).

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-5-carboxamide (**247**)



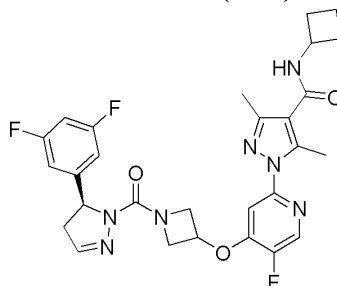
The titled compound **247** was prepared from **245** in a yield of 27% according to the procedure outlined for compound **68**. Mass (m/z) 598.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 2.8 Hz, 1H), 7.31-7.18 (m, 1H), 6.83-6.62 (m, 4H), 5.82-5.80 (m, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.14 (td, *J* = 6.5, 3.4 Hz, 1H), 4.66-4.58 (m, 2H), 4.42-4.31 (m, 1H), 4.31-4.14 (m, 3H), 4.08 (s, 3H), 4.01 (dt, *J* = 11.9, 3.5 Hz, 2H), 3.55 (td, *J* = 11.7, 2.2 Hz, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.75-2.66 (m, 1H), 2.51 (s, 3H), 2.13-1.97 (m, 2H), 1.70-1.53 (m, 2H).

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-methoxy-3,5-dimethyl-1H-pyrazole-4-sulfonamide (**248**)



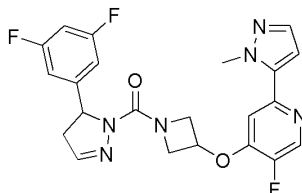
The titled compound **248** was prepared from **220-01** in a yield of 10.4% according to the procedure outlined for compound **220**. Mass (m/z) 580.4 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, $J = 2.4$ Hz, 1H), 7.17 (d, $J = 6.0$ Hz, 1H), 7.00 (s, 1H), 6.80 (t, $J = 1.6$ Hz, 1H), 6.78 – 6.65 (m, 3H), 5.28 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.15 (ddd, $J = 10.4, 6.4, 4.0$ Hz, 1H), 4.70 – 4.56 (m, 2H), 4.40 – 4.23 (m, 2H), 3.81 (s, 3H), 3.36 (ddd, $J = 18.4, 12.0, 1.6$ Hz, 1H), 2.83 (s, 3H), 2.79 – 2.65 (m, 1H), 2.47 (s, 3H).

(S)-N-cyclobutyl-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (**249**)



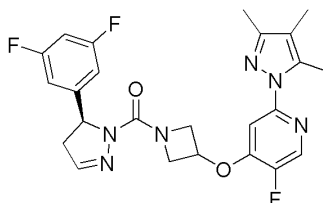
The titled compound **249** was prepared from **245** in a yield of 39.2% according to the procedure outlined for compound **68**. 1H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, $J = 2.5$ Hz, 1H), 7.15 (d, $J = 6.1$ Hz, 1H), 6.81 – 6.78 (m, 1H), 6.75 (dt, $J = 6.5, 2.1$ Hz, 2H), 6.70 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.71 (d, $J = 7.9$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.14 (dd, $J = 8.8, 5.0$ Hz, 1H), 4.70 – 4.51 (m, 3H), 4.32 (dd, $J = 32.7, 10.3$ Hz, 2H), 3.36 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.76 (s, 3H), 2.71 (ddd, $J = 18.7, 6.5, 1.8$ Hz, 1H), 2.44 (s, 3H), 2.50 – 2.40 (m, 2H), 1.92 (dt, $J = 11.0, 8.8$ Hz, 2H), 1.84 – 1.71 (m, 2H). Mass (m/z) 568.4 $[M+H]^+$.

(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (250)



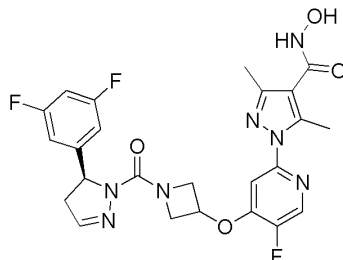
5 The titled compound **250** was prepared according to the procedure outlined for compound **3**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, J = 2.9 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 6.4 Hz, 1H), 6.81 (t, J = 1.7 Hz, 1H), 6.75 (dt, J = 6.4, 2.1 Hz, 2H), 6.70 (tt, J = 8.8, 2.3 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 5.015 – 5.04 (m, 1H), 4.66 – 4.53 (m, 2H), 4.41 – 4.25 (m, 2H), 4.17 (s, 3H), 3.37 (ddd, J = 18.7, 12.2, 1.7 Hz, 1H), 2.72 (ddd, J = 18.6, 6.4, 1.8 Hz, 1H). Mass (m/z) 457.2 $[\text{M}+\text{H}]^+$.

15 **(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(3,4,5-trimethyl-1H-pyrazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (251)**



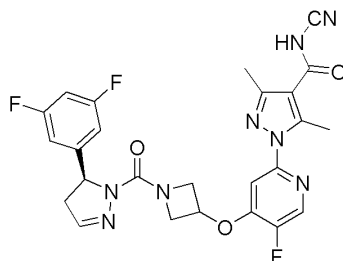
20 The titled compound **251** was prepared from **3-04** in a yield of 10.2% according to the procedure outlined for compound **167-03**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 6.2 Hz, 1H), 6.79 (d, J = 1.7 Hz, 1H), 6.75 (dt, J = 6.5, 2.0 Hz, 2H), 6.70 (td, J = 8.9, 4.4 Hz, 1H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 5.15 (td, J = 6.4, 3.3 Hz, 1H), 4.69 – 4.55 (m, 2H), 4.31 (dd, J = 30.7, 10.5 Hz, 2H), 3.35 (ddd, J = 18.7, 12.2, 1.7 Hz, 1H), 2.70 (ddd, J = 18.7, 6.5, 1.8 Hz, 1H), 2.50 (s, 3H), 2.23 (s, 3H), 1.95 (s, 3H). Mass (m/z) 485.3 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-hydroxy-3,5-dimethyl-1H-pyrazole-4-carboxamide (252)



