PYRIDAZINONE C5AR1 ANTAGONISTS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 63/565,212 filed March 14, 2024, the entirety of which is incorporated herein by reference.

BACKGROUND

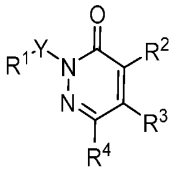
[0002] The C5a receptor, also known as complement component 5a receptor 1 (C5aR1) or CD88 (Cluster of Differentiation 88) is a G protein-coupled receptor for C5a. It functions as a complement receptor.

[0003] C5a is a potent immunomodulator, but also has emerging roles outside of immunity during embryonic development. Its production is tightly controlled in order to produce a rapid response to tissue injury/pathogens yet protect against unwanted activity on host tissue. The disruption of this control can lead to the overproduction of C5a, which can lead to an uncontrolled inflammatory response. C5a has been associated with a number of autoimmune, inflammatory, and neurodegenerative disorders. Thus, targeting C5aR1 with effective small molecule modulators would be useful in the treatment of several types of diseases (*e.g.*, neurodegenerative disorders).

SUMMARY

[0004] The present disclosure provides compounds that are modulators of C5aR1 (*e.g.*, antagonists). These compounds provide new compositions and methods for the treatment of diseases associated with C5aR1 activity.

[0005] In one aspect, provided are compounds of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein:

R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 is optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^3 is hydrogen, halogen, optionally substituted alkyl, or optionally substituted aryl;

R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,$-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, $-C(=NR^A)NR^AOR^A$, or $-NR^AC(=O)R^A$;

Y is $-C(R^5)_2-$ or a bond;

each R^5 is independently hydrogen, halogen, or optionally substituted alkyl; and

each R^A is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

[0006] In another aspect, provided are pharmaceutical compositions comprising a compound of Formula (**I**), or a tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007] In another aspect, provided are methods of treating a disease or disorder in a subject in need thereof, the methods comprising administering an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) to the subject.

[0008] In another aspect, provided are methods of antagonizing C5aR1, the methods comprising contacting C5aR1 with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**).

[0009] In another aspect, provided is a kit comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**), and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

[0010] The details of certain embodiments of the invention are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the invention will be apparent from the Definitions, Examples, and Claims. It should be understood that the aspects described herein are not limited to specific embodiments, methods, or configurations, and as such can, of course, vary. It is also to be

understood that the terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

DEFINITIONS

Chemical Definitions

[0011] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0012] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including high pressure liquid chromatography (HPLC) using chiral columns and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen *et al.*, Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H., Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers. While compounds may be depicted as racemic or as one or more diastereomers, enantiomers, or other isomers, all such racemic, diastereomer, enantiomer, or other isomer forms of that depicted are included in the present disclosure.

[0013] In a formula, ~~~ is a single bond where the stereochemistry of the moieties immediately attached thereto is not specified, - - - is absent or a single bond, and ═ or ═ is a single or double bond.

[0014] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of ^{12}C with ^{13}C or ^{14}C are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0015] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0016] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0017] The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, n-propyl, isopropyl), butyl (C_4) (*e.g.*, n-butyl, tert-butyl, sec-butyl, iso-butyl), pentyl (C_5) (*e.g.*, n-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C_6) (*e.g.*, n-hexyl). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr),

unsubstituted isopropyl (i-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted n-butyl (n-Bu), unsubstituted tert-butyl (tert-Bu or t-Bu), unsubstituted sec-butyl (sec-Bu), unsubstituted isobutyl (i-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CF_3$, Bn).

[0018] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

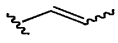
[0019] The term "alkoxy" refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. In some embodiments, the alkoxy moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 3 carbon atoms ("C_{1-3} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxy"). Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0020] The term "alkoxyalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by an alkoxy group, as defined herein. In some embodiments, the alkoxyalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxyalkyl").

[0021] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In some embodiments, a heteroalkyl group is a saturated

group having 1 to 18 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-18} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 16 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-16} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 14 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-14} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, the heteroalkyl group defined herein is a partially unsaturated group having 1 or more heteroatoms within the parent chain and at least one unsaturated carbon, such as a carbonyl group. For example, a heteroalkyl group may comprise an amide or ester functionality in its parent chain such that one or more carbon atoms are unsaturated carbonyl groups. Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl.

[0022] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl").

In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-10} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-CH=CHCH_3$ or ) may be an (E)- or (Z)-double bond.

[0023] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2

heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0024] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0025] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group

has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0026] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8),

cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0027] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0028] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3-14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3-14 membered heterocyclyl.

[0029] In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0030] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0031] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10}

aryl"; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0032] "Arylalkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0033] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0034] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered

aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0035] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0036] "Heteroarylalkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0037] The term "unsaturated bond" refers to a double or triple bond.

[0038] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0039] The term "saturated" refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[0040] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0041] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For

purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The disclosure is not intended to be limited in any manner by the exemplary substituents described herein.

[0042] When substituted, exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-SF_5$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_3$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_3^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, $-R^{aa}$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$,

$-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3{}^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl,

heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1-6}$ alkyl, $–ON(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_3^+X^–$, $–NH(C_{1-6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1-6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), $–N(OH)(C_{1-6}$ alkyl), –NH(OH), –SH, $–SC_{1-6}$ alkyl, $–SS(C_{1-6}$ alkyl), $–C(=O)(C_{1-6}$ alkyl), $–CO_2H$, $–CO_2(C_{1-6}$ alkyl), $–OC(=O)(C_{1-6}$ alkyl), $–OCO_2(C_{1-6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1-6}$ alkyl$)_2$, $–OC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)(C_{1-6}$ alkyl), $–N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl), $–NHCO_2(C_{1-6}$ alkyl), $–NHC(=O)N(C_{1-6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1-6}$ alkyl), $–OC(=NH)(C_{1-6}$ alkyl), $–OC(=NH)OC_{1-6}$ alkyl, $–C(=NH)N(C_{1-6}$ alkyl$)_2$, $–C(=NH)NH(C_{1-6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1-6}$ alkyl$)_2$, $–OC(=NH)NH(C_{1-6}$ alkyl), $–OC(=NH)NH_2$, $–NHC(=NH)N(C_{1-6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1-6}$ alkyl), $–SO_2N(C_{1-6}$ alkyl$)_2$, $–SO_2NH(C_{1-6}$ alkyl), $–SO_2NH_2$, $–SO_2(C_{1-6}$ alkyl), $–SO_2O(C_{1-6}$ alkyl), $–OSO_2(C_{1-6}$ alkyl), $–SO(C_{1-6}$ alkyl), $–Si(C_{1-6}$ alkyl$)_3$, $–OSi(C_{1-6}$ alkyl$)_3$ $–C(=S)N(C_{1-6}$ alkyl$)_2$, $C(=S)NH(C_{1-6}$ alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1-6}$ alkyl), $–C(=S)SC_{1-6}$ alkyl, $–SC(=S)SC_{1-6}$ alkyl, $–P(=O)(OC_{1-6}$ alkyl$)_2$, $–P(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(OC_{1-6}$ alkyl$)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[0043] The term “halo” or “halogen” refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0044] The term “hydroxyl” or “hydroxy” refers to the group –OH. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–OR^{aa}$, $–ON(R^{bb})_2$, $–OC(=O)SR^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–OC(=O)N(R^{bb})_2$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$,

$-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0045] The term "amino" refers to the group $-NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0046] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, and $-NHP(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-NH(R^{bb})$ is not hydrogen.

[0047] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, and $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0048] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $-N(R^{bb})_3$ and $-N(R^{bb})_3{}^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0049] The term "sulfonyl" refers to a group selected from $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, and $-SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0050] The term "sulfinyl" refers to the group $-S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0051] The term "acyl" refers to a group having the general formula: $-C(=O)R^{X1}$, $-C(=O)OR^{X1}$, $-C(=O)-O-C(=O)R^{X1}$, $-C(=O)SR^{X1}$, $-C(=O)N(R^{X1})_2$, $-C(=S)R^{X1}$, $-C(=S)N(R^{X1})_2$, $-C(=S)O(R^{X1})$, $-C(=S)S(R^{X1})$, $-C(=NR^{X1})R^{X1}$, $-C(=NR^{X1})OR^{X1}$, $-C(=NR^{X1})SR^{X1}$, or $-C(=NR^{X1})N(R^{X1})_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or

unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (–CHO), carboxylic acids ($–CO_2H$), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0052] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0053] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)(OR^{cc})_2$, $–P(=O)(R^{aa})_2$, $–P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{2-10}alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein.

[0054] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$,

$-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0055] For example, nitrogen protecting groups such as amide groups (*e.g.*, $-C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzyloxyacylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine derivative, o-nitrobenzamide and o-(benzoyloxymethyl)benzamide.

[0056] Nitrogen protecting groups such as carbamate groups (*e.g.*, $-C(=O)OR^{aa}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2′- and 4′-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz),

p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0057] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4′,8′-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0058] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N′-p-toluenesulfonylaminoacyl derivative, N′-phenylaminothioacyl derivative, N-benzoylphenylalanyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N-(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In certain embodiments, a nitrogen protecting group is benzyl (Bn), tert-butyloxycarbonyl (BOC), carbobenzyloxy (Cbz), 9-flurenylmethyloxycarbonyl (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl (Ac), benzoyl (Bz), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethyloxycarbonyl (Troc), triphenylmethyl (Tr), tosyl (Ts), brosyl (Bs), nosyl (Ns), mesyl (Ms), triflyl (Tf), or dansyl (Ds).

[0059] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen

protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0060] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t-butyldimethylsilyl (TBDMS), t-

butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, t-butyl carbonate (BOC or Boc), p-nitrophenyl carbonate, benzyl carbonate, p-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, o-nitrobenzyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate, o-(methoxyacyl)benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, alkyl N-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). In certain embodiments, an oxygen protecting group is silyl. In certain embodiments, an oxygen protecting group is t-butyldiphenylsilyl (TBDPS), t-butyldimethylsilyl (TBDMS), triisoproylsilyl (TIPS), triphenylsilyl (TPS), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsiloxymethyl (TOM), acetyl (Ac), benzoyl (Bz), allyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-trimethylsilylethyl carbonate, methoxymethyl (MOM), 1-ethoxyethyl (EE), 2-methyoxy-2-propyl (MOP), 2,2,2-trichloroethoxyethyl, 2-methoxyethoxymethyl (MEM), 2-trimethylsilylethoxymethyl (SEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), tetrahydrofuranyl (THF), p-methoxyphenyl (PMP), triphenylmethyl (Tr), methoxytrityl (MMT), dimethoxytrityl (DMT), allyl, p-methoxybenzyl (PMB), t-butyl, benzyl (Bn), allyl, or pivaloyl (Piv).

[0061] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$,

$-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. In certain embodiments, a sulfur protecting group is acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl.

[0062] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*i.e.*, including one formal negative charge). An anionic counterion may also be multivalent (*i.e.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0063] A "leaving group" (LG) is an art-understood term referring to an atomic or molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. *See e.g.*, Smith, March Advanced Organic Chemistry 6th ed. (501–502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, fluoro, chloro, bromo, iodo) and activated substituted hydroxyl groups (*e.g.*, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-OP(=O)_2R^{aa}$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-OP(=O)_2N(R^{bb})_2$, and $-OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein). Additional examples of suitable leaving groups include, but are not limited to, halogen alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy,

aryloxy, methoxy, *N*,*O*-dimethylhydroxylamino, pixyl, and haloformates. In some embodiments, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, –OTs), methanesulfonate (mesylate, –OMs), *p*-bromobenzenesulfonyloxy (brosylate, –OBs), –$OS(=O)_2(CF_2)_3CF_3$ (nonaflate, –ONf), or trifluoromethanesulfonate (triflate, –OTf). In some embodiments, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some embodiments, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. In some embodiments, the leaving group is a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

[0064] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[0065] The term "antagonist" refers to an agent that (i) decreases or suppresses one or more effects of another agent; and/or (ii) decreases or suppresses one or more biological events. In some embodiments, an antagonist may reduce level and/or activity or one or more agents that it targets. An antagonist may be direct (in which case it exerts its influence directly upon its target) or indirect (in which case it exerts its influence by other than binding to its target; *e.g.*, by interacting with a regulator of the target, for example so that level or activity of the target is altered). In some embodiments, an antagonist may be a receptor antagonist, *e.g.*, a receptor ligand or drug that blocks or dampens a biological response by binding to and blocking a receptor rather than activating it like an agonist. In certain embodiments, compounds of Formula (**I**) are antagonists of C5aR1.

[0066] The term "agonist" refers to an agent that (i) increases or induces one or more effects of another agent; and/or (ii) increases or induces one or more biological events. In some embodiments, an agonist may increase level and/or activity or one or more agents that it targets. In various embodiments, agonists may be or include agents of various chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or other entity that shows the relevant agonistic activity. An agonist may be direct (in which case it exerts its influence directly upon its target) or indirect (in which case it

exerts its influence by other than binding to its target; *e.g.,* by interacting with a regulator of the target, for example so that level or activity of the target is altered). A partial agonist can act as a competitive antagonist in the presence of a full agonist, as it competes with the full agonist to interact with its target and/or a regulator thereof, thereby producing (i) a decrease in one or more effects of another agent, and/or (ii) a decrease in one or more biological events, as compared to that observed with the full agonist alone.

[0067] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts.

[0068] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and/or animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}\ alkyl)_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine

cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0069] The term "solvate" refers to forms of the compound, or a salt thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0070] The term "hydrate" refers to a compound that is associated with water molecules. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x\ H_2O$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2\ H_2O$) and hexahydrates ($R \cdot 6\ H_2O$)).

[0071] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0072] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[0073] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers".

When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (–)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0074] The term "polymorph" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). Many compounds can adopt a variety of different crystal forms (*i.e.*, different polymorphs). Typically, such different crystalline forms have different X-ray diffraction patterns, infrared spectra, and/or can vary in some or all properties such as melting points, density, hardness, crystal shape, optical and electrical properties, stability, solubility, and bioavailability. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate a given preparation. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0075] The term "co-crystal" refers to a crystalline structure composed of at least two components. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more other component(s), including, but not limited to, atoms, ions, molecules, or solvent molecules. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more solvent molecules. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more acid or base. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more components related to said compound, including, but not limited to, an isomer, tautomer, salt, solvate, hydrate, synthetic precursor, synthetic derivative, fragment, or impurity of said compound.

[0076] The term "prodrugs" refers to compounds that have cleavable groups that are removed, by solvolysis or under physiological conditions, to provide the compounds described herein, which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgaard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the

parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, C_{7-12} substituted aryl, and C_{7-12} arylalkyl esters of the compounds described herein may be preferred.

[0077] The terms "composition" and "formulation" are used interchangeably.

[0078] The term "modulate" means decreasing or inhibiting activity and/or increasing or augmenting activity. For example, modulating C5aR1 activity means decreasing or inhibiting C5aR1 activity and/or increasing or augmenting C5aR1 activity. The compounds disclosed herein may be administered to modulate C5aR1 for example, as an antagonist.

[0079] A "subject" to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term "patient" refers to a human subject in need of treatment of a disease. The subject may also be a plant. In certain embodiments, the plant is a land plant. In certain embodiments, the plant is a non-vascular land plant. In certain embodiments, the plant is a vascular land plant. In certain embodiments, the plant is a seed plant. In certain embodiments, the plant is a cultivated plant. In certain embodiments, the plant is a dicot. In certain embodiments, the plant is a monocot. In certain embodiments, the plant is a flowering plant. In some embodiments, the plant is a cereal plant, *e.g.*, maize, corn, wheat, rice, oat, barley, rye, or millet. In some embodiments, the plant is a legume, *e.g.*, a bean plant, *e.g.*, soybean plant. In some embodiments, the plant is a tree or shrub.

[0080] The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles

(such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucous, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample.

[0081] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[0082] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0083] The terms "condition," "disease," and "disorder" are used interchangeably.

[0084] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses.

[0085] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for C5aR1 deactivation (*e.g.*, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least

80%, at least 90%, at least 95%, at least 100%, at least 150%, at least 200%, at least 250%, at least 300%, or at least 500% decrease in the activity of C5aR1). In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder). In certain embodiments, a therapeutically effective amount is an amount sufficient for C5aR1 deactivation and treating a disease or disorder (*e.g.*, neurological disorder).

[0086] A "prophylactically effective amount" of a compound described herein is an amount sufficient to prevent a condition, or one or more signs or symptoms associated with the condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. In certain embodiments, a prophylactically effective amount is an amount sufficient for C5aR1 deactivation. In certain embodiments, a prophylactically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder). In certain embodiments, a prophylactically effective amount is an amount sufficient for C5aR1 deactivation and treating a disease or disorder (*e.g.*, neurological disorder).

[0087] As used herein, the term "activate" or "activation" in the context of proteins, for example, in the context of C5aR1, refers to an increase in the activity of the protein. In some embodiments, the term refers to an increase of the level of activity to a level that is statistically significantly higher than an initial level, which may, for example, be a baseline level of activity (*e.g.*, of wild-type C5aR1). In some embodiments, the term refers to an increase in the level of activity to a level that is greater than 1%, greater than 5%, greater than 10%, greater than 25%, greater than 50%, greater than 75%, greater than 100%, greater than 150%, greater than 200%, greater than 300%, greater than 400%, greater than 500%, or greater than 1000% of an initial level, which may, for example, be a baseline level of activity.

[0088] The term "immunotherapy" refers to a therapeutic agent that promotes the treatment of disease by inducing, enhancing, or suppressing an immune response. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies. Immunotherapies are typically, but not always, biotherapeutic agents. Numerous immunotherapies are used to treat cancer. These include, but are not

limited to, monoclonal antibodies, adoptive cell transfer, cytokines, chemokines, vaccines, and small molecule inhibitors.

[0089] The terms "biologic," "biologic drug," and "biological product" refer to a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, nucleic acids, and proteins. Biologics may include sugars, proteins, or nucleic acids, or complex combinations of these substances, or may be living entities, such as cells and tissues. Biologics may be isolated from a variety of natural sources (*e.g.*, human, animal, microorganism) and may be produced by biotechnological methods and other technologies.

[0090] The term "small molecule" or "small molecule therapeutic" refers to molecules, whether naturally occurring or artificially created (*e.g.*, via chemical synthesis) that have a relatively low molecular weight. Typically, a small molecule is an organic compound (*i.e.*, it contains carbon). The small molecule may contain multiple carbon-carbon bonds, stereocenters, and other functional groups (*e.g.*, amines, hydroxyl, carbonyls, and heterocyclic rings, etc.). In certain embodiments, the molecular weight of a small molecule is not more than about 1,000 g/mol, not more than about 900 g/mol, not more than about 800 g/mol, not more than about 700 g/mol, not more than about 600 g/mol, not more than about 500 g/mol, not more than about 400 g/mol, not more than about 300 g/mol, not more than about 200 g/mol, or not more than about 100 g/mol. In certain embodiments, the molecular weight of a small molecule is at least about 100 g/mol, at least about 200 g/mol, at least about 300 g/mol, at least about 400 g/mol, at least about 500 g/mol, at least about 600 g/mol, at least about 700 g/mol, at least about 800 g/mol, or at least about 900 g/mol, or at least about 1,000 g/mol. Combinations of the above ranges (*e.g.*, at least about 200 g/mol and not more than about 500 g/mol) are also possible. In certain embodiments, the small molecule is a therapeutically active agent such as a drug (*e.g.*, a molecule approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (C.F.R.)). The small molecule may also be complexed with one or more metal atoms and/or metal ions. In this instance, the small molecule is also referred to as a "small organometallic molecule." Preferred small molecules are biologically active in that they produce a biological effect in animals, preferably mammals, more preferably humans. Small molecules include, but are not limited to, radionuclides and imaging agents. In certain embodiments, the small molecule is a drug. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use in humans or animals by the appropriate governmental agency or regulatory body. For example, drugs approved for human use are listed by the FDA under 21

C.F.R. §§ 330.5, 331 through 361, and 440 through 460, incorporated herein by reference; drugs for veterinary use are listed by the FDA under 21 C.F.R. §§ 500 through 589, incorporated herein by reference. All listed drugs are considered acceptable for use in accordance with the present disclosure.

[0091] The term "therapeutic agent" refers to any substance having therapeutic properties that produce a desired, usually beneficial, effect. For example, therapeutic agents may treat, ameliorate, and/or prevent disease. Therapeutic agents, as disclosed herein, may be biologics or small molecule therapeutics, or combinations thereof.

[0092] Use of the phrase "at least one instance" refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0093] Other than in the examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." "About" and "approximately" shall generally mean an acceptable degree of error for the quantity measu

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

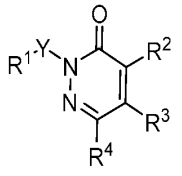
Compounds

[0094] Provided herein are compounds (e.g., a compound of any of the formulae herein) that are modulators of C5aR1 (*e.g.*, C5aR1 antagonists). In one aspect, the provided C5aR1 modulators are compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and pharmaceutical compositions thereof. Accordingly, the compounds are useful for the treatment and/or prevention of diseases and disorders associated with C5aR1 (*e.g.*, neurological diseases and disorders) in a subject in need thereof.

[0095] The compounds described herein interact with C5aR1. As described herein, the therapeutic effect may be a result of modulation (e.g., antagonism), binding, and/or modification of C5aR1 by the compounds described herein. The compounds may be provided for use in any composition, kit, or method described herein as a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

Compounds of Formula (I)

[0096] In one aspect, disclosed is a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein:

R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 is optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^3 is hydrogen, halogen, optionally substituted alkyl, or optionally substituted aryl;

R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,–OR^A, –$N(R^A)_2$, –$C(=O)N(R^A)_2$, –$C(=NR^A)NR^AOR^A$, or –$NR^AC(=O)R^A$;

Y is –$C(R^5)_2$– or a bond;

each R^5 is independently hydrogen, halogen, or optionally substituted alkyl; and

each R^A is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

[0097] In certain embodiments:

R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 is optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^3 is hydrogen, halogen, optionally substituted alkyl, or optionally substituted aryl;

R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,–OR^A, –$N(R^A)_2$, –$C(=O)N(R^A)_2$, or –$NR^AC(=O)R^A$;

Y is –$C(R^5)_2$– or a bond;

each R^5 is independently hydrogen, halogen, or optionally substituted alkyl; and

each R^A is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

Y

[0098] As described herein, Y is $–C(R^5)_2–$ or a bond; and each R^5 is independently hydrogen, halogen, or optionally substituted alkyl. In certain embodiments, Y is $–C(R^5)_2–$ or a bond. In certain embodiments, Y is $–C(R^5)_2–$; and each R^5 is independently hydrogen or optionally substituted alkyl. In certain embodiments, Y is $–C(R^5)_2–$. In some embodiments, each R^5 is independently hydrogen or optionally substituted alkyl. In certain embodiments, Y is $–CH_2–$. In certain embodiments, Y is a bond.

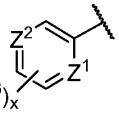
R^1

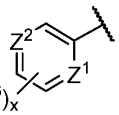
[0099] As described herein, R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl. In some embodiments, R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

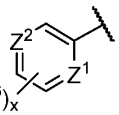
[00100] In certain embodiments, R^1 is optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted carbocyclyl. In certain embodiments, R^1 is optionally substituted aryl or optionally substituted heteroaryl.

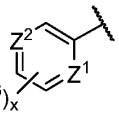
[00101] In certain embodiments, R^1 is optionally substituted aryl. In certain embodiments, R^1 is optionally substituted phenyl.

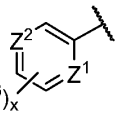
[00102] In certain embodiments, R^1 is optionally substituted heteroaryl. In certain embodiments, R^1 is optionally substituted pyridinyl, optionally substituted pyrazinyl, optionally substituted pyrimidinyl, or optionally substituted pyridazinyl. In certain embodiments, R^1 is optionally substituted pyridinyl or optionally substituted pyrazinyl. In certain embodiments, R^1 is optionally substituted phenyl, optionally substituted pyridinyl, or optionally substituted pyrazinyl. In certain embodiments, R^1 is optionally substituted pyridinyl. In certain embodiments, R^1 is optionally substituted pyrazinyl.

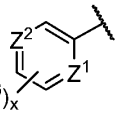
[00103] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and x is 0, 1, 2, 3, or 4. In some embodiments, x is 0. In certain embodiments, x is 1. In certain embodiments, x is 2. In certain embodiments, x is 3. In certain embodiments, x is 4.

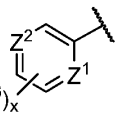
[00104] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, or $–OR^A$; and x is 0, 1, 2, or 3.

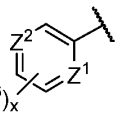
[00105] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and x is 0 or 1.

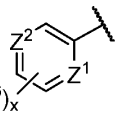
[00106] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, or $–OR^A$; and x is 0 or 1.

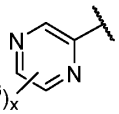
[00107] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, alkyl, haloalkyl, optionally substituted cycloalkyl, or $–OR^A$; R^A is alkyl or haloalkyl; and x is 0 or 1.

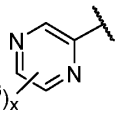
[00108] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, alkyl, haloalkyl, or $–OR^A$; R^A is alkyl or haloalkyl; and x is 0 or 1.

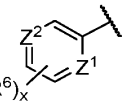
[00109] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently haloalkyl, or $–OR^A$; and x is 0, 1, 2, 3, or 4.

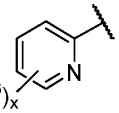
[00110] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently -F, cyclopropyl, $-CH_3$, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, -O-cyclopropyl, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CF_3$, $–OCH_2CHF_2$, $–OCF_3$, or $–OCHF_2$; and x is 0, 1, 2, 3, or 4.

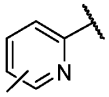
[00111] In certain embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently -F, $-CH_3$, $-CF_3$, $-CHF_2$, $–OCH_2CF_3$, $–OCH_3$, $–OCF_3$, or $–OCHF_2$; and x is 0, 1, 2, 3, or 4.

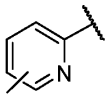
[00112] In certain embodiments, R^1 is , wherein each R^6 is independently -F, cyclopropyl, $-CH_3$, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, -O-cyclopropyl, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CF_3$, $–OCH_2CHF_2$, $–OCF_3$, or $–OCHF_2$; and x is 0 or 1.

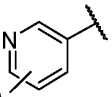
[00113] In certain embodiments, R^1 is , wherein each R^6 is independently -F, $-CH_3$, $-CF_3$, $-CHF_2$, $–OCH_2CF_3$, $–OCH_3$, $–OCF_3$, or $–OCHF_2$; and x is 0 or 1.

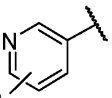
[00114] In some embodiments, R^1 is , wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently cyclopropyl, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–OCF_3$, or $–OCHF_2$; and x is 0, 1, 2, 3, or 4.

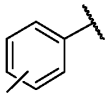
[00115] In certain embodiments, R^1 is , wherein each R^6 is independently haloalkyl or optionally substituted cycloalkyl; and x is 0 or 1.

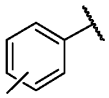
[00116] In certain embodiments, R^1 is , wherein each R^6 is independently -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCF_3, –OCH_2CHF_2, or –$OCHF_2$; and x is 0 or 1.

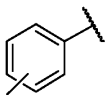
[00117] In certain embodiments, R^1 is , wherein each R^6 is independently -F, -CH_3, -CF_3, -CHF_2, –OCH_2CF_3, –OCH_3, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

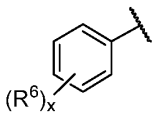
[00118] In certain embodiments, R^1 is , wherein each R^6 is independently -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCH_2CHF_2, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

[00119] In certain embodiments, R^1 is , wherein each R^6 is independently -F, -CH_3, -CF_3, -CHF_2, –OCH_2CF_3, –OCH_3, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

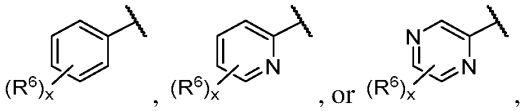
[00120] In certain embodiments, R^1 is , wherein each R^6 is independently -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCH_2CHF_2, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

[00121] In certain embodiments, R^1 is , wherein each R^6 is independently -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCH_2CHF_2, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

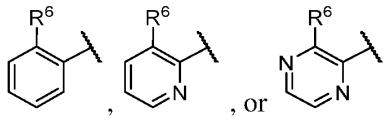
[00122] In certain embodiments, R^1 is , wherein each R^6 is independently -F, -CH_3, -CF_3, -CHF_2, –OCH_2CF_3, –OCH_3, –OCF_3, or –$OCHF_2$; and x is 0 or 1.

[00123] In certain embodiments, R^1 is , wherein each R^6 is independently cyclopropyl, -CF_3, –CF_2CH_3, or –CH_2CF_3; and x is 0 or 1.

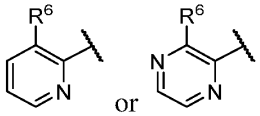
[00124] In some embodiments, R^1 is



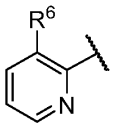
wherein each R^6 is independently cyclopropyl, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, –OCF_3, or –$OCHF_2$; and x is 0, 1, 2, 3, or 4.

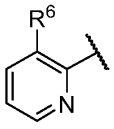
[00125] In some embodiments, R^1 is , wherein R^6 is cyclopropyl, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, –OCF_3, or –$OCHF_2$.

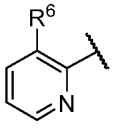
[00126] In some emodiments, R^1 is

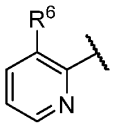


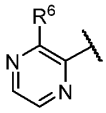
wherein R^6 is cyclopropyl, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, –OCF_3, or –$OCHF_2$.

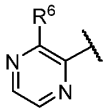
[00127] In certain embodiments, R^1 is , wherein R^6 is halogen, alkyl, haloalkyl, optionally substituted cycloalkyl, or –OR^A; and R^A is alkyl or haloalkyl.

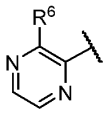
[00128] In certain embodiments, R^1 is , wherein R^6 is haloalkyl or optionally substituted cycloalkyl.

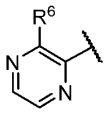
[00129] In certain embodiments, R^1 is , wherein R^6 is -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCH_2CHF_2, –OCF_3, or –$OCHF_2$.

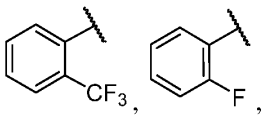
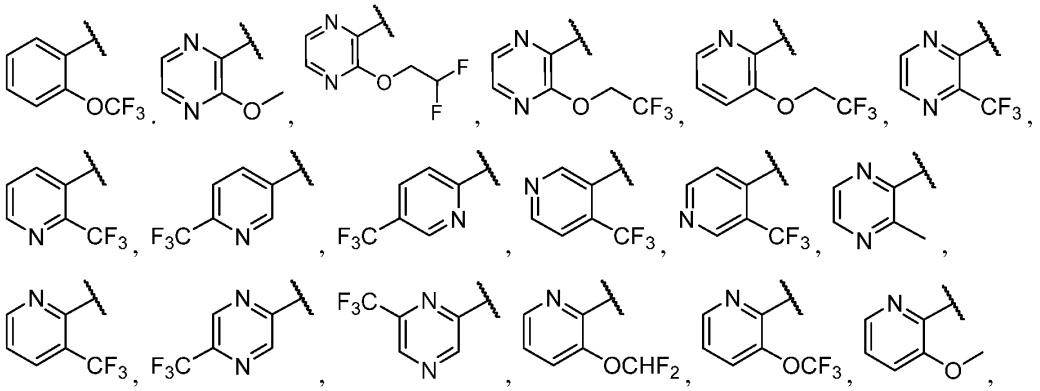
[00130] In certain embodiments, R^1 is , wherein R^6 is cyclopropyl, -CF_3, –CF_2CH_3, or –CH_2CF_3.

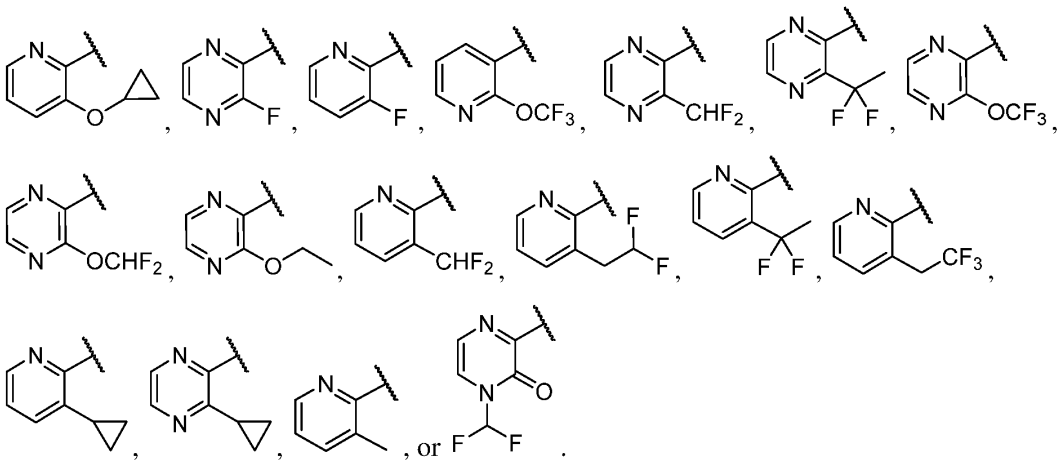
[00131] In certain embodiments, R^1 is , wherein R^6 is halogen, alkyl, haloalkyl, optionally substituted cycloalkyl, or –OR^A; and R^A is alkyl or haloalkyl.

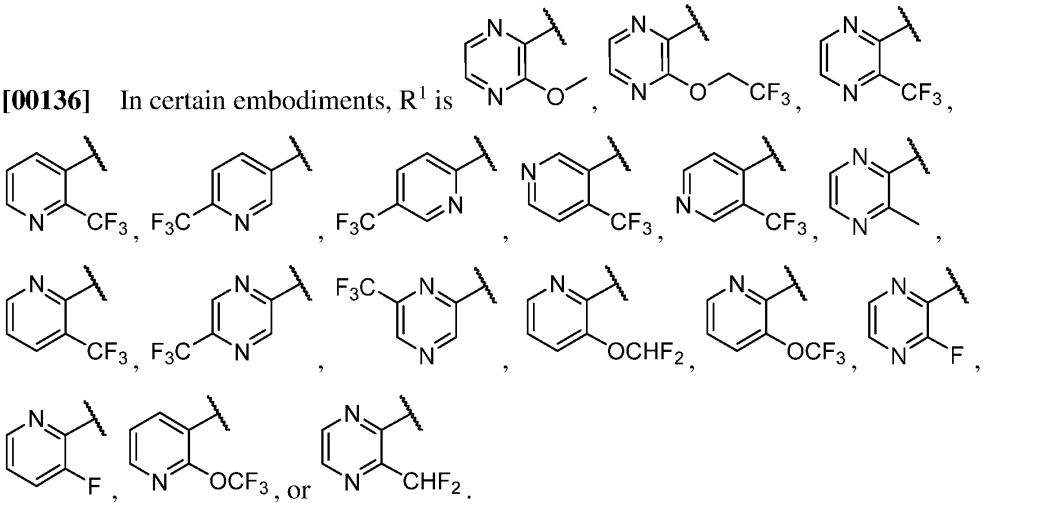
[00132] In certain embodiments, R^1 is , wherein R^6 is haloalkyl or optionally substituted cycloalkyl.

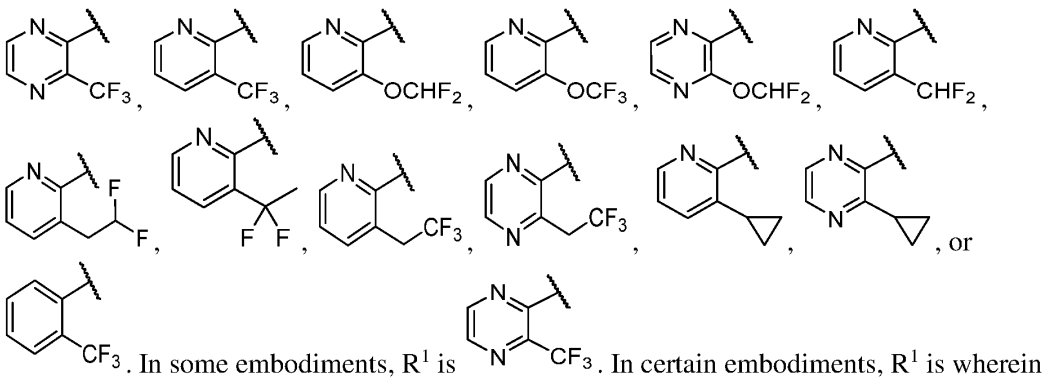
[00133] In certain embodiments, R^1 is , wherein R^6 is -F, cyclopropyl, -CH_3, -CF_3, -CHF_2, –CF_2CH_3, –CH_2CF_3, –CH_2CHF_2, -O-cyclopropyl, –OCH_3, –OCH_2CH_3, –OCH_2CF_3, –OCH_2CHF_2, –OCF_3, or –$OCHF_2$.

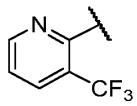
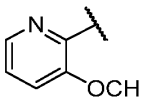
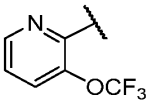
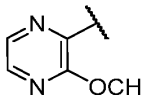
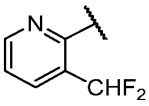
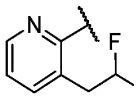
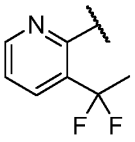
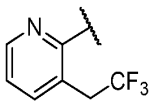
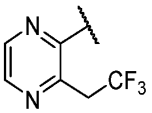
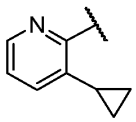
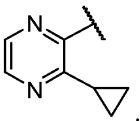
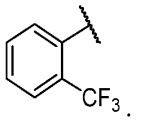
[00134] In certain embodiments, R^1 is , wherein R^6 is cyclopropyl, -CF_3, –CF_2CH_3, or –CH_2CF_3.

[00135] In certain embodiments, R^1 is , or 



[00136] In certain embodiments, R^1 is 

[00137] In certain embodiments, R^1 is . In some embodiments, R^1 is . In certain embodiments, R^1 is wherein R^1 is

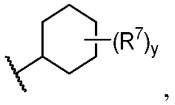
. In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is .

[00138] In certain embodiments, R^1 is optionally substituted carbocyclyl. In certain embodiments, R^1 is optionally substituted carbocyclyl, wherein the carbocyclyl is fused with a heteroaryl ring. In certain embodiments, R^1 is optionally substituted C_{8-14} carbocyclyl, wherein the carbocyclyl is fused with a heteroaryl ring.

R^2

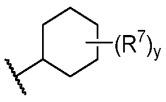
[00139] As described herein, R^2 is an optionally substituted carbocyclyl or optionally substituted heterocyclyl. In certain embodiments, R^2 is optionally substituted carbocyclyl. In certain embodiments, R^2 is optionally substituted cycloalkyl. In certain embodiments, R^2 is optionally substituted C_{3-12} cycloalkyl. In certain embodiments, R^2 is optionally substituted C_{3-8} cycloalkyl. In certain embodiments, R^2 is optionally substituted C_{3-6} cycloalkyl. In certain embodiments, R^2 is optionally substituted C_{4-6} cycloalkyl. In certain embodiments, R^2 is optionally substituted C_{5-6} cycloalkyl. In certain embodiments, R^2 is optionally substituted cyclopentyl. In certain embodiments, R^2 is optionally substituted cyclobutyl. In certain embodiments, R^2 is optionally substituted cyclohexyl.

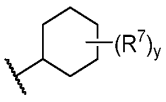
[00140] In some embodiments, R^2 is

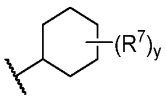


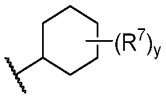
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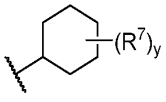
wherein each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted aryl; and y is 0, 1, or 2.

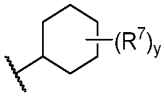
[00141] In certain embodiments, R^2 is , wherein each R^7 is independently halogen, optionally substituted alkyl, or optionally substituted aryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

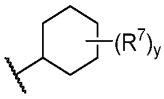
[00142] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

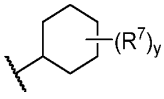
[00143] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl or optionally substituted heteroaryl; and y is 1.

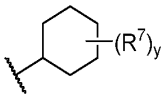
[00144] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

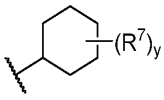
[00145] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 1 or 2.

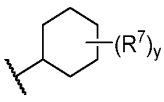
[00146] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 1 or 2.

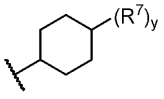
[00147] In certain embodiments, R^2 is , wherein R^7 is optionally substituted aryl; and y is 1.

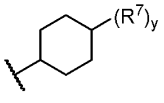
[00148] In certain embodiments, R^2 is , wherein R^7 is substituted phenyl; and y is 1.

[00149] In certain embodiments, R^2 is , wherein R^7 is optionally substituted heteroaryl; and y is 1.

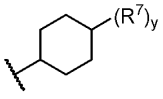
[00150] In certain embodiments, R^2 is , wherein R^7 is substituted heteroaryl; and y is 1.

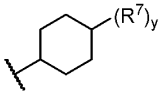
[00151] In certain embodiments, R^2 is , wherein R^7 is substituted pyridine, substituted thiazole, substituted isothiazole, substituted pyrazole, or substituted indazole; and y is 1.

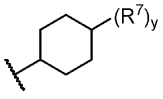
[00152] In certain embodiments, R^2 is , wherein each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

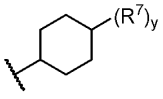
[00153] In certain embodiments, R^2 is , wherein each R^7 is independently halogen, optionally substituted alkyl, or optionally substituted aryl, or two instances of R^7

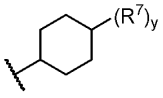
together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

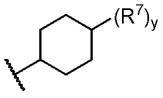
[00154] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

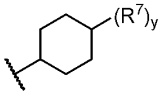
[00155] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl or optionally substituted heteroaryl; and y is 1.

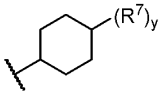
[00156] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

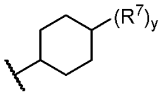
[00157] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted aryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 1 or 2.

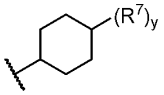
[00158] In certain embodiments, R^2 is , wherein each R^7 is independently optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 1 or 2.

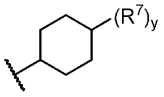
[00159] In certain embodiments, R^2 is , wherein R^7 is optionally substituted aryl; and y is 1.

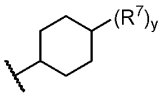
[00160] In certain embodiments, R^2 is , wherein R^7 is substituted aryl; and y is 1.

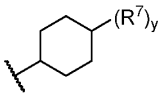
[00161] In certain embodiments, R^2 is , wherein R^7 is substituted phenyl; and y is 1.

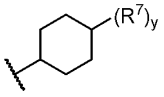
[00162] In certain embodiments, R^2 is , wherein R^7 is optionally substituted heteroaryl; and y is 1.

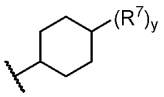
[00163] In certain embodiments, R^2 is , wherein R^7 is substituted heteroaryl; and y is 1.

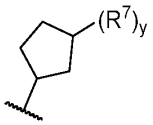
[00164] In certain embodiments, R^2 is , wherein R^7 is substituted pyridine, substituted thiazole, substituted isothiazole, substituted pyrazole, or substituted indazole; and y is 1.

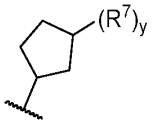
[00165] In certain embodiments, R^2 is , wherein two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl; and y is 2.

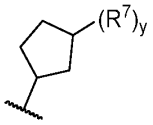
[00166] In certain embodiments, R^2 is , wherein two instances of R^7 together with the atoms to which they are attached form a substituted heterocyclyl; and y is 2.

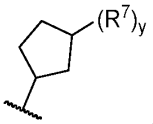
[00167] In certain embodiments, R^2 is , wherein two instances of R^7 together with the atoms to which they are attached form a substituted 4-6 membered heterocyclyl; and y is 2.

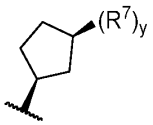
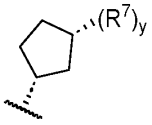
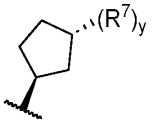
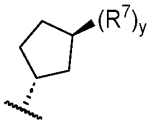
[00168] In certain embodiments, R^2 is , wherein two instances of R^7 together with the atoms to which they are attached form a substituted azetidine; and y is 2.

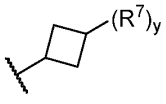
[00169] In certain embodiments, R^2 is , wherein each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

[00170] In certain embodiments, R^2 is ,wherein R^7 is optionally substituted aryl; and y is 1.

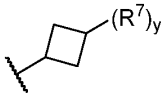
[00171] In certain embodiments, R^2 is , wherein R^7 is substituted aryl; and y is 1.

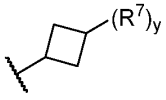
[00172] In certain embodiments, R^2 is ,wherein R^7 is substituted phenyl; and y is 1.

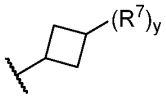
[00173] In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is .

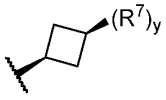
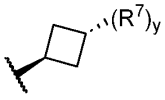
[00174] In certain embodiments, R^2 is , wherein each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a

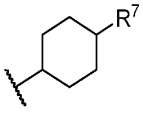
substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

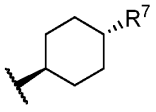
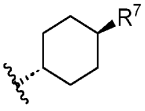
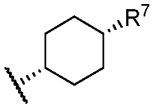
[00175] In certain embodiments, R^2 is , wherein R^7 is optionally substituted aryl; and y is 1.

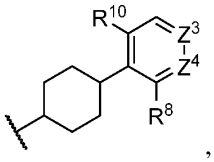
[00176] In certain embodiments, R^2 is , wherein R^7 is substituted aryl; and y is 1.

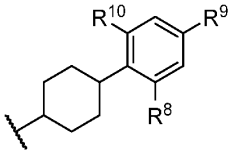
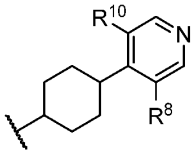
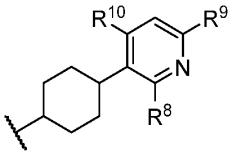
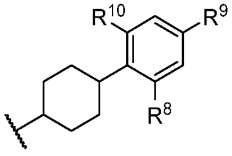
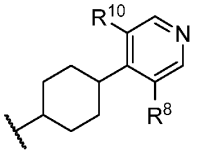
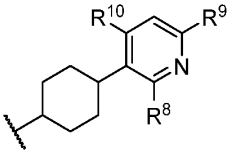
[00177] In certain embodiments, R^2 is , wherein R^7 is substituted phenyl; and y is 1.

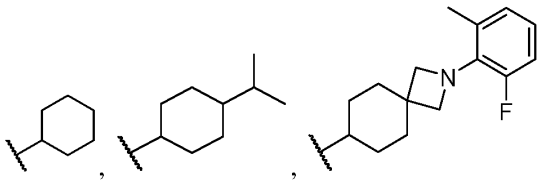
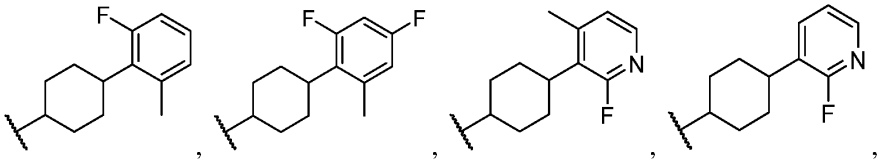
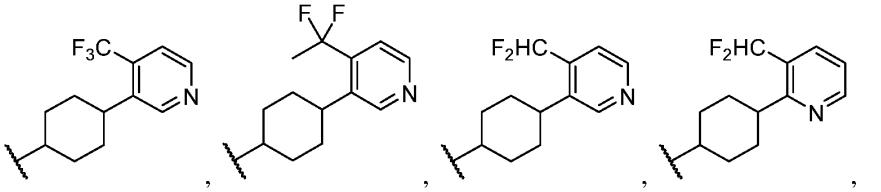
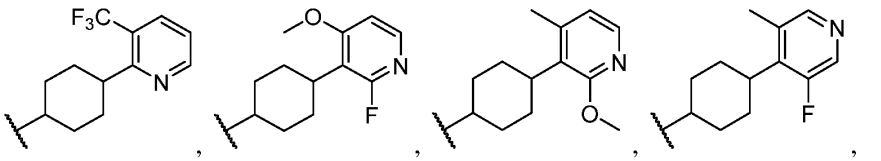
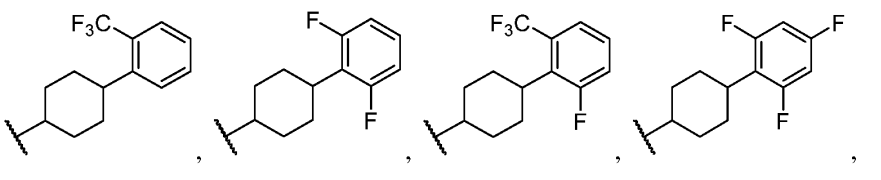
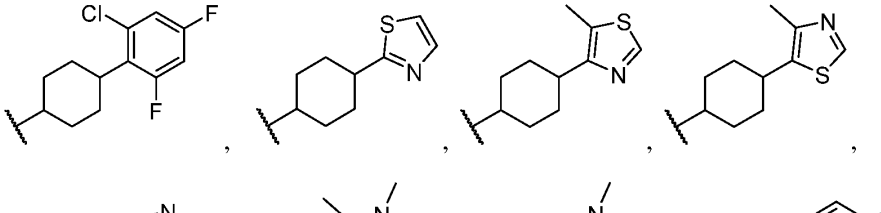
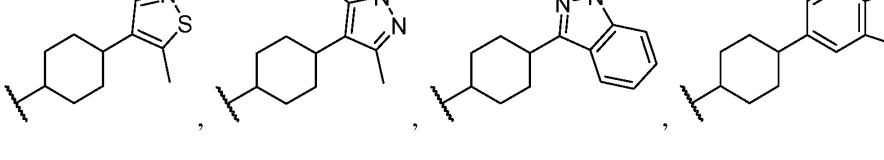
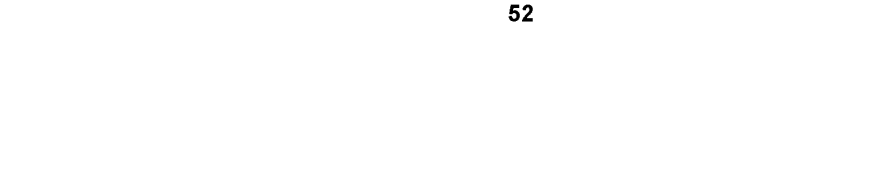
[00178] In certain embodiments, R^2 is . In certain embodiments, R^2 is .

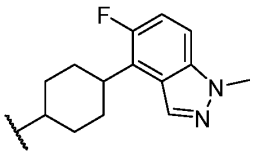
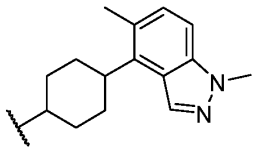
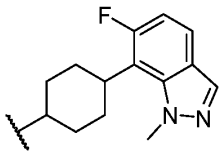
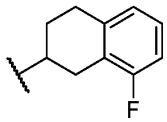
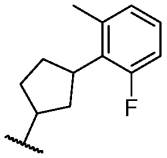
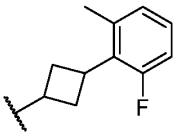
[00179] In some embodiments, wherein R^2 is , wherein R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

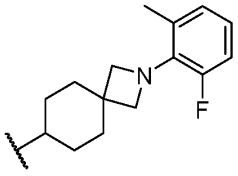
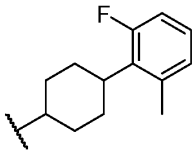
[00180] In certain embodiments, R^2 is , wherein R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl . In some embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is .

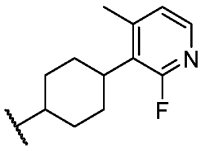
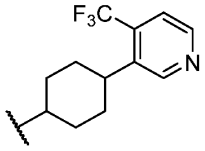
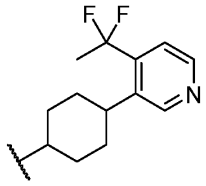
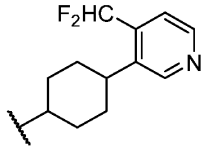
[00181] In certain embodiments, R^2 is , wherein Z^3 and Z^4 are each independently -N- or -CR^9-; and R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

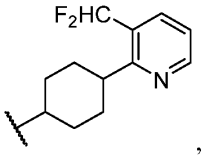
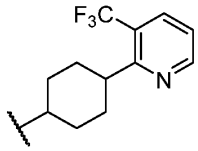
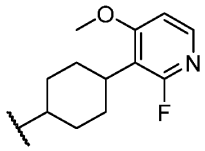
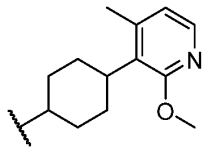
[00182] In some embodiments, R^2 is , , or  wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A. In some embodiments, R^2 is  wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A. In some embodiments, R^2 is  wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A. In some embodiments, R^2 is  wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

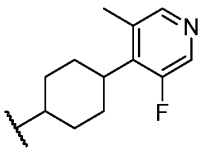
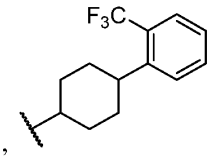
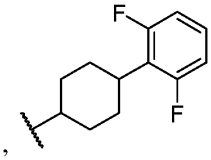
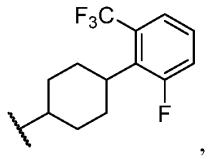
[00183] In certain embodiments, R^2 is , , , , , , , , , , .

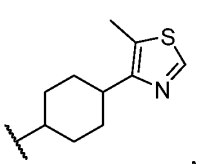
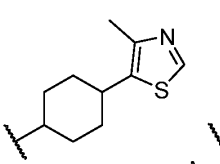
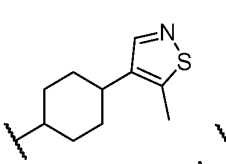
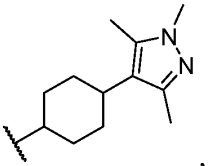






, or .

[00184] In certain embodiments, R^2 is 


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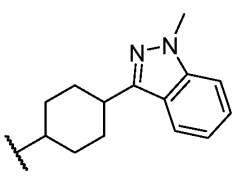
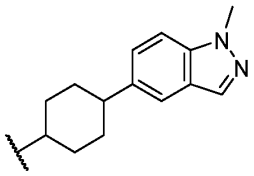
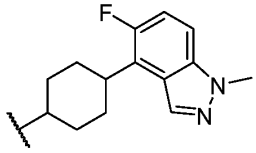
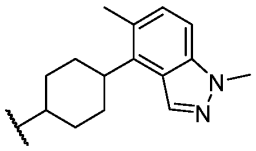
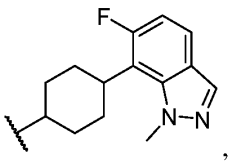
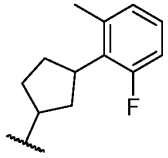
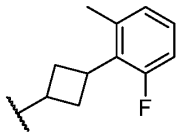




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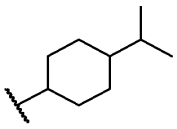
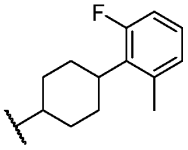
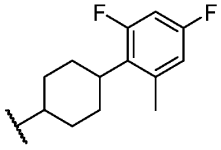
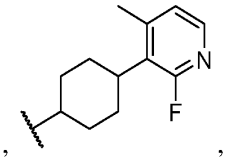
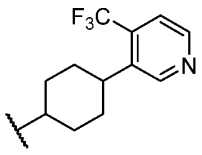
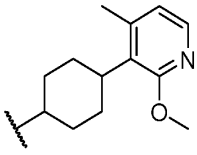
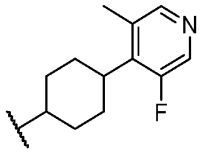
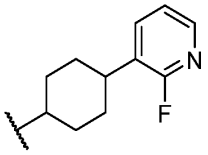
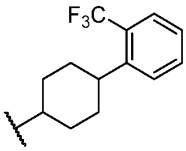
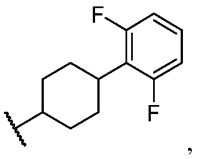
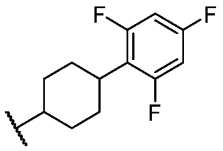
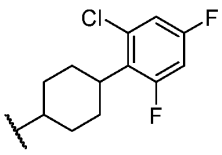
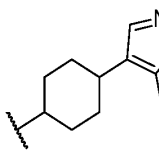
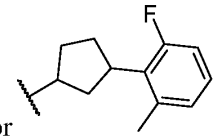




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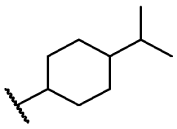
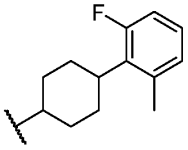
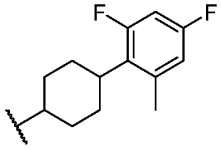
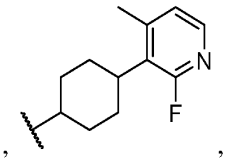
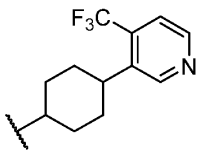
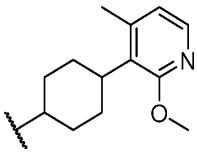
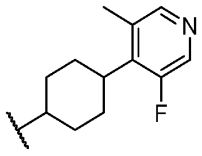





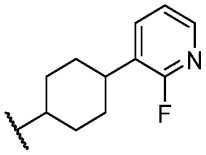
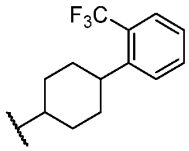
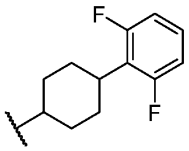
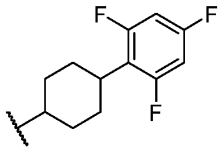
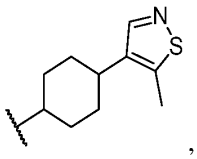
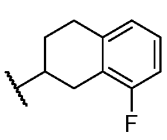
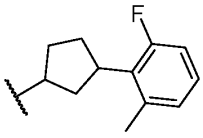
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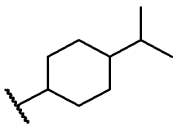
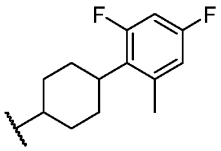
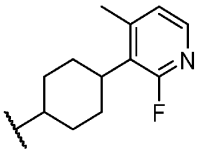
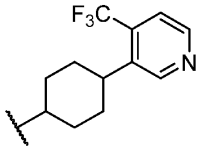
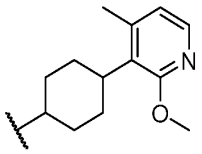
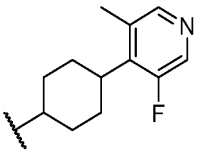
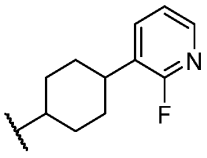
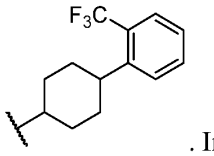
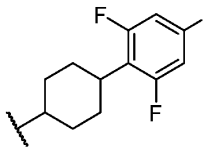
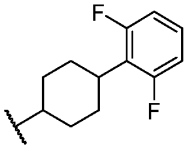
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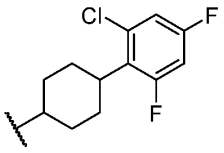






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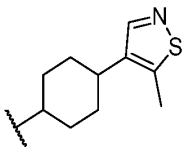
[00185] In some embodiments, R^2 is 












, or .

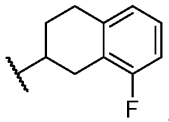
[00186] In some embodiments, R^2 is 







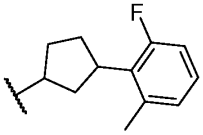

, 
, 
, 
, 
, 
, or 
.

[00187] In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is

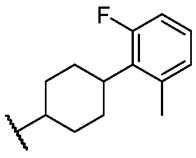


. In some embodiments, R^2 is 

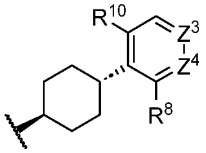
. In some embodiments, R^2 is 

. In some embodiments, R^2 is 

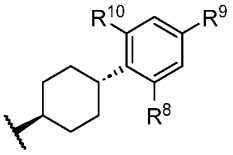
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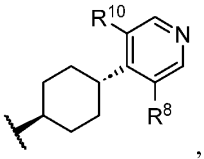
[00188] In certain embodiments, R^2 is 

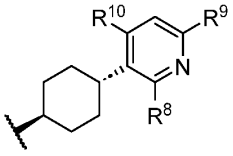
.

[00189] In some embodiments, R^2 is 

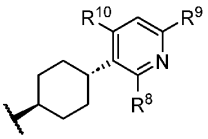
, wherein Z^3 and Z^4 are each independently -N- or -CR^9-; and R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

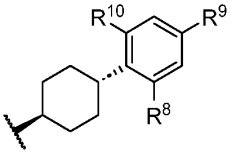
[00190] In some embodiments, R^2 is 

, 

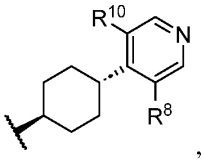
, or 

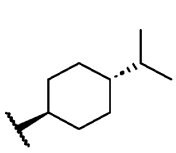
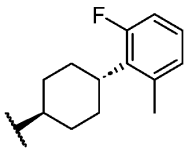
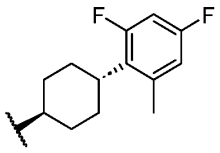
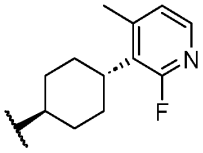
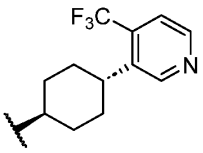
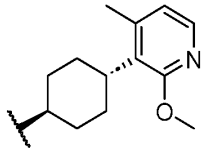
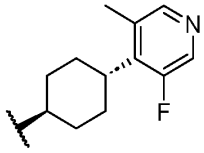
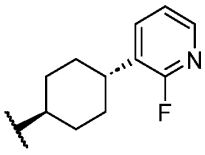
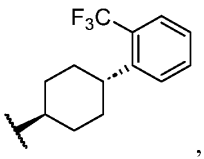
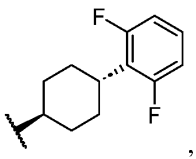
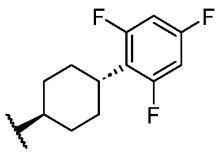
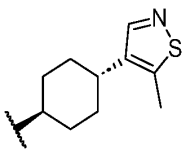
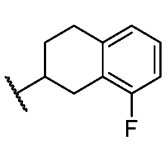
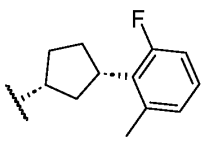
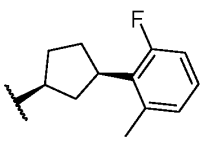
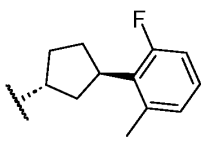
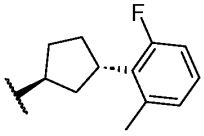
, wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

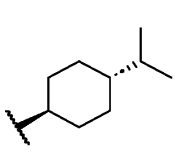
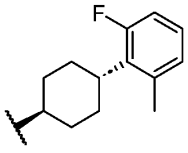
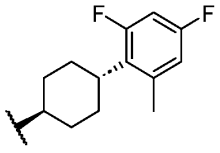
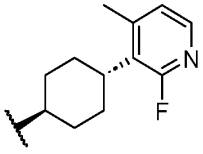
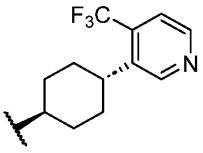
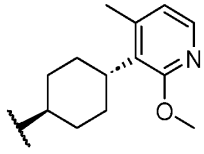
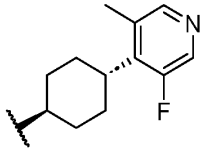
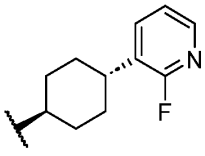
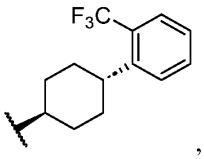
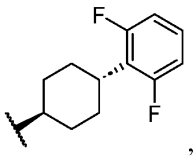
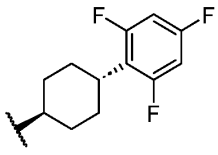
[00191] In certain embodiments, R^2 is 

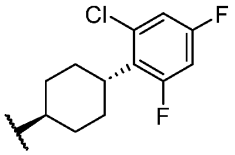
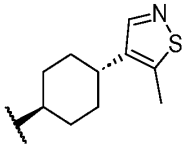
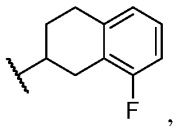
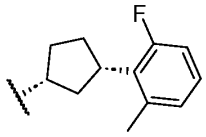
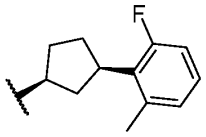
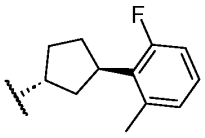
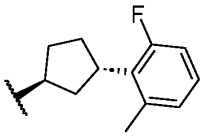
,wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A. In some embodiments, R^2 is 

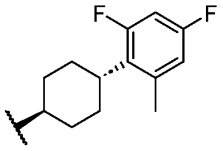
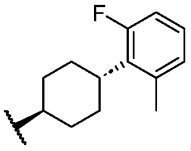
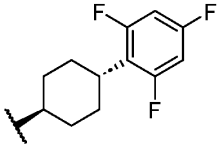
, wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A. In some embodiments, R^2 is

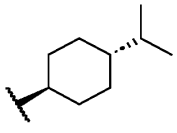
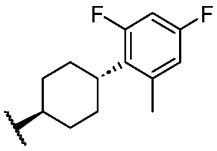
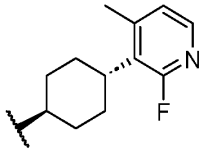
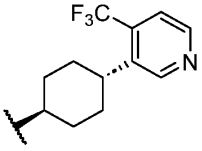
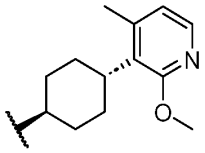
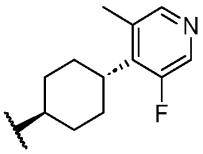
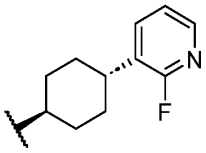
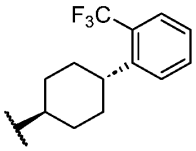

, wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

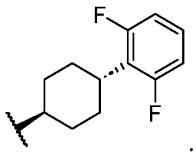
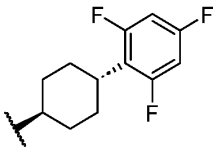
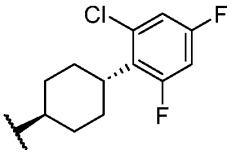
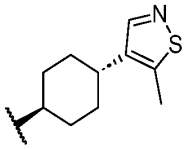
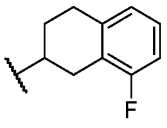
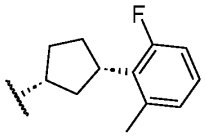
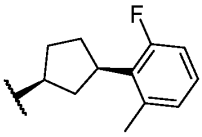
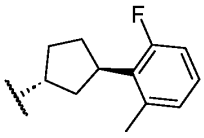
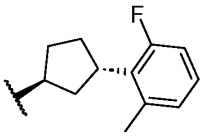
[00192] In some embodiments, R^2 is , , , , , , , , , , , , , , , , or .

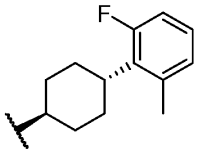
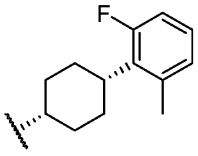
[00193] In some embodiments, R^2 is , , , , , , , , , , .

[00194] In certain embodiments, R^2 is , , or .

[00195] In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments, R^2 is . In certain embodiments,

R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  . In certain embodiments, R^2 is  .

[00196] In certain embodiments, R^2 is  . In certain embodiments, R^2 is  .

[00197] In certain embodiments, R^2 is optionally substituted heterocyclyl. In certain embodiments, R^2 is optionally substituted 4-7 membered heterocyclyl comprising 1 or 2 nitrogen atoms in the ring. In certain embodiments, R^2 is optionally substituted azetidine, pyrrolidine, piperidine, or piperazine. In certain embodiments, R^2 is optionally substituted azetidine. In certain embodiments, R^2 is optionally substituted pyrrolidine. In certain embodiments, R^2 is optionally substituted piperidine. In certain embodiments, R^2 is optionally substituted piperazine.

R^3

[00198] As described herein, R^3 is hydrogen, halogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^3 is hydrogen or optionally substituted aryl. In certain embodiments, R^3 is optionally substituted aryl. In certain embodiments, R^3 is hydrogen or optionally substituted phenyl. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is optionally substituted phenyl. In certain embodiments, R^3 is unsubstituted phenyl.

R^4

[00199] As described herein, R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, $-C(=NR^A)NR^AOR^A$, or $-NR^AC(=O)R^A$. In certain embodiments, R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, or $-NR^AC(=O)R^A$. In certain embodiments, R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, $-C(=NR^A)NR^AOR^A$, or $-NR^AC(=O)R^A$. In certain embodiments, R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, or $-NR^AC(=O)R^A$. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is haloalkyl. In certain embodiments, R^4 is optionally substituted alkyl. In certain embodiments, R^4 is optionally substituted C_{4-6} cycloalkyl. In certain embodiments, R^4 is optionally substituted 4-6-membered heterocyclyl. In certain embodiments, R^4 is optionally substituted 5-6-membered heteroaryl. In certain embodiments, R^4 is $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, $-C(=NR^A)NR^AOR^A$, or $-NR^AC(=O)R^A$. In certain embodiments, R^4 is $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, or $-NR^AC(=O)R^A$.

[00200] In certain embodiments, R^4 is optionally substituted 5-membered heteroaryl.

[00201] In certain embodiments, R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $-OR^A$, $-N(R^A)_2$, $-C(=O)N(R^A)_2$, or $-NR^AC(=O)R^A$; and each R^A is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl, or two instances of

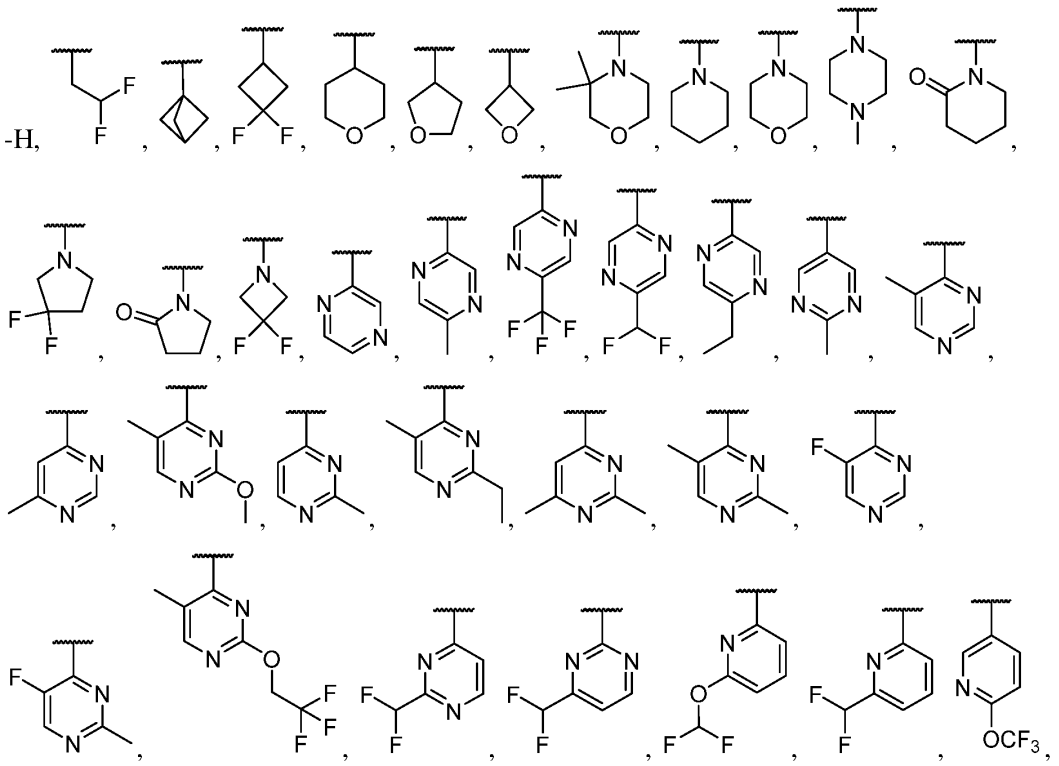
R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

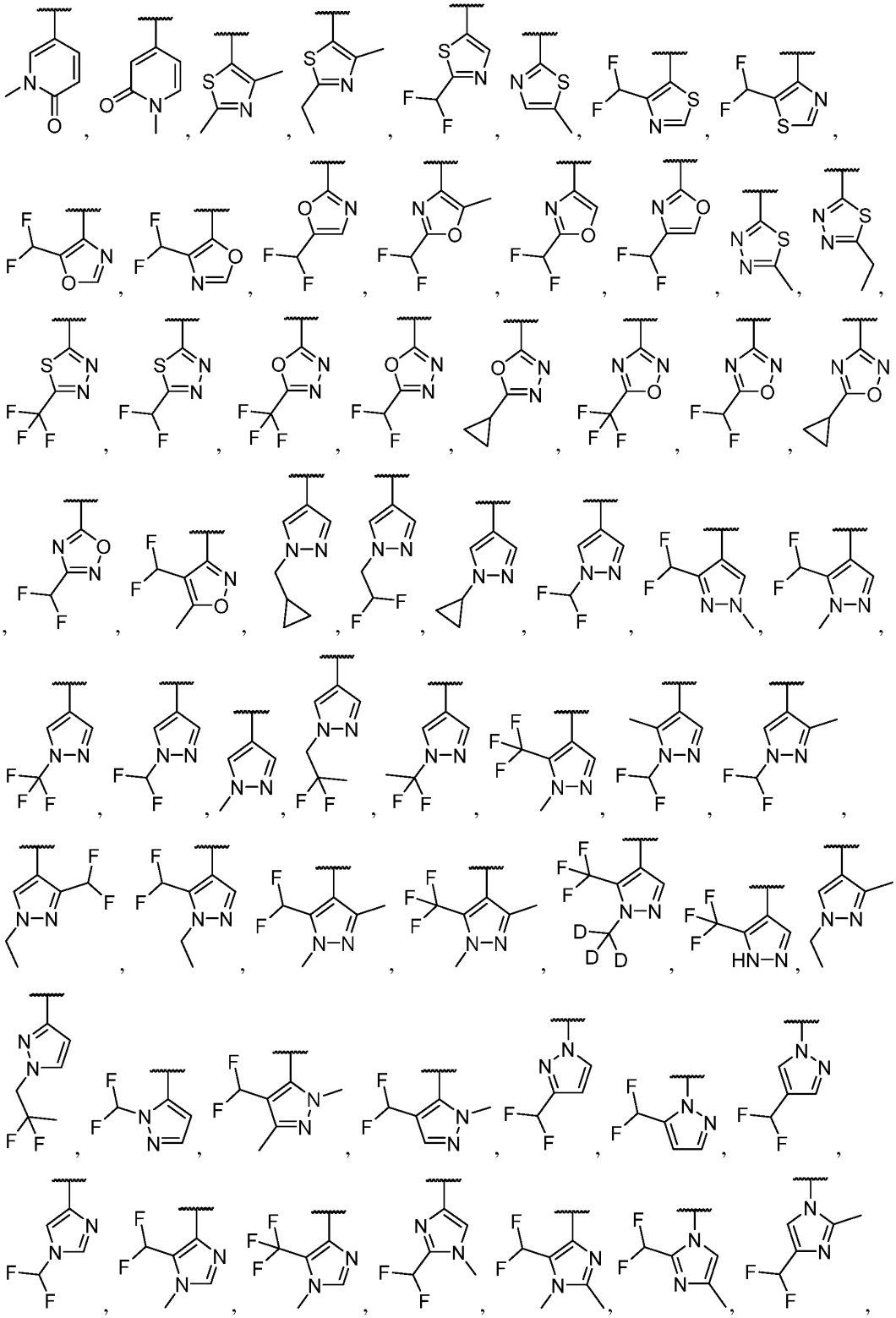
[00202] In certain embodiments, R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $–OR^A$, $–N(R^A)_2$, $–C(=O)N(R^A)_2$, $–C(=NR^A)NR^AOR^A$, or $–NR^AC(=O)R^A$; and each R^A is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

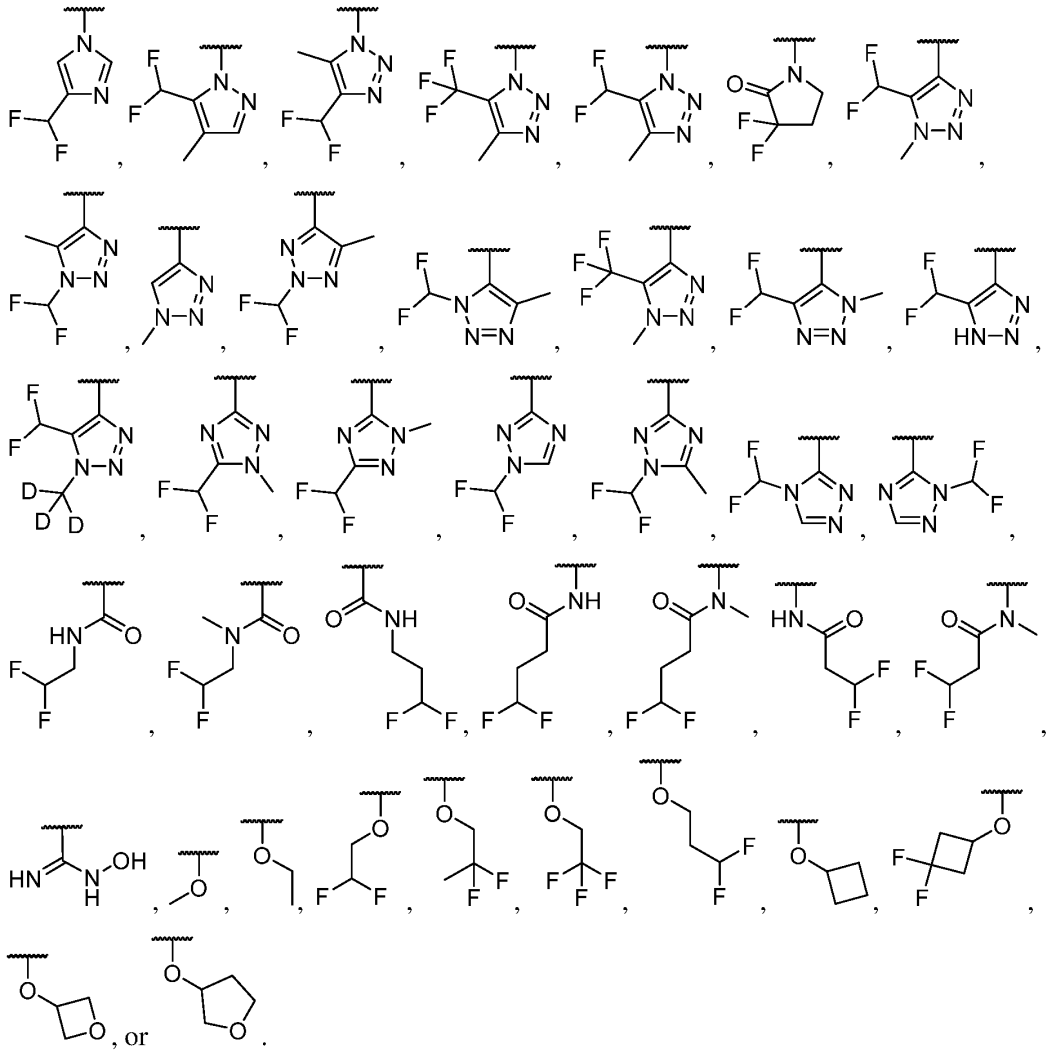
[00203] In certain embodiments, R^4 is optionally substituted thiazole, optionally substituted pyrazole, optionally substituted triazole, optionally substituted dithiazole, optionally substituted imidazole, optionally substituted oxadiazole, or optionally substituted oxazole.

[00204] In certain embodiments, R^4 is optionally substituted thiazole. In certain embodiments, R^4 is optionally substituted pyrazole. In certain embodiments, R^4 is optionally substituted triazole. In certain embodiments, R^4 is optionally substituted dithiazole. In certain embodiments, R^4 is optionally substituted imidazole. In certain embodiments, R^4 is optionally substituted oxadiazole. In certain embodiments, R^4 is optionally substituted oxazole.