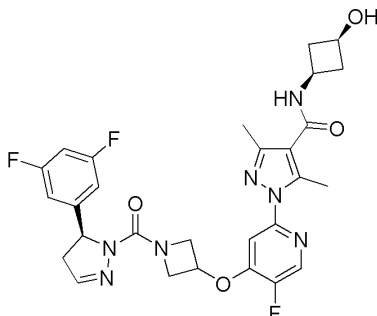
5 The titled compound **252** was prepared in 15% yield according to the procedure outlined for compound **225**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 6.1 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.73 – 6.67 (m, 1H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 5.20 – 5.09 (m, 2H), 4.71 – 4.53 (m, 3H), 4.32 (dd, J = 32.1, 10.4 Hz, 3H), 3.42 – 3.32 (m, 1H), 2.79 (s, 3H), 2.78 – 2.68 (m, 1H), 2.44 (s, 3H).
 10 Mass (m/z) 530.2 $[\text{M}+\text{H}]^+$.

(S)-N-cyano-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (253)



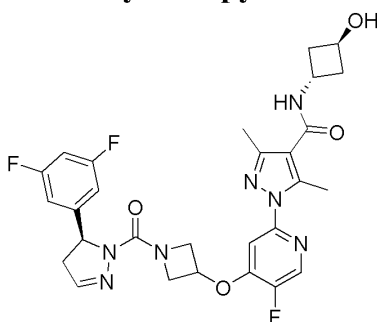
15 The titled compound **253** was prepared in 10.2% yield according to the procedure outlined for compound **225**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, J = 2.4 Hz, 1H), 7.37 (s, 1H), 7.15 (d, J = 6.1 Hz, 1H), 6.81 (t, J = 1.7 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.74 – 6.68 (m, 1H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 5.18 – 5.09 (d, J = 4.1 Hz, 2H), 4.69 – 4.56 (s, 2H), 4.40 – 4.23 (m, 2H), 3.37 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.82 (s, 3H), 2.76 – 2.68 (m, 1H), 2.49 (s, 3H). Mass (m/z) 539.3 $[\text{M}+\text{H}]^+$.
 20

1-(4-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-((1s,3s)-3-hydroxycyclobutyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (254)



5 The titled compound **254** was prepared in 37.8% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.15 (d, *J* = 6.1 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.77 – 6.73 (m, 2H), 6.73 – 6.66 (m, 1H), 5.72 (d, *J* = 7.6 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.14 (td, *J* = 6.5, 3.4 Hz, 1H), 4.63 (s, 2H), 4.32 (dd, *J* = 33.4, 9.1 Hz, 2H), 4.15 (dq, *J* = 14.8, 7.8, 7.3 Hz, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.91 (dtd, *J* = 9.8, 6.9, 3.0 Hz, 2H), 2.76 (s, 2H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 2H), 2.44 (s, 3H), 1.98 – 1.86 (m, 2H). Mass (*m/z*) 584.4 [M+H]⁺.

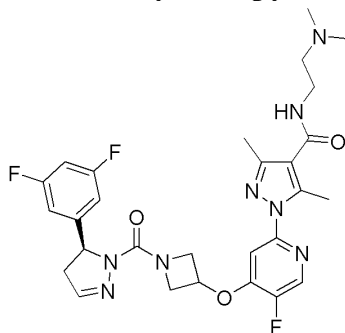
15 **1-(4-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-((1r,3r)-3-hydroxycyclobutyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (255)**



The titled compound **255** was prepared in 54.3% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz,

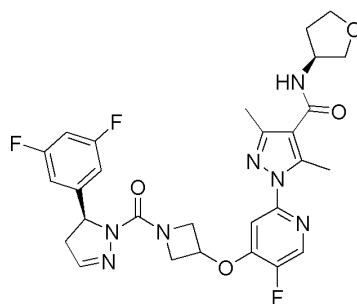
Chloroform-*d*) δ 8.20 (d, $J = 2.4$ Hz, 1H), 7.15 (d, $J = 6.1$ Hz, 1H), 6.81 – 6.79 (m, 1H), 6.78 – 6.73 (m, 2H), 6.70 (tt, $J = 8.8$, 2.4 Hz, 1H), 5.73 (d, $J = 6.5$ Hz, 1H), 5.28 (dd, $J = 12.2$, 6.4 Hz, 1H), 5.15 (ddd, $J = 10.3$, 6.5, 4.0 Hz, 1H), 4.69 – 4.55 (m, 4H), 4.32 (dd, $J = 33.4$, 10.2 Hz, 2H), 3.36 (ddd, $J = 18.6$, 12.2, 1.7 Hz, 2H), 2.76 (s, 2H), 2.71 (ddd, $J = 18.6$, 6.4, 1.8 Hz, 2H), 2.53 – 2.45 (m, 2H), 2.44 (s, 3H), 2.38 – 2.30 (m, 2H). Mass (m/z) 584.4 $[M+H]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(2-(dimethylamino)ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (256)



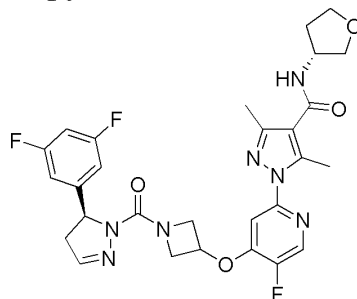
The titled compound **256** was prepared in 16% yield according to the procedure outlined for compound **225**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, $J = 2.4$ Hz, 1H), 7.33 (s, 1H), 7.11 (d, $J = 6.1$ Hz, 1H), 6.79 (t, $J = 1.7$ Hz, 1H), 6.75 (dt, $J = 6.4$, 2.1 Hz, 2H), 6.70 (tt, $J = 8.8$, 2.3 Hz, 1H), 5.28 (dd, $J = 12.2$, 6.3 Hz, 1H), 5.14 (dq, $J = 6.7$, 4.0, 3.4 Hz, 1H), 4.72 – 4.53 (m, 2H), 4.32 (dd, $J = 26.5$, 10.7 Hz, 2H), 3.87 (d, $J = 5.4$ Hz, 2H), 3.41 – 3.30 (m, 3H), 2.92 (s, 6H), 2.74 (s, 3H), 2.72 – 2.66 (m, 1H), 2.45 (s, 3H). Mass (m/z) 585.4 $[M+H]^+$.

1-(4-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-((S)-tetrahydrofuran-3-yl)-1H-pyrazole-4-carboxamide (257)



The titled compound **257** was prepared in 39.8% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 2.5 Hz, 1H), 7.15 (d, *J* = 6.1 Hz, 1H), 6.83 – 6.66 (m, 4H), 5.78 (d, *J* = 7.6 Hz, 1H), 5.28 (dd, *J* = 12.1, 6.4 Hz, 1H), 5.14 (td, *J* = 6.5, 3.3 Hz, 1H), 4.78 – 4.56 (m, 3H), 4.32 (dd, *J* = 32.6, 10.6 Hz, 2H), 4.07 – 3.74 (m, 4H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.76 (s, 3H), 2.71 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.43 (s, 3H), 2.42 – 2.32 (m, 1H), 1.96 – 1.86 (m, 1H). Mass (*m/z*) 584.4 [*M*+H]⁺.

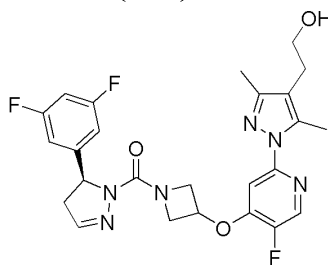
1-(4-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-N-((R)-tetrahydrofuran-3-yl)-1H-pyrazole-4-carboxamide (258)



The titled compound **258** was prepared in 45.4% yield according to the procedure outlined for compound **225**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 6.1 Hz, 1H), 6.86 – 6.66 (m, 4H), 5.81 (d, *J* = 7.5 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.15 (tt, *J* = 6.4, 4.0 Hz, 1H), 4.81 – 4.54 (m, 3H), 4.32 (dd, *J* = 32.2, 10.3 Hz, 2H), 4.07 – 3.72 (m, 4H), 3.36 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.76 (s, 3H), 2.71 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 2.43 (s, 3H), 2.36 (ddt, *J* =

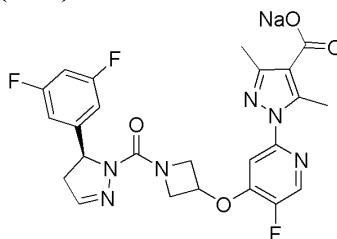
13.2, 8.6, 7.1 Hz, 1H), 1.91 (dddd, $J = 13.2, 8.0, 5.4, 3.1$ Hz, 1H). Mass (m/z) 584.4 $[M+H]^+$.

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(4-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-1-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (259)



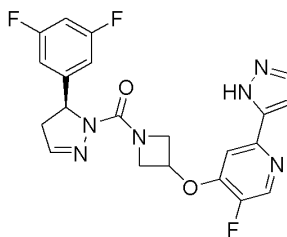
The titled compound **259** was prepared in 28.9% yield according to the procedure outlined for compound **202**. ^1H NMR (400 MHz, Chloroform- d) δ 8.15 (d, $J = 2.5$ Hz, 1H), 7.19 (d, $J = 6.2$ Hz, 1H), 6.81 – 6.64 (m, 4H), 5.32 – 5.25 (m, 1H), 5.15 (td, $J = 6.5, 3.3$ Hz, 1H), 4.71 – 4.56 (m, 3H), 4.31 (dd, $J = 31.4, 10.3$ Hz, 2H), 3.72 (t, $J = 6.7$ Hz, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.76 – 2.66 (m, 3H), 2.55 (s, 3H), 2.27 (s, 2H). Mass (m/z) 514.30 $[M+H]^+$

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxylate (260)



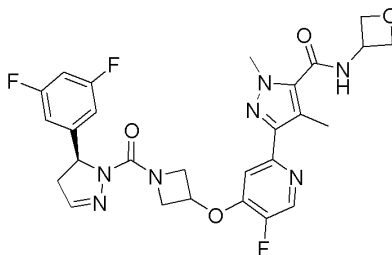
The titled compound **260** was prepared from compound **233**. Mass (m/z) 537.2 $[M+H]^+$

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(1H-pyrazol-5-yl)pyridin-4-yl)oxy)azetidin-1-yl)methanone (261)



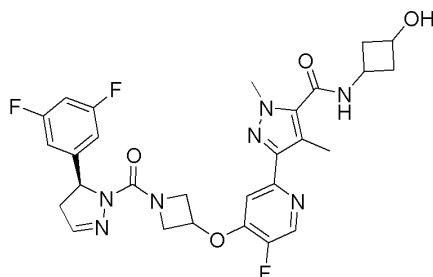
The titled compound **261** was prepared from **3-04** in a yield of 3.4% according to the procedure outlined for compound **3**. Mass (m/z) 443.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.06 (brs, 1H), 8.47 (s, 1H), 7.82 (s, 1H), 7.39 (d, *J* = 0.8 Hz, 1H), 7.14-7.08 (m, 1H), 7.03 (t, *J* = 1.6 Hz, 1H), 6.98 – 6.86 (m, 2H), 6.78 (s, 1H), 5.37-5.27 (m, 1H), 5.25 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.68 – 4.43 (m, 2H), 4.17-3.97 (m, 2H), 3.39 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.64 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H).