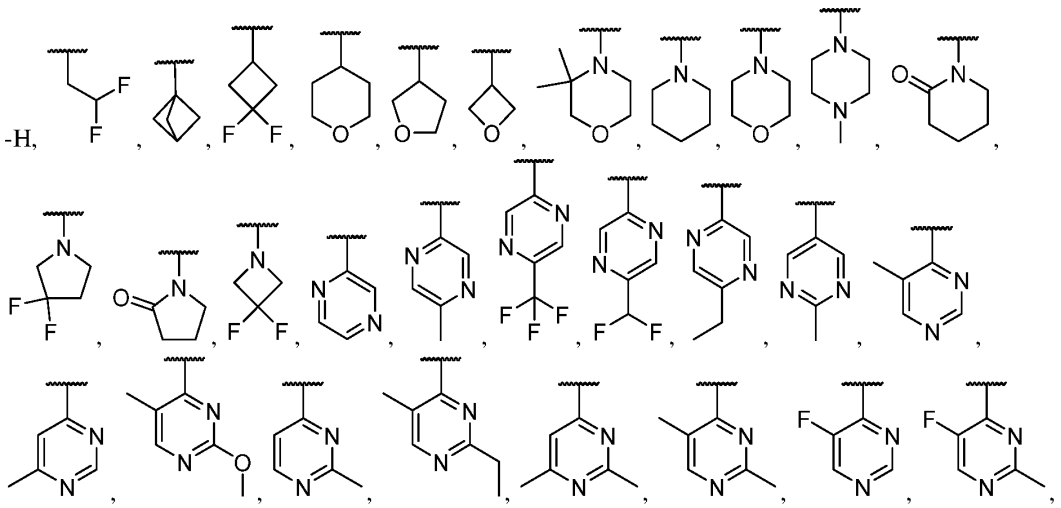
[00205] In some embodiments, R^4 is:

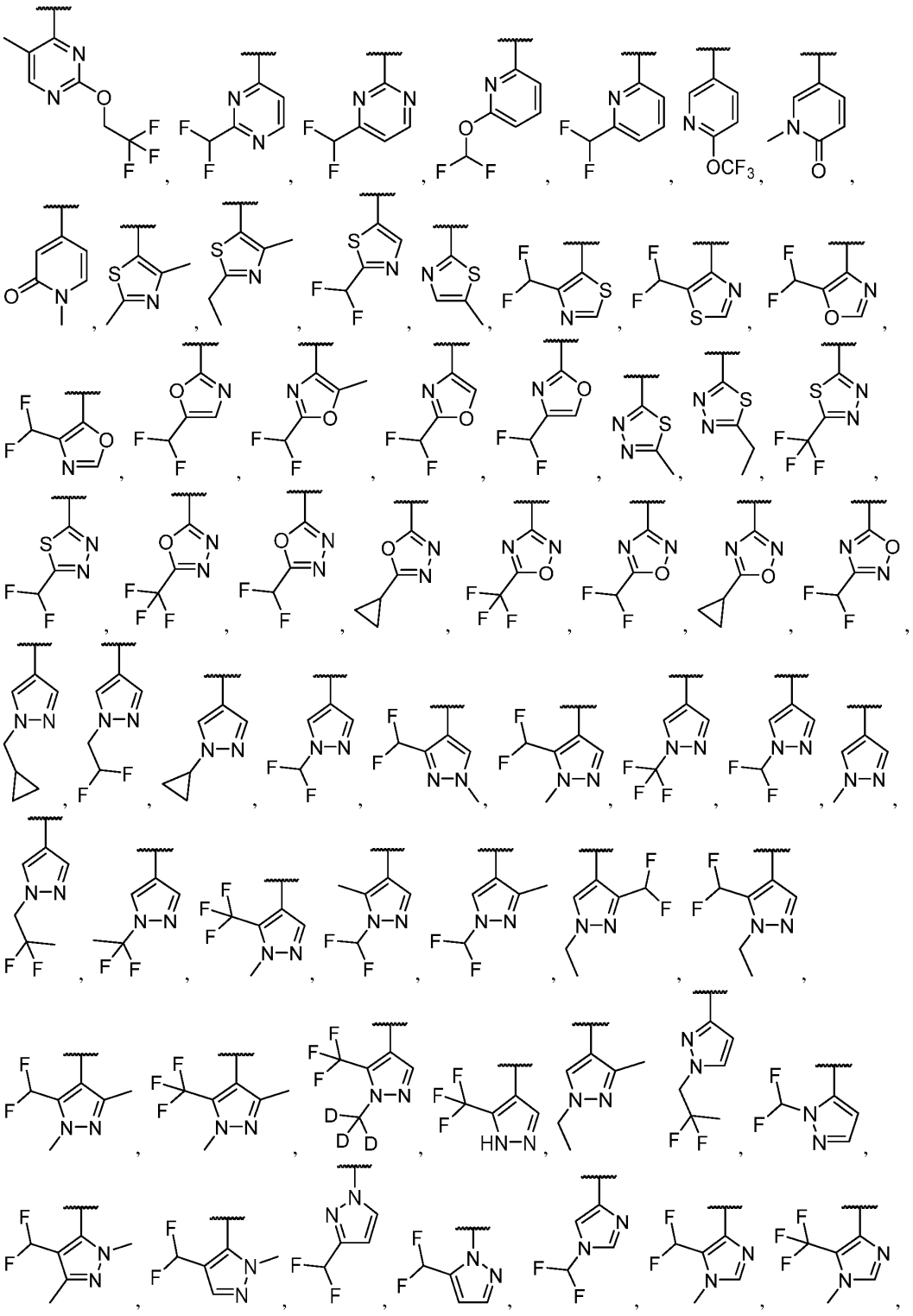


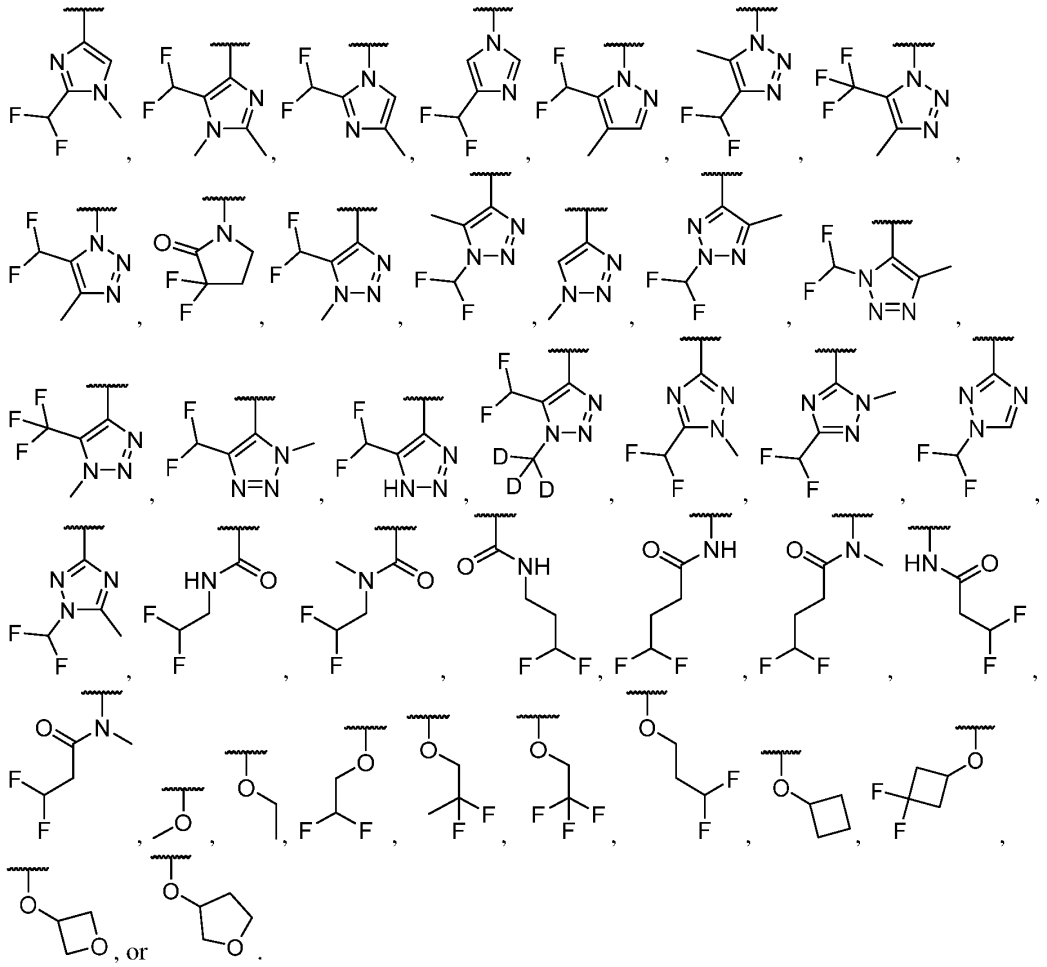




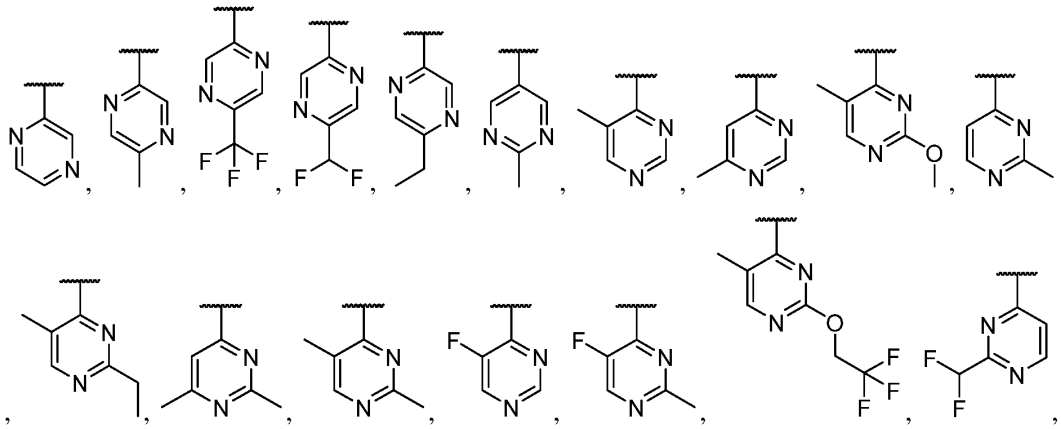
[00206] In some embodiments, R^4 is:

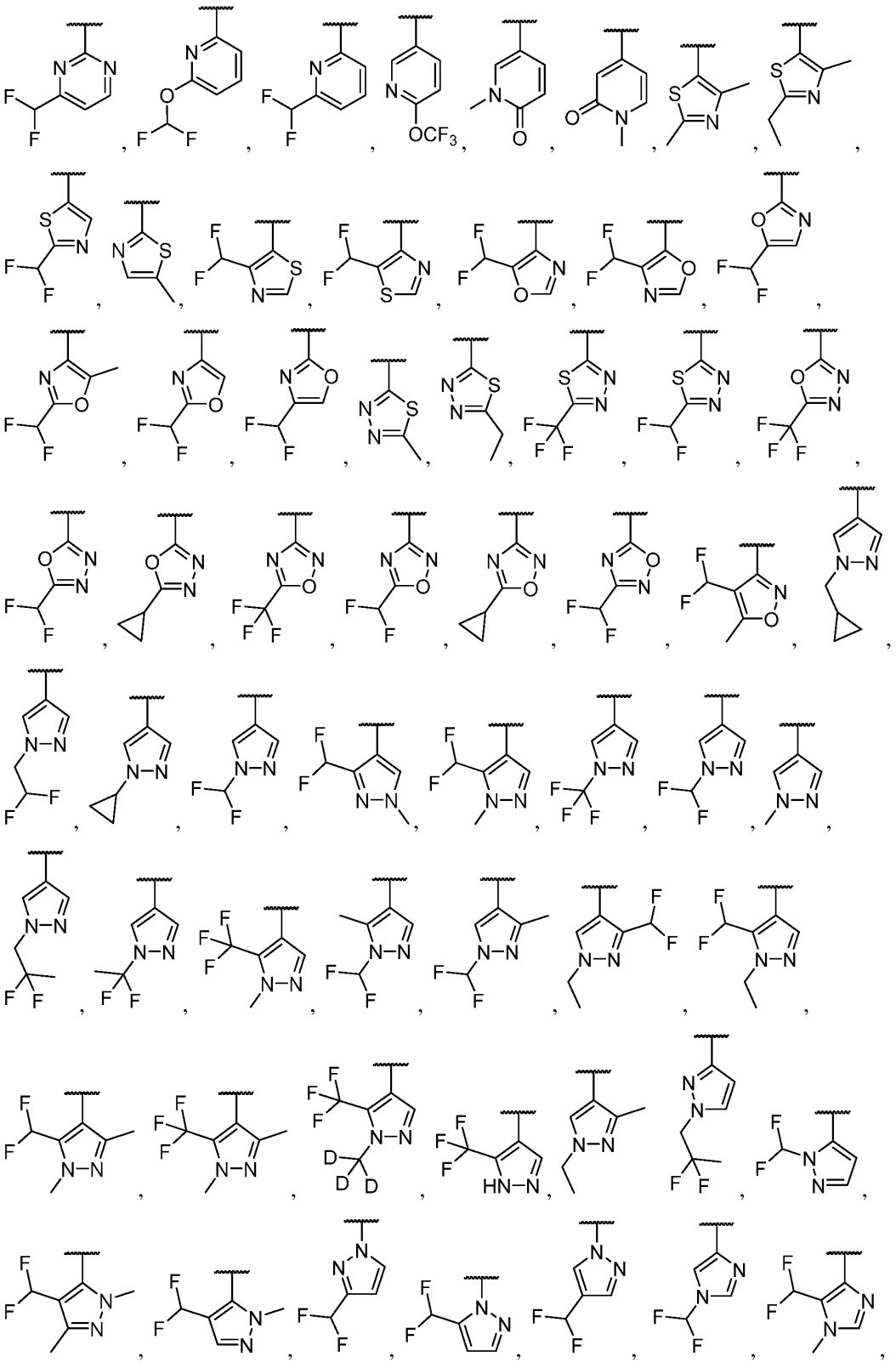


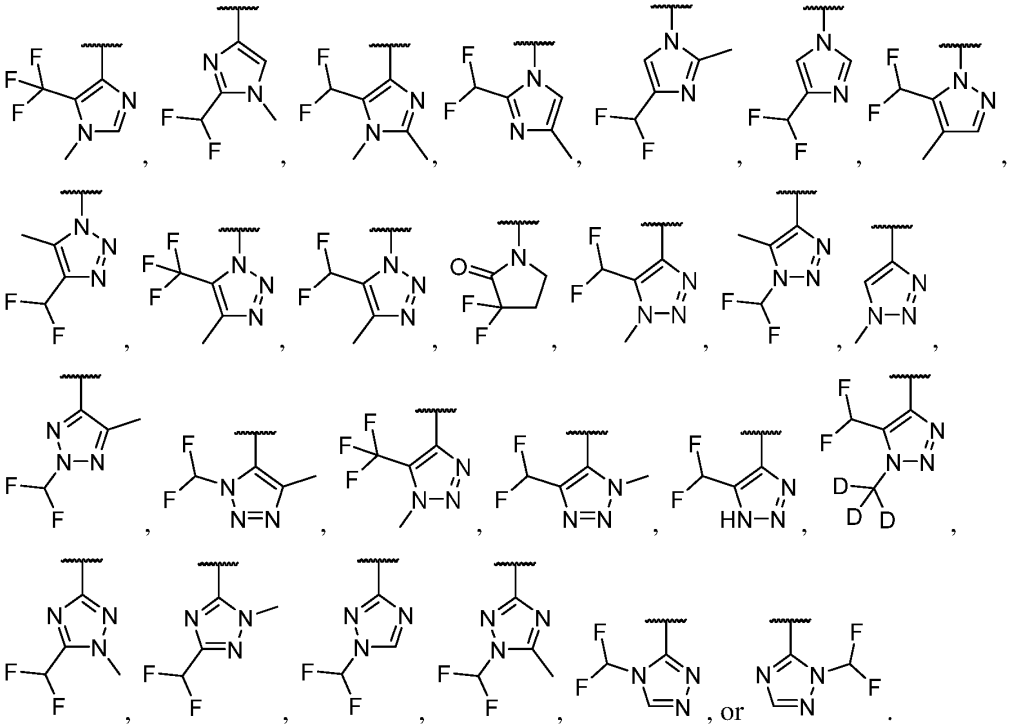




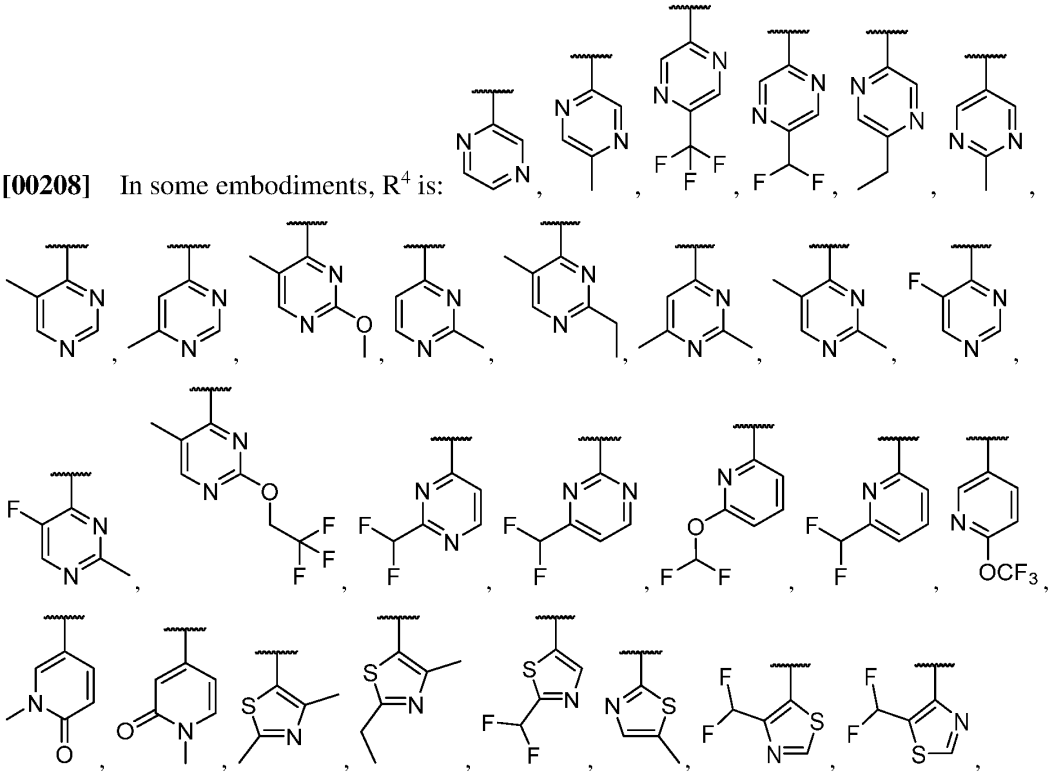
[00207] In some embodiments, R^4 is:

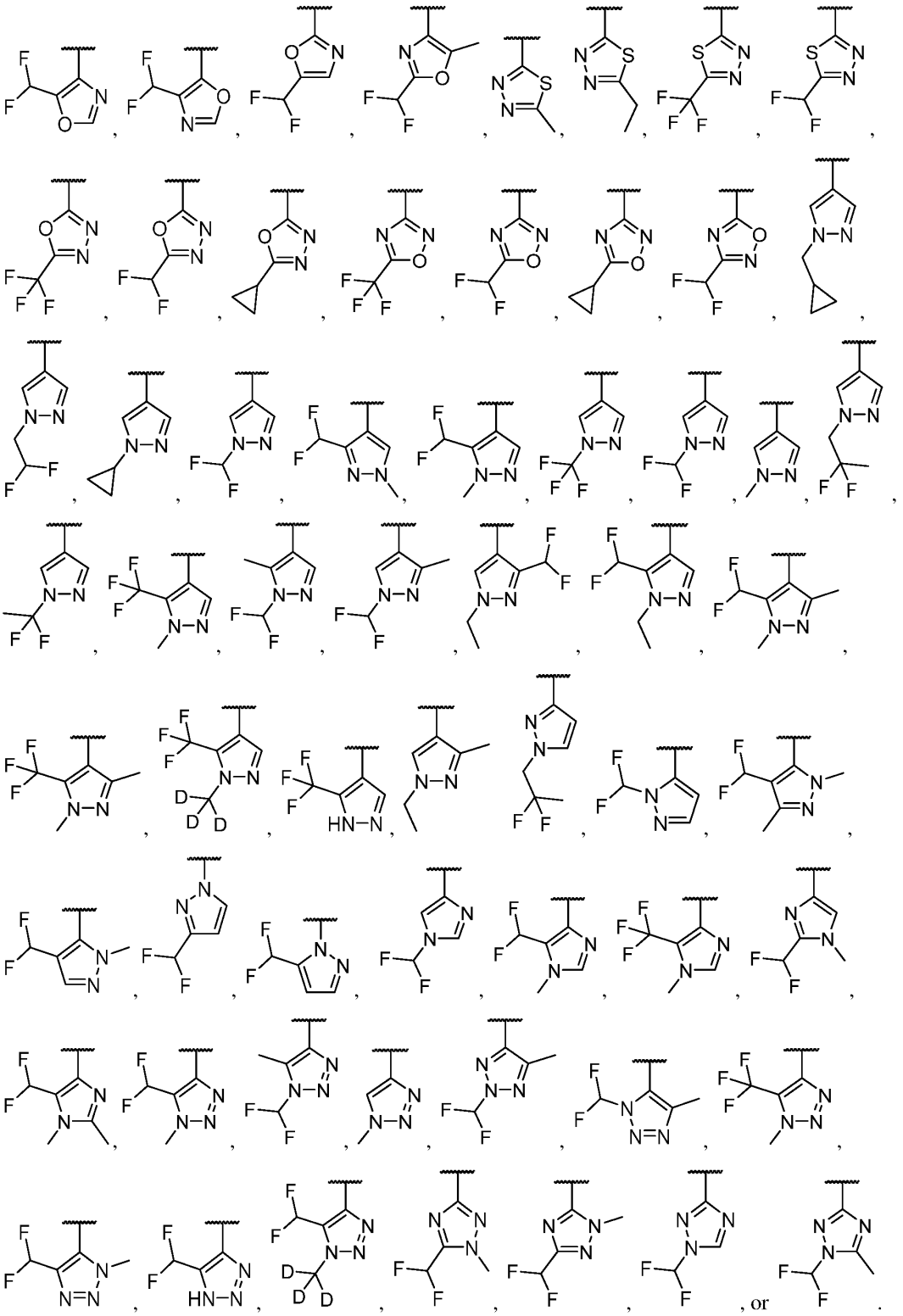


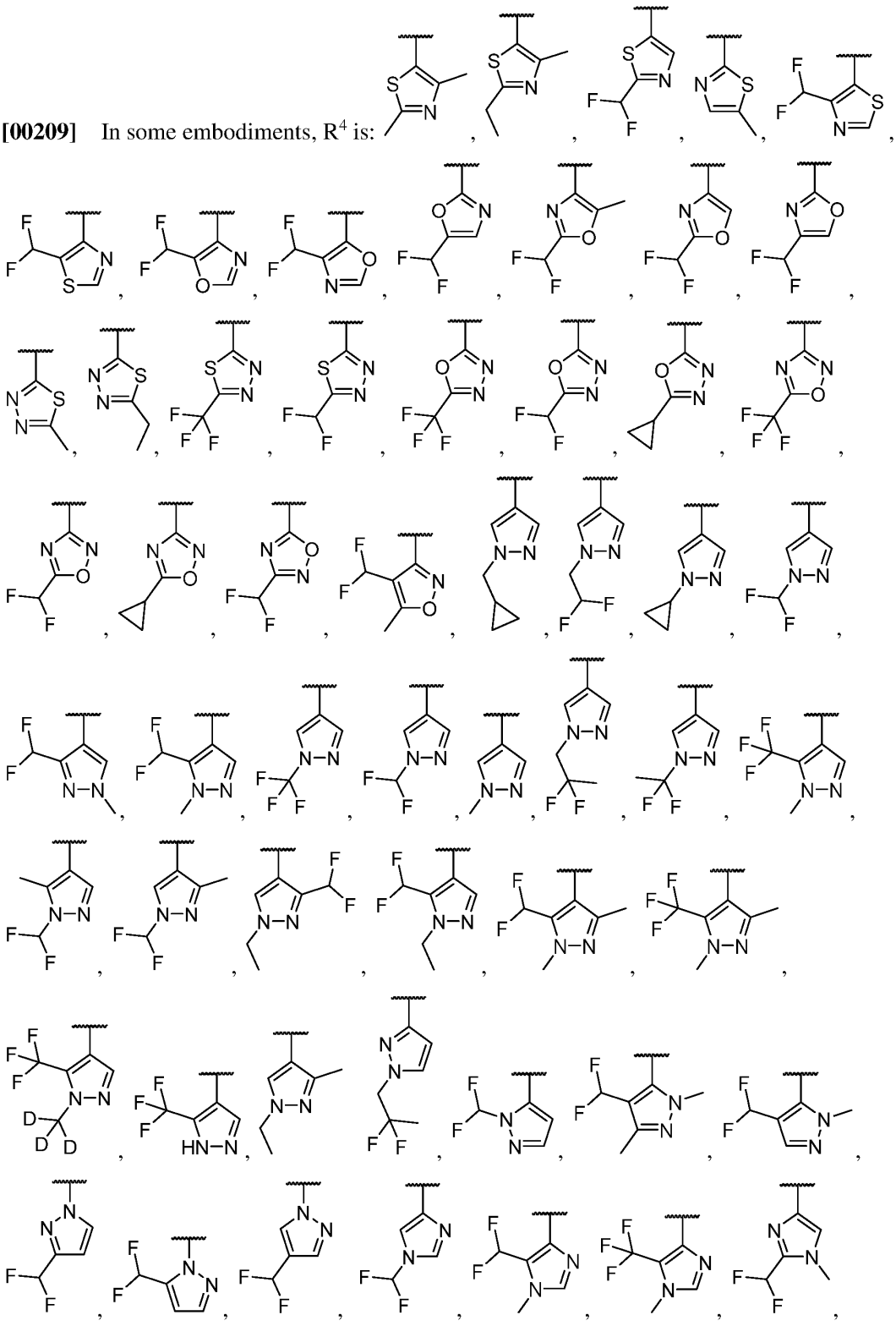


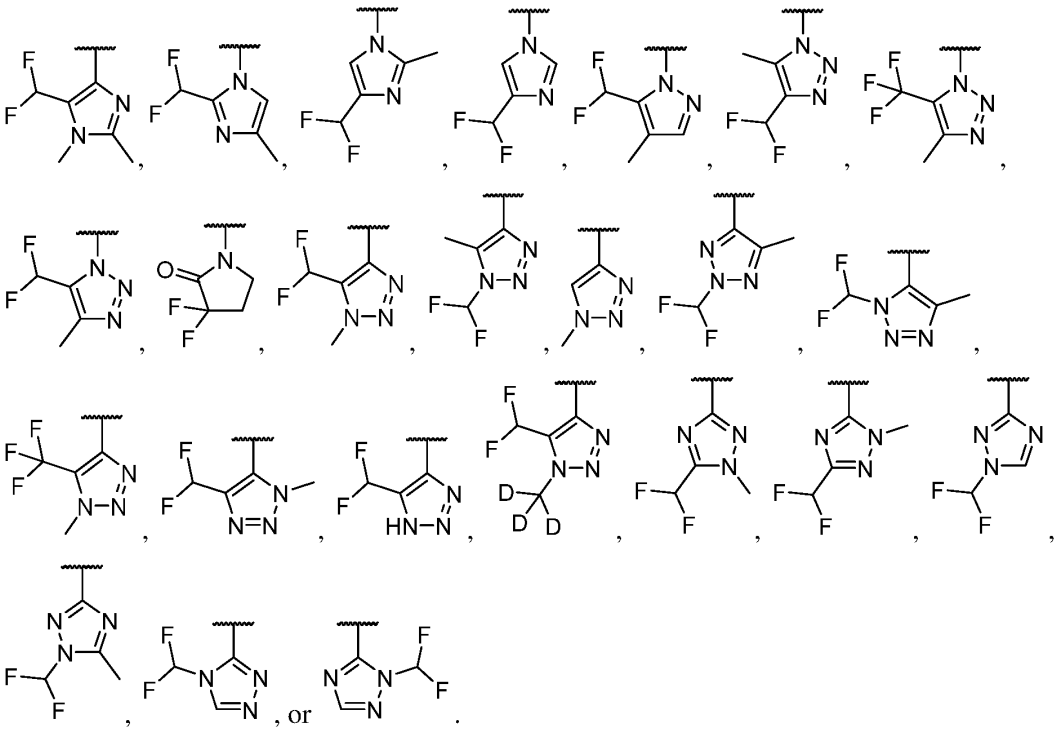


[00208] In some embodiments, R^4 is:

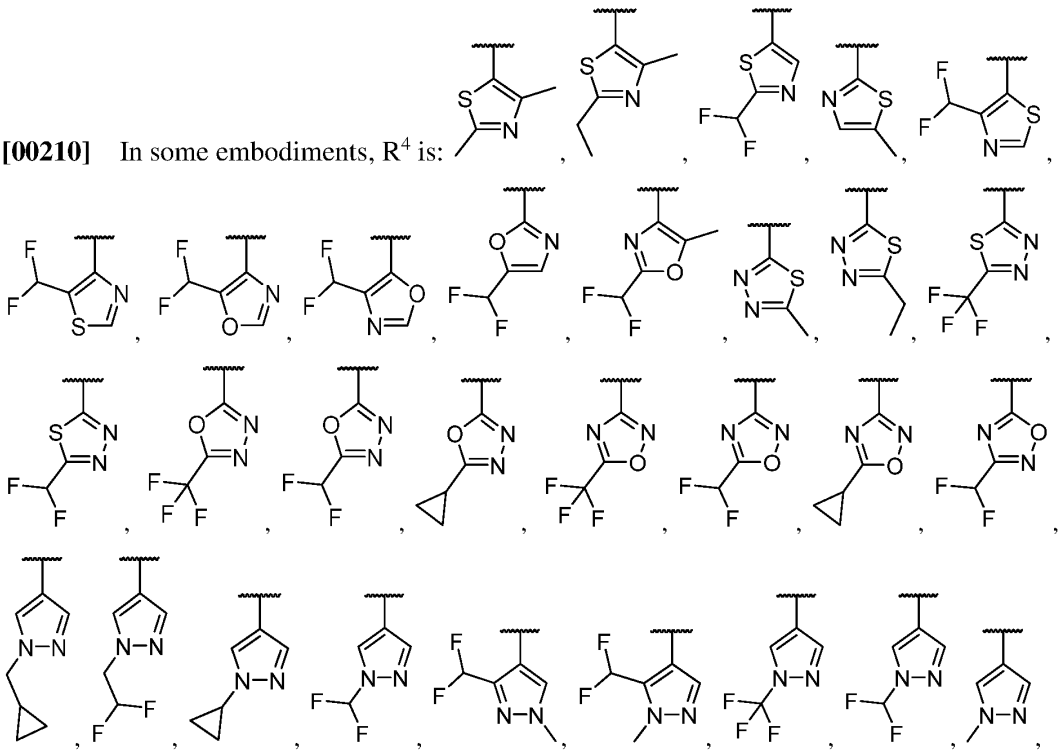


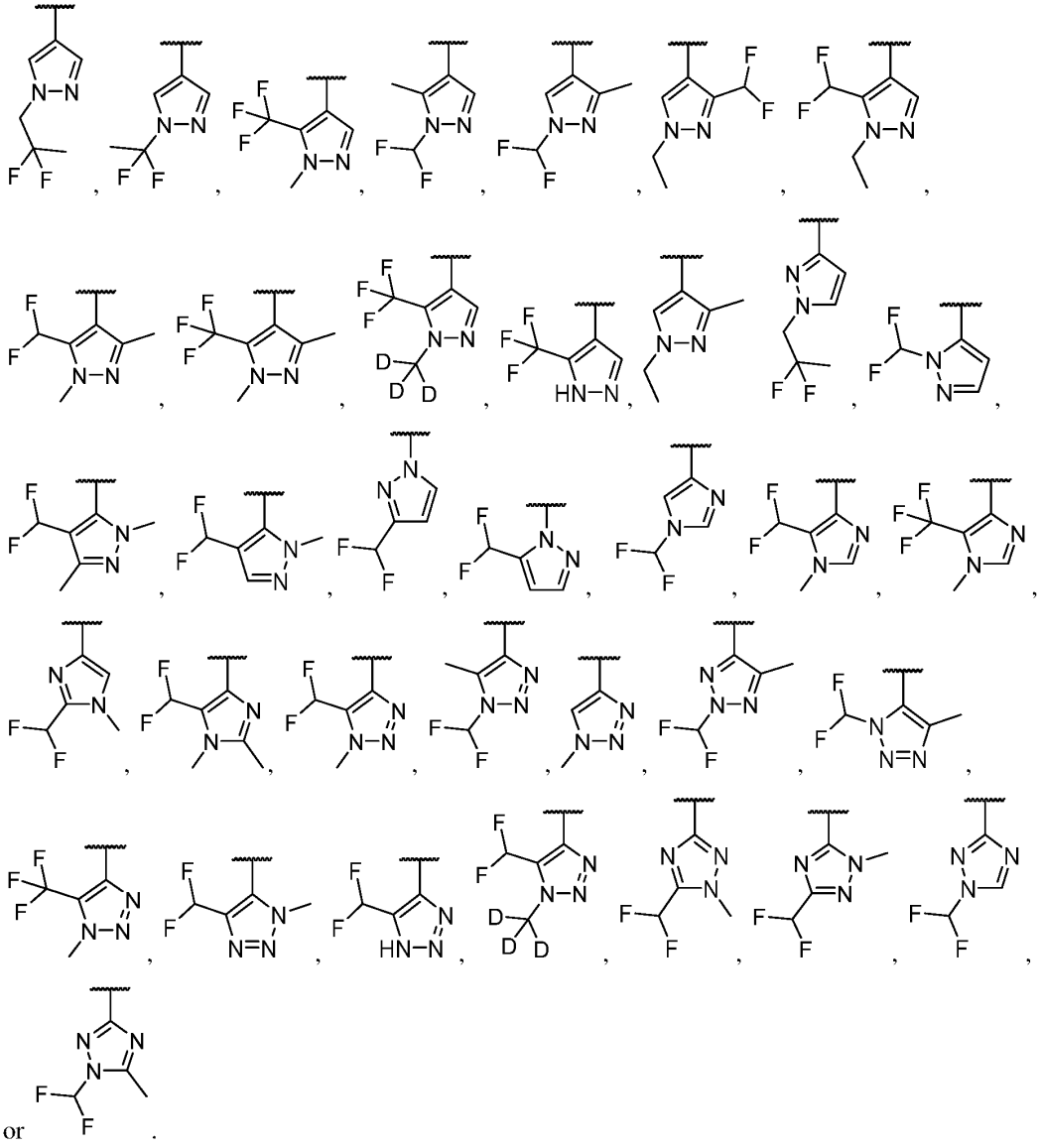


[00209] In some embodiments, R^4 is: 

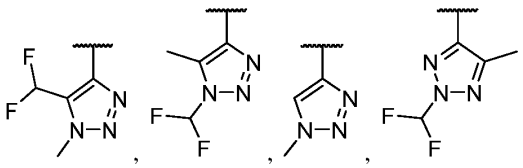
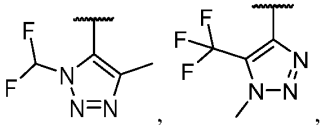
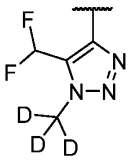


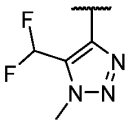
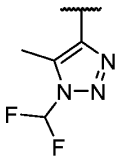
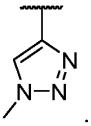
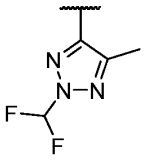
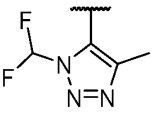
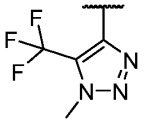
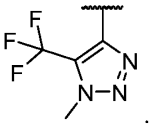
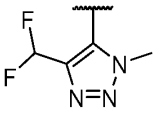
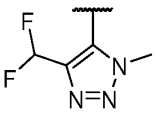
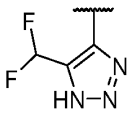
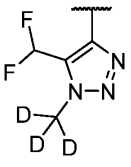
[00210] In some embodiments, R^4 is:





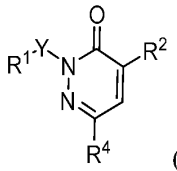
or .

[00211] In certain embodiments, R^4 is , , or . In certain

embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is . In certain embodiments, R^4 is .

Certain Embodiments

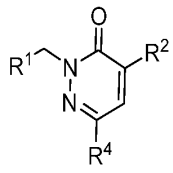
[00212] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-a**):



(**I-a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein R^1, Y, R^2, and R^4 are as defined herein.

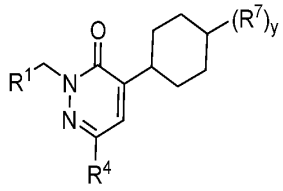
[00213] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-b**):



(**I-b**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^4 are as defined herein.

[00214] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-c**):



(**I-c**),

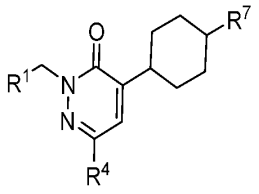
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein R^1 and R^4 are as defined herein;

each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

[00215] In certain embodiments of the compound of Formula (**I-c**), each R^7 is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

[00216] In certain embodiments of the compound of Formula (**I-c**), each R^7 is independently optionally substituted aryl or optionally substituted heteroaryl; and y is 1.

[00217] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-d**):



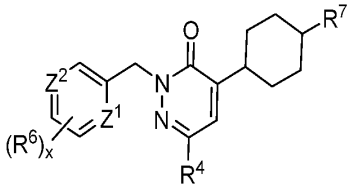
(**I-d**),

[00218] or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 and R^4 are as defined herein; and

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

[00219] In certain embodiments of the compound of Formula (**I-d**), R^7 is optionally substituted heteroaryl or optionally substituted aryl. In certain embodiments of the compound of Formula (**I-d**), R^7 is optionally substituted heteroaryl. In certain embodiments of the compound of Formula (**I-d**), R^7 is optionally substituted aryl.

[00220] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-e**):



(**I-e**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof wherein R^4 is as defined herein;

Z^1 and Z^2 are each independently CH, CR^6, or N;

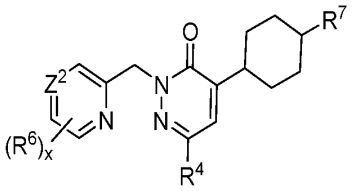
each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl,; and

x is 0, 1 , or 2.

[00221] In certain embodiments of the compound of Formula (**I-e**), Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and R^7 is optionally substituted heteroaryl, or optionally substituted aryl.

[00222] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-f**):



(**I-f**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein.

r a pharmaceutically acceptable salt thereof, wherein:

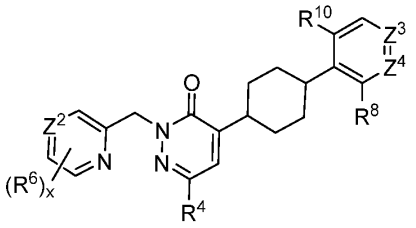
Z^2 is CH, CR^6, or N;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl; and

x is 0, 1, or 2.

[00223] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-f-1**):



(**I-f-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

Z^2 is CH, CR^6, or N;

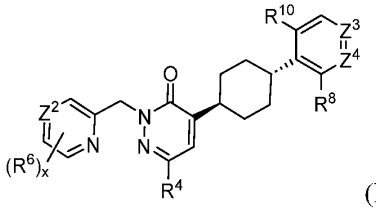
Z^3 and Z^4 are each independently -N- or $-CR^9-$;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $–OR^A$; and

x is 0, 1, or 2.

[00224] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-f-2**):



(**I-f-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

Z^2 is CH, CR^6, or N;

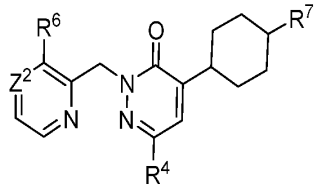
Z^3 and Z^4 are each independently -N- or -CR^9-;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A;

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or –OR^A; and

x is 0, 1, or 2.

[00225] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g**):



(**I-g**),

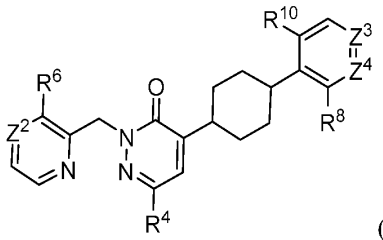
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

Z^2 is CH or N;

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A; and

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

[00226] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g-1**):



(**I-g-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

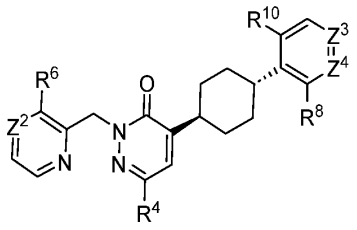
Z^2 is CH or N;

Z^3 and Z^4 are each independently -N- or -CR^9-; and

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or –OR^A.

[00227] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g-2**):



(**I-g-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

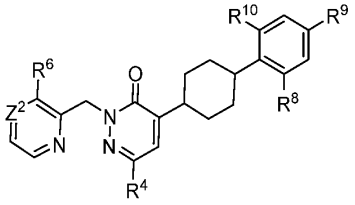
Z^2 is CH or N;

Z^3 and Z^4 are each independently -N- or -CR^9-; and

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or –OR^A.

[00228] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g-3**):



(**I-g-3**),

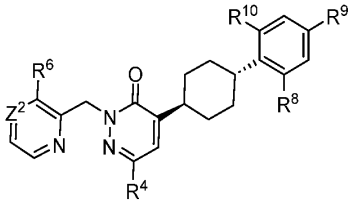
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

Z^2 is CH or N;

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $-OR^A$; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $-OR^A$.