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-N-(oxetan-3-yl)-1H-pyrazole-5-carboxamide (262)



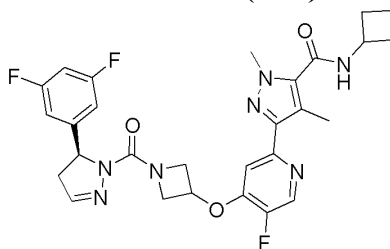
The titled compound **262** was prepared from **245** in a yield of 30% according to the procedure outlined for compound **68**. Mass (m/z) 570.1 [M+H]⁺.

(S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(3-hydroxycyclobutyl)-1,4-dimethyl-1H-pyrazole-5-carboxamide (263)



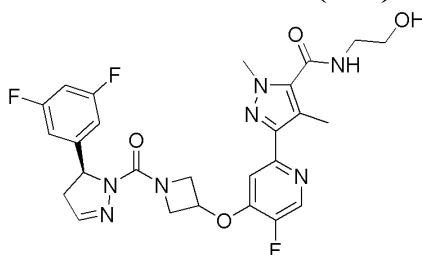
The titled compound **263** was prepared from **245** in a yield of 31% according to the procedure outlined for compound **68**. Mass (m/z) 584.1 $[M+H]^+$.

- 5 **(S)-N-cyclobutyl-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-1,4-dimethyl-1H-pyrazole-5-carboxamide (264)**



- 10 The titled compound **264** was prepared from **245** in a yield of 29% according to the procedure outlined for compound **68**. Mass (m/z) 568.1 $[M+H]^+$.

- (S)-3-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-N-(2-hydroxyethyl)-1,4-dimethyl-1H-pyrazole-5-carboxamide (265)**

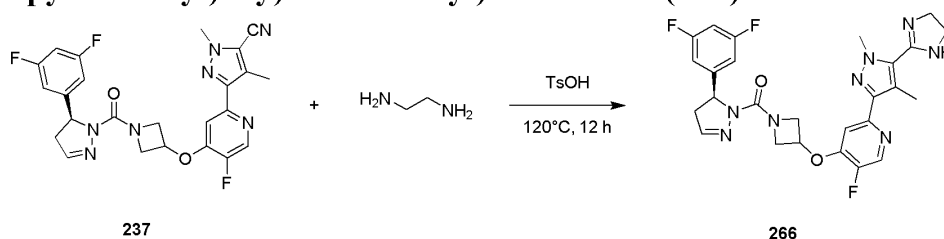


- 15

The titled compound **265** was prepared from **245** in a yield of 22% according to the procedure outlined for compound **68**. Mass (m/z) 558.1

[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J* = 2.8 Hz, 1H), 7.24 (d, *J* = 6.8 Hz, 1H), 6.86-6.59 (m, 4H), 6.40 (m, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.14 (td, *J* = 6.4, 3.3 Hz, 1H), 4.62 (d, *J* = 9.7 Hz, 2H), 4.32 (dd, *J* = 32.8, 10.3 Hz, 2H), 4.10 (s, 3H), 3.91-3.80 (m, 2H), 3.65 (q, *J* = 5.3 Hz, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.8 Hz, 1H), 2.54 (s, 3H).

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(5-(4,5-dihydro-1H-imidazol-2-yl)-1,4-dimethyl-1H-pyrazol-3-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (266)

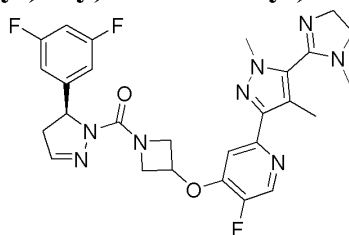


10

To a solution of compound **237** (30 mg, 60.6 μmol) in ethane-1,2-diamine (2 mL) was added TsOH (105 mg, 605.5 μmol). The reaction mixture was stirred at 120°C for 12 h. The crude mixture was purified by Pre-HPLC to give compound **266** (4 mg, 12%) as a white solid MS (*m/z*) 539.1 [M+H]⁺.

15

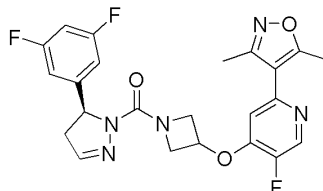
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(1,4-dimethyl-5-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazol-3-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (267)



The titled compound **267** was prepared from **237** in a yield of 8% according to the procedure outlined for compound **266**. Mass (*m/z*) 553.1 [M+H]⁺.

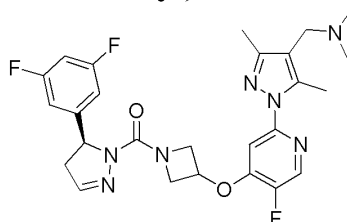
20

(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(3,5-dimethylisoxazol-4-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (268)



5 The titled compound **268** was prepared from **3-02** in a yield of 20.2% according to the procedure outlined for compound **3**. MS (m/z) 472.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.54 (d, $J = 3.0$ Hz, 1H), 7.08 (tt, $J = 9.3, 2.4$ Hz, 1H), 7.01 – 6.98 (m, 2H), 6.91 – 6.86 (m, 2H), 5.28 – 5.17 (m, 2H), 4.52 (s, 2H), 4.07 (d, $J = 14.5$ Hz, 2H), 3.36 (ddd, $J = 18.4,$
10 12.0, 1.6 Hz, 1H), 2.62 (ddd, $J = 18.7, 6.6, 1.7$ Hz, 1H), 2.50 (s, 3H), 2.31 (s, 3H).

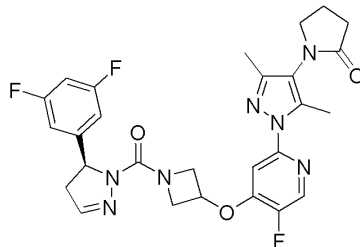
(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2-(4-((dimethylamino)methyl)-3,5-dimethyl-1H-pyrazol-1-yl)-5-fluoropyridin-4-yl)oxy)azetidin-1-yl)methanone (269)



15

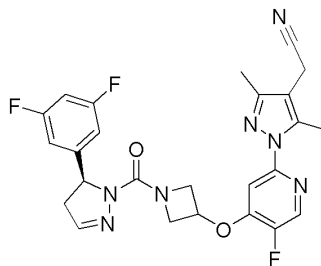
The titled compound **269** was prepared in a yield of 16.8% according to the procedure outlined for compound **110**. 1H NMR (400 MHz, DMSO- d_6) δ 8.37 (d, $J = 2.7$ Hz, 1H), 7.25 (d, $J = 6.3$ Hz, 1H), 7.10 (tt, $J = 9.3, 2.4$ Hz, 1H), 7.02 (d, $J = 1.7$ Hz, 1H), 6.96 – 6.88 (m, 2H), 5.32 (tt, $J = 6.5, 3.6$ Hz, 1H), 5.25 (dd, $J = 12.1, 6.6$ Hz, 1H), 4.52 (s, 2H), 4.08 (s, 2H), 3.39 (ddd, $J = 18.7, 12.1, 1.8$ Hz, 1H), 3.18 (s, 2H), 2.62 (dd, $J = 6.5, 1.8$ Hz, 1H), 2.52 (s, 3H) 2.19 (s, 3H), 2.12 (s, 6H). Mass (m/z) 528.2 $[M+H]^+$.
20

(S)-1-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)pyrrolidin-2-one (270)



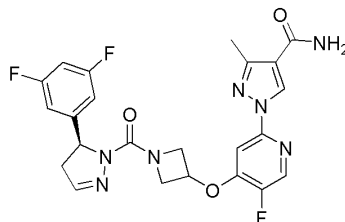
5 The titled compound **270** was prepared in a yield of 20.1% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.40 (d, J = 2.6 Hz, 1H), 7.25 (d, J = 6.3 Hz, 1H), 7.10 (tt, J = 9.2, 2.3 Hz, 1H), 7.03 (d, J = 1.7 Hz, 1H), 6.93 (qd, J = 6.6, 3.3 Hz, 2H), 5.34 (tt, J = 6.6, 3.6 Hz, 1H), 5.25 (dd, J = 12.1, 6.6 Hz, 1H), 4.53 (s, 2H), 4.09 (s, 2H), 3.59 (t, J = 6.9 Hz, 2H), 3.39 (ddd, J = 18.8, 12.2, 1.8 Hz, 1H), 2.62 (dd, J = 6.7, 1.8 Hz, 1H), 2.42 (t, J = 8.0 Hz, 2H), 2.37 (s, 3H), 2.12 (d, J = 6.7 Hz, 5H). Mass (m/z) 554.2 [$\text{M}+\text{H}$] $^+$.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)acetonitrile (271)



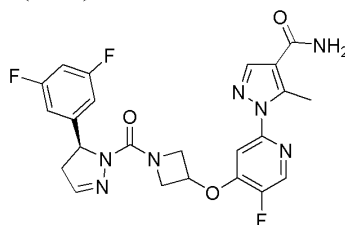
The titled compound **271** was prepared in a yield of 35.4% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform- d) δ 8.15 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 6.1 Hz, 1H), 6.82 – 6.63 (m, 4H), 5.30 – 5.23 (m, 1H), 5.15 (s, 1H), 4.62 (s, 2H), 4.31 (dd, J = 31.6, 10.2 Hz, 2H), 3.47 (s, 2H), 3.41 – 3.30 (m, 1H), 2.74 – 2.66 (m, 1H), 2.59 (s, 3H), 2.31 (s, 3H). Mass (m/z) 510.3 [$\text{M}+\text{H}$] $^+$

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3-methyl-1H-pyrazole-4-carboxamide (272)



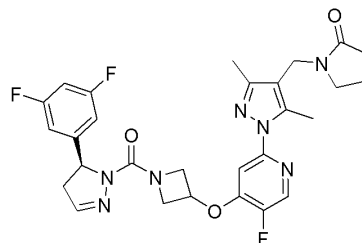
5 The titled compound **272** was prepared in a yield of 73.2% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.14 (d, $J = 2.5$ Hz, 1H), 7.30 (d, $J = 6.1$ Hz, 1H), 6.85 – 6.63 (m, 4H), 5.63 (s, 2H), 5.27 (dd, $J = 12.1, 6.4$ Hz, 1H), 5.20-5.22 (m, 1H), 4.72 – 4.58 (m, 2H), 4.32 (dd, $J = 30.4, 9.4$ Hz, 2H),
 10 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H), 2.55 (s, 3H). Mass (m/z) 500.30 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxamide (273)