[00229] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g-4**):



(**I-g-4**),

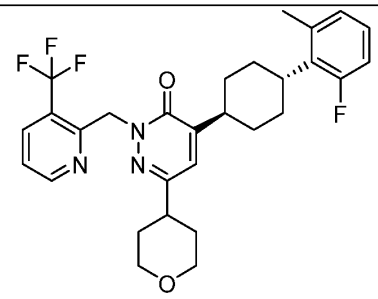
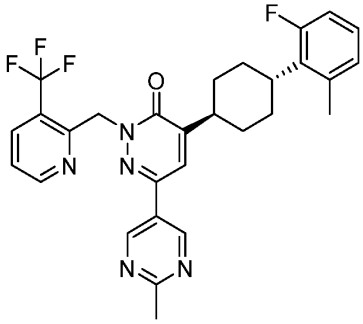
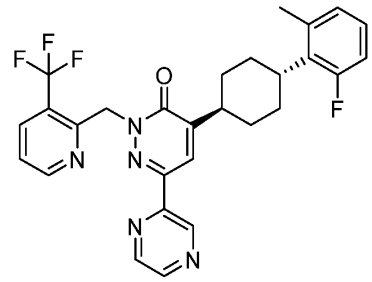
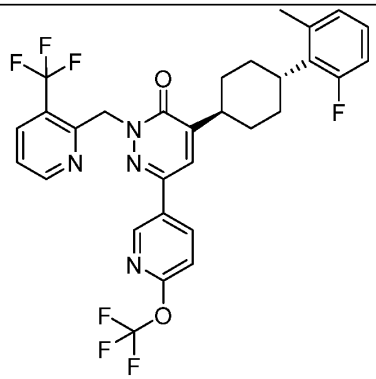
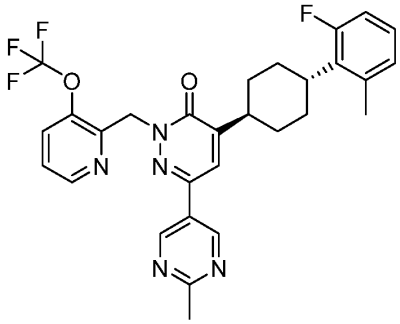
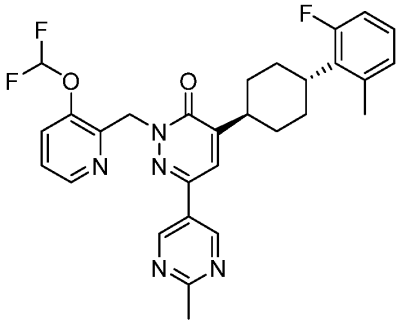
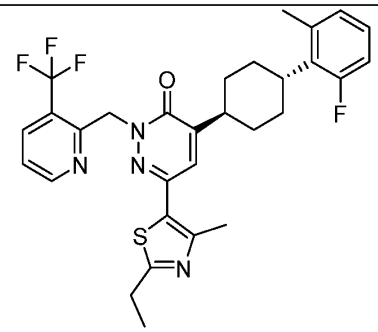
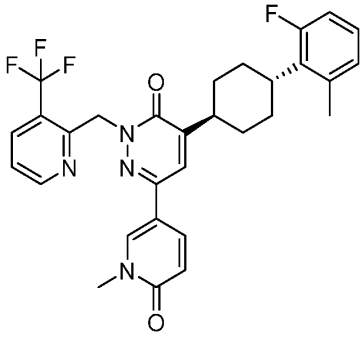
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^4 is as defined herein;

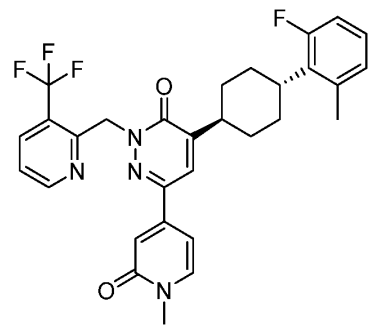
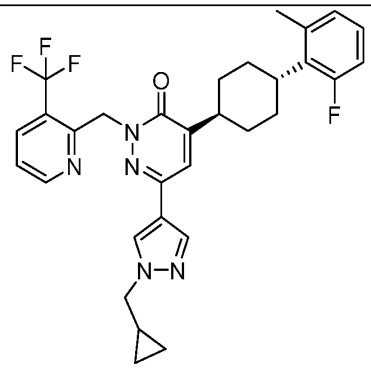
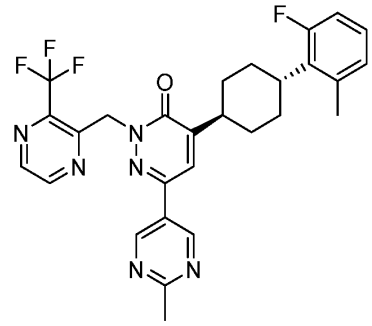
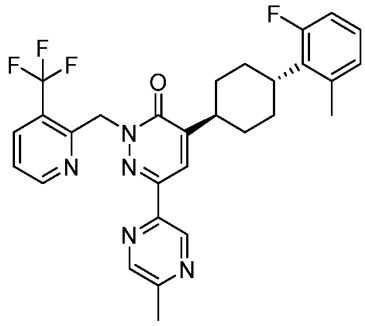
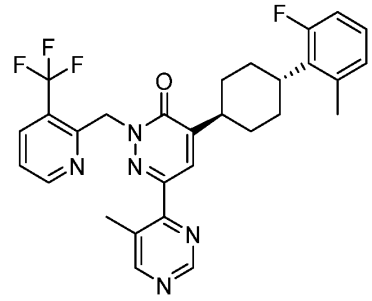
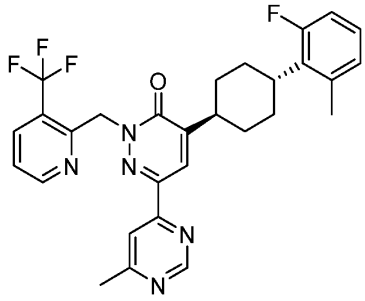
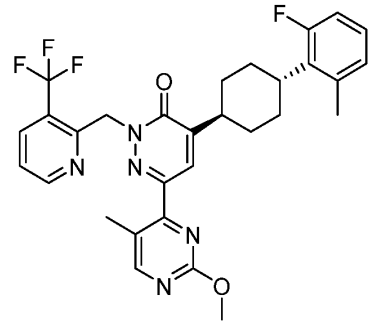
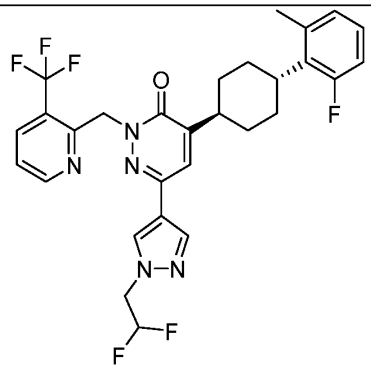
Z^2 is CH or N;

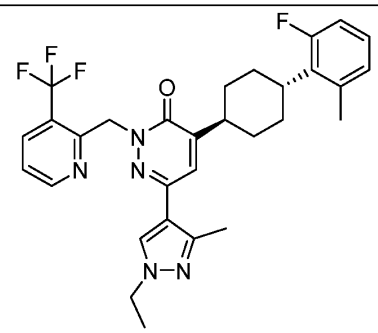
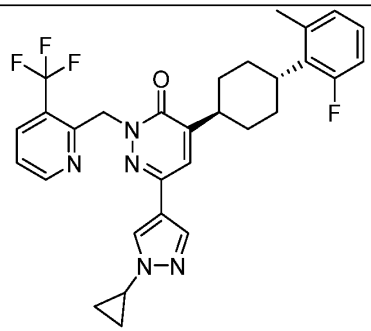
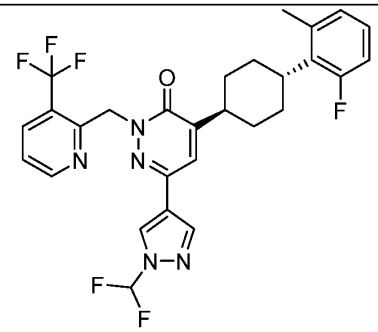
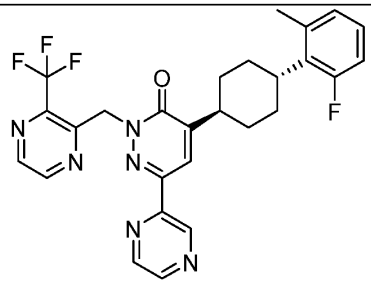
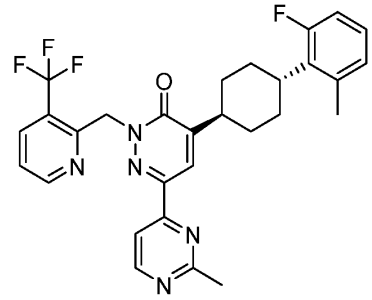
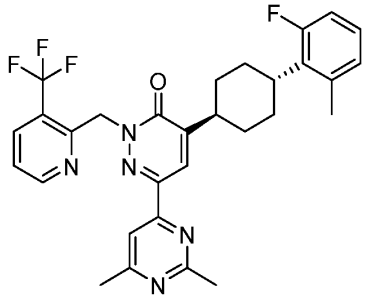
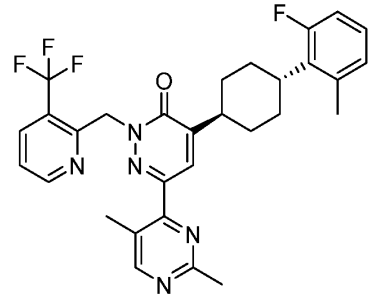
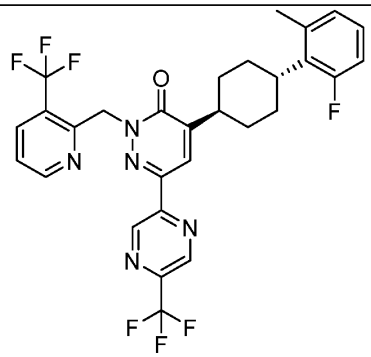
R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $-OR^A$; and

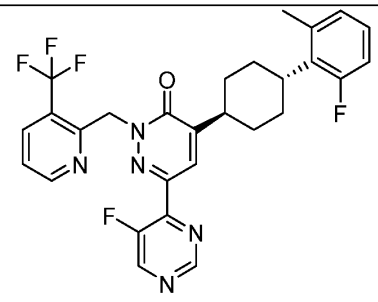
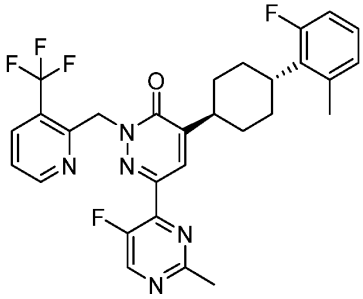
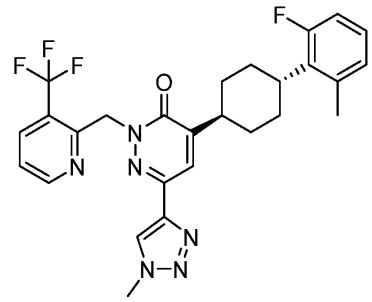
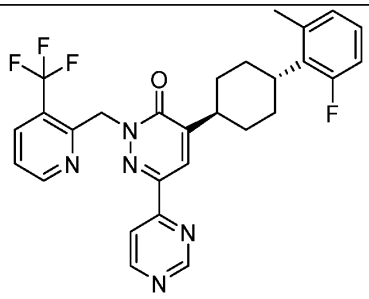
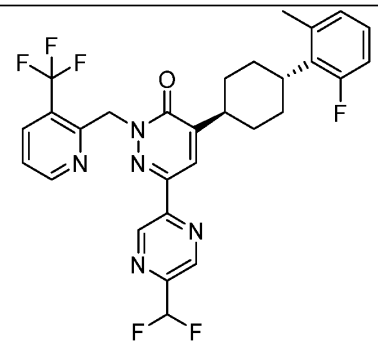
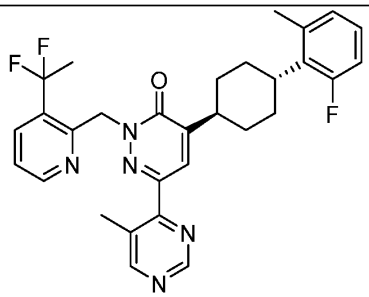
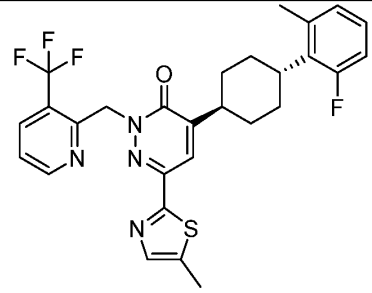
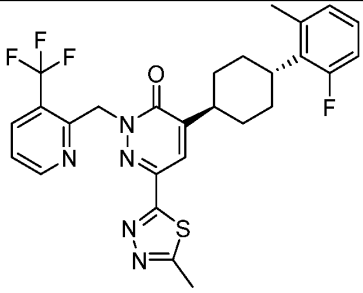
each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $-OR^A$.

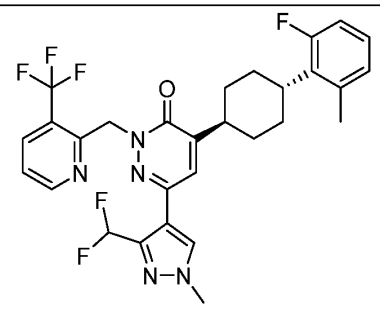
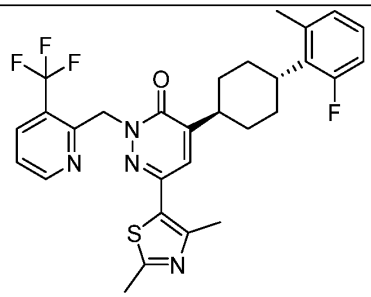
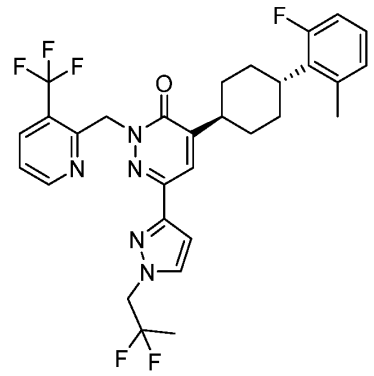
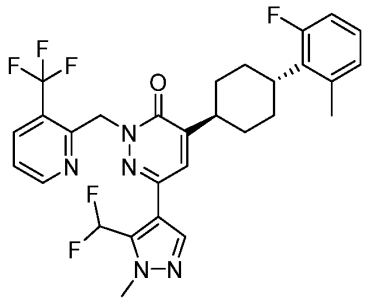
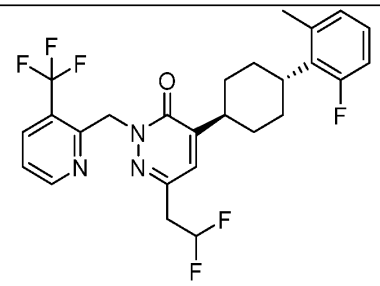
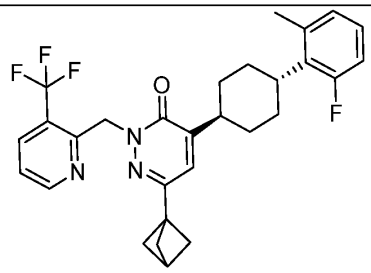
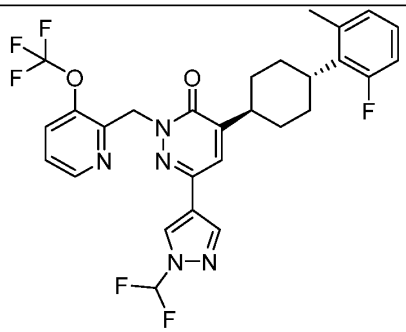
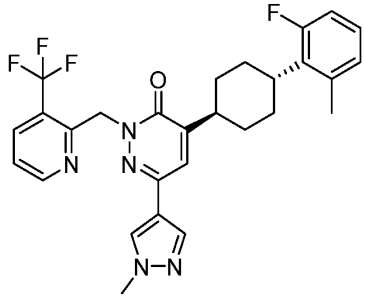
[00230] In certain embodiments, the compound of Formula (**I**) is of formula:

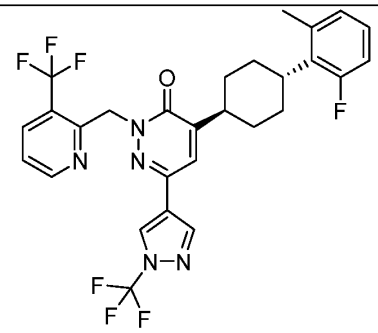
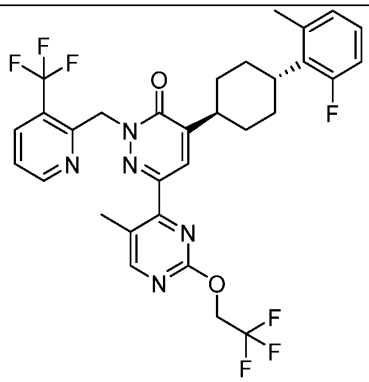
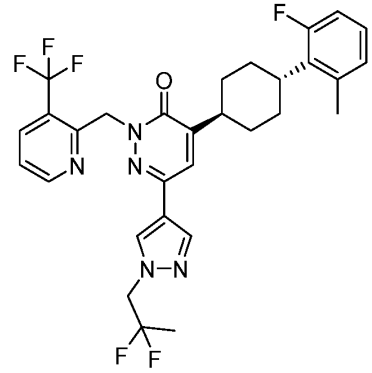
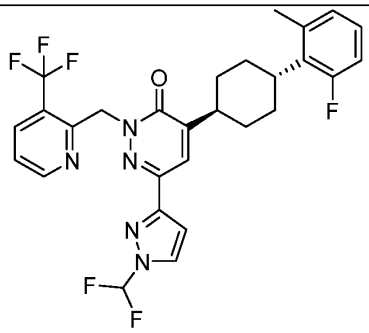
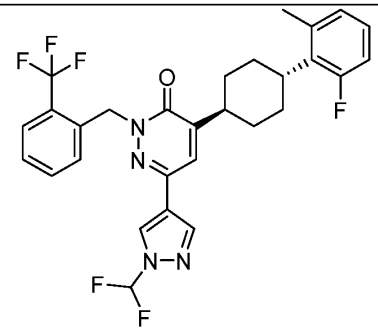
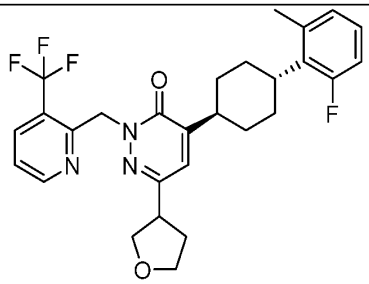
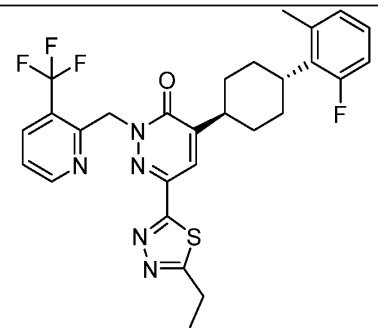
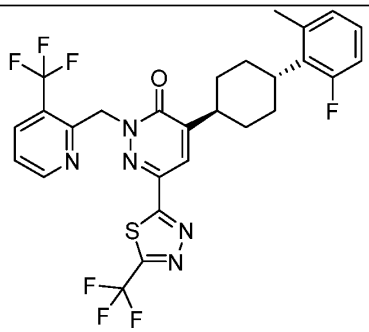
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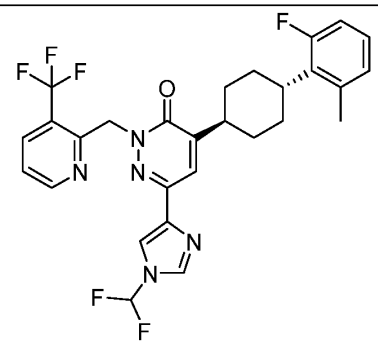
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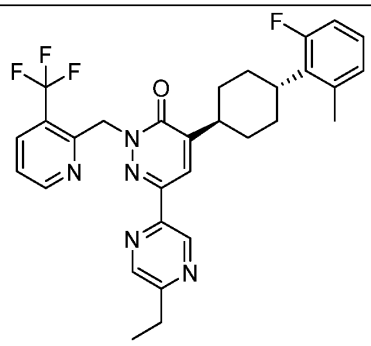
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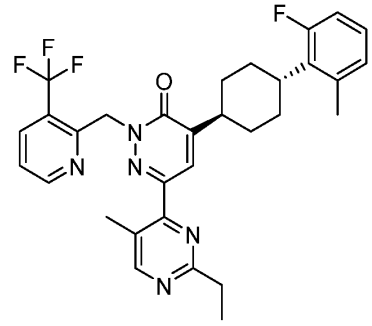
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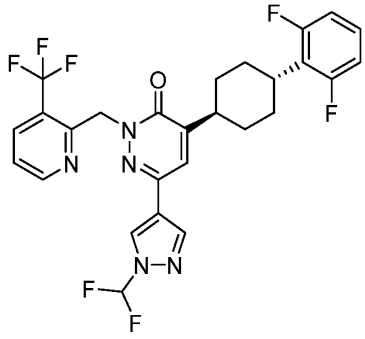
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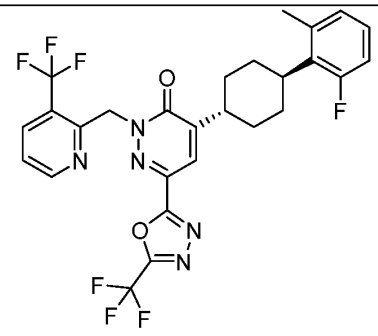
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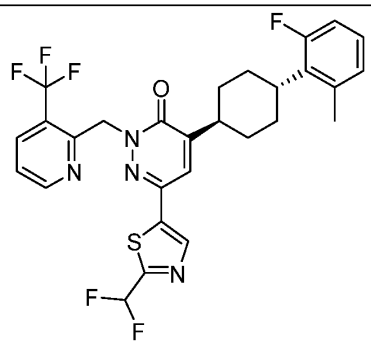
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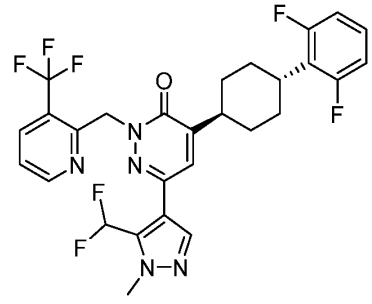
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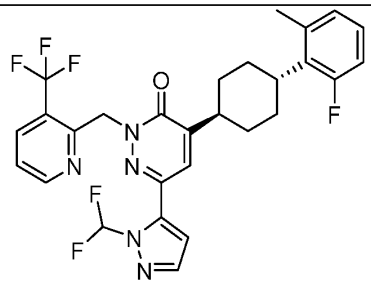
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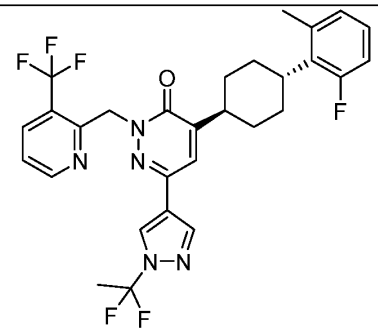
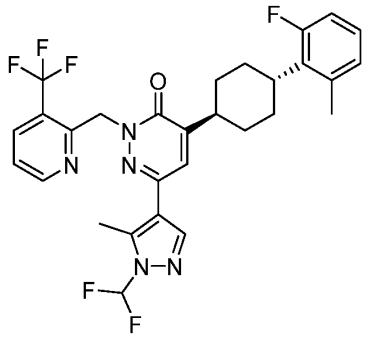
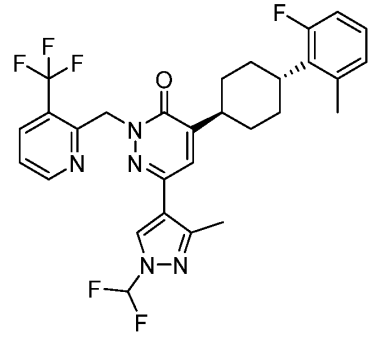
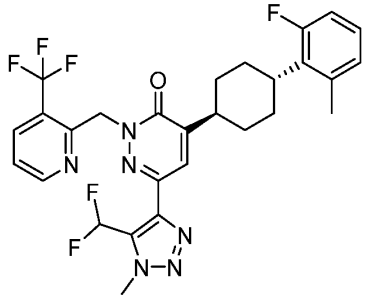
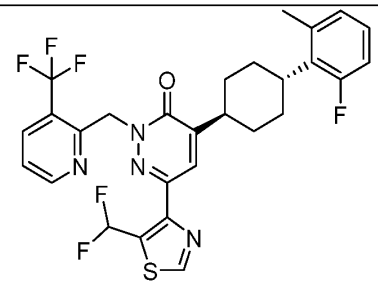
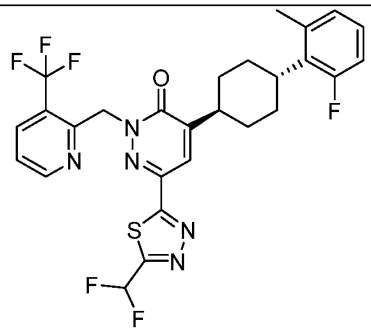
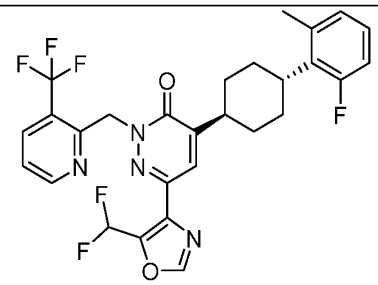
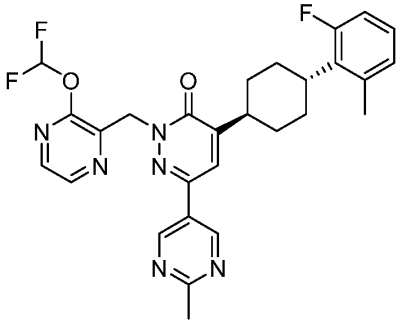
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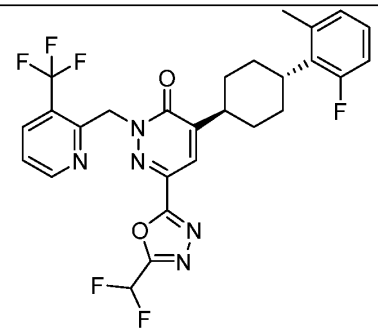
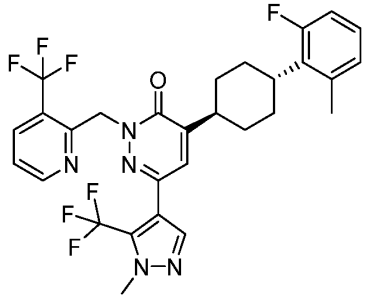
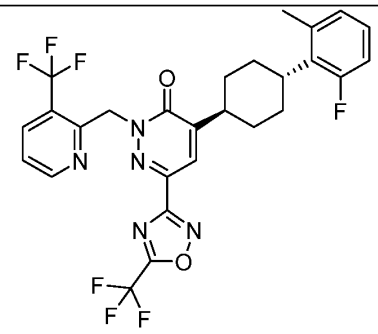
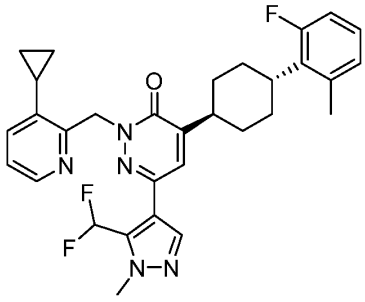
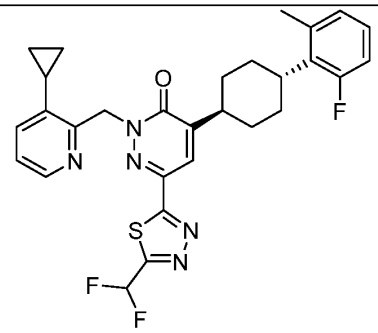
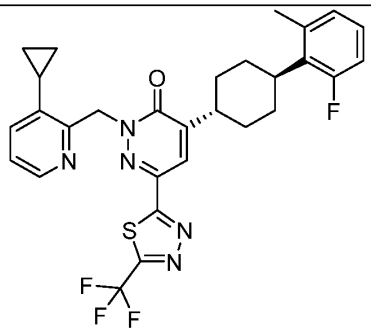
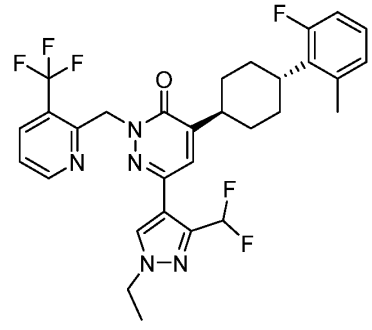
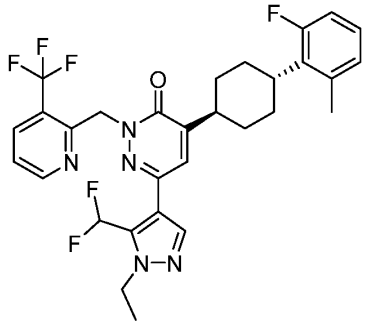


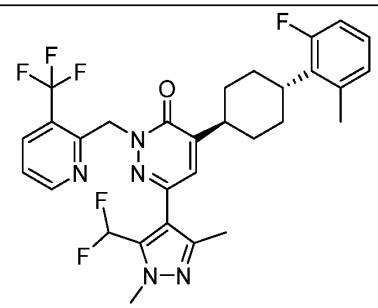
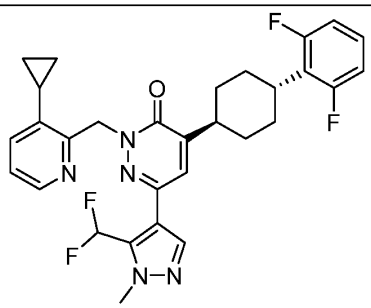
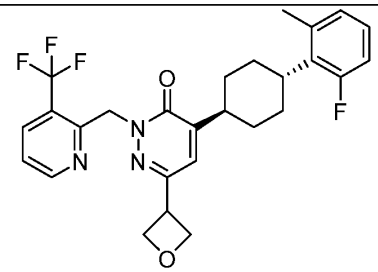
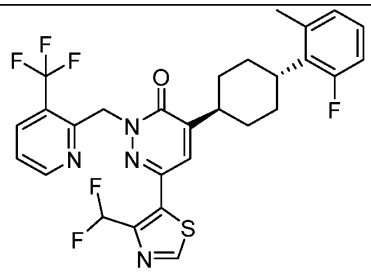
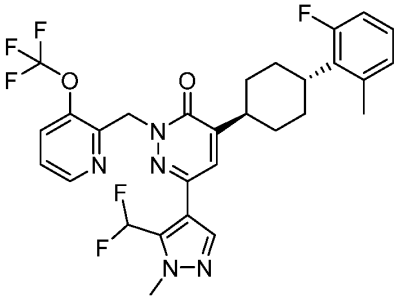
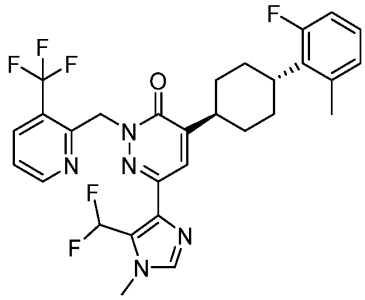
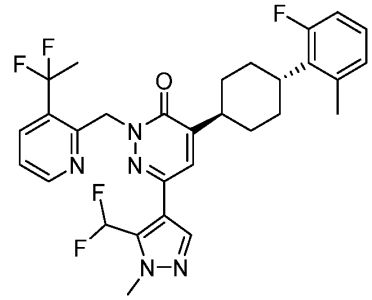
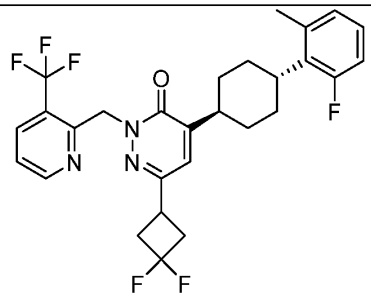
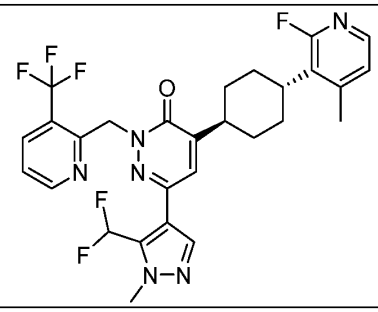
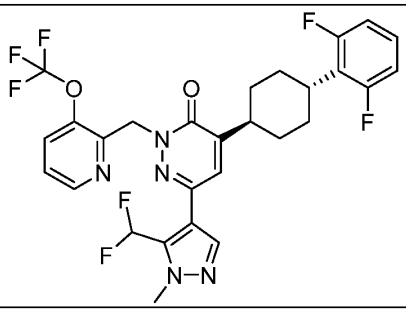
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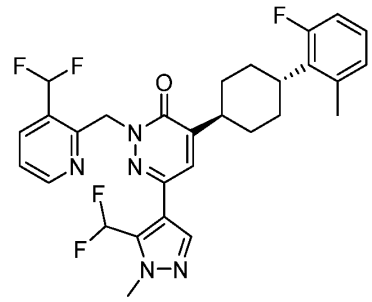
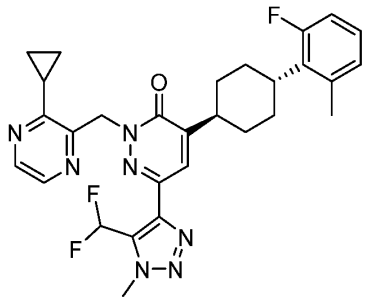
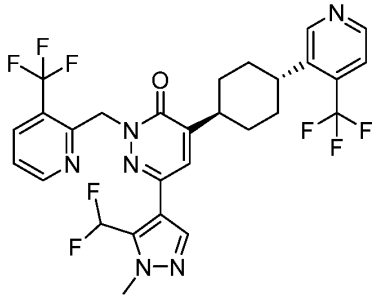
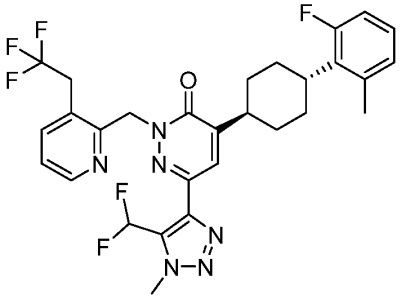
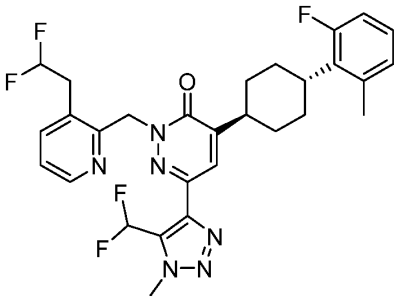
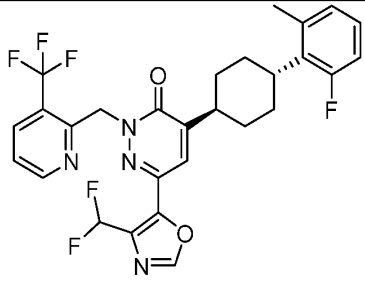
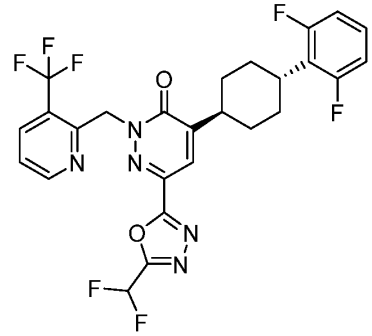
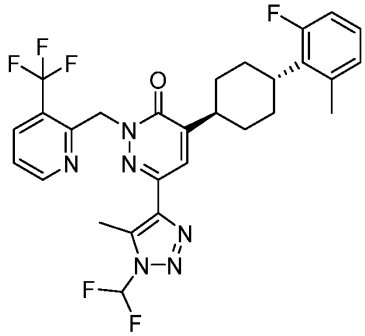