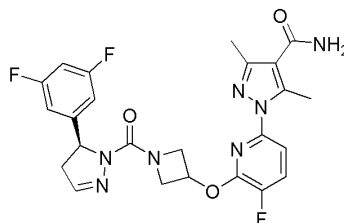
15 The titled compound **273** was prepared in a yield of 21.2% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, $J = 2.4$ Hz, 1H), 7.79 (s, 1H), 7.17 (d, $J = 6.1$ Hz, 1H), 6.82 – 6.65 (m, 4H), 5.61 (m, 2H), 5.27 (dd, $J = 12.6, 6.8$ Hz, 1H), 5.18 – 5.08 (m, 1H), 4.62 (m, 2H), 4.31 (dd, $J = 28.8, 10.4$ Hz, 2H), 3.35
 20 (ddd, $J = 18.6, 12.1, 1.7$ Hz, 1H), 2.89 (s, 3H), 2.70 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H). Mass (m/z) 500.30 $[\text{M}+\text{H}]^+$

(S)-1-((1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)pyrrolidin-2-one (274)



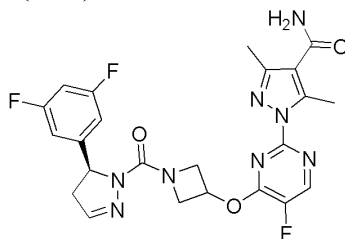
5 The titled compound **274** was prepared in a yield of 28.1% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 6.2 Hz, 1H), 6.82 – 6.62 (m, 4H), 5.31 – 5.23 (m, 1H), 5.148-5.10(m, 1H), 4.69-4.54 (m, 2H), 4.39-4.22 (m, 2H), 4.32 (s, 2H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H),
 10 3.23 (t, J = 7.1 Hz, 2H), 2.69 (ddd, J = 18.6, 6.4, 1.7 Hz, 1H), 2.57 (s, 3H), 2.41 (t, J = 8.1 Hz, 2H), 2.26 (s, 3H), 1.96 (p, J = 7.6 Hz, 2H). Mass (m/z) 568.40 $[\text{M}+\text{H}]^+$

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (275)



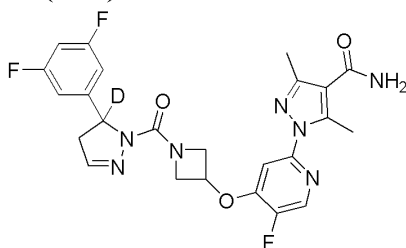
The titled compound **275** was prepared in a yield of 58.2% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.53 (dd, J = 9.1, 8.4 Hz, 1H), 7.37 (dd, J = 8.4, 2.7 Hz, 1H), 6.79 – 6.74 (m, 3H), 6.72-6.65 (m, 1H), 5.69 (s, 2H), 5.40-5.34 (m, 1H), 5.27 (dd, J = 12.2, 6.5 Hz, 1H), 4.65 – 4.52 (m, 2H), 4.38 – 4.22 (m, 2H), 3.34 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.77 (s, 3H), 2.69 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.48 (s, 3H). Mass (m/z) 514.3 $[\text{M}+\text{H}]^+$

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (276)



5 The titled compound **276** was prepared in a yield of 82.3% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 6.84 – 6.64 (m, 4H), 5.62 (s, 2H), 5.52 (tt, J = 6.6, 4.0 Hz, 1H), 5.26 (dd, J = 12.2, 6.4 Hz, 1H), 4.70 – 4.55 (m, 2H), 4.31 (dd, J = 28.4, 10.5 Hz, 2H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.84 (s, 3H), 2.70 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.52 (s, 3H). Mass (m/z) 515.4 $[\text{M}+\text{H}]^+$.

1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl-5-d)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazole-4-carboxamide (277)

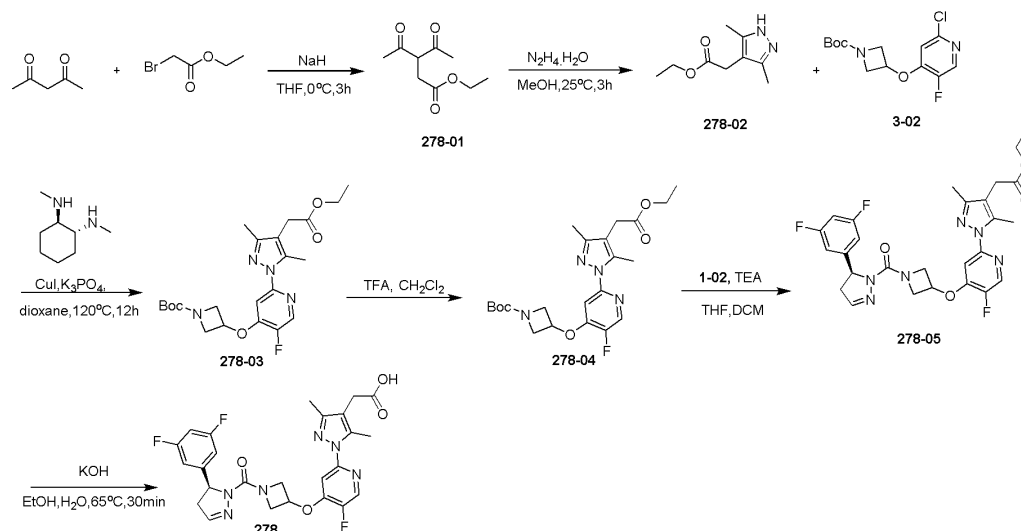


15

The titled compound **277** was prepared in a yield of 26% according to the procedure outlined for compound **110**. Mass (m/z) 515.1 $[\text{M}+\text{H}]^+$.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)acetic acid (278)

20



Step 1: Pentane-2,4-dione (10 g, 100 mmol) was dissolved in 100 ml of dry THF, NaH (3.6 g, 150 mmol) was added to the above solution at 0°C, the mixture was stirred for 1h. Then ethyl 2-bromoacetate (16.7g, 100 mmol) was added to the above solution, the mixture was stirred for 3 h. The mixture was added water and extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography gave compound **278-01** (15 g, 80.6%) as a yellow oil. Mass (m/z) 186.2 [M+H]⁺.

Step 2: **278-01** (15 g, 80.6 mmol), N₂H₄·H₂O (4 g, 120 mmol) were placed in MeOH (200 mL). The mixture was stirred rt for 3 h, was added water and extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **278-02** (10 g, 79.4%) as a yellow oil. Mass (m/z) 183.2 [M+H]⁺.

Step 3: **278-02** (10 g, 33.1 mmol) and **3-02** (10 g, 54 mmol) was dissolved in 200 mL of dry dioxane, CuI (10.7g, 56.3 mmol), K₃PO₄ (12 g, 56.3 mmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (7.9 g, 56.3 mmol) was added to the above solution, the mixture was stirred for 12 h at 120°C. Water was added and extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel

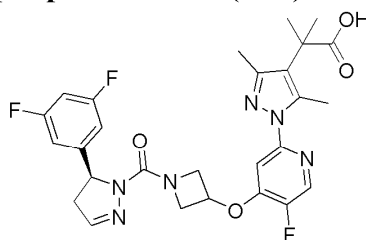
chromatography gave the compound **278-03** (6 g, 40.5%). Mass (m/z) 449.2 $[M+H]^+$.

Step 4: 278-03 (1 g, 2.23 mmol) was dissolved in 10mL of DCM, trifluoroacetic acid (1mL) was added, the mixture was stirred at r.t. for 30 min. Concentrated to give the desired product **278-04**, which was used for next step without further purification.

Step 5: 278-04 (crude), **1-02** (616 mg, 2.23 mmol) and TEA (1 mL) were dissolved in THF (30 mL) DMF (5mL) and stirred at 65°C for 6 h. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **278-05** (600 mg, 49.5%). Mass (m/z) 556.4 $[M+H]^+$.

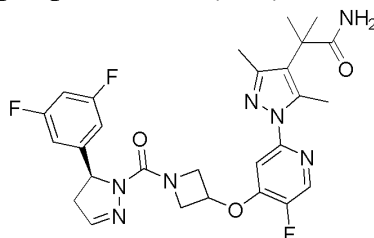
Step 6: 278-05 (600 mg, 1.08 mmol), were dissolved in EtOH (10 mL), KOH (5 mL, 2M) was added, stirred at 65°C for 12h. Water and was added and extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. purification by prep-HPLC to give the titled compound **278** (300 mg, 52.6%). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.35 (d, $J = 2.6$ Hz, 1H), 7.19 (d, $J = 6.3$ Hz, 1H), 7.08 (tt, $J = 9.3, 2.4$ Hz, 1H), 7.00 – 6.99 (m, 1H), 6.92 – 6.87 (m, 2H), 5.29 (tt, $J = 6.5, 3.5$ Hz, 1H), 5.21 (dd, $J = 12.1, 6.6$ Hz, 1H), 4.49 (s, 2H), 4.05 (s, 2H), 3.42-3.35 (m, 1H), 3.33 (s, 2H), 2.66 – 2.57 (m, 1H), 2.42 (s, 3H), 2.12 (s, 3H). Mass (m/z) 528.4 $[M+H]^+$.

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-2-methylpropanoic acid (279)



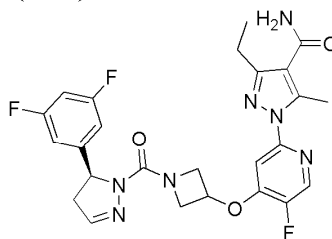
The titled compound **279** was prepared in a yield of 15.8% according to the procedure outlined for compound **110**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.37 (d, J = 2.7 Hz, 1H), 7.15 (d, J = 6.3 Hz, 1H), 7.08 (tt, J = 9.3, 2.4 Hz, 1H), 7.01 – 6.99 (m, 1H), 6.93 – 6.83 (m, 2H), 5.28 (dq, J = 6.4, 3.3, 2.9 Hz, 1H), 5.21 (dd, J = 12.1, 6.6 Hz, 1H), 4.48 (s, 2H), 4.04 (s, 2H), 3.35-3.20 (m, 1H), 2.65 – 2.58 (m, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.45 (s, 6 H). Mass (m/z) 557.4 $[\text{M}+\text{H}]^+$

(S)-2-(1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3,5-dimethyl-1H-pyrazol-4-yl)-2-methylpropanamide (**280**)



The titled compound **280** was prepared in a yield of 16.3% according to the procedure outlined for compound **68**. ^1H NMR (400 MHz, Chloroform- d) δ 8.17 (d, J = 2.5 Hz, 1H), 7.10 (d, J = 6.1 Hz, 1H), 6.84 – 6.63 (m, 4H), 5.59 (s, 1H), 5.32 (s, 1H), 5.26 (dd, J = 12.2, 6.5 Hz, 1H), 5.14 (tt, J = 6.4, 4.0 Hz, 1H), 4.61 (s, 2H), 4.30 (dd, J = 32.0, 10.2 Hz, 2H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, J = 18.6, 6.5, 1.8 Hz, 1H), 2.51 (s, 3H), 2.35 (s, 3H), 1.58 (s, 6H). Mass (m/z) 556.4 $[\text{M}+\text{H}]^+$.