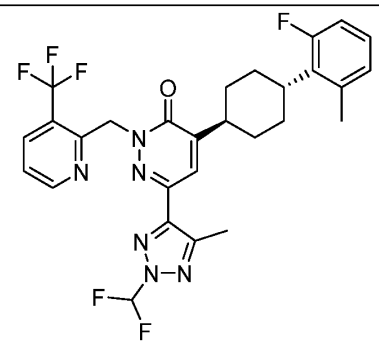
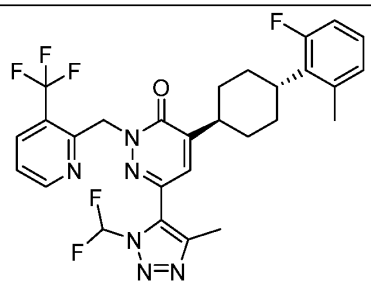
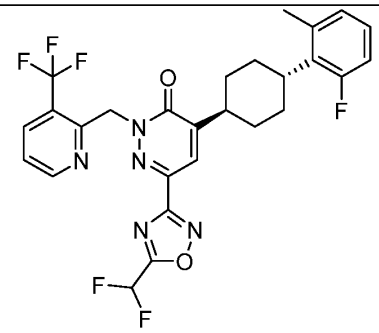
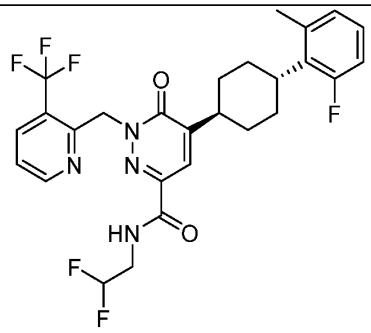
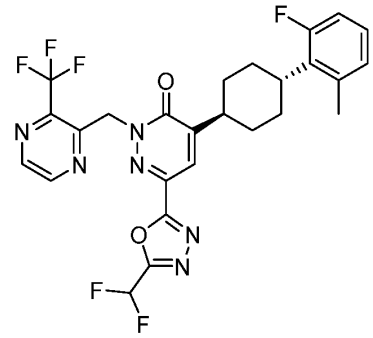
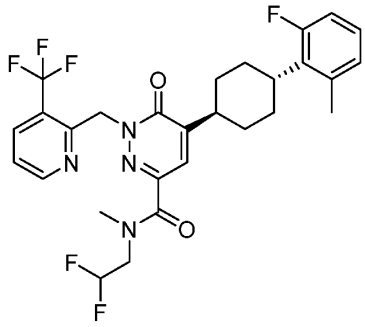
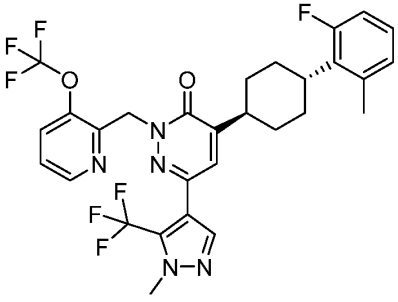
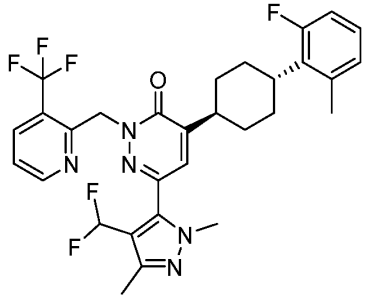
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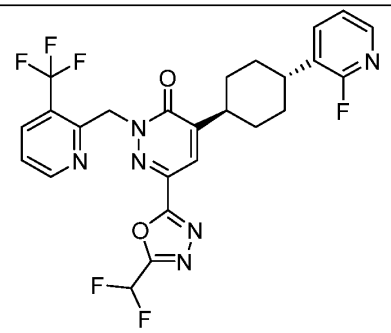
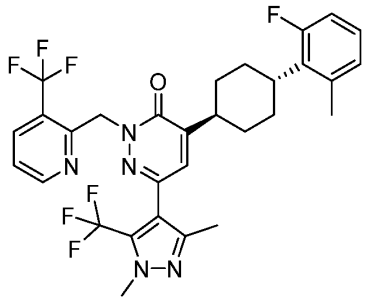
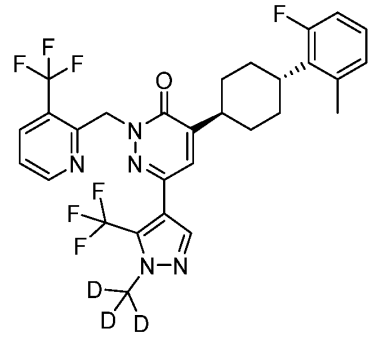
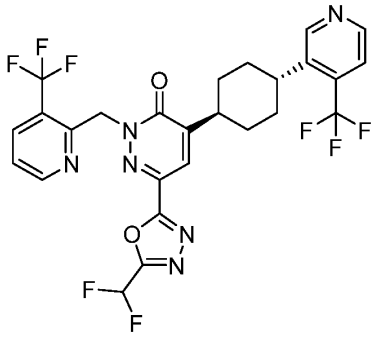
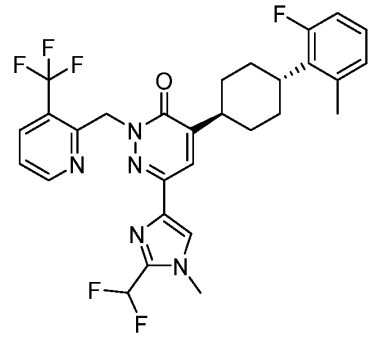
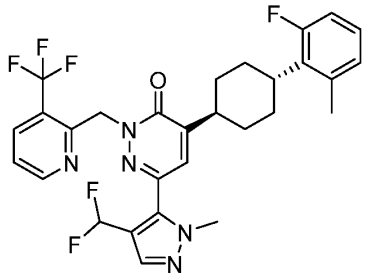
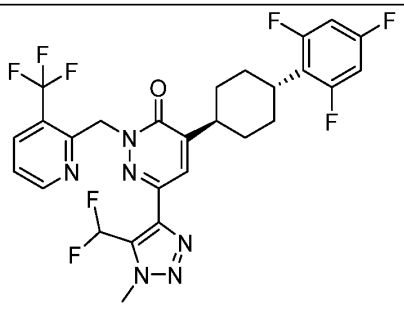
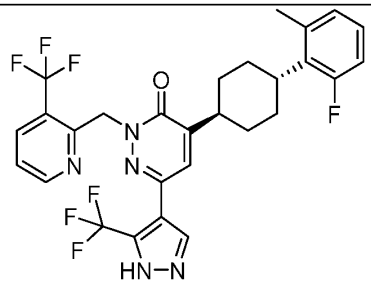
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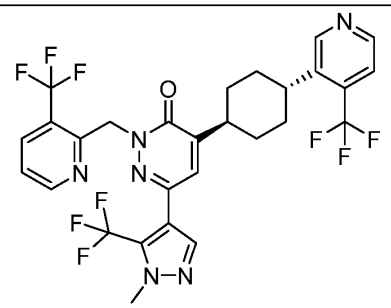
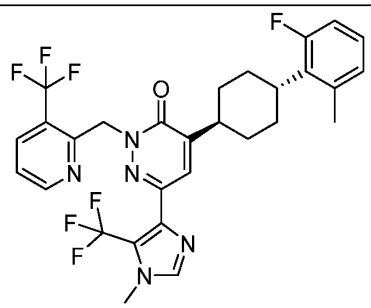
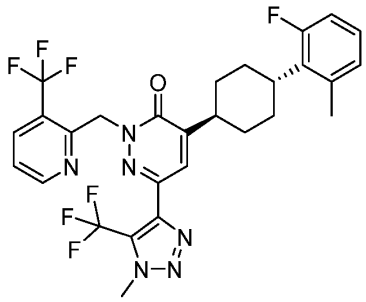
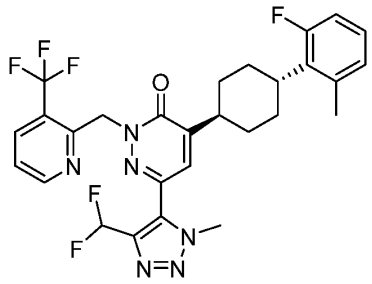
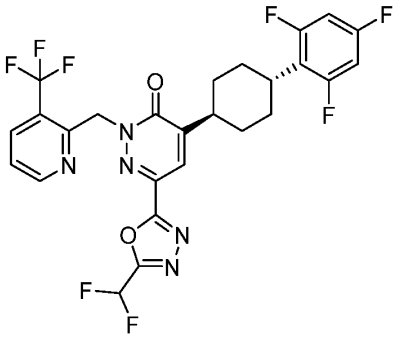
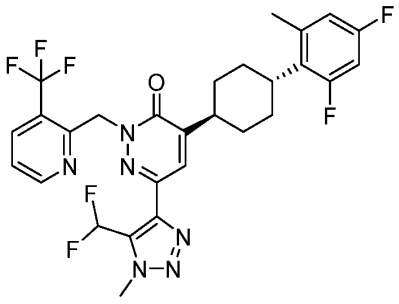
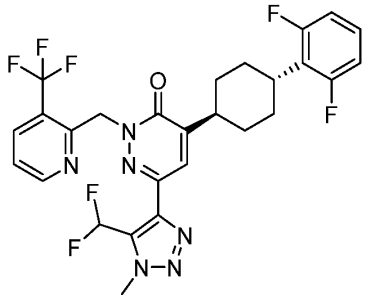
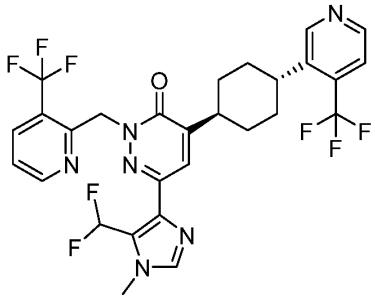
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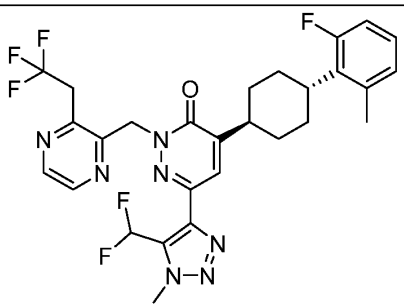
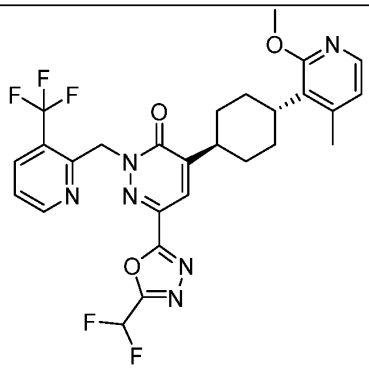
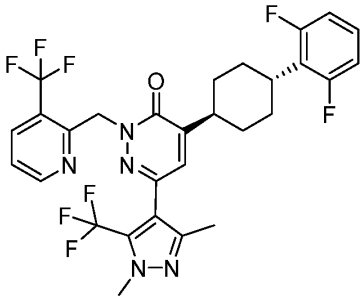
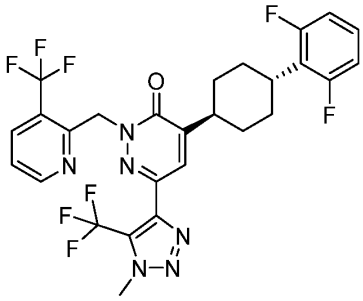
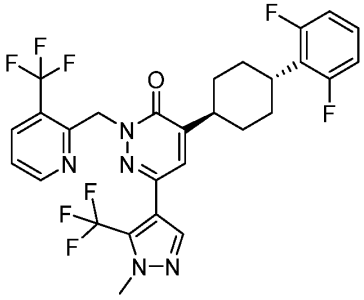
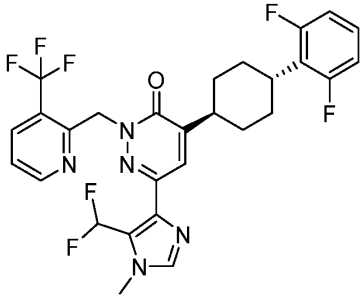
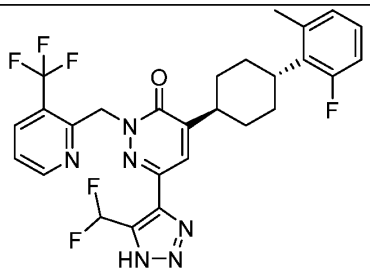
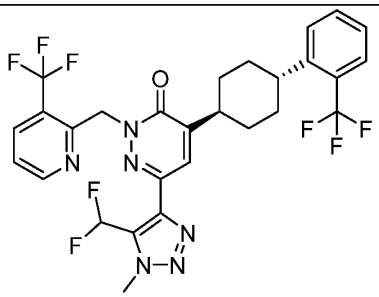
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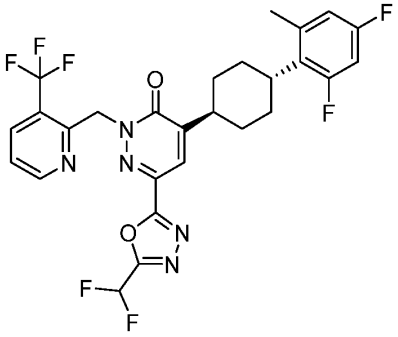
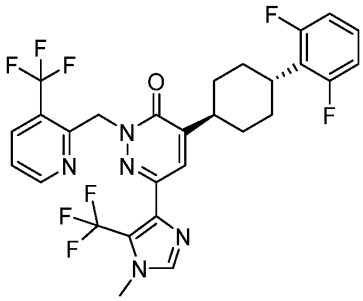
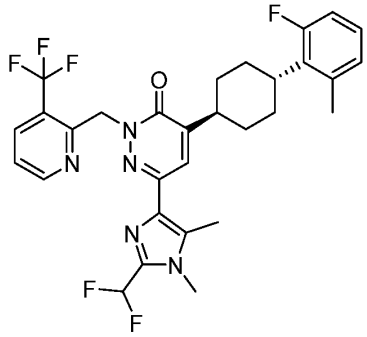
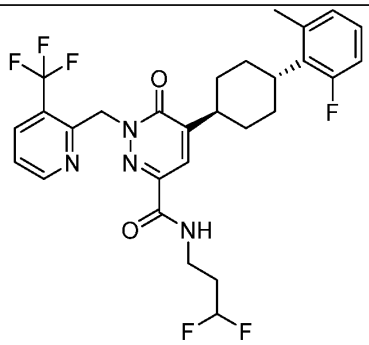
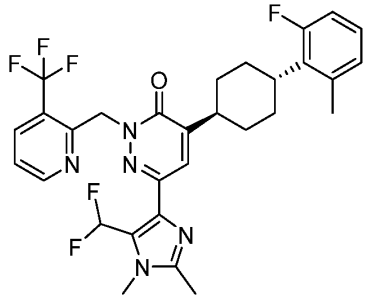
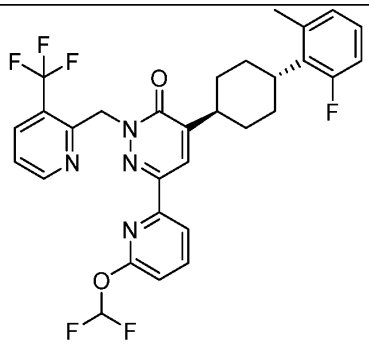
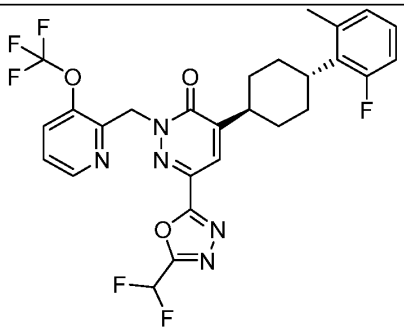
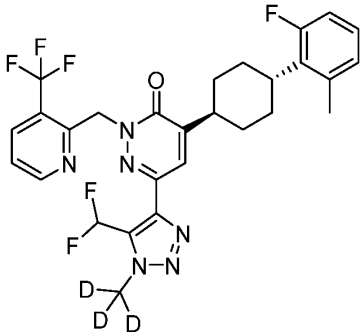
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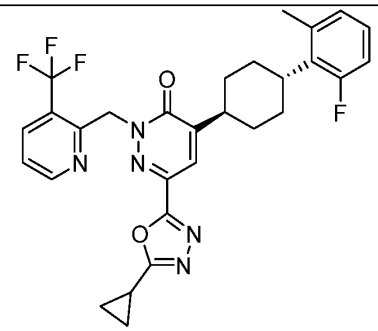
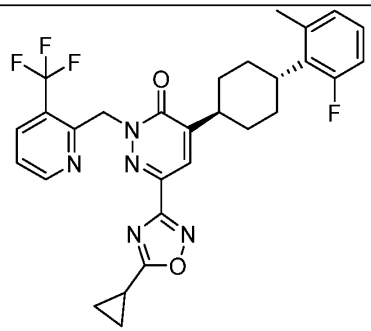
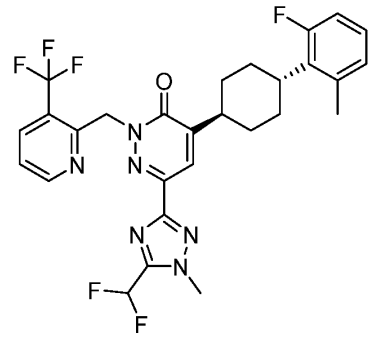
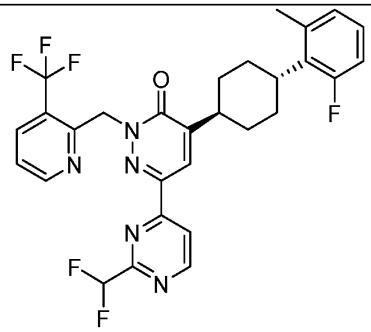
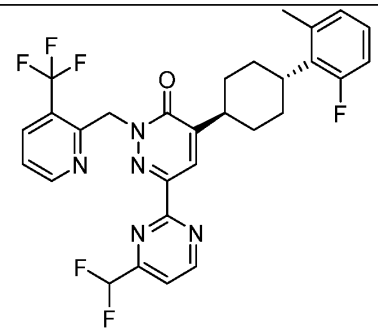
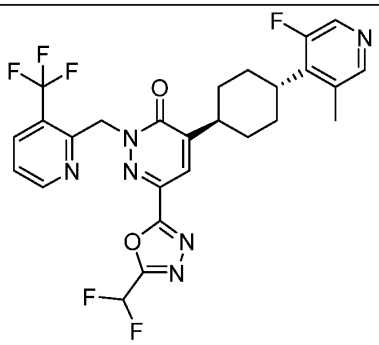
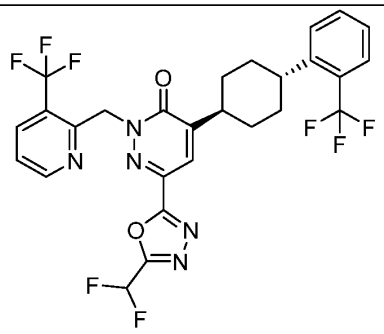
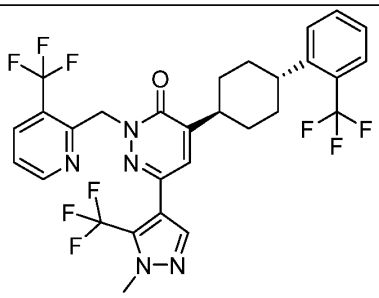
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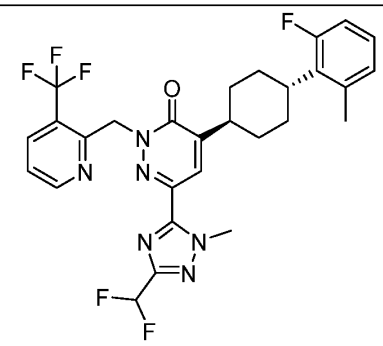
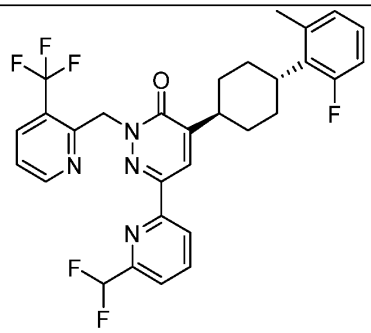
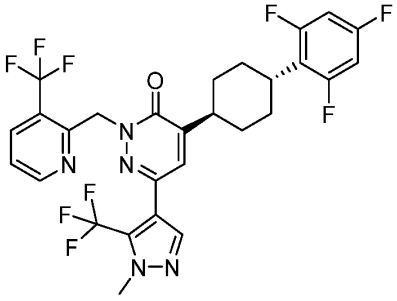
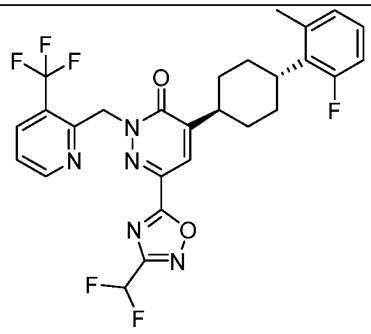
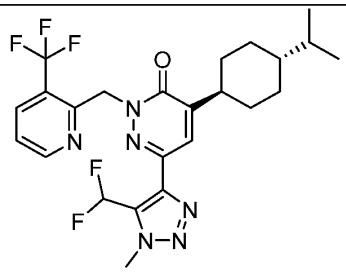
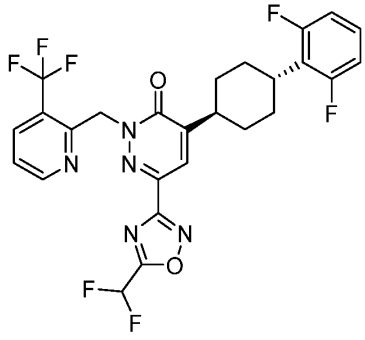
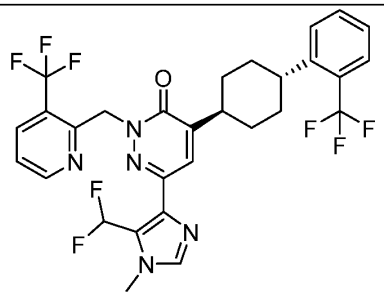
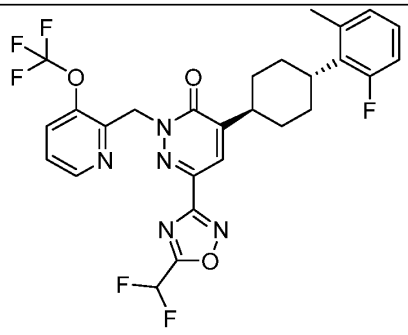
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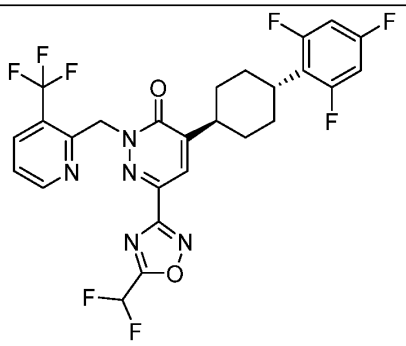
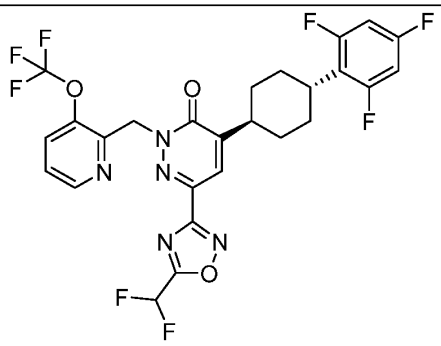
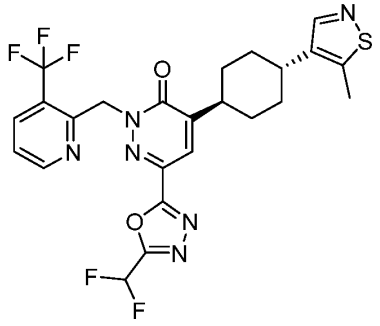
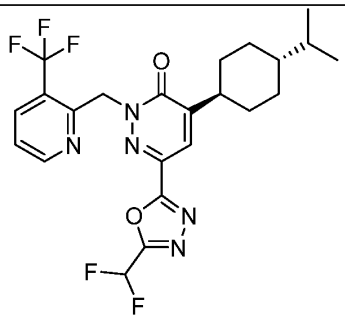
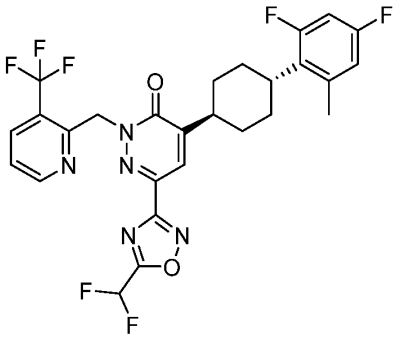
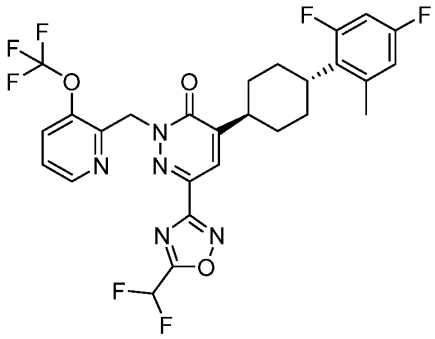
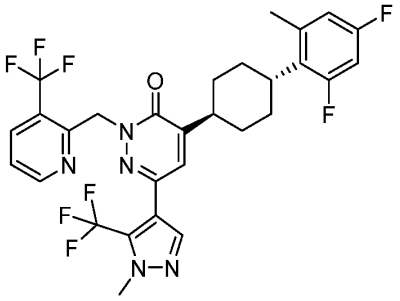
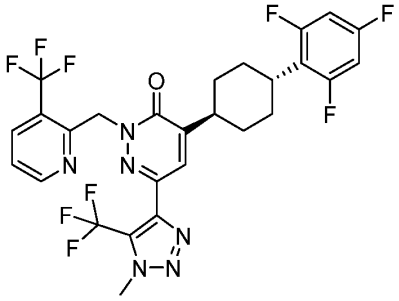
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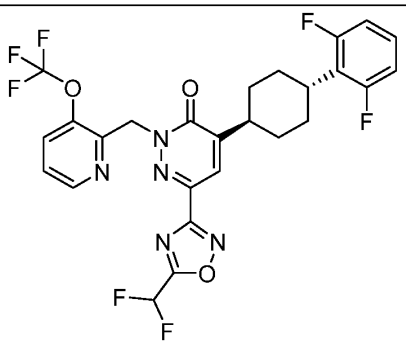
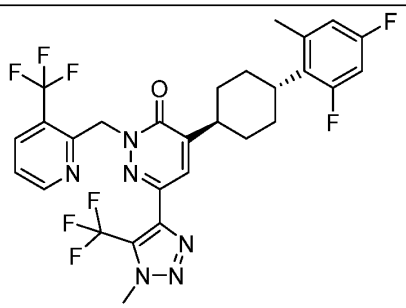
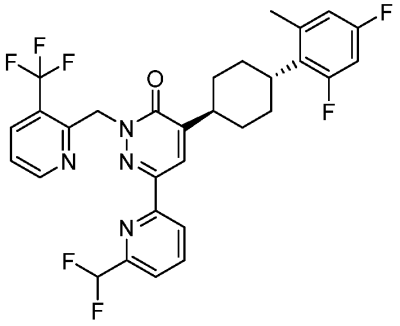
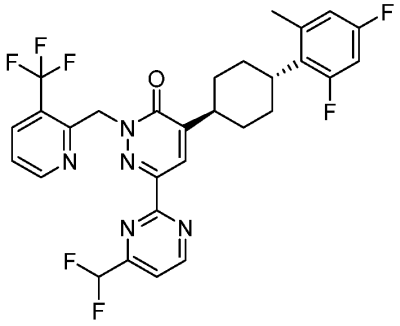
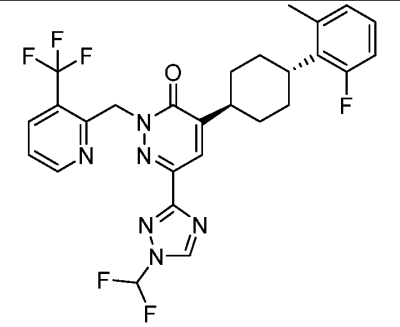
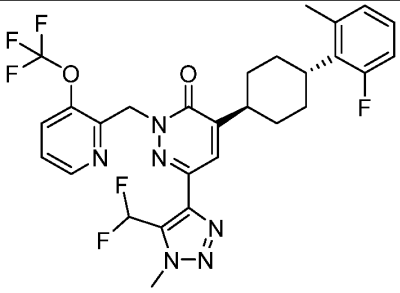
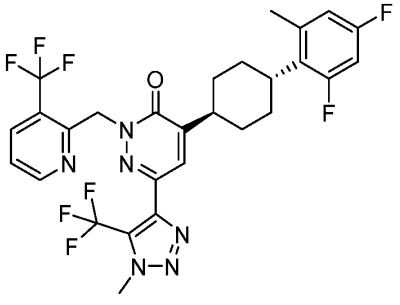
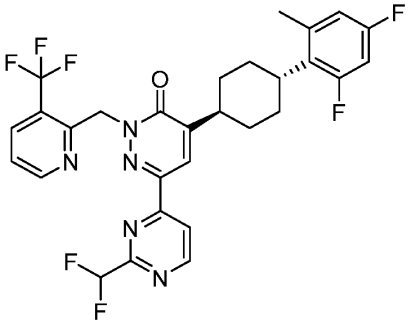
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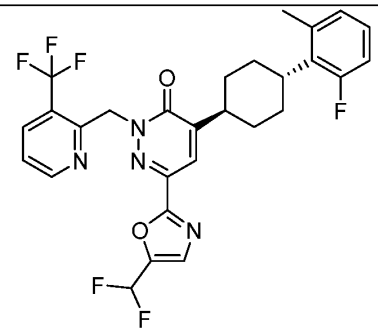
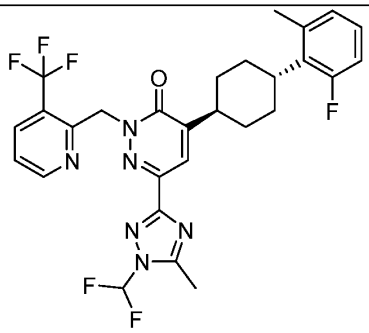
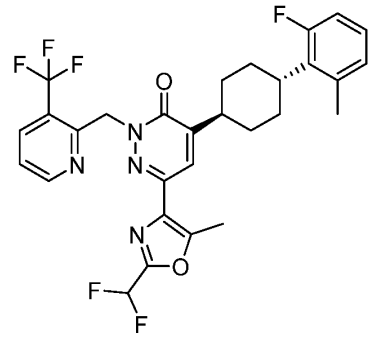
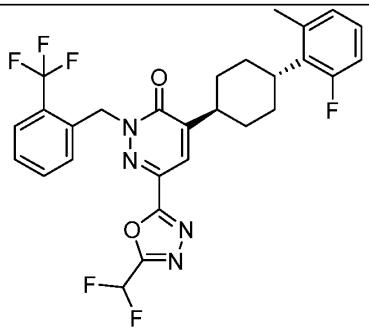
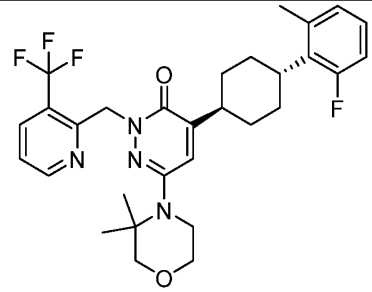
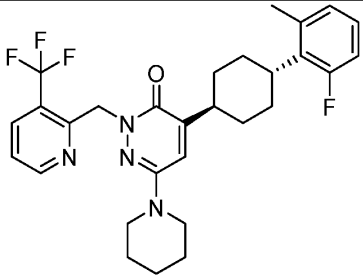
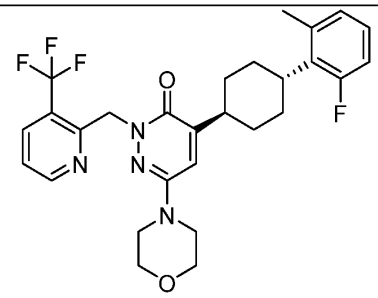
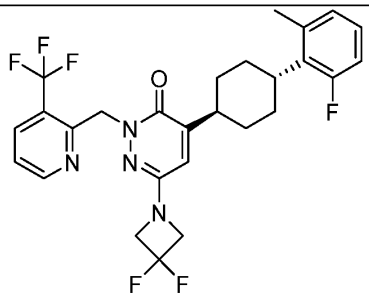
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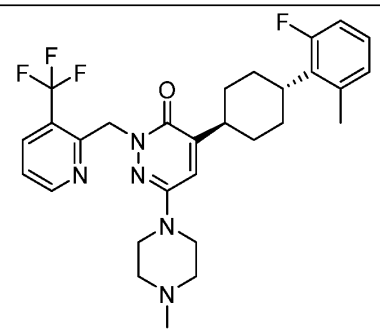
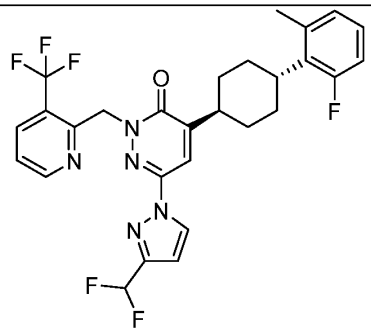
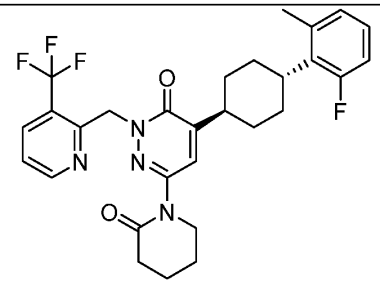
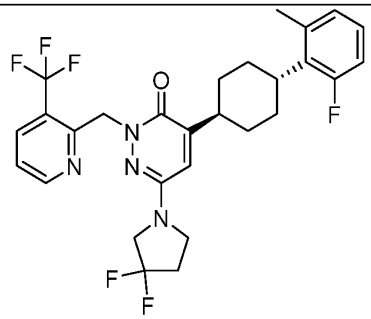
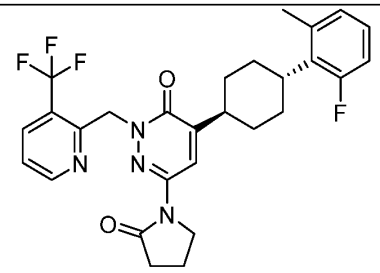
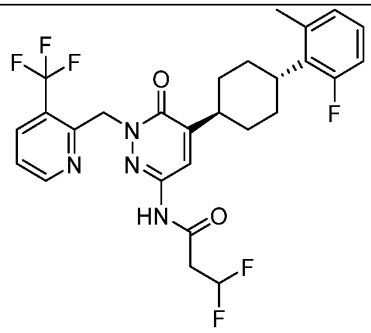
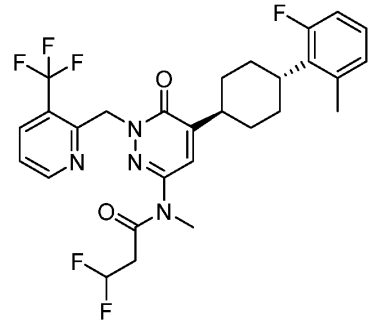
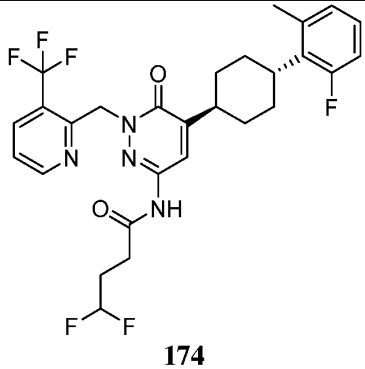
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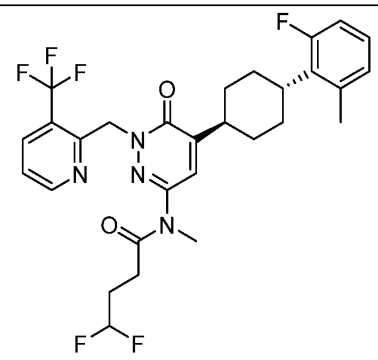
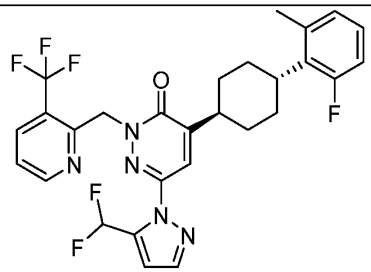
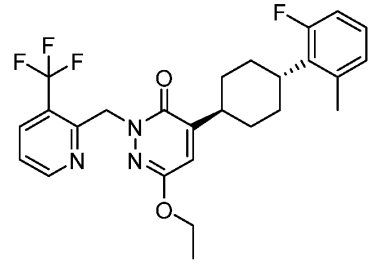
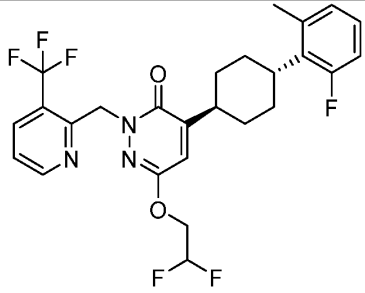
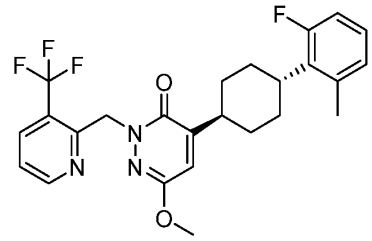
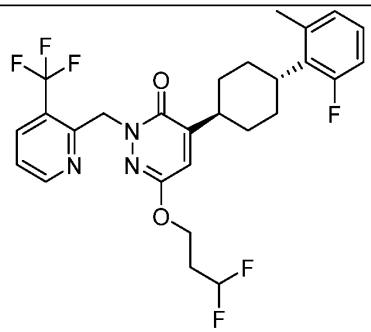
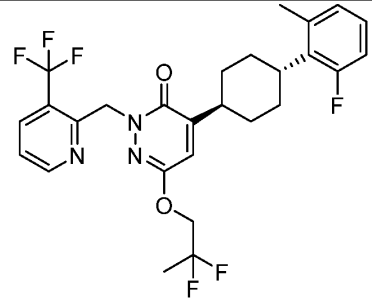
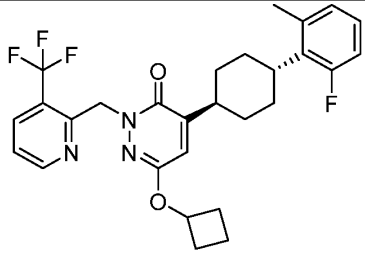
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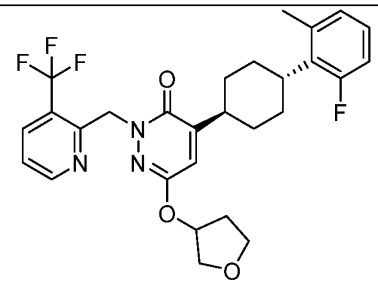
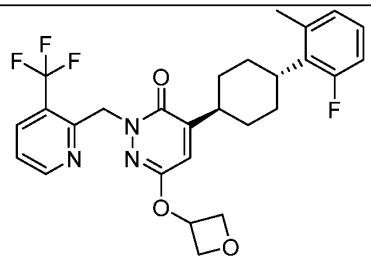
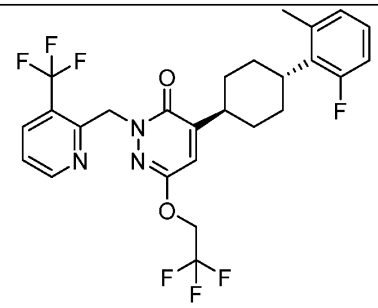
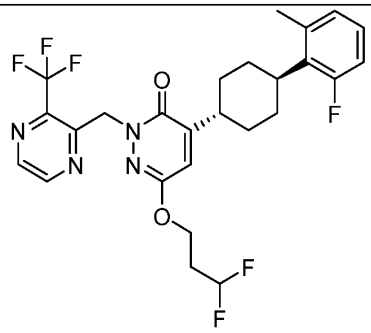
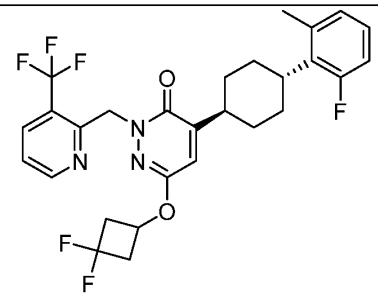
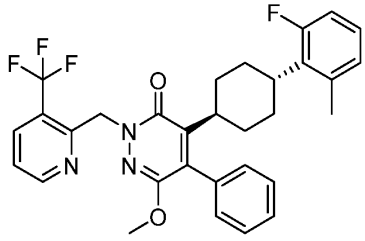
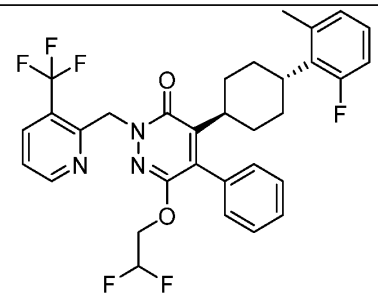
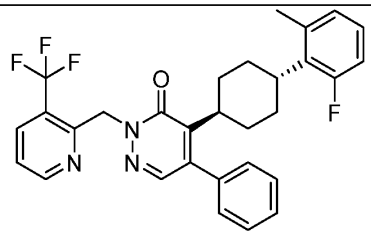
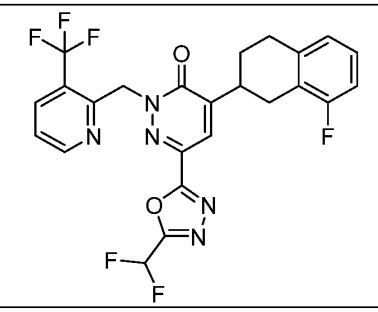
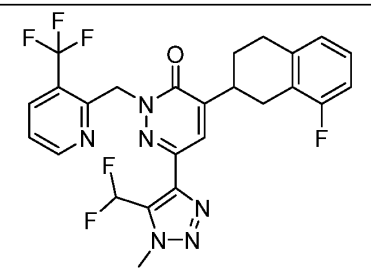
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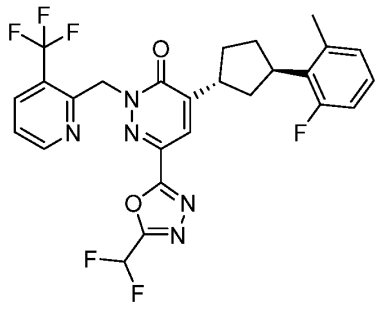
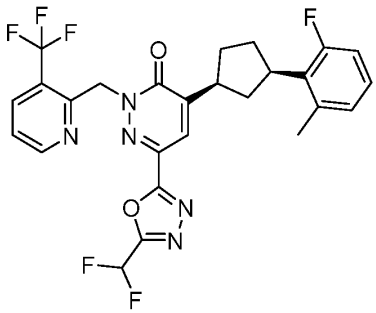
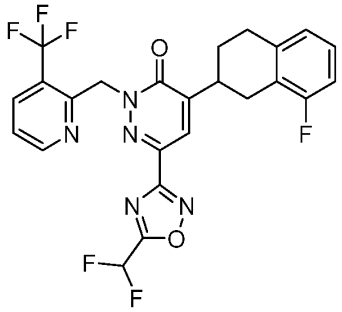
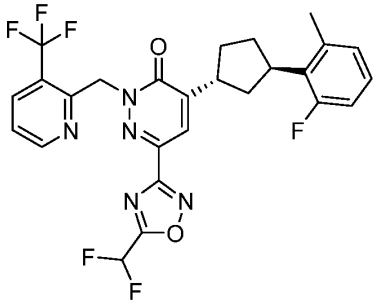
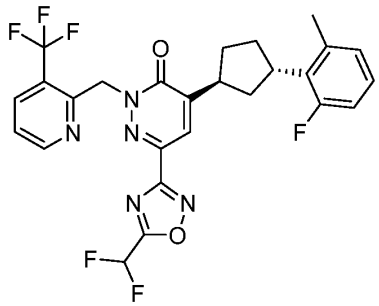
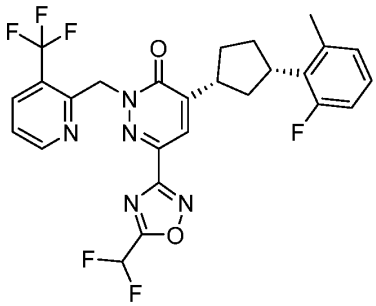
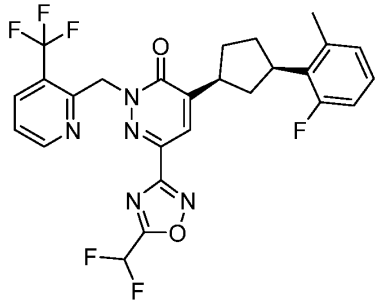
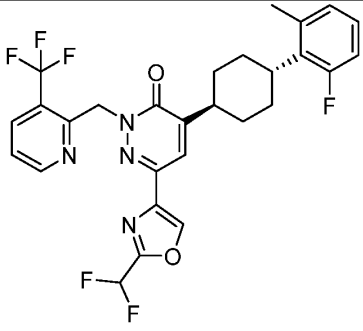
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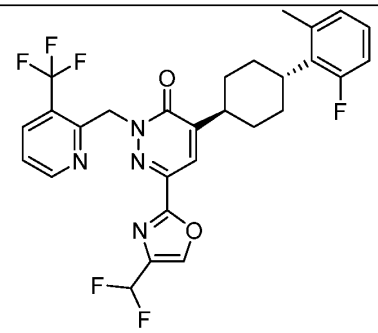
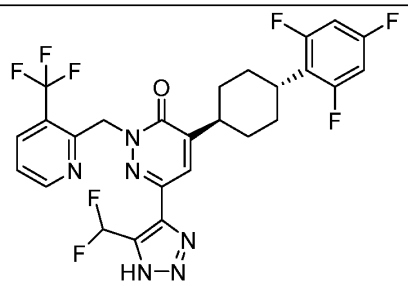
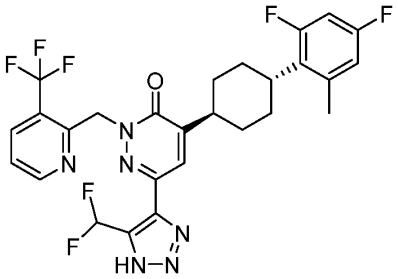
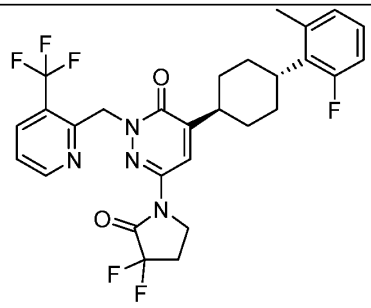
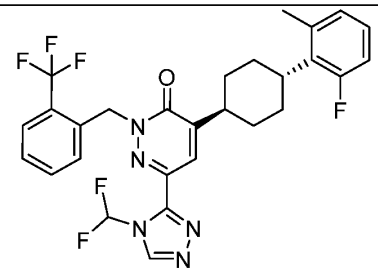
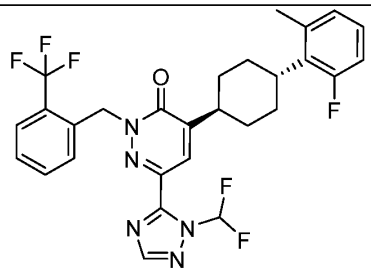
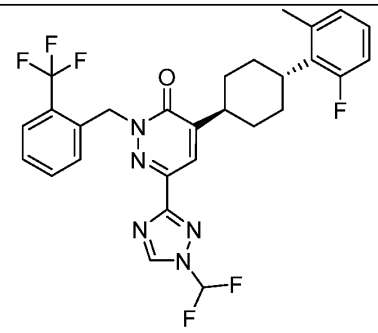
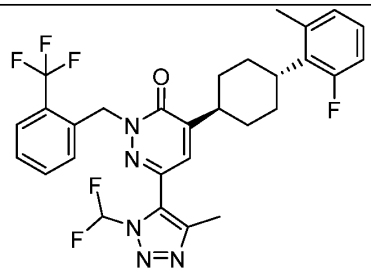
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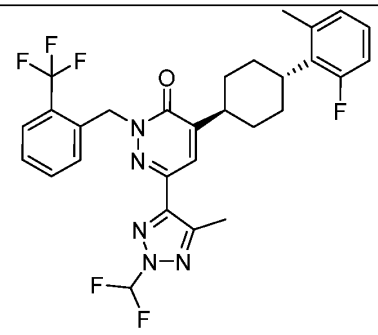
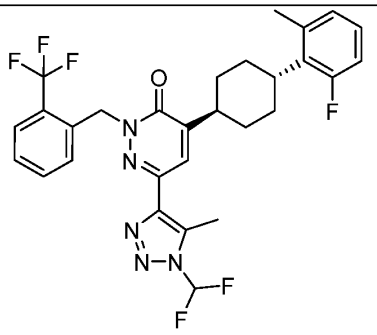
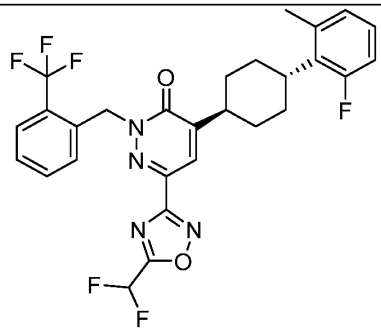
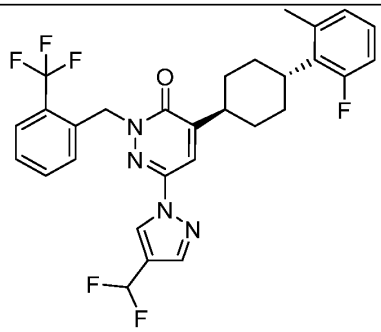
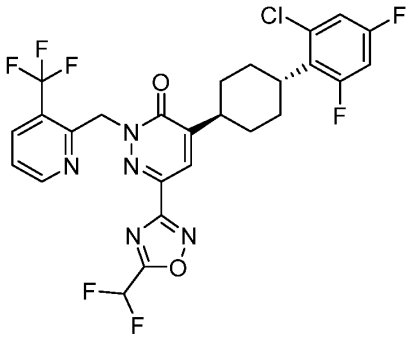
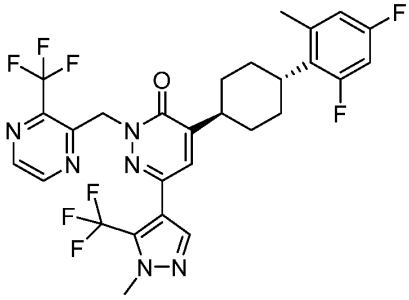
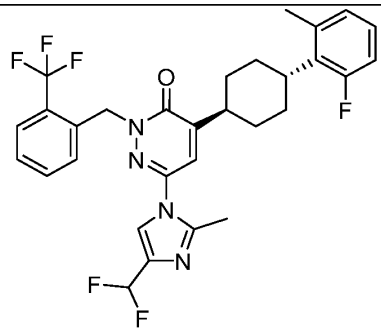
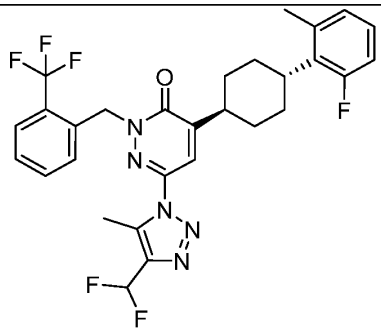
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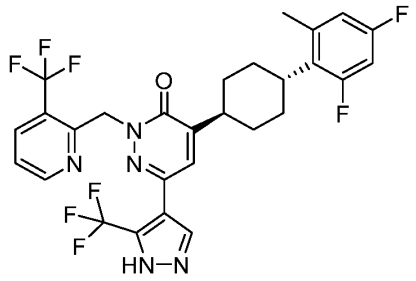
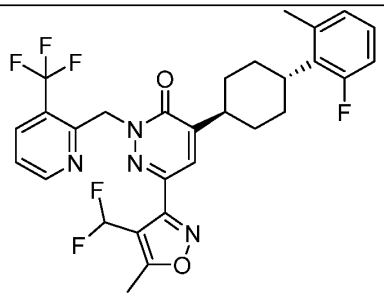
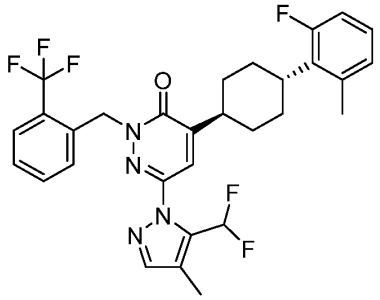
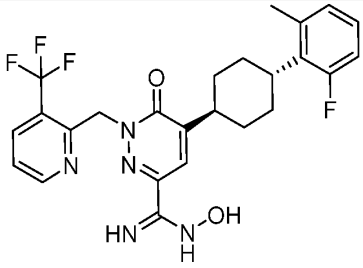
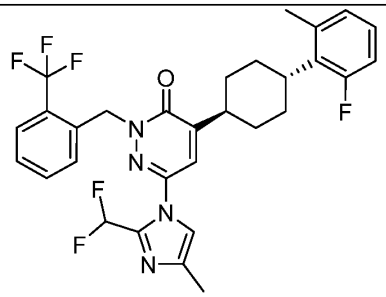
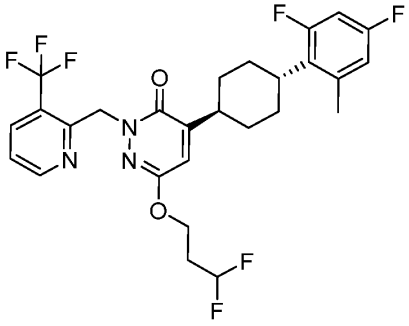
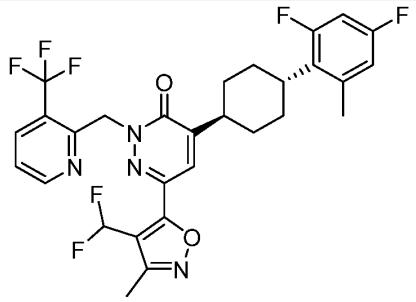
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 **197**	 **198**
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or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00231] In certain embodiments, the provided compounds (*e.g.*, compounds of Formula (**I**)), antagonize C5aR1 with an IC_{50} of less than 100,000 nM, less than 50,000 nM, less than 20,000 nM, less than 10,000 nM, less than 5,000 nM, less than 2,500 nM, less than 1,000 nM,

less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM.