(S)-1-(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)-3-ethyl-5-methyl-1H-pyrazole-4-carboxamide (**281**)



The titled compound **281** was prepared in a yield of 25.2% according to the procedure outlined for compound **110**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.17 (d, *J* = 6.0 Hz, 1H), 6.84 – 6.65 (m, 4H), 5.58 (s, 2H), 5.26 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.14 (td, *J* = 6.4, 3.3 Hz, 1H), 4.61 (s, 2H), 4.31 (dd, *J* = 34.9, 9.8 Hz, 2H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.85 (q, *J* = 7.5 Hz, 2H), 2.78 (s, 3H), 2.70 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 1.31 (t, *J* = 7.5 Hz, 3H). Mass (m/z) 510.1 [M+H]⁺.

Protocol for HT29 cells 0FBS assay in vitro

1. Materials

Cell line: HT-29 (ATCC® HTB-38™)
Culture medium: McCoy's 5A, Gibco, Cat No. 16600-082
FBS, Gibco, Cat No. 10099-141C
Trypsin: Gibco, Cat No. 25200-056
DMSO: Sigma, Cat No. 67-68-5, 1L
Assay plate: Corning#3903
Compound dilution plate: Corning#3357
Inducers: TNF α , GenScript, Cat No. Z01001-50,
SmacM, Cat. No., HY-15989, MedChemExpress (MCE)
Z_VAD FMK, TargetMol, T6013
Cell Titer-Glo® Luminescent Cell Viability Assay Kit: Promega, Cat No. G7573
EnVision: PerkinElmer, 2105-0010

2. Cell seeding of HT-29 cells

1) HT-29 cells were checked every day to make sure they are healthy and growing as expected. They were split sub-culturing when were approximately 80% confluent.

2) First pre-warm the culture medium of McCoy's 5A medium (Gibco, Cat No. 16600-082) with 10% FBS (Gibco, Cat No. 10099-141C) in 37°C water bath for at least 30 min.

3) Growing cells to desired level of confluency 80% in a T75 flask, aspirate the medium, and wash with warm PBS two times.

4) Add 2-3 ml fresh warm trypsin (Gibco, Cat No. 25200-056) solution. Transfer the flask to a 37°C incubator.

5) After 5 minutes, tap the side of the flask, and examine the flask under a microscope for lifting. If necessary, return the cells to the incubator for an additional 5-10 minutes, with occasional tapping, until lifting is complete.

6) Quickly neutralize the trypsin reaction by adding 6-9 ml cell culture medium, then transfer the cells to sterile 15 ml conical tubes. Pellet the cells by centrifugation at 300 x g for 7 minutes, then decant the supernatant.

7) Resuspend the cells in fresh cell culture medium. Do cell counting with hemocytometer.

8) Seed 100µl of 5,000 cells into each well of the sterile 96-well cell culture plate (Corning 3903) and culture overnight at 37 °C with 5% CO₂.

3. Compounds titration and treatment of HT-29 cells

1) All batches of compounds (CPDs) (e.g., compound 1-281) were dissolved in DMSO (Dimethyl sulfoxide) as 20mM stock solution.

2) Take 3µl 20mM stock solution of CPDs to 27µl DMSO and mix well, continue the titration ratio of 1:3 (20µl CPDs+ 40µl DMSO), e.g., to give solutions of CPDS at 6.6 mM, 2.2 mM, etc., till the 10 points end.

3) Take out assay plates with HT-29 cells from incubator, remove all culture medium then wash 1 time with 1xPBS, and change fresh McCoy's 5A medium of FBS free with a cocktail of TNF-α(10ng/ml), the SMAC mimetic(6µM) and zVAD-FMK (10µM) to stimulate the HT-29 cells to increase pRIPK1 levels and necroptosis.

4) Add 0.5 µL of the diluted compound to the corresponding 96-well assay plates.

5) Incubate the assay plates for 20 hours at 37 °C with 5% CO₂.

4. Performing cell viability detection of HT-29 cells after treated with compounds

1) The CellTiter-Glo® Luminescent Cell Viability Assay was employed to detect the ATP levels of viable HT-29 cells.

5 2) Equilibrate the CellTiter-Glo® buffer and the lyophilized substrate to room temperature prior to use.

3) Resuspend the CellTiter-Glo® substrate with CellTiter-Glo® buffer, mix by gently vortexing to obtain a homogeneous solution.

4) Pipette 20 µl the enzyme/substrate mixture by multi-channel pipette
10 into the 96-well assay plates from step 5) under the Compounds titration and treatment stage.

5) Place the plates on an orbital shaker and mix the contents for 3 minutes to induce cell lysis.

6) Then allow the plates to incubate at room temperature for 10
15 minutes to stabilize luminescent signal.

7) Read and record luminescence signal with EnVision.

8) The geometric mean EC₅₀ of the compounds were calculated from
10 points response dose with duplicate. RIP1 inhibitory activity of compounds 1-281 is summarized in Tables 2 and 4. In Tables 2 and 4,
20 activity is provided as follows: +++ = 0.1 nM ≤ EC₅₀ < 100 nM; ++ = 100 nM ≤ EC₅₀ < 1000 nM; + = 1000 nM ≤ EC₅₀ < 10000 nM.