[00232] In certain embodiments, the provided compounds (*e.g.*, compounds of Formula (**I**)), inhibit C5aR1 with an IC_{50} of less than 100,000 nM, less than 50,000 nM, less than 20,000 nM, less than 10,000 nM, less than 5,000 nM, less than 2,500 nM, less than 1,000 nM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM.

Pharmaceutical Compositions, Kits, and Administration

[00233] The present disclosure provides pharmaceutical compositions comprising a disclosed compound (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00234] In certain embodiments, the compound of Formula (**I**) is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a disease or disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating cancer, an infectious disease, an autoimmune disease or disorder, an inflammatory disease or disorder, a cardiovascular disease or disorder, a cerebrovascular disease or disorder, a vasculitis disease or disorder, or a neurodegenerative disease or disorder. In certain embodiments, the effective amount is an amount effective for treating an autoimmune, inflammatory, or neurological disease or disorder. In certain embodiments, the effective amount is an amount effective for treating a neurological disease or disorder in a subject in need thereof. In certain

embodiments, the effective amount is an amount effective for preventing cancer, an infectious disease, an autoimmune disease or disorder, an inflammatory disease or disorder, a cardiovascular disease or disorder, a cerebrovascular disease or disorder, a vasculitis disease or disorder, or a neurodegenerative disease or disorder. In certain embodiments, the effective amount is an amount effective for preventing an autoimmune, inflammatory, or neurological disease or disorder. In certain embodiments, the effective amount is an amount effective for preventing a neurological disease or disorder in a subject in need thereof.

[00235] In certain embodiments, the effective amount is an amount effective for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof.

[00236] In certain embodiments, the effective amount is an amount effective for antagonizing C5aR1 in a subject, tissue, biological sample, or cell.

[00237] In certain embodiments, the subject being treated or administered a compound described herein is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[00238] In certain embodiments, the effective amount is an amount effective for decreasing the activity of C5aR1 by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, or at least about 1000%. In certain embodiments, the effective amount is an amount effective for decreasing the activity of C5aR1 by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00239] The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, activates) C5aR1 for use in treating a C5aR1-related disease or disorder in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, antagonizes) C5aR1 for use in treating a disease or disorder associated with aberrant activity of C5aR1 in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, antagonizes) C5aR1 for use in treating a disease or disorder associated with mutated C5aR1 in a subject in need thereof.

[00240] In certain embodiments, the composition is for use in treating a disease or disorder. In certain embodiments, the composition is for use in treating an autoimmune, inflammatory, or neurological disease or disorder. In certain embodiments, the composition is for use in treating a neurological disease or disorder.

[00241] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, and/or in reducing the risk to develop a disease in a subject in need thereof), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an additional pharmaceutical agent exhibit a synergistic effect that is absent in a pharmaceutical composition including one of the compounds and the additional pharmaceutical agent, but not both.

[00242] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic

polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease (*e.g.*, neurological disease or disorder). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00243] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the composition comprising a compound of Formula (**I**) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[00244] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as, for example, one-half or one-third of such a dosage.

[00245] The compound and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical, mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol.

[00246] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable

container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

[00247] Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for decreasing the activity of C5aR1 in a subject or cell. In certain embodiments, the kits are useful for antagonizing C5aR1 in a subject or cell.

[00248] In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for decreasing the activity of C5aR1 in a subject or cell. In certain embodiments, the kits and instructions provide for antagonizing C5aR1 in a subject or cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment

[00249] The present disclosure provides methods for treating a disease or disorder in a subject in need thereof. In certain embodiments, the present disclosure provides methods for treating a disease or disorder associated with C5aR1 (*e.g.*, C5aR1 activity).

[00250] In certain embodiments, the disease or disorder is any of the following:

[00251] Autoimmune disorders (*e.g.*, Rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barre syndrome, pancreatitis, lupus nephritis, lupus glomerulonephritis, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, aHUS (Atypical Hemolytic Uremic Syndrome), Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), immunovasculitis, tissue graft rejection, hyperacute rejection of transplanted organs).

[00252] Inflammatory disorders and related conditions (*e.g.*, Neutropenia, sepsis, septic shock, Alzheimer's disease, multiple sclerosis, stroke, inflammatory bowel disease (IBD), age-related macular degeneration (AMD, both wet and dry forms), inflammation associated with severe burns, lung injury, and ischemia-reperfusion injury, osteoarthritis, as well as acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary obstructive disorder (COPD), systemic inflammatory response syndrome (SIRS), atopic dermatitis, psoriasis, chronic urticaria and multiple organ dysfunction syndrome (MODS). Also included are pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), lupus nephropathy, Heyman nephritis, membranous nephritis and other forms of glomerulonephritis, IGA nephropathy, contact sensitivity responses, and inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (*e.g.*, during hemodialysis or via a heart-lung machine, for example, in association with vascular surgery such as coronary artery bypass grafting or heart valve replacement), or in association with contact with other artificial vessel or container surfaces (*e.g.*, ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, plasmapheresis, plateletpheresis, and the like), diseases related to ischemia/reperfusion injury, such as those resulting from transplants, including solid organ transplant, and syndromes such as ischemic reperfusion injury, ischemic colitis and cardiac ischemia. Compounds of the instant disclosure may also be useful in the treatment of age-related macular degeneration (Hageman et al, P.N.A.S. 102: 7227-7232, 2005).

[00253] Cardiovascular and cerebrovascular disorders (*e.g.*, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, atherosclerosis, traumatic central nervous system injury, and ischemic heart disease. In one embodiment, an effective amount of a compound of the disclosure may be administered to a patient at risk for myocardial infarction or thrombosis (*i.e.*, a patient who has one or more recognized risk factor for myocardial infarction or thrombosis, such as, but not limited to, obesity, smoking,

high blood pressure, hypercholesterolemia, previous or genetic history of myocardial infarction or thrombosis) in order reduce the risk of myocardial infarction or thrombosis).

[00254] Diseases of vasculitis: vasculitic diseases are characterized by inflammation of the vessels. Infiltration of leukocytes leads to destruction of the vessel walls, and the complement pathway is believed to play a major role in initiating leukocyte migration as well as the resultant damage manifested at the site of inflammation (Vasculitis, Second Edition, Edited by Ball and Bridges, Oxford University Press, pp 47-53, 2008). The compounds provided in the present disclosure can be used to treat ANCA vasculitis (anti-neutrophil cytoplasmic autoantibody vasculitis). The compounds provided in the present disclosure can be used to treat leukoclastic vasculitis, urticarial vasculitis, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, Henoch-Schonlein purpura, polyateritis nodosa, Rapidly Progressive Glomerulonephritis (RPGN), cryoglobulinaemia, giant cell arteritis (GCA), Behcet's disease and Takayasu's arteritis (TAK).

[00255] HIV infection and AIDS (*e.g.*, C5a receptor modulators provided herein may be used to inhibit HIV infection, delay AIDS progression or decrease the severity of symptoms or HIV infection and AIDS).

[00256] Neurodegenerative disorders and related diseases (*e.g.*, Alzheimer's disease, multiple sclerosis, and cognitive function decline associated with cardiopulmonary bypass surgery and related procedures).

[00257] Cancer and precancerous conditions (*e.g.*, melanomas, lung cancer, lymphomas, sarcomas, carcinomas, and mixed tumors. Exemplary conditions that may be treated according to the present disclosure include fibrosarcomas, liposarcomas, chondrosarcomas, osteogenic sarcomas, angiosarcomas, lymphangiosarcomas, synoviomas, mesotheliomas, meningiomas, leukemias, lymphomas, leiomyosarcomas, rhabdomyosarcomas, squamous cell carcinomas, basal cell carcinomas, adenocarcinomas, papillary carcinomas, cystadenocarcinomas, bronchogenic carcinomas, melanomas, renal cell carcinomas, hepatocellular carcinomas, transitional cell carcinomas, choriocarcinomas, seminomas, embryonal carcinomas, Wilm's tumors, pleomorphic adenomas, liver cell papillomas, renal tubular adenomas, cystadenomas, papillomas, adenomas, leiomyomas, rhabdomyomas, hemangiomas, lymphangiomas, osteomas, chondromas, lipomas and fibromas. In some embodiments, the disease or disorder is selected from the group consisting of glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate

cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, asbestosis, and carcinoma).

[00258] In one embodiment, an effective amount of a compound of the disclosure may be administered to a patient at risk for myocardial infarction or thrombosis (*i.e.*, a patient who has one or more recognized risk factor for myocardial infarction or thrombosis, such as, but not limited to, obesity, smoking, high blood pressure, hypercholesterolemia, previous or genetic history of myocardial infarction or thrombosis) in order reduce the risk of myocardial infarction or thrombosis.

[00259] In another embodiment, the compounds of the present disclosure are useful in the treatment of cisplatin induced nephrotoxicity. In this embodiment, compound treatment can alleviate the nephrotoxicity induced by cisplatin chemotherapy of malignancies (Hao Pan et al, *Am J Physiol Renal Physiol,* 296, F496-504, 2009).

[00260] In one embodiment, the compounds of the disclosure can be used for the treatment of diseases selected from the group consisting of sepsis (and associated disorders), COPD, rheumatoid arthritis, lupus nephritis and multiple sclerosis.

[00261] Provided herein is a method of treating a human suffering from or susceptible to a disease or disorder involving pathologic activation of C5a receptors, comprising administering a therapeutically effective amount of a compound of the disclosure or a pharmaceutical composition thereof.

[00262] Provided herein is a method of inhibiting C5a receptor-mediated cellular chemotaxis comprising contacting mammalian white blood cells with a C5a receptor modulatory amount of an active metabolite of a compound of the disclosure.

[00263] In some embodiments, the disease or disorder is an inflammatory disease or disorder, a cardiovascular or cerebrovascular disorder, an autoimmune disease, or an oncologic disease or disorder.

[00264] In some embodiments, the disease or disorder is selected from the group consisting of neutropenia, neutrophilia, C3-glomerulopathy, C3-glomerulonephritis, dense deposit disease, membranoproliferative glomerulonephritis, Kawasaki disease, sepsis, septic shock, Hemolytic uremic syndrome, atypical hemolytic uremic syndrome (aHUS), Alzheimer's disease, multiple sclerosis, stroke, inflammatory bowel disease, chronic obstructive pulmonary disorder, inflammation associated with burns, lung injury, osteoarthritis, atopic dermatitis, chronic urticaria, ischemia-reperfusion injury, acute respiratory distress syndrome, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, Uveitis, tissue graft rejection, hyperacute rejection of transplanted organs, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis, polypoidal choroidal vasculopathy, traumatic central nervous system injury, ischemic heart disease, rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barre syndrome, pancreatitis, lupus nephritis, lupus glomerulonephritis, psoriasis, Crohn's disease, vasculitis, ANCA vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, immuno vasculitis, Graft versus host disease, Paroxysmal nocturnal hemoglobinuria, Sjoegrens syndrome, insulin-dependent diabetes, mellitus, lupus nephropathy, Heyman nephritis, membranous nephritis, glomerulonephritis, IGA nephropathy, Membranoproliferative glomerulonephritis, Antiphospholipid syndrome, Age related macular degeneration; Dry age related macular degeneration, Wet age related macular degeneration, Motor neurone disease, contact sensitivity responses, and inflammation resulting from contact of blood with artificial surfaces.

[00265] In some embodiments, the disease or disorder is selected from the group consisting of neutropenia, neutrophilia, C3-glomerulopathy, C3-glomerulonephritis, dense deposit disease, membranoproliferative glomerulonephritis, Kawasaki disease, Hemolytic uremic syndrome, atypical hemolytic uremic syndrome (aHUS), tissue graft rejection, hyperacute rejection of transplanted organs, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, lupus glomerulonephritis, vasculitis, ANCA vasculitis, autoimmune hemolytic and thrombocytopenic states, immuno vasculitis, Graft versus host disease, lupus nephropathy, Heyman nephritis, membranous nephritis, glomerulonephritis, IGA nephropathy, Membranoproliferative and glomerulonephritis.

[00266] In some embodiments, the disease or disorder is selected from the group consisting of melanoma, lung cancer, lymphoma, sarcoma, carcinoma, fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, mesothelioma, meningioma, leukemia, lymphoma, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatocellular carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma. In some embodiments, the disease or disorder is selected from the group consisting of glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian

cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, asbestosis, and carcinoma.

[00267] In certain embodiments, the autoimmune disease or disorder is acquired aplastic anemia, acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis (AHLE) / Hurst's disease, gammaglobulinemia, (primary), alopecia areata, ankylosing spondylitis (AS), anti-NMDA receptor encephalitis, antiphospholipid syndrome (APS), arteriosclerosis, autism spectrum disorders (ASD), autoimmune Addison's disease (AAD), autoimmune dysautonomia / Autoimmune autonomic ganglionopathy (AAG), autoimmune encephalitis, autoimmune gastritis, autoimmune hemolytic anemia (AIHA), autoimmune hepatitis (AIH), autoimmune hyperlipidemia, autoimmune hypophysitis / lymphocytic hypophysitis, autoimmune inner ear disease (AIED), autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis (AIP) / Immunoglobulin G4- Related Disease (IgG4-RD), autoimmune polyglandular syndromes (Types I, II, & III), autoimmune progesterone dermatitis, autoimmune sudden sensorineural hearing loss (SNHL), balo disease, Behcet's disease, birdshot chorioretinopathy / birdshot uveitis, bullous pemphigoid, castleman disease, celiac disease, chagas disease, chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME), chronic inflammatory demyelinating polyneuropathy (CIDP), chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS), chronic urticaria (CU), churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, CREST syndrome / limited cutaneous systemic sclerosis, Crohn's disease (CD), cronkhite- Canada syndrome (CSS), cryptogenic organizing pneumonia (COP), dermatitis herpetiformis, dermatomyositis, type 1 diabetes, discoid lupus, Dressler's syndrome/ postmyocardial infarction / postpericardiotomy syndrome, endometriosis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibrosing alveolitis, giant cell arteritis / temporal arteritis / Horton's disease,

glomerulonephritis, Goodpasture's syndrome / anti-GBM/anti-TBM disease, granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis, Graves' disease, Guillain-Barre syndrome (GBS), Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis, Henoch-Schonlein purpura / IgA vasculitis, herpes gestationis / pemphigoid gestationis, hypogammaglobulinemia, IgA nephropathy / Berger's disease, immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura, interstitial cystitis juvenile idiopathic arthritis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD) / linear IgA bullous dermatosis (LABD), lupus nephritis, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis (MS), myasthenia gravis (MG), neuromyelitis optica (NMO) / Devic's disease, narcolepsy, non-length-dependent small fiber sensory neuropathy (SFSN), ocular cicatricial pemphigoid, opsoclonus-myoclonus syndrome (OMS), palindromic rheumatism, palmoplantar pustulosis (type of psoriasis), paraneoplastic cerebellar degeneration, paraneoplastic pemphigus, paroxysmal nocturnal hemoglobinuria (PNH), peripheral uveitis / pars planitis, parsonage turner syndrome, pemphigus foliaceus, pemphigus vulgaris, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polymyalgia rheumatica, polymyositis, postural orthostatic tachychardia syndrome (POTS), primary biliary cholangitis (PBC) / primary biliary cirrhosis, primary sclerosing cholangitis (PSC), psoriasis, psoriatic arthritis, pulmonary fibrosis, idiopathic (IPF), pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis / Reiter's syndrome, reflex sympathetic dystrophy syndrome, relapsing polychondritis, leg syndrome / Willis-Ekbom disease, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome / autoimmune poly endocrine syndrome type II, systemic sclerosis, scleritis, scleroderma, serpiginous choroidopathy, Sjogren's syndrome, stiff person syndrome (SPS), systemic lupus erythematosus (SLE), subacute bacterial endocarditis (SBE), Sydenham's chorea, sympathetic ophthalmia, Takayasu's arteritis (vasculitis), testicular autoimmunity (vasculitis / orchitis), Tolosa-Hunt syndrome, transverse myelitis (TM), tubulointerstitial nephritis uveitis syndrome (TINU), ulcerative colitis (UC), undifferentiated connective tissue disease (UCTD), uveitis (anterior), uveitis (intermediate), uveitis (posterior), vasculitis, vitiligo, or Vogt-Koyanagi-Harada syndrome (VKH). In one embodiment, the autoimmune trigger is lupus nephritis. In another embodiment, the autoimmune trigger is systemic sclerosis.

[00268] In certain embodiments, the disease or disorder is age-related macular degeneration, Alzheimer's disease, amyotrophic lateral sclerosis, anaphylaxis, anthrax

poisoning, anti-neutrophil cytoplasmic antibody-associated vasculitis, antiphospholipid syndrome, asthma, atherosclerosis, atopic dermatitis, atypical hemolytic uremic syndrome, autism, autoantibody-mediated disease, Berger disease, brain ischaemia, bronchiectasis, C3 glomerulopathy, cancer, Carnevale syndrome, CHAPLEE syndrome, chron disease, chronic obstructive pulmonary disease, cold agglutin disease, cutaneous lupus erythematosus, dementia, dermatomyositis, diabetic angiopathy, Ehlers-Danlos, epilepsy, frontotemporal dementia, generalized myasthenia gravis, geographic atrophy, glaucoma, glomerulonephritis, Guillain-Barre syndrome, hematopoetic stem cell transplant, complement mediated rejection, hereditary angioedema, hidradenitis supprativa, Huntington's disease, IgA nephropathy, immune thrombocytopenia, lupus nephritis, Malpuech syndrome, membranous glomerulonephritis, Michels syndrome, microscopic polyangiitis, Mingarelli syndrome, mood disorders, multifocal motor neuropathy, multiple sclerosis, myocardial infarction, neonatal HIE, neuromyelitis, optica spectrum disorder, neurotrauma, osteoarthritis, palmoplantar pustulosis, Parkinson's disorder, paroxysmal nocturnal haemoglobinuria, pemphigus, polytrauma, preeclampsia, primary membranous nephropathy, psoriasis, pyoderma gangraenosum, rare neutrophilic dermatoses, rheumatoid arthritis, schizophrenia, sepsis, severe thrombocytopenia, Shiga toxin associated hemolytic uremic syndrome, spinal cord injury, Stargardt disease, stroke, Sweet syndrome, systemic lupus erythematosus, systemic sclerosis, thrombotic microangiopathies, transplant rejection, Traumatic brain injury, ulcerative colitis, or vasculitis.

[00269] In certain embodiments, the application provides a method of treating cancer, an infectious disease, an autoimmune disease or disorder, an inflammatory disease or disorder, a cardiovascular disease or disorder, a cerebrovascular disease or disorder, a vasculitis disease or disorder, or a neurodegenerative disease or disorder.

[00270] In certain embodiments, the application provides a method of treating an autoimmune, inflammatory, or neurological disease or disorder. In certain embodiments, the application provides a method of treating a neurological disease or disorder.

[00271] The present disclosure provides a method of antagonizing C5aR1. The present disclosure provides a method of decreasing the activity of C5aR1. In certain embodiments, the application provides a method of antagonizing C5aR1 (*e.g.*, decreasing the activity of C5aR1) *in vitro*. In certain embodiments, the application provides a method of antagonizing C5aR1 (*e.g.*, decreasing the activity of C5aR1) *in vivo*. In certain embodiments, the application provides a method of antagonizing C5aR1 in a cell. In certain embodiments, the application provides a method of antagonizing C5aR1 in a human cell.

[00272] In certain embodiments, the methods comprise administering to a subject in need thereof (*e.g.*, a subject with a neurological disease or disorder) a compound that interacts with C5aR1, for example, a compound that is a modulator of C5aR1 (*e.g.*, an antagonist of C5aR1), a binder of C5aR1, or a compound that modifies C5aR1. In certain embodiments, the methods comprise administering a compound of the disclosure (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound of the disclosure (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof.

[00273] Another object of the present disclosure is the use of a compound as described herein (*e.g.*, of any formulae herein) in the manufacture of a medicament for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein (*e.g.*, of any formulae herein) for use in the treatment of a disorder or disease described herein.

EXAMPLES

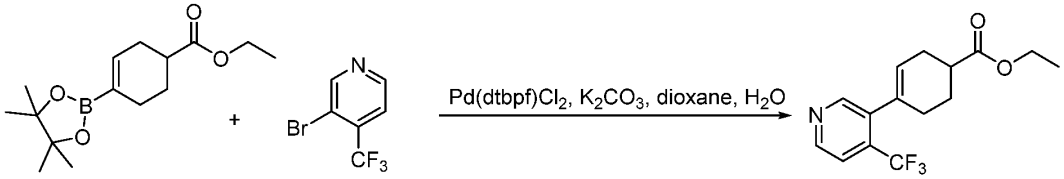
[00274] In order that the present disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting in their scope.

Example 1: Synthetic Methods

[00275] Compounds of Formula (**I**) were prepared following the synthetic schemes and procedures described in detail below. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope. Compounds of the disclosure that are not explicitly described in the following procedures may be prepared by analogous methods. Those having ordinary skill in the art would understand how to make such compounds from the disclosure provided herein and by means known in the art of organic synthesis. For example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups

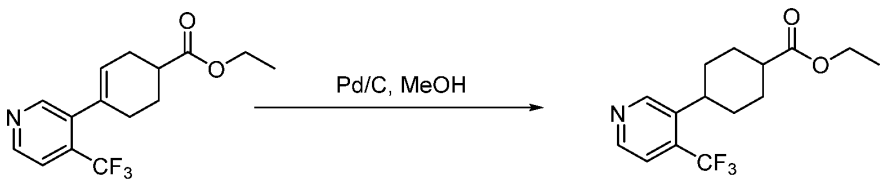
in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof are representative and instructive. Methods for optimizing reaction conditions, if necessary minimizing competing by products, are known in the art. Embodiments of this disclosure include methods of synthesizing compounds delineated herein using any of the compounds, reactants, and/or processes delineated herein.

General Procedure A



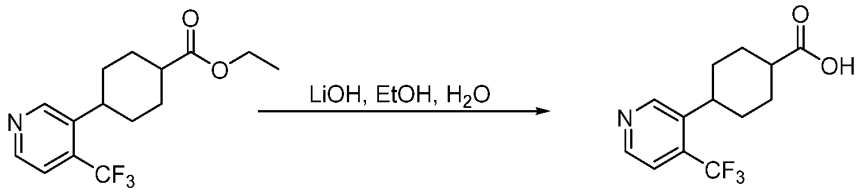
[00276] Ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate: To a stirred solution of ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (2.00 g, 7.14 mmol, 1.0 equiv) and 3-bromo-4-(trifluoromethyl)pyridine (1.94 g, 8.56 mmol, 1.2 equiv) in dioxane (20 mL) and H_2O (4 mL) were added $Pd(dtbpf)Cl_2$ (0.470 g, 0.714 mmol, 0.1 equiv) and K_2CO_3 (2.96 g, 21.4 mmol, 3.0 equiv) in portions at room temperature. The resulting mixture was stirred for overnight at 80 °C under argon atmosphere and monitored by LCMS. The resulting mixture was diluted with water (200 mL), extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/5 to afford ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate (1.91 g, 89%) as a light orange oil.

General Procedure B



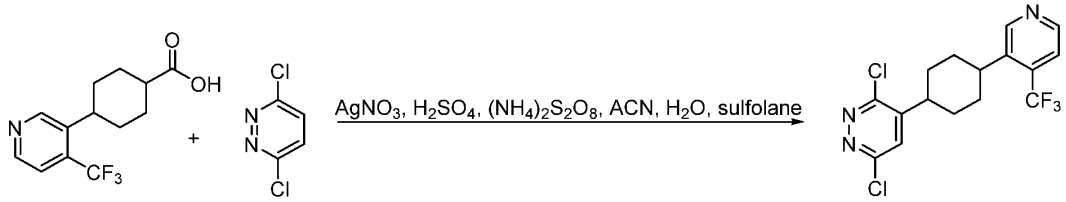
[00277] Ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate. A solution of ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate (1.9 g, 6.3 mmol, 1.0 equiv) and Pd/C (600 mg, 10% Pd on carbon, wetted with water) in MeOH (200 mL) was stirred for 2 days at room temperature under H_2 atmosphere using a hydrogen balloon. The reaction was monitored by LCMS. After the complete disappearance of the starting material, the resulting mixture was filtered through a Celite pad and concentrated under reduced pressure. This resulted in ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate (1 g, crude) as a light yellow oil.

General Procedure C



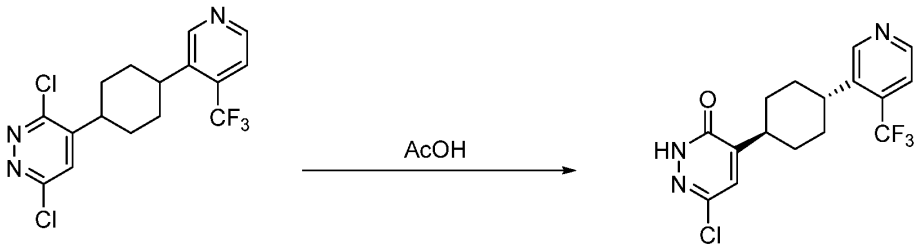
[00278] 4-(4-(Trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid. A solution of ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate (1.05 g, 3.48 mmol, 1.0 equiv) and LiOH (0.500 g, 20.9 mmol, 6.0 equiv) in EtOH (10 mL) and H2O (10 mL) was stirred for 4 h at 50 °C and monitored by LCMS. After the complete disappearance of the starting material, the mixture was acidified to pH ~ 6 with HCl (aq., 2M), extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid (900 mg, crude) as a white solid.

General Procedure D



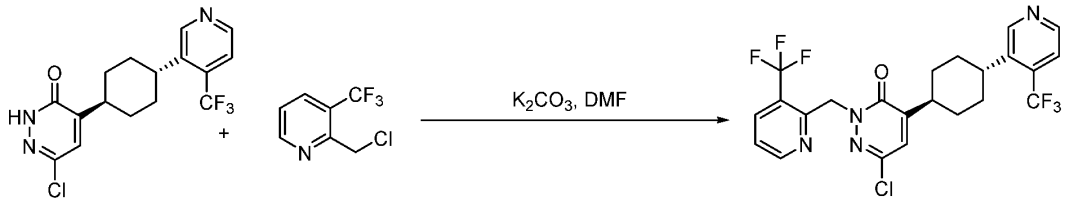
[00279] 3,6-Dichloro-4-(4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine. To a stirred solution of 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid (1.09 g, 3.99 mmol, 1.0 equiv) and 3,6-dichloropyridazine (0.590 g, 3.99 mmol, 1.0 equiv) in ACN (5 mL), H_2O (5 mL) and sulfolane (5 mL) were added $AgNO_3$ (0.680 g, 3.99 mmol, 1.0 equiv) and H_2SO_4 (1.17 g, 12.0 mmol, 3.0 equiv) in portions at 60 °C. To the above mixture was added $(NH_4)_2S_2O_8$ (2.28 g, 9.97 mmol, 2.5 equiv) in H_2O (5 mL) dropwise over 3 min at 60 °C. The resulting mixture was stirred for an additional 1 h at 60 °C and monitored by LCMS. The resulting mixture was diluted with water (100 mL), extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/5 to afford 3,6-dichloro-4-(4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine (320 mg, 21%) as a white solid.

General Procedure E



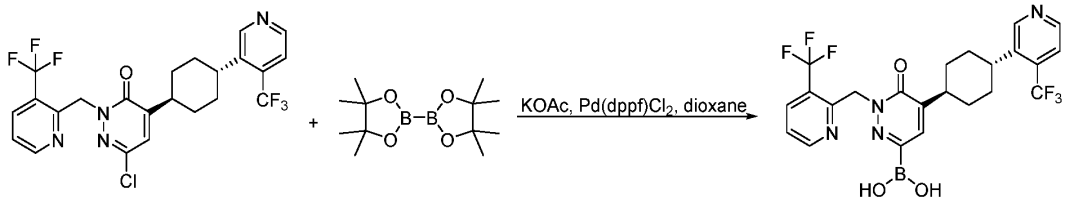
[00280] 6-Chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one. A solution of 3,6-dichloro-4-(4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine (310 mg, 0.824 mmol, 1.0 equiv) in AcOH (3 mL) was stirred for overnight at 100 °C and monitored by LCMS. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 6-chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (80 mg, 27%) as a white solid.

General Procedure F



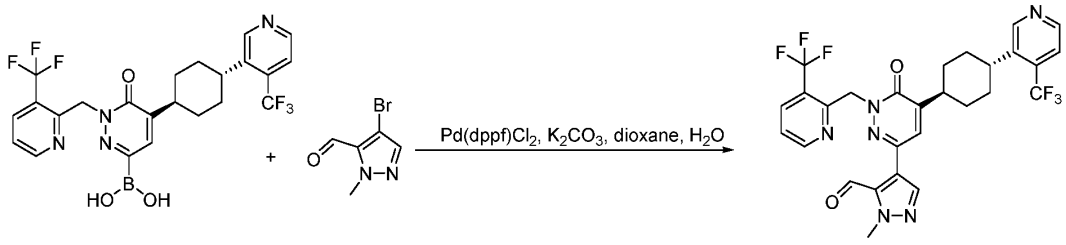
[00281] 6-Chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one. To a stirred solution of 6-chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (80 mg, 0.22 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (52 mg, 0.27 mmol, 1.2 equiv) in DMF (2 mL) was added K_2CO_3 (92 mg, 0.67 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred overnight at 60 °C. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/1 to afford 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (65 mg, 56%) as a white solid.

General Procedure G



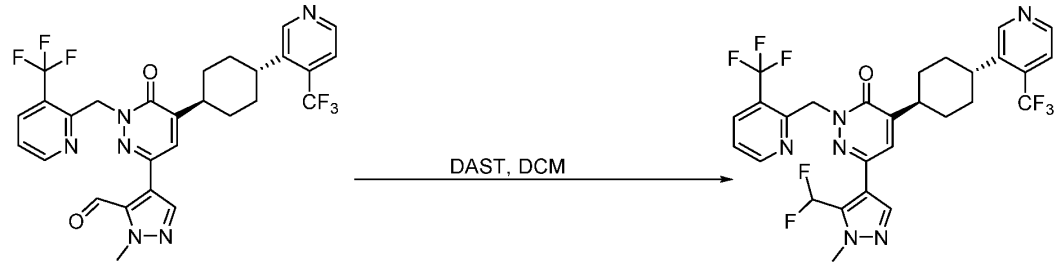
[00282] (6-Oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid. To a stirred solution of 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2H)-one (60 mg, 0.12 mmol, 1.0 equiv) and bis(pinacolato)diboron (58.9 mg, 0.232 mmol, 2.0 equiv) in dioxane (2 mL) were added $Pd(dppf)Cl_2$ (8.5 mg, 0.012 mmol, 0.1 equiv) and KOAc (34 mg, 0.35 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under argon atmosphere and monitored by LCMS. After the complete disappearance of the starting material, the resulting mixture was used in the next step directly without further purification.

General Procedure H



[00283] 1-Methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde. To a stirred solution of (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.12 mmol, 1.0 equiv) and 4-bromo-2-methylpyrazole-3-carbaldehyde (43 mg, 0.24 mmol, 2.0 equiv) in dioxane (2 mL) and H_2O (0.4 mL) were added Pd(dppf)Cl_2 (8.5 mg, 0.012 mmol, 0.1 equiv) and K_2CO_3 (48 mg, 0.36 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/1 to afford 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (25 mg, 37%) as a white solid.

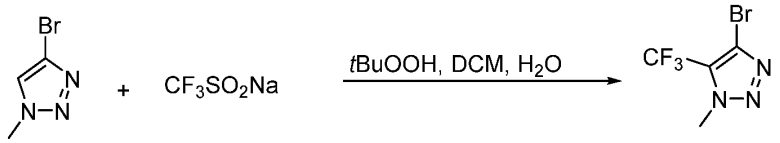
General Procedure I



[00284] 6-(5-(Difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one. To a stirred solution of 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-

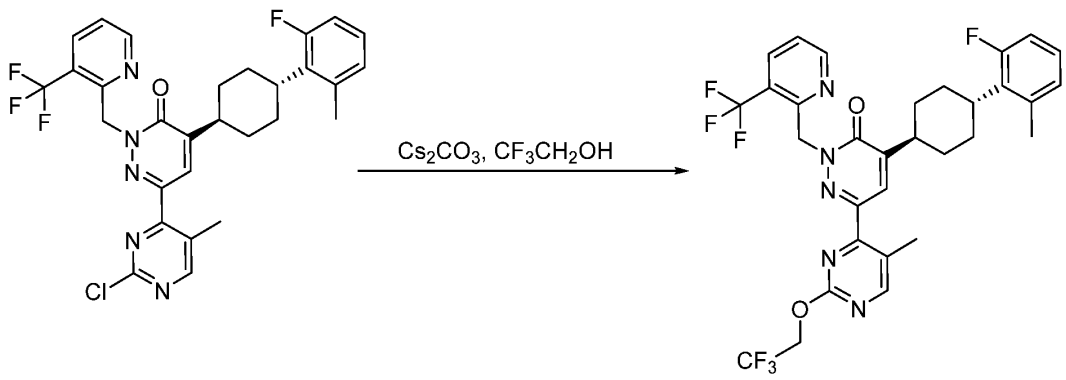
yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (40 mg, 0.068 mmol, 1.0 equiv) in DCM (2 mL) was added DAST (54 mg, 0.34 mmol, 5.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 4 h at room temperature. The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/ Hexane = 1/2) to afford 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1r,4r)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (20.4 mg, 48%) as a white solid.

General Procedure J



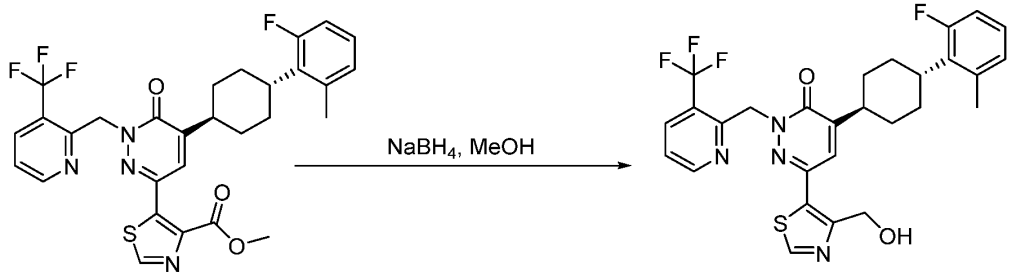
[00285] 4-Bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole. To a stirred mixture of 4-bromo-1-methyl-1,2,3-triazole (1.00 g, 6.17 mmol, 1.0 equiv) and sodium trifluoromethanesulfinate (2.89 g, 18.5 mmol, 3.0 equiv) in DCM (10 mL) and H_2O (4 mL) was added *tert*-butyl hydroperoxide (3.97 g, 30.8 mmol, 5.0 equiv, 70%) dropwise at 0 °C. The resulting mixture was stirred for 2 days at room temperature. The reaction was monitored by GCMS. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0% to 80% gradient in 30 min) to afford 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (150 mg, 10%) as a light yellow oil.

General Procedure K



[00286] 4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. A solution of 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.087 mmol, 1.0 equiv) and Cs_2CO_3 (85.4 mg, 0.261 mmol, 3.0 equiv) in CF_3CH_2OH (2 mL) was stirred for 2 h at 60 °C. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/ Hexane = 1/2) to afford 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (26.5 mg, 44%) as a white solid.

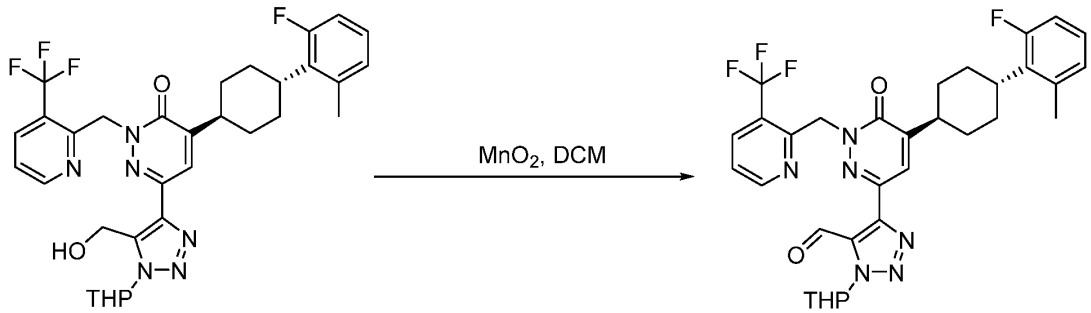
General Procedure L



[00287] 4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)thiazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred mixture of methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carboxylate (90 mg, 0.15 mmol, 1.0 equiv) in MeOH (3 mL) was added $NaBH_4$ (58 mg, 1.5 mmol, 10 equiv) in portions at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by LCMS.

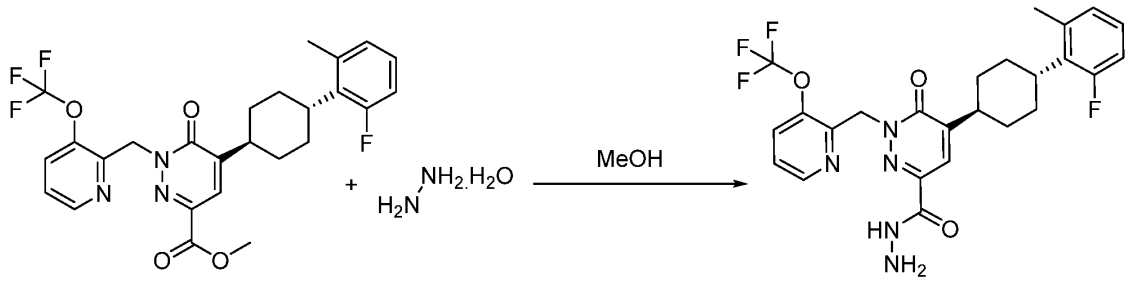
After the complete disappearance of the starting material, the reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (2 x 60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to dry. The resulting crude product was used in the next step directly without further purification.

General Procedure M



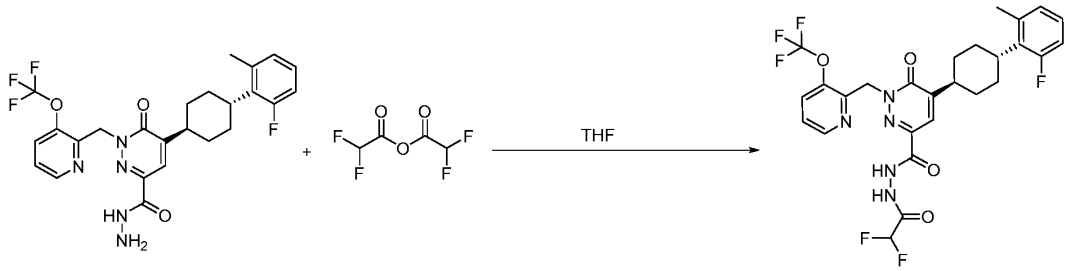
[00288] 4-(5-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde. To a stirred mixture of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (75 mg, 0.12 mmol, 1.0 equiv) in DCM (2 mL) was added MnO_2 (104 mg, 1.2 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 6 h at room temperature and monitored by LCMS. After the complete disappearance of the starting material, the resulting mixture was filtered, the filter cake was washed with DCM (3 x 5 mL). The filtrate was concentrated under reduced pressure to dry. The resulting crude product was used in the next step directly without further purification.

General Procedure N



[00289] **5-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3 (trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide**. To a stirred mixture of methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (100 mg, 0.192 mmol, 1.0 equiv) in MeOH (2 mL) was added hydrazine hydrate (29.5 mg, 0.576 mmol, 3.0 equiv, 98%) dropwise at room temperature. The resulting mixture was stirred for 1 h at 80 °C and monitored by LCMS. After the complete disappearance of the starting material, the resulting mixture was concentrated under reduced pressure to dry. The resulting crude product was used in the next step directly without further purification.

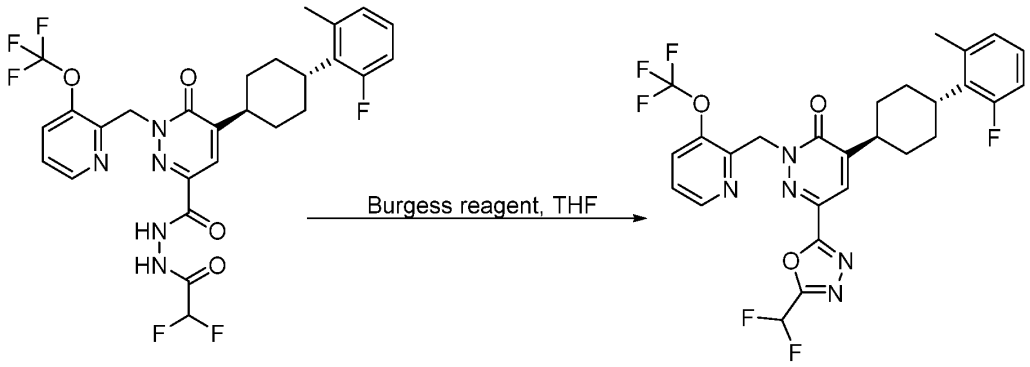
General Procedure O



[00290] ***N*'-(2,2-Difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide.** To a stirred mixture of 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 0.192 mmol, 1.0 equiv) in THF (2 mL) was added 2,2-difluoroacetyl 2,2-difluoroacetate (100 mg, 0.576 mmol, 3.0 equiv) dropwise at room temperature. The resulting mixture was stirred for 2 h at 60 °C and monitored by LCMS. After complete disappearance of the starting material, the resulting mixture was diluted with water (80 mL), extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.

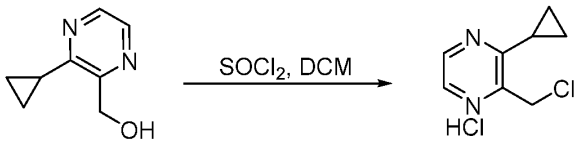
The residue was purified by silica gel column chromatography, eluted with PE / EA (30% to 90% gradient in 20 min) to afford *N*'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 86%) as a light yellow solid.

General Procedure P



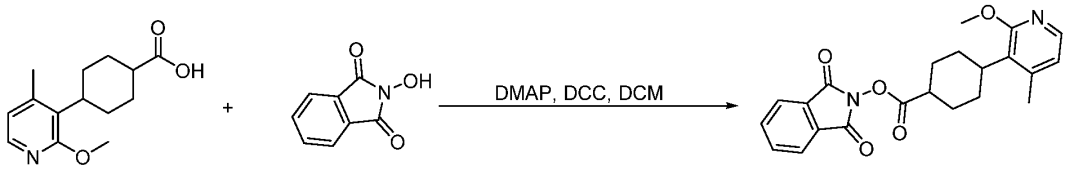
[00291] 6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred mixture of *N*'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (55 mg, 0.092 mmol, 1.0 equiv) in THF (1.5 mL) was added Burgess reagent (109 mg, 0.46 mmol, 5.0 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 60 °C under and monitored by LCMS. The resulting mixture was diluted with water (80 mL), extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane / EA 3:1) to afford 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.9 mg, 27%) as a white solid.

General Procedure Q



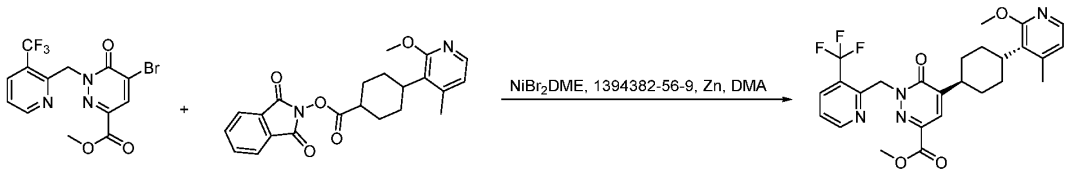
[00292] 2-(Chloromethyl)-3-cyclopropylpyrazine hydrochloride. A solution of (3-cyclopropylpyrazin-2-yl)methanol (220 mg, 1.46 mmol, 1.0 equiv) and $SOCl_2$ (871 mg, 7.32 mmol, 5.0 equiv) in DCM (3 mL) was stirred for 1 h at room temperature under air atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

General Procedure R



[00293] 1,3-Dioxoisoindolin-2-yl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate. To a stirred mixture of 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid (600 mg, 2.41 mmol, 1.0 equiv) and N-hydroxyphthalimide (431 mg, 2.64 mmol, 1.1 equiv) in DCM (6 mL) were added DMAP (29 mg, 0.24 mmol, 0.1 equiv) and DCC (595 mg, 2.88 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature and monitored by LCMS. The resulting mixture was purified by silica gel column chromatography, eluted with PE / EA (0% to 100%) to afford 1,3-dioxoisoindolin-2-yl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (800 mg, 84%) as a white solid.

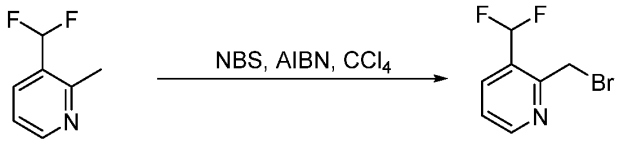
General Procedure S



[00294] Methyl 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate. To a stirred mixture of methyl 5-bromo-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (300 mg, 0.765 mmol, 1.0 equiv) and 1,3-dioxoisoindol-2-yl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (452 mg, 1.14 mmol, 1.5 equiv) in DMA (5 mL) was added Zn (150 mg, 2.29 mmol, 3.0 equiv) at room temperature

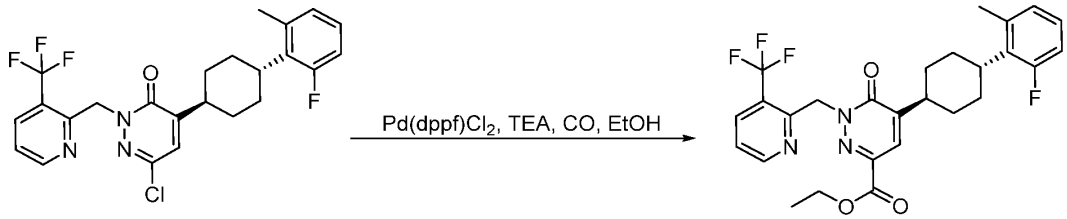
under argon atmosphere. $NiBr_2DME$ (47 mg, 0.15 mmol, 0.2 equiv) and pyridine-2,6-dicarboximidamide dihydrochloride (36 mg, 0.15 mmol, 0.2 equiv) were premixed for 30 min in DMA (0.5 mL) at 60 °C under argon atmosphere and subsequently added to the above mixture. The resulting mixture was stirred for overnight at 30 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (100 mL), extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (0% to 100% in 30 min) to afford methyl 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (200 mg, 50%) as a white solid.

General Procedure T



[00295] 2-(Bromomethyl)-3-(difluoromethyl)pyridine. To a stirred mixture of 3-(difluoromethyl)-2-methylpyridine (500 mg, 3.49 mmol, 1.0 equiv) and NBS (1.24 g, 6.98 mmol, 2.0 equiv) in CCl_4 (5 mL) was added AIBN (57 mg, 0.35 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C. The reaction was monitored by LCMS. The resulting mixture was purified by silica gel column chromatography, eluted with PE / EA (0% to 100% in 30 min) to afford 2-(bromomethyl)-3-(difluoromethyl)pyridine (160 mg, 20%) as a light yellow oil.

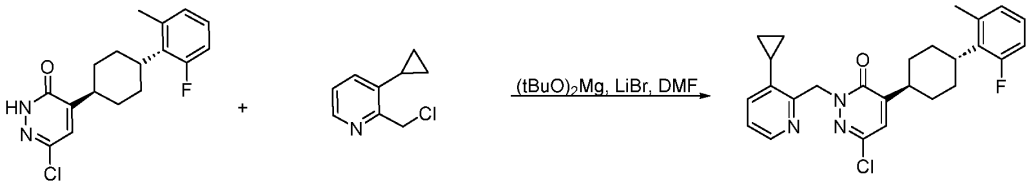
General Procedure U



[00296] Ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate. To a stirred mixture of 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120 mg, 0.250 mmol, 1.0 equiv) and $Pd(dppf)Cl_2$ (18 mg, 0.025 mmol, 0.1 equiv) in EtOH (10 mL) was added TEA (76 mg, 0.75 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C under carbon monoxide atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with EtOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 61%) as a white solid.

General Procedure V



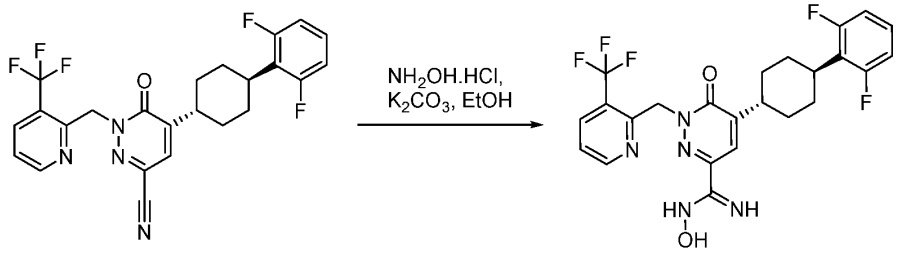
[00297] 6-Chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) pyridazin-3(2*H*)-one. To a stirred solution of 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (150 mg, 0.468 mmol, 1.0 equiv) and 2-(chloromethyl)-3-cyclopropylpyridine (94.0 mg, 0.562 mmol, 1.2 equiv) in DMF (3 mL) were added $(tBuO)_2Mg$ (399 mg, 2.34 mmol, 5.0 equiv) and LiBr (201 mg, 2.34 mmol, 5.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at 60 °C and monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane / EA 5:1) to afford 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) pyridazin-3(2*H*)-one (150 mg, 70%) as a pink solid.

General Procedure W



[00298] 5-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. To a stirred solution of 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.413 mmol, 1.0 equiv) and $Zn(CN)_2$ (72.8 mg, 0.619 mmol, 1.5 equiv) in DMSO (3 mL) were added $Pd(dppf)Cl_2$ (60.5 mg, 0.083 mmol, 0.2 equiv) and Zn (16.2 mg, 0.248 mmol, 0.6 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C under air atmosphere and monitored by LCMS. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/1 to afford 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (160 mg, 81.5%) as a white solid.

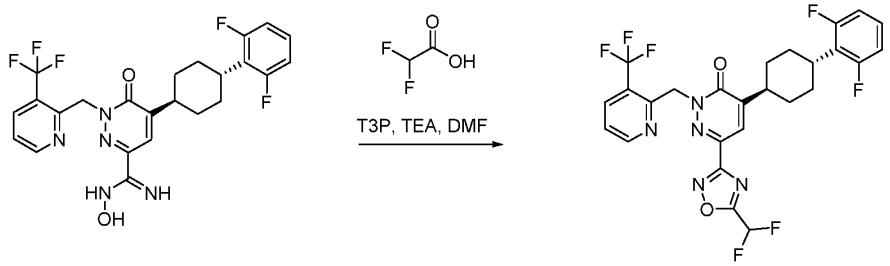
General Procedure X



[00299] **5-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide.** To a stirred solution of 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (160 mg, 0.337 mmol, 1.0 equiv) and hydroxylamine hydrochloride (28.1 mg, 0.404 mmol, 1.2 equiv) in EtOH (3 mL) were added K_2CO_3 (139 mg, 1.01 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C and monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting mixture was filtered, the filter cake was

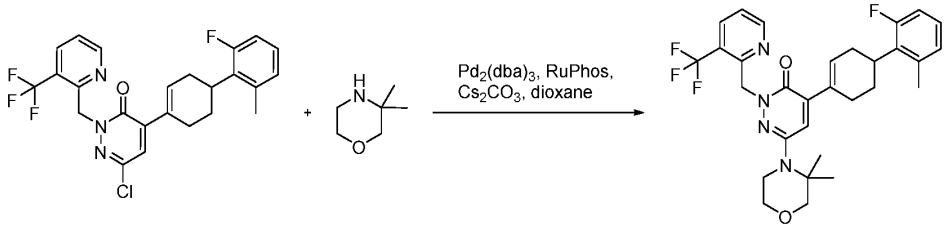
washed with water (3 x 5 mL). This resulted in 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (140 mg) as a white solid.

General Procedure Y



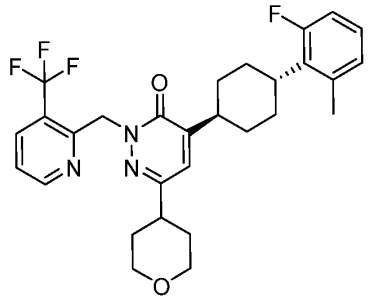
[00300] 6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred solution of 2,2-difluoroacetic acid (34.0 mg, 0.354 mmol, 3.0 equiv) and TEA (36.0 mg, 0.354 mmol, 3.0 equiv) in DMF (3 mL) were added T3P (56.4 mg, 0.177 mmol, 1.5 equiv) in portions at room temperature. The resulting mixture was stirred for 5 min at room temperature under nitrogen atmosphere followed by adding. 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (60.0 mg, 0.118 mmol, 1.0 equiv) in portions at room temperature over 1 min. The resulting mixture was stirred for an additional 1 h at 80 °C and monitored by LCMS. The resulting mixture was diluted with water (10 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 3:2) to afford 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52.7 mg, 74.3%) as a white solid.

General Procedure Z



[00301] 6-(3,3-Dimethylmorpholino)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred solution of 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.42 mmol, 1.0 equiv) and 3,3-dimethylmorpholine (72.3 mg, 0.63 mmol, 1.5 equiv) in dioxane (5 mL) were added $Pd_2(dba)_3$ (76.6 mg, 0.08 mmol, 0.2 equiv), RuPhos (39.1 mg, 0.08 mmol, 0.2 equiv) and Cs_2CO_3 (409 mg, 1.26 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under argon atmosphere and monitored by LCMS. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/2 to afford 6-(3,3-dimethylmorpholino)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (130 mg, 56%) as a white solid. MS *m/z*: 557 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydro-2*H*-pyran-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (1)

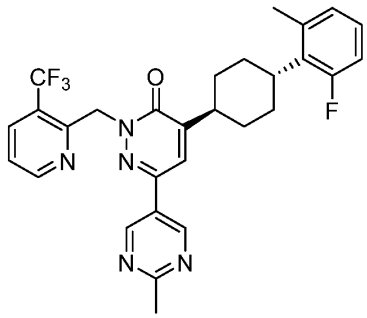


[00302] Step 1: 6-(3,6-dihydro-2*H*-pyran-4-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.209 mmol, 1.0 equiv) and 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (65.9 mg, 0.314 mmol, 1.5 equiv) as the starting materials to give 6-(3,6-dihydro-2*H*-pyran-4-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120 mg, 72%) as a colorless oil. MS *m/z*: 526 $[M+H]^+$.

[00303] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydro-2H-pyran-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using6-(3,6-dihydro-2*H*-pyran-4-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120 mg, 0.228 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydro-2*H*-pyran-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (16.1 mg, 12.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 7.33 (s, 1H), 7.02 (d, *J* = 11.7 Hz, 2H), 6.94 – 6.80 (m, 2H), 5.65 (s, 2H), 4.10 – 4.00 (m, 2H), 3.53 – 3.44 (m, 2H), 3.04 (t, *J* = 11.7 Hz, 1H), 2.92 – 2.74 (m, 2H), 2.36 (s, 3H), 2.11 (t, *J* = 13.4 Hz, 4H), 1.86 – 1.78 (m, 6H), 1.46 (d, *J* = 12.7 Hz, 2H). MS *m/z*: 530.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (2)

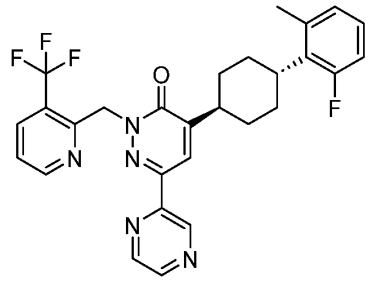


[00304] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (80.0 mg, 0.249 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (58.5 mg, 0.299 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 80%) as a white solid. MS *m/z*: 480 $[M+H]^+$.

[00305] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

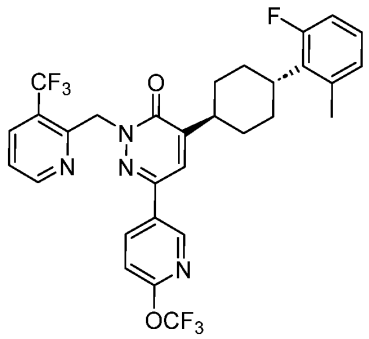
(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.063 mmol, 1.0 equiv) and (2-methylpyrimidin-5-yl)boronic acid (11.2 mg, 0.082 mmol, 1.3 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23 mg, 67%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.05 (s, 2H), 8.69 – 8.57 (m, 1H), 8.08 – 7.96 (m, 1H), 7.53 (s, 1H), 7.35 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.12 – 7.00 (m, 1H), 7.00 – 6.80 (m, 2H), 5.79 (s, 2H), 3.15 (t, *J* = 11.8 Hz, 1H), 2.91 (d, *J* = 12.6 Hz, 1H), 2.83 (s, 3H), 2.39 (s, 3H), 2.18 (d, *J* = 12.1 Hz, 4H), 1.89 (d, *J* = 12.3 Hz, 2H), 1.59 (t, *J* = 12.3 Hz, 2H). MS *m/z*: 538.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (3)



[00306] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.083 mmol, 1.0 equiv) and pyrazin-2-ylboronic acid (51.6 mg, 0.415 mmol, 5.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.6 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.29 (s, 1H), 8.70 – 8.49 (m, 3H), 8.18 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.33 (s, 1H), 7.07 – 7.00 (m, 1H), 6.94 – 6.81 (m, 2H), 5.79 (s, 2H), 3.13 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 11.7 Hz, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 11.1 Hz, 4H), 1.90 – 1.81 (m, 2H), 1.59 (s, 2H). MS *m/z*: 524.15 $[M+H]^+$.

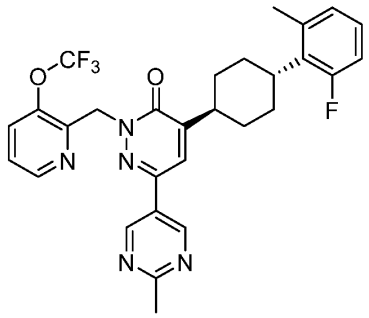
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (4)



[00307] Step 1: 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (125 mg, 0.262 mmol, 1.0 equiv) and (6-(trifluoromethoxy)pyridin-3-yl)boronic acid (81.2 mg, 0.392 mmol, 1.5 equiv) as the starting materials, using XPhos (25 mg, 0.052 mmol, 0.2 equiv) and XPhos Pd G4 (45 mg, 0.052 mmol, 0.2 equiv) as the catalyst to give 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70 mg, 44%) as a withe solid. MS *m/z*: 605 $[M+H]^+$.

[00308] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70.0 mg, 0.116 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(6-(trifluoromethoxy)pyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.1 mg, 14.4%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.76 – 8.64 (m, 2H), 8.23 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.38 (t, *J* = 6.5 Hz, 1H), 7.13 – 6.99 (m, 2H), 6.96 – 6.79 (m, 2H), 5.78 (s, 2H), 3.11 (t, *J* = 11.9 Hz, 1H), 2.89 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.15 (d, *J* = 12.1 Hz, 4H), 1.88 (s, 2H), 1.52 (q, *J* = 12.7 Hz, 2H). MS *m/z*: 607.10 $[M+H]^+$.

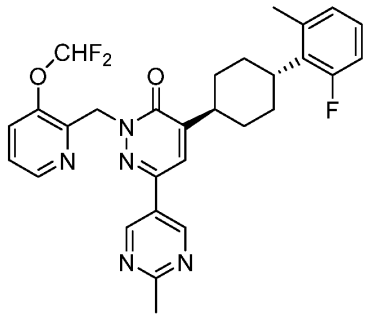
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5)



[00309] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (35.0 mg, 0.109 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (27.7 mg, 0.131 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 52%) as a white solid. MS *m/z*: 496 $[M+H]^+$.

[00310] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25 mg, 0.050 mmol, 1.0 equiv) and (2-methylpyrimidin-5-yl)boronic acid (8.3 mg, 0.06 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.0 mg, 45.1%) as a light yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.03 (s, 2H), 8.47 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.51 (s, 1H), 7.32 (dd, *J* = 8.3, 4.7 Hz, 1H), 7.13 – 7.01 (m, 1H), 6.98 – 6.81 (m, 2H), 5.70 (s, 2H), 3.14 (t, *J* = 12.0 Hz, 1H), 2.92 (t, *J* = 12.4 Hz, 1H), 2.83 (s, 3H), 2.39 (s, 3H), 2.17 (t, *J* = 11.1 Hz, 4H), 1.88 (d, *J* = 13.0 Hz, 2H), 1.57 (t, *J* = 12.4 Hz, 2H). MS *m/z*: 554.10 $[M+H]^+$.

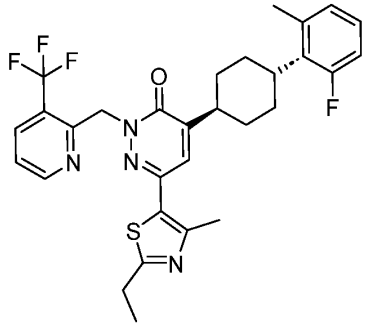
[00311] 2-((3-(Difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one (6)



[00312] Step 1: 6-chloro-2-((3-(difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40.0 mg, 0.125 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(difluoromethoxy)pyridine (31.4 mg, 0.162 mmol, 1.3 equiv) as the starting materials to give 6-chloro-2-((3-(difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 67%) as a white solid. MS *m/z*: 478 $[M+H]^+$.

[00313] Step 2: 2-((3-(difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-2-((3-(difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 0.084 mmol, 1.0 equiv) and (2-methylpyrimidin-5-yl)boronic acid (15.0 mg, 0.108 mmol, 1.3 equiv) as the starting materials to give 2-((3-(difluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one (8.8 mg, 19.6%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.08 (s, 2H), 8.39 (s, 1H), 7.53 (d, *J* = 20.6 Hz, 2H), 7.38 – 7.28 (m, 1H), 7.04 (q, *J* = 7.1, 6.6 Hz, 1H), 6.98 – 6.39 (m, 3H), 5.66 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 3.01 – 2.82 (m, 4H), 2.37 (s, 3H), 2.12 (d, *J* = 11.5 Hz, 4H), 1.86 (d, *J* = 12.8 Hz, 2H), 1.52 (d, *J* = 10.5 Hz, 2H). MS *m/z*: 536.15 $[M+H]^+$.

6-(2-Ethyl-4-methylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (7)

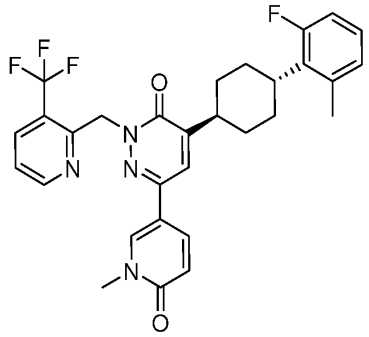


[00314] Step 1: 6-(2-ethyl-4-methylthiazol-5-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred mixture of 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.209 mmol, 1.0 equiv) and 2-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole (158 mg, 0.627 mmol, 3.0 equiv) in 1,4-dioxane (2 mL) were added XPhos (19.9 mg, 0.042 mmol, 0.2 equiv), XPhos Pd G4 (36 mg, 0.042 mmol, 0.2 equiv) and $NaHCO_3$ (52.7 mg, 0.627 mmol, 3.0 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 8 h at 80 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 1:1) to afford 6-(2-ethyl-4-methylthiazol-5-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 50%) as a light yellow oil. MS *m/z*: 569 $[M+H]^+$.

[00315] Step 2: 6-(2-ethyl-4-methylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 6-(2-ethyl-4-methylthiazol-5-yl)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80.0 mg, 0.141 mmol, 1.0 equiv) as the starting material to give 6-(2-ethyl-4-methylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.3 mg, 11.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 2H), 7.04 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.70 (s, 2H), 3.17 – 2.97 (m, 3H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H),

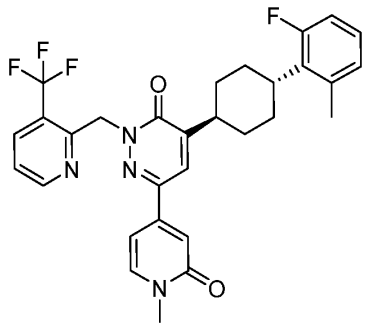
2.14 (t, *J* = 11.4 Hz, 4H), 1.87 – 1.82 (m, 2H), 1.48 (d, *J* = 12.4 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 3H). MS *m/z*: 571.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8)



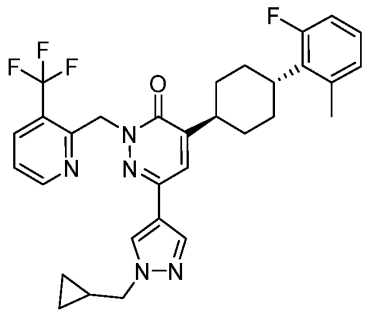
[00316] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.063 mmol, 1.0 equiv) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (22.0 mg, 0.095 mmol, 1.5 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8.5 mg, 24%) as a light brown solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.63 – 8.57 (m, 1H), 8.33 (d, *J* = 2.6 Hz, 1H), 8.17 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.03 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.78 (s, 1H), 7.48 (dd, *J* = 8.1, 4.9 Hz, 1H), 7.05 (td, *J* = 7.9, 5.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 12.1, 8.1 Hz, 1H), 6.59 (d, *J* = 9.5 Hz, 1H), 5.72 (s, 2H), 3.65 (s, 3H), 3.02 (dt, *J* = 15.3, 5.0 Hz, 2H), 2.38 (s, 3H), 2.19 – 2.02 (m, 4H), 1.90 – 1.82 (m, 2H), 1.66 (q, *J* = 12.8 Hz, 2H). MS *m/z*: 553.15 $[M+H]^+$.

[00317] 4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9)



[00318] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.063 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (14.7 mg, 0.063 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.4 mg, 18%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.33 (s, 2H), 7.09 – 6.99 (m, 2H), 6.95 – 6.83 (m, 2H), 6.77 (s, 1H), 5.75 (s, 2H), 3.60 (s, 2H), 3.15 – 2.82 (m, 2H), 2.38 (s, 3H), 2.12 (d, *J* = 11.5 Hz, 4H), 1.86 (d, *J* = 13.1 Hz, 2H), 1.50 (d, *J* = 12.2 Hz, 2H), 1.26 (s, 1H). MS *m/z*: 553.15 $[M+H]^+$.

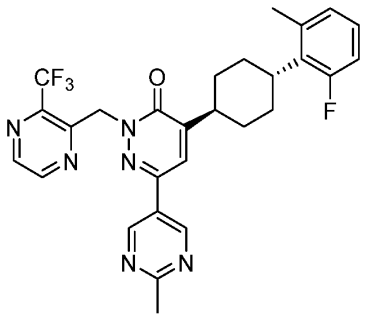
[00319] 6-(1-(Cyclopropylmethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10)



[00320] Step 1: 6-(1-(cyclopropylmethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.042 mmol, 1.0 equiv) and 1-(cyclopropylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (20.6 mg, 0.084 mmol, 2.0 equiv) as the starting materials to give 6-(1-(cyclopropylmethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.5 mg, 47.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.07 (s, 1H), 7.97 (s, 1H), 7.48 (s, 1H), 7.30 (s, 1H), 7.06 – 6.99 (m, 1H), 6.94 – 6.81 (m, 2H), 5.77 (s, 2H), 4.22 (d, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.89 (s, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 11.7 Hz, 4H), 1.85 (d, *J* = 13.2 Hz, 2H), 1.26 (s, 1H), 0.74 (d, *J* = 7.6 Hz, 2H), 0.74 (d, *J* = 7.6 Hz, 2H), 0.50 (d, *J* = 5.0 Hz, 2H). MS *m/z*: 566.20 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (11)

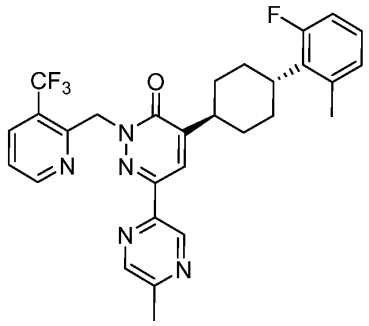


[00321] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.156 mmol, 1.0 equiv) and 2-(bromomethyl)-3-(trifluoromethyl)pyrazine hydrochloride (56.2 mg, 0.203 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 53%) as a white solid. MS *m/z*: 481 [M+H]$^+$.

[00322] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.083 mmol, 1.0 equiv) and (2-methylpyrimidin-5-yl)boronic acid (13.8 mg, 0.1 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-

yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (34 mg, 88%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.04 (s, 2H), 8.59 (d, *J* = 10.2 Hz, 2H), 7.52 (s, 1H), 7.05 – 7.01 (m, 1H), 6.94 – 6.82 (m, 2H), 5.82 (s, 2H), 3.12 – 3.09 (m, 1H), 2.91 – 2.81 (m, 4H), 2.36 (s, 3H), 2.16 – 2.13 (m, 4H), 1.89 – 1.85 (m, 2H), 1.56 –1.53 (m, 2H). MS *m/z*: 539.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12)



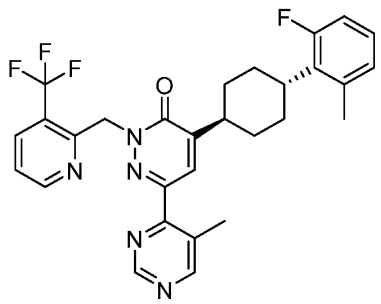
[00323] Step 1: (5-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid**:** Followed the general procedure G using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (160 mg, 0.335 mmol, 1.0 equiv) as the starting material to give (5-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 488 $[M+H]^+$.

[00324] Step 2: 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one**:** Followed the general procedure H using (5-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.334 mmol, 1.0 equiv) and 2-bromo-5-methylpyrazine (116 mg, 0.669 mmol, 2.0 equiv) as the starting materials to give 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 83%) as a light yellow solid. MS *m/z*: 536 $[M+H]^+$.

[00325] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general

procedure B using 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.280 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.5 mg, 11.5%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.14 (d, *J* = 1.5 Hz, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 8.47 (d, *J* = 1.5 Hz, 1H), 8.15 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.33 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.03 (td, *J* = 7.8, 5.4 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.78 (s, 2H), 3.18 – 3.06 (m, 1H), 2.90 (t, *J* = 12.3 Hz, 1H), 2.63 (s, 3H), 2.36 (s, 3H), 2.22 – 2.08 (m, 4H), 1.90 – 1.80 (m, 2H), 1.66 – 1.50 (m, 2H). MS *m/z*: 538.10[M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13)

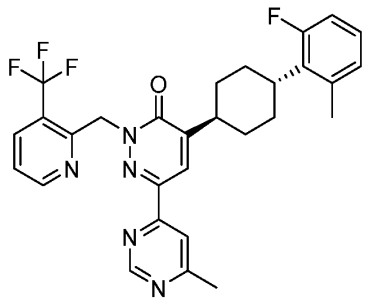


[00326] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (42 mg, 0.088 mmol, 1.0 equiv) the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 [M+H]$^+$.

[00327] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.088 mmol, 1.0 equiv) and 4-chloro-5-methylpyrimidine (28.1 mg, 0.22 mmol, 2.5 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-

methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23.4 mg, 49.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 8.64 – 8.59 (m, 2H), 8.12 (s, 1H), 8.00 – 7.99 (m, 1H), 7.36 – 7.32 (m, 1H), 7.06 – 7.01 (m, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.76 (s, 2H), 3.12 (t, *J* = 12.4 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 2.37 (d, *J* = 4.8 Hz, 6H), 2.21 – 2.10 (m, 4H), 1.88 – 1.83 (m, 2H), 1.63 – 1.53 (m, 2H). MS *m/z*: 538.15 $[M+H]^+$.

4-((1r,4r)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(6-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (14)

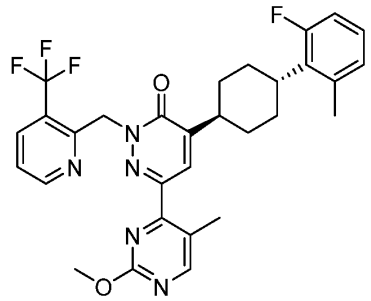


[00328] Step 1: (5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS m/z: 490 [M+H]+.

[00329] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(6-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-6-methylpyrimidine (13.2 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give 4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(6-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (23.3 mg, 48.4%) as a white solid. 1H NMR (300 MHz, Chloroform-d) δ 9.07 (s, 1H), 8.57 – 8.49 (m, 1H), 8.19 (s, 1H), 7.98 – 7.88 (m, 1H), 7.84 (s, 1H), 7.30 – 7.20 (m, 1H), 7.03 – 6.90 (m, 1H), 6.89 – 6.72 (m, 2H), 5.72 (s, 2H), 3.04 (t, J = 12.0 Hz, 1H), 2.83 (t, J = 12.0 Hz, 1H),

2.52 (s, 3H), 2.29 (s, 3H), 2.05 (t, J = 11.5 Hz, 4H), 1.84 – 1.73 (m, 2H), 1.61 – 1.42 (m, 2H), 1.24 – 1.13 (m, 1H). MS m/z: 538. 15 [M+H]+.

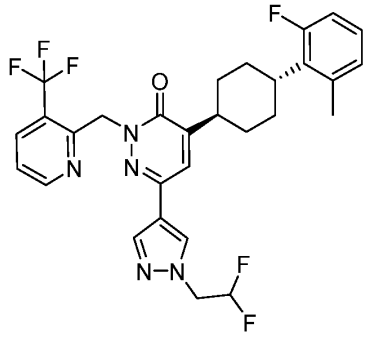
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-methoxy-5-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (15)



[00330] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

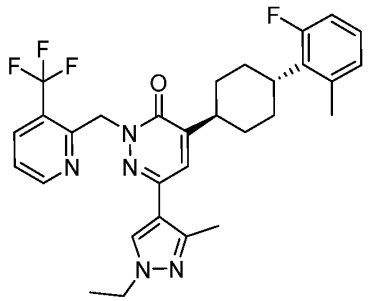
[00331] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methoxy-5-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-2-methoxy-5-methylpyrimidine (24.6 mg, 0.156 mmol, 1.5 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methoxy-5-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (24.0 mg, 57.9%) as a light yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.66 – 8.60 (m, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 8.08 (d, *J* = 1.0 Hz, 1H), 8.04 – 7.95 (m, 1H), 7.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.94 – 6.80 (m, 2H), 5.75 (s, 2H), 4.08 (s, 3H), 3.17 – 3.05 (m, 1H), 2.95 – 2.84 (m, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 2.22 – 2.07 (m, 4H), 1.85 (dd, *J* = 13.7, 3.7 Hz, 2H), 1.63 – 1.51 (m, 2H). MS *m/z*: 568.20 $[M+H]^+$.

6-(1-(2,2-Difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (16)



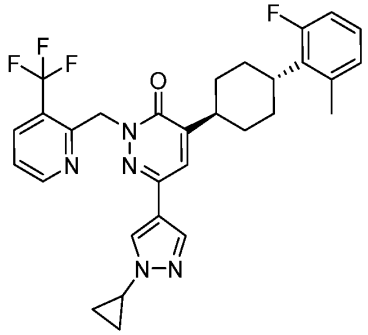
[00332] Step 1: 6-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.06 mmol, 1.0 equiv) and 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (16.1 mg, 0.06 mmol, 1.0 equiv) as the starting materials to give 6-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.3 mg, 28.5%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.08 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.41 (s, 1H), 7.29 (s, 1H), 7.10 – 6.97 (m, 1H), 6.94 – 6.80 (m, 2H), 6.11 (t, *J* = 55.3 Hz, 1H), 5.74 (s, 2H), 4.57 – 4.41 (m, 2H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.89 (t, *J* = 12.2 Hz, 1H), 2.36 (s, 3H), 2.13 (s, 4H), 1.91 – 1.79 (m, 2H), 1.51 (q, *J* = 12.1 Hz, 2H). MS *m/z*: 576.15 $[M+H]^+$.

6-(1-Ethyl-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (17)



[00333] Step 1: 6-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (45 mg, 0.094 mmol, 1.0 equiv) and 1-ethyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (26.7 mg, 0.113 mmol, 1.2 equiv) as the starting materials to give 6-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.9 mg, 21.0%) as a grey white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.8 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.64 (s, 1H), 7.31 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.24 (s, 1H), 7.04 (td, *J* = 7.9, 5.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.79 (m, 1H), 5.70 (s, 2H), 4.13 (q, *J* = 7.3 Hz, 2H), 3.17 – 3.02 (m, 1H), 2.88 (t, *J* = 12.6 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 2.14 (t, *J* = 11.5 Hz, 4H), 1.90 – 1.77 (m, 2H), 1.49 (t, *J* = 7.3 Hz, 5H). MS *m/z*: 554.15 $[M+H]^+$.

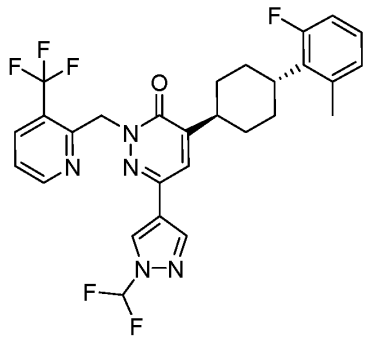
6-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18)



[00334] Step 1: 6-(1-cyclopropyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.063 mmol, 1.0 equiv) and 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (17.6 mg, 0.076 mmol, 1.2 equiv) as the starting materials to give 6-(1-cyclopropyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.8 mg, 59.9%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 9.6 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.10 – 6.97 (m, 1H), 6.93 – 6.80 (m, 2H), 5.69 (s, 2H), 3.69 – 3.56 (m, 1H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.89 (t, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 9.5 Hz, 4H), 1.84 (d, *J* = 13.1 Hz, 2H), 1.51 (q, *J* = 12.6 Hz, 2H), 1.21 – 1.10 (m, 2H), 1.10 – 0.99 (m, 2H). MS *m/z*: 552.25 $[M+H]^+$.

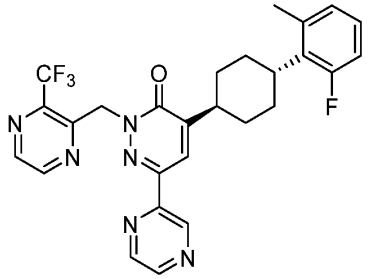
6-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19)



[00335] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 0.063 mmol, 1.0 equiv) and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (18.0 mg, 0.076 mmol, 1.2 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.7 mg, 63.8%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.4 Hz, 1H), 8.17 (s, 1H), 8.02 – 7.97 (m, 2H), 7.36 – 7.30 (m, 2H), 7.22 – 6.99 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J*

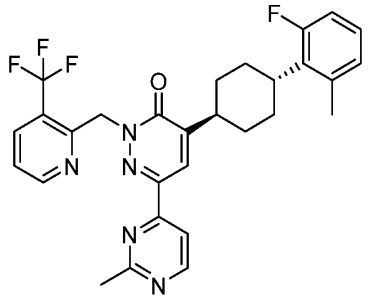
= 11.6, 7.9 Hz, 1H), 5.71 (s, 2H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 11.4 Hz, 4H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.59 – 1.44 (m, 2H). MS *m/z*: 562.05 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (20)



[00336] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (25 mg, 0.052 mmol, 1.0 equiv) and pyrazin-2-ylboronic acid (9.6 mg, 0.078 mmol, 1.5 equiv) as the starting materials to give 4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrazin-2-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (5.3 mg, 19%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 8.66 – 8.57 (m, 4H), 8.20 (s, 1H), 7.11 – 6.98 (m, 1H), 6.96 – 6.79 (m, 2H), 5.84 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.15 (d, *J* = 12.5 Hz, 4H), 1.86 (d, *J* = 13.2 Hz, 2H), 1.43 (d, *J* = 13.7 Hz, 2H). MS *m/z*: 525.20 $[M+H]^+$.

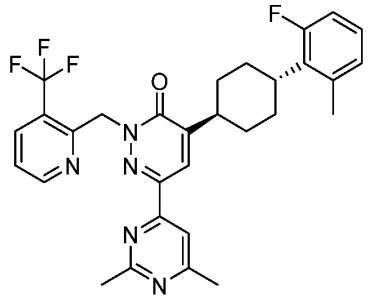
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (21)



[00337] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00338] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-2-methylpyrimidine (26.9 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (28.4 mg, 59.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 5.2 Hz, 1H), 8.60 (d, *J* = 4.8 Hz, 1H), 8.26 (s, 1H), 8.04 – 7.95 (m, 1H), 7.82 (d, *J* = 4.9 Hz, 1H), 7.32 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.04 (td, *J* = 7.8, 5.4 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.78 (s, 2H), 3.17 – 3.05 (m, 1H), 2.93 (t, *J* = 12.2 Hz, 1H), 2.83 (s, 3H), 2.37 (s, 3H), 2.16 (d, *J* = 11.9 Hz, 4H), 1.92 – 1.80 (m, 2H), 1.68 – 1.52 (m, 2H). MS *m/z*: 538.20 $[M+H]^+$.

6-(2,6-Dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22)

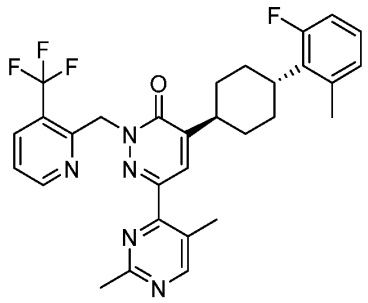


[00339] Step 1 : (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00340] Step 2 : 6-(2,6-dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-2,6-dimethylpyrimidine (29.4 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(2,6-dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (34.8 mg, 71.6%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.9 Hz, 1H), 8.25 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.77 (s, 1H), 7.36 – 7.29 (m, 1H), 7.08 – 7.00 (m, 1H), 6.95 – 6.80 (m, 2H), 5.78 (s, 2H), 3.10 (t, *J* = 12.0 Hz, 1H), 3.01 – 2.82 (m, 4H), 2.61 (s, 3H), 2.37 (s, 3H), 2.15 (d, *J* = 12.2 Hz, 4H), 1.86 (d, *J* = 12.2 Hz, 2H), 1.26 (s, 2H). MS *m/z*: 552.20 $[M+H]^+$.

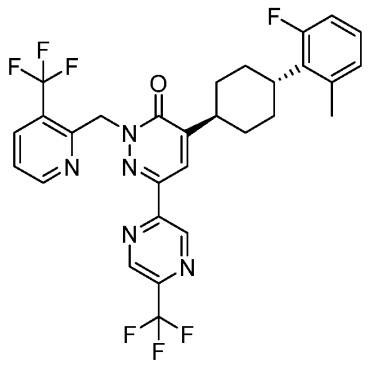
6-(2,5-Dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23)



[00341] Step 1 : (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00342] Step 2 : 6-(2,5-dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-2,5-dimethylpyrimidine (29.4 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(2,5-dimethylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (29.8 mg, 61.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.61 (m, 1H), 8.51 (s, 1H), 8.09 (d, *J* = 0.8 Hz, 1H), 8.03 – 7.99 (m, 1H), 7.37 – 7.32 (m, 1H), 7.08 – 6.99 (m, 1H), 6.95 – 6.82 (m, 2H), 5.76 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 3.01 – 2.81 (m, 4H), 2.36 (d, *J* = 5.1 Hz, 6H), 2.16 (d, *J* = 10.5 Hz, 4H), 1.87 (d, *J* = 12.4 Hz, 2H), 1.59 (d, *J* = 12.4 Hz, 2H). MS *m/z*: 552.15 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (24)

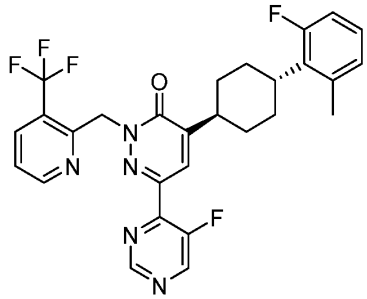


[00343] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00344] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using 4-((1*r*,4*r*)-4-(2-fluoro-6-

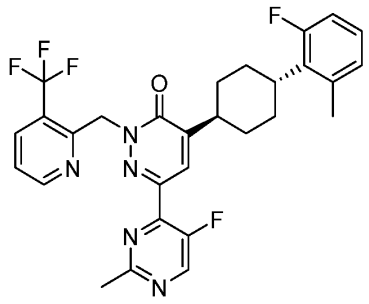
methylphenyl)cyclohexyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (crude, 104 mmol, 1.0 equiv) and 2-chloro-5-(trifluoromethyl)pyrazine (37.7 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)pyrazin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (41.5 mg, 78.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.36 (s, 1H), 8.91 (s, 1H), 8.63 (d, *J* = 4.8 Hz, 1H), 8.19 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.06 – 7.01 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.87– 6.82 (m, 1H), 5.81 (s, 2H), 3.12 (t, *J* = 11.9 Hz, 1H), 2.91 (t, *J* = 12.3 Hz, 1H), 2.36 (d, *J* = 1.6 Hz, 3H), 2.15 (d, *J* = 12.0 Hz, 4H), 1.88 – 1.84 (m, 2H), 1.62 – 1.51 (m, 2H). MS *m/z*: 592.10 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-fluoropyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25)



[00345] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-fluoropyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (50.0 mg, 0.102 mmol, 1.0 equiv) and 4-chloro-5-fluoropyrimidine (16.3 mg, 0.122 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-fluoropyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23.2 mg, 41.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.08 (d, *J* = 2.5 Hz, 1H), 8.64 (dd, *J* = 14.3, 4.0 Hz, 2H), 8.09 (s, 1H), 8.04 – 7.94 (m, 1H), 7.33 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.04 (td, *J* = 7.8, 5.4 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.79 (s, 2H), 3.11 (tt, *J* = 12.1, 2.9 Hz, 1H), 2.99 – 2.83 (m, 1H), 2.36 (s, 3H), 2.17 (dd, *J* = 15.0, 11.6 Hz, 4H), 1.96 – 1.79 (m, 2H), 1.64 – 1.49 (m, 2H). MS *m/z*: 542.20 [M+H]$^+$.

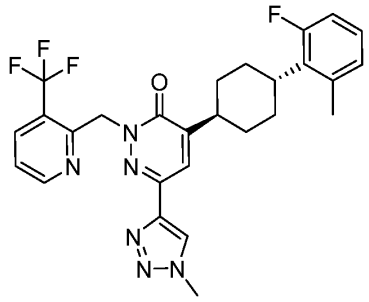
6-(5-Fluoro-2-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (26)



[00346] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00347] Step 2: 6-(5-fluoro-2-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-5-fluoro-2-methylpyrimidine (18.2 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(5-fluoro-2-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.6 mg, 57.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.53 (d, *J* = 3.3 Hz, 1H), 8.02 (d, *J* = 17.8 Hz, 2H), 7.38 – 7.30 (m, 1H), 7.09 – 6.99 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.80 (m, 1H), 5.78 (s, 2H), 3.10 (t, *J* = 12.0 Hz, 1H), 2.91 (t, *J* = 12.3 Hz, 1H), 2.81 (d, *J* = 1.2 Hz, 3H), 2.37 (s, 3H), 2.15 (d, *J* = 11.9 Hz, 4H), 1.86 (d, *J* = 12.6 Hz, 2H), 1.59 (t, *J* = 12.5 Hz, 2H). MS *m/z*: 556.15 $[M+H]^+$.

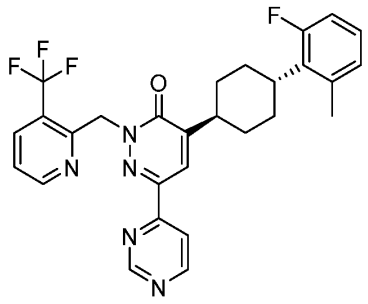
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (27)



[00348] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00349] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1H-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-1,2,3-triazole (33.6 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (44.3 mg, 85.4%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 8.05 – 7.91 (m, 3H), 7.32 (s, 1H), 7.09 – 6.96 (m, 1H), 6.94 – 6.82 (m, 2H), 5.71 (s, 2H), 4.14 (s, 3H), 3.12 (t, *J* = 11.6 Hz, 1H), 2.89 (t, *J* = 12.1 Hz, 1H), 2.36 (s, 3H), 2.14 (d, *J* = 11.8 Hz, 4H), 1.84 (d, *J* = 12.4 Hz, 2H), 1.59 (t, *J* = 12.3 Hz, 2H). MS *m/z*: 527.25 $[M+H]^+$.

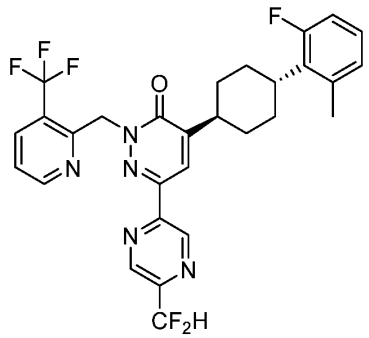
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (28)



[00350] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00351] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (40.0 mg, 0.082 mmol, 1.0 equiv) and 4-chloropyrimidine (21.0 mg, 0.098 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (16.0 mg, 37.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (d, *J* = 1.3 Hz, 1H), 8.76 (d, *J* = 5.4 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.27 (d, *J* = 0.9 Hz, 1H), 8.06 (dd, *J* = 5.4, 1.4 Hz, 1H), 8.01 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.09 – 6.99 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.79 (m, 1H), 5.79 (s, 2H), 3.18 – 3.05 (m, 1H), 2.91 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.23 – 2.08 (m, 4H), 1.92 – 1.81 (m, 2H), 1.66 – 1.50 (m, 2H). MS *m/z*: 524.15 $[M+H]^+$.

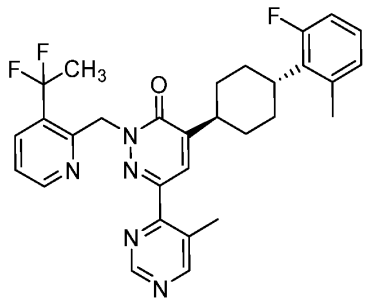
6-(5-(Difluoromethyl)pyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (29)



[00352] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00353] Step 2: 6-(5-(difluoromethyl)pyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-chloro-5-(difluoromethyl)pyrazine (20.7 mg, 0.122 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)pyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (26.0 mg, 44.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 8.89 (s, 1H), 8.66 (d, J = 4.9 Hz, 1H), 8.20 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.38 (s, 1H), 7.04 (td, J = 7.8, 5.4 Hz, 1H), 6.95 – 6.71 (m, 3H), 5.81 (s, 2H), 3.12 (t, J = 12.1 Hz, 1H), 2.91 (t, J = 12.3 Hz, 1H), 2.36 (s, 3H), 2.15 (d, J = 12.1 Hz, 4H), 1.89 – 1.84 (m, 2H), 1.59 (t, J = 12.5 Hz, 2H). MS *m/z*: 574.10 $[M+H]^+$.

2-((3-(1,1-Difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrimidin-4-yl)pyridazin-3(2*H*)-one (30)



[00354] Step 1: 2-chloro-3-(1,1-difluoroethyl)pyridine: Followed the general procedure I using 1-(2-chloropyridin-3-yl)ethan-1-one (5.00 g, 32.1 mmol, 1.0 equiv) as the starting materials to give 2-chloro-3-(1,1-difluoroethyl)pyridine (5.0 g, 87%) as a light yellow oil. MS *m/z*: 178 $[M+H]^+$.

[00355] Step 2: (3-(1,1-difluoroethyl)pyridin-2-yl)methanol: To a stirred solution of 2-chloro-3-(1,1-difluoroethyl)pyridine (2.5 g, 14.1 mmol, 1.0 equiv) and $Pd(PPh_3)_2Cl_2$ (0.99 g, 1.41 mmol, 0.1 equiv) in toluene (20 mL) was added (tributylstannyl)methanol (5.42 g, 16.9 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford (3-(1,1-difluoroethyl)pyridin-2-yl)methanol (560 mg, 23%) as a light yellow oil. MS *m/z*: 174 $[M+H]^+$.

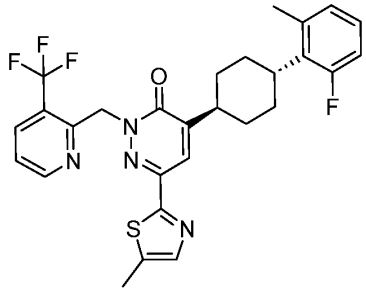
[00356] Step 3: 2-(chloromethyl)-3-(1,1-difluoroethyl)pyridine: Followed the general procedure Q using (3-(1,1-difluoroethyl)pyridin-2-yl)methanol (560 mg, 3.23 mmol, 1.0 equiv) and $SOCl_2$ (3 mL) as the starting materials to give 2-(chloromethyl)-3-(1,1-difluoroethyl)pyridine (550 mg, 89%) as a yellow oil. MS *m/z*: 192 $[M+H]^+$.

[00357] Step 4: 6-chloro-2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure V using 2-(chloromethyl)-3-(1,1-difluoroethyl)pyridine (50.0 mg, 0.260 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.313 mmol, 1.2 equiv) as the starting materials to give 6-chloro-2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 40%) as a light yellow solid. MS *m/z*: 476 $[M+H]^+$.

[00358] Step 5: (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.105 mmol, 1.0 equiv) as the starting material to give (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 486 $[M+H]^+$.

[00359] Step 6: 2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrimidin-4-yl)pyridazin-3(2*H*)-one: Followed the general procedure H using (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.105 mmol, 1.0 equiv) and 4-chloro-5-methylpyrimidine (16.3 mg, 0.126 mmol, 1.2 equiv) as the starting materials to give 2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylpyrimidin-4-yl)pyridazin-3(2*H*)-one (6.5 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 8.62 (s, 1H), 8.54 (d, *J* = 4.0 Hz, 1H), 8.15 (d, *J* = 0.9 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.04 (td, *J* = 7.8, 5.5 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 11.9, 8.2 Hz, 1H), 5.71 (d, *J* = 1.6 Hz, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 12.3 Hz, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 2.20 (s, 1H), 2.14 (d, *J* = 18.5 Hz, 6H), 1.85 (dd, *J* = 12.7, 3.8 Hz, 2H), 1.64 – 1.49 (m, 2H). MS *m/z*: 534.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylthiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (31)

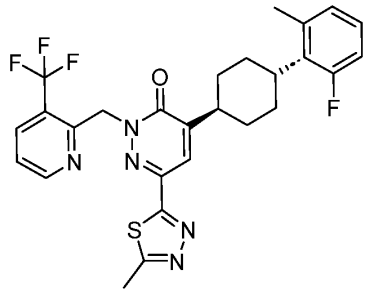


[00360] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid*:* Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv)

as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00361] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylthiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-bromo-5-methylthiazole (38.9 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methylthiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25.2 mg, 52.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 – 8.61 (m, 1H), 8.02 – 7.98 (m, 2H), 7.52 (d, *J* = 1.3 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.05 – 7.00 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.86 – 6.81 (m, 1H), 5.71 (s, 2H), 3.13 – 3.07 (m, 1H), 2.90 – 2.84 (m, 1H), 2.49 (d, *J* = 1.2 Hz, 3H), 2.35 (s, 3H), 2.17 – 2.09 (m, 4H), 1.85 – 1.81 (m, 2H), 1.60 – 1.50 (m, 2H). MS *m/z*: 543.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32)

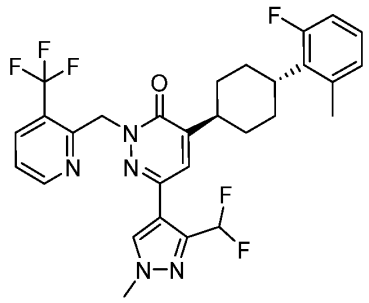


[00362] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00363] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed

the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-bromo-5-methyl-1,3,4-thiadiazole (27.6 mg, 0.156 mmol, 1.5 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.9 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 8.09 (s, 1H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.39 (s, 1H), 7.05 – 7.00 (m, 1H), 6.91 (s, 1H), 6.87 – 6.81 (m, 1H), 5.74 (s, 2H), 3.10 (t, *J* = 11.9 Hz, 1H), 2.89 (t, *J* = 12.0 Hz, 1H), 2.82 (s, 3H), 2.37 (s, 3H), 2.13 (d, *J* = 12.2 Hz, 4H), 1.85 (d, *J* = 12.8 Hz, 2H), 1.56 (t, *J* = 12.5 Hz, 2H). MS *m/z*: 544.10 [M+H]$^+$.

6-(3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (33)

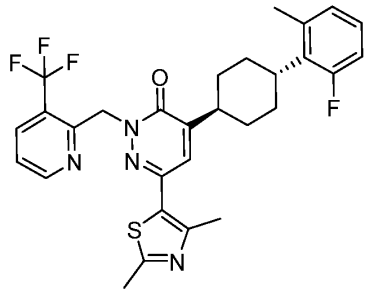


[00364] Step 1: 4-bromo-3-(difluoromethyl)-1-methyl-1*H*-pyrazole hydrogen chloride: Followed the general procedure I using 4-bromo-1-methyl-1*H*-pyrazole-3-carbaldehyde (500 mg, 2.64 mmol, 1.0 equiv) as the starting material to give 4-bromo-3-(difluoromethyl)-1-methyl-1*H*-pyrazole hydrochloride (310 mg, 55%) as a white solid. MS *m/z*: 211 [M+H]$^+$.

[00365] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00366] Step 3: 6-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-3-(difluoromethyl)-1-methyl-1*H*-pyrazole hydrochloride (32.7 mg, 0.156 mmol, 1.5 equiv) as the starting materials to give 6-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (36.4 mg, 60.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 8.12 (s, 1H), 7.77 (s, 1H), 7.43 (d, *J* = 29.4 Hz, 2H), 7.07 – 6.94 (m, 2H), 6.93 – 6.83 (m, 2H), 5.76 (s, 2H), 3.96 (s, 3H), 3.08 (s, 1H), 2.88 (s, 1H), 2.36 (s, 3H), 2.14 (s, 4H), 1.83 (s, 2H). 1.49 (s, 2H). MS *m/z*: 576.10 $[M+H]^+$.

6-(2,4-Dimethylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (34)

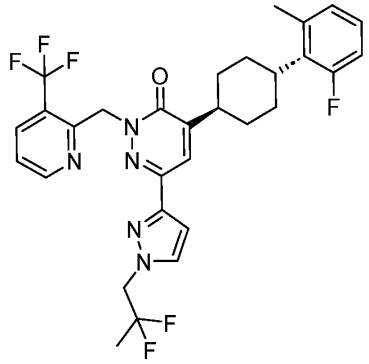


[00367] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00368] Step 2: 6-(2,4-dimethylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 5-bromo-2,4-dimethylthiazole (24.2 mg, 0.124 mmol, 1.2

equiv) as the starting materials to give 6-(2,4-dimethylthiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.4 mg, 36.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 8.02 – 7.95 (m, 1H), 7.36 – 7.28 (m, 2H), 7.09 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.70 (s, 2H), 3.08 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.2 Hz, 1H), 2.73 (s, 3H), 2.54 (s, 3H), 2.36 (s, 3H), 2.14 (t, *J* = 11.4 Hz, 4H), 1.85 (d, *J* = 13.0 Hz, 2H), 1.51 – 1.42 (m, 2H). MS *m/z*: 557.10 [M+H]$^+$.

6-(1-(2,2-Difluoropropyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) -2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (35)



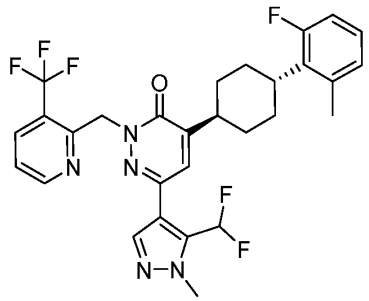
[00369] Step 1: 3-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole: Followed the general procedure F using 3-bromo-1*H*-pyrazole (300 mg, 2.04 mmol, 1.0 equiv) and 2,2-difluoropropyl trifluoromethanesulfonate (558 mg, 2.44 mmol, 1.2 equiv) as the starting materials to give 3-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole (80 mg, 17%) as a brown oil. MS *m/z*: 225 [M+H]$^+$.

[00370] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00371] Step 3: 6-(1-(2,2-difluoropropyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 3-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole (46.4 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(1-(2,2-difluoropropyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19.2 mg, 36.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.06 – 7.00 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.81 (m, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 5.73 (s, 2H), 4.53 – 4.47 (m, 2H), 3.13 – 3.05 (m, 1H), 2.93 – 2.85 (m, 1H), 2.36 (s, 3H), 2.19 – 2.10 (m, 4H), 1.88 – 1.80 (m, 3H), 1.59 (d, *J* = 18.6 Hz, 4H). MS *m/z*: 590.10 [M+H]$^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (36)

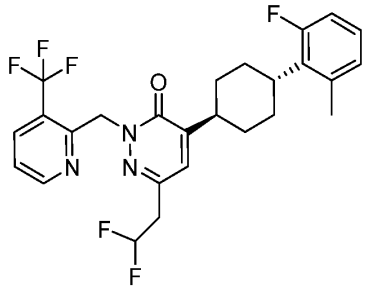


[00372] Step 1: 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-pyrazole: Followed the general procedure I using 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (500 mg, 2.64 mmol, 1.0 equiv) as the starting material to give 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-pyrazole (260 mg, 46%) as a colorless oil.MS *m/z*: 211 [M+H]$^+$.

[00373] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00374] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-pyrazole (26.1 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (38.1 mg, 74.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 – 8.67 (m, 1H), 8.06 – 8.03 (m, 1H), 7.71 (d, *J* = 1.1 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.30 (d, *J* = 0.9 Hz, 1H), 7.11 – 6.95 (m, 2H), 6.95 – 6.82 (m, 2H), 5.70 (s, 2H), 4.06 (s, 3H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.37 (s, 3H), 2.14 (t, *J* = 12.5 Hz, 4H), 1.85 (d, *J* = 11.0 Hz, 2H), 1.51 (d, *J* = 12.4 Hz, 2H).MS *m/z*: 576.15 $[M+H]^+$.

6-(2,2-Difluoroethyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (37)



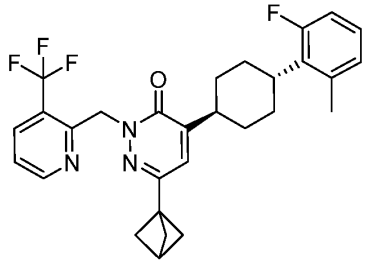
[00375] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00376] Step 2: 6-(2,2-difluorovinyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104

mmol, 1.0 equiv) and 2-bromo-1,1-difluoroethene (17.7 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(2,2-difluorovinyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl) pyridazin-3(2*H*)-one (19.2 mg, 36%) as a brown oil. MS *m/z*: 507 $[M+H]^+$.

[00377] Step 3: 6-(2,2-difluoroethyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B 6-(2,2-difluorovinyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.059 mmol, 1.0 equiv) as the starting material to give 6-(2,2-difluoroethyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.2 mg, 20%) as a white solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.10 – 7.00 (m, 2H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.88 – 6.80 (m, 1H), 6.22 – 5.91 (m, 1H), 5.66 (s, 2H), 3.20 – 2.86 (m, 4H), 2.36 (d, *J* = 9.9 Hz, 3H), 2.17 – 2.06 (m, 4H), 1.83 (s, 2H), 1.51 – 1.39 (m, 2H). MS *m/z*: 510.10$[M+H]^+$.

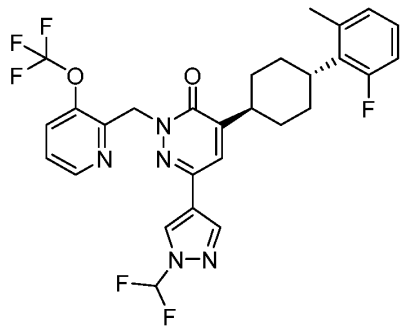
6-(Bicyclo[1.1.1]pentan-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (38)



[00378] Step 1: 6-(bicyclo[1.1.1]pentan-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl) pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 2-(bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.2 mg, 0.125 mmol, 1.2 equiv) as the starting materials to give 6-(1-(2,2-difluoropropyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridine-2-yl) methyl)pyridazin-3(2*H*)-one (13.7 mg, 25.1%) as a light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.91 – 5.78 (m, 1H), 5.65 (d, *J* = 20.0 Hz, 3H), 5.33 (s,

1H), 5.08 – 4.98 (m, 2H), 3.16 (d, *J* = 6.8 Hz, 2H), 3.11 – 3.01 (m, 1H), 2.93 – 2.83 (m, 1H), 2.36 (s, 3H), 2.20 – 2.06 (m, 4H), 1.88 – 1.79 (m, 2H), 1.55 – 1.43 (m, 2H). MS *m/z*: 512.15[M+H]$^+$.

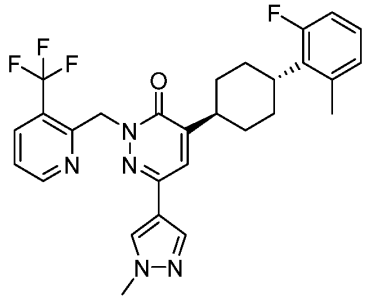
6-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (39)



[00379] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (80.0 mg, 0.249 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (68.7 mg, 0.324 mmol, 1.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 40%) as a white solid. MS *m/z*: 496 [M+H]$^+$.

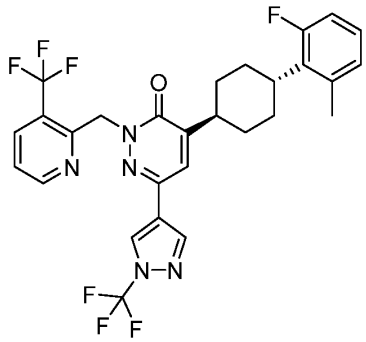
[00380] Step 2: 6-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.101 mmol, 1.0 equiv) and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (24.6 mg, 0.101 mmol, 1.0 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.3 mg, 54.8 %) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.6 Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.21 (s, 1H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.63 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.87 (t, *J* = 10.9 Hz, 1H), 2.36 (s, 3H), 2.20 – 2.10 (m, 4H), 1.85 (d, *J* = 12.7 Hz, 2H), 1.50 (d, *J* = 12.6 Hz, 2H).MS *m/z*: 578.10 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40)



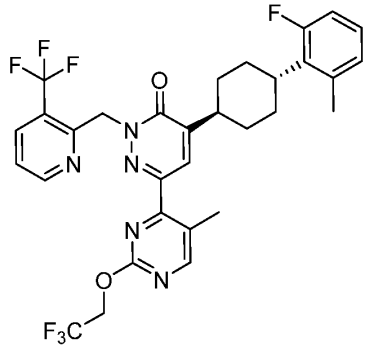
[00381] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (26.0 mg, 0.125 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (48.4 mg, 87.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 9.7 Hz, 1H), 7.75 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.81 (m, 1H), 5.69 (s, 2H), 3.94 (s, 3H), 3.09 (t, *J* = 11.9 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 11.1 Hz, 4H), 1.83 (s, 2H), 1.51 (d, *J* = 12.5 Hz, 2H).MS *m/z*: 526.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (41)



[00382] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trifluoromethyl)-1*H*-pyrazole (32.7 mg, 0.125 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (43.3 mg, 71.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 4.8 Hz, 1H), 8.18 (s, 1H), 8.11 – 8.05 (m, 2H), 7.44 – 7.37 (m, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.74 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 11.1 Hz, 4H), 1.89 – 1.81 (m, 2H), 1.57 – 1.46 (m, 2H).MS *m/z*: 580.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (42)



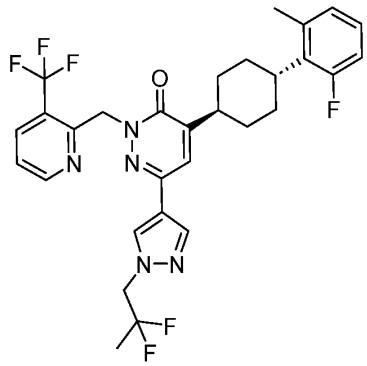
[00383] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 $[M+H]^+$.

[00384] Step 2: 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2,4-dichloro-5-methylpyrimidine (20.1 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 86%) as a colorless oil. MS *m/z*: 572 $[M+H]^+$.

[00385] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure K using 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.087 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (26.5 mg, 44.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 – 8.62 (m, 1H), 8.38 (d, *J* = 0.8 Hz, 1H), 8.06 – 8.01 (m, 2H), 7.40 – 7.34 (m, 1H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.80 (m, 1H), 5.76 (s, 2H), 4.92 – 4.79 (m, 2H), 3.14 – 3.03 (m, 1H), 2.91 (t, *J* = 12.3 Hz, 1H), 2.37 (s, 3H), 2.32 – 2.28 (m, 3H), 2.14 (t, *J* = 11.6 Hz, 4H), 1.89 – 1.84 (m, 2H), 1.63 – 1.51 (m, 2H). MS *m/z*: 636.15 $[M+H]^+$.

6-(1-(2,2-Difluoropropyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) -2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (43)



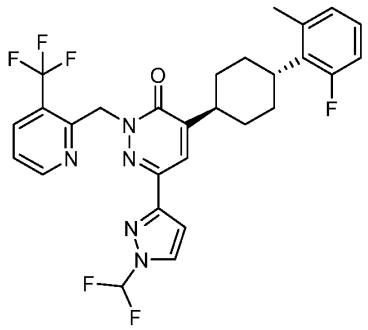
[00386] Step 1: 4-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole: Followed the general procedure F using 4-bromo-1*H*-pyrazole (500 mg, 3.40 mmol, 1.0 equiv) and 2,2-difluoropropyl trifluoromethanesulfonate (931 mg, 4.08 mmol, 1.2 equiv) as the starting

materials to give 4-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole (200 mg, 26%) as a brown oil. MS *m/z*: 225 $[M+H]^+$.

[00387] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 $[M+H]^+$.

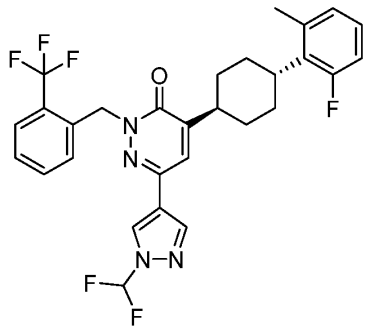
[00388] Step 3: 6-(1-(2,2-difluoropropyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl) -2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-1-(2,2-difluoropropyl)-1*H*-pyrazole e (39.3 mg, 0.176 mmol, 1.7 equiv) as the starting materials to give 6-(1-(2,2-difluoropropyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (42 mg, 81%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 2H), 7.41 (s, 1H), 7.30 (s, 1H), 7.06 – 7.00 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.82 (m, 1H), 5.74 (s, 2H), 4.52 – 4.45 (m, 2H), 3.11 – 3.04 (m, 1H), 2.89 (s, 1H), 2.36 (s, 3H), 2.20 – 2.09 (m, 4H), 1.84 (d, *J* = 12.7 Hz, 2H), 1.64(s, 1H), 1.57 – 1.49 (m, 4H). MS *m/z*: 590.10 $[M+H]^+$.

6-(1-(Difluoromethyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (44)



[00389] Step 1: 6-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 1-(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (38.1 mg, 0.156 mmol, 1.5 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (31.6 mg, 54.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.60 (m, 1H), 8.03 – 7.98 (m, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.23 (s, 1H), 7.10 – 7.00 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.81 (m, 2H), 5.74 (s, 2H), 3.14 – 3.06 (m, 1H), 2.94 – 2.84 (m, 1H), 2.36 (s, 3H), 2.21 – 2.08 (m, 4H), 1.89 – 1.81 (m, 2H), 1.62 – 1.49 (m, 2H). MS *m/z*: 562.15[M+H]$^+$.

6-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (45)

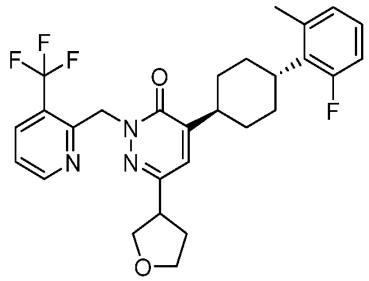


[00390] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl) pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.156 mmol, 1.0 equiv) and 1-(bromomethyl)-2-(trifluoromethyl)benzene (44.7 mg, 0.187 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl) pyridazin-3(2*H*)-one (50 mg, 66%)as a white solid. MS *m/z*: 479 [M+H]$^+$.

[00391] Step 2: 6-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl) -2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl) pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 1-

(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (50.9 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (44 mg, 75%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.98 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.30 (d, *J* = 0.9 Hz, 1H), 7.21 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.08 – 7.02 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.83 (m, 1H), 5.63 (s, 2H), 3.13 (t, *J* = 11.9 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 2.37 (s, 3H), 2.15 (t, *J* = 14.6 Hz, 4H), 1.87 (d, *J* = 12.7 Hz, 2H), 1.47 (s, 2H). MS *m/z*: 561.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydrofuran-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (46)

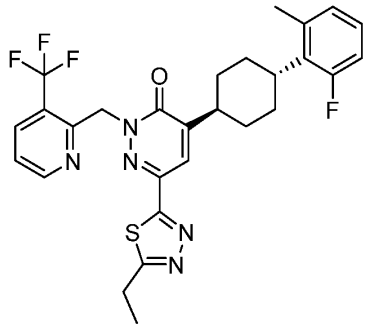


[00392] Step 1: 6-(2,5-dihydrofuran-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.5 mg, 0.125 mmol, 1.2 equiv) as the starting materials to give 6-(2,5-dihydrofuran-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 56%) as a white solid. MS *m/z*: 514 $[M+H]^+$.

[00393] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydrofuran-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 6-(2,5-dihydrofuran-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 0.058 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(tetrahydrofuran-3-yl)-2-((3-(trifluoromethyl)pyridin-2-

yl)methyl)pyridazin-3(2*H*)-one (11.2 mg, 35.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.64 (s, 2H), 4.11 – 3.96 (m, 2H), 3.91 – 3.80 (m, 2H), 3.47 – 3.35 (m, 1H), 3.03 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.3 Hz, 1H), 2.35 (s, 3H), 2.34 – 2.26 (m, 1H), 2.19 – 2.03 (m, 5H), 1.84 (s, 1H), 1.80 (s, 1H), 1.53 – 1.39 (m, 2H). MS *m/z*: 516.25 [M+H]$^+$.

6-(5-Ethyl-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (47)



[00394] Step 1: 2-bromo-5-vinyl-1,3,4-thiadiazole: Followed the general procedure A using 2,5-dibromo-1,3,4-thiadiazole (500 mg, 2.05 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (157 mg, 1.02 mmol, 0.5 equiv) as the starting materials to give 2-bromo-5-vinyl-1,3,4-thiadiazole (180 mg, 45%) as a light brown oil. MS *m/z*: 191 [M+H]$^+$.

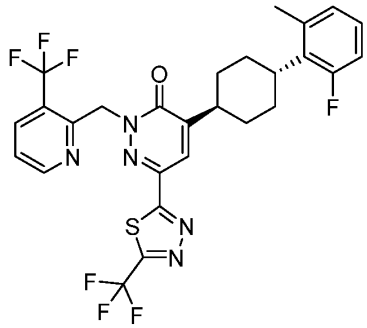
[00395] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00396] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinyl-1,3,4-thiadiazol-2-yl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-bromo-5-vinyl-1,3,4-thiadiazole (32.0 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinyl-1,3,4-thiadiazol-2-yl)pyridazin-3(2H)-one (20 mg, 35%) as a colorless oil. MS *m/z*: 556 $[M+H]^+$.

[00397] Step 4: 6-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinyl-1,3,4-thiadiazol-2-yl)pyridazin-3(2*H*)-one (20 mg, 0.036 mmol, 1.0 equiv) as the starting material to give 6-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8.9 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 4.8 Hz, 1H), 8.08 (d, *J* = 17.8 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.80 (m, 1H), 5.75 (s, 2H), 3.19 (t, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.91 (d, *J* = 12.8 Hz, 1H), 2.37 (s, 3H), 2.13 (d, *J* = 12.9 Hz, 4H), 1.85 (d, *J* = 12.4 Hz, 2H), 1.55 (d, *J* = 12.6 Hz, 2H), 1.44 (d, *J* = 7.6 Hz, 3H).MS *m/z*: 558.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (48)

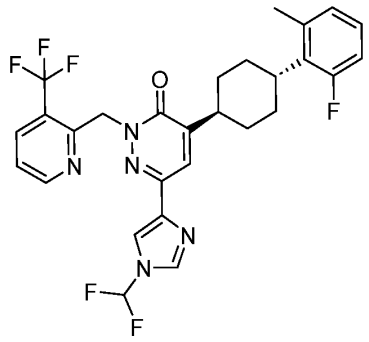


[00398] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00399] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-

6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropy- ridazin-3-yl)boronic acid (crude, 0.102 mmol, 1.0 equiv) and 2-chloro-5-(trifluoromethyl)-1,3,4-thiadiazole (38.5 mg, 0.204 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (39.8 mg, 65.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.7 Hz, 1H), 8.11 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.08 – 6.99 (m, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.74 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 12.2 Hz, 1H), 2.37 (s, 3H), 2.14 (d, *J* = 12.1 Hz, 4H), 1.87 (d, *J* = 12.4 Hz, 2H), 1.52 (d, *J* = 12.4 Hz, 2H). MS *m/z*: 598.05 $[M+H]^+$.

6-(1-(Difluoromethyl)-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (49)

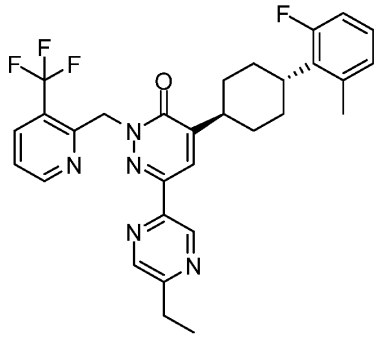


[00400] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid**:** Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40.0 mg, 0.083 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00401] Step 2: 6-(1-(difluoromethyl)-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one**:** Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.083 mmol, 1.0 equiv) and 4-bromo-1-(difluoromethyl)-1*H*-imidazole (19.5 mg,

0.099 mmol, 1.2 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.3 mg, 33.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (d, *J* = 4.2 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 11.3 Hz, 2H), 7.65 (s, 1H), 7.30 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.13 – 6.79 (m, 4H), 5.72 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.5 Hz, 1H), 2.35 (s, 3H), 2.13 (d, *J* = 12.1 Hz, 4H), 1.83 (d, *J* = 12.9 Hz, 2H), 1.56 (q, *J* = 12.6 Hz, 2H). MS *m/z*: 562.15[M+H]$^+$.

6-(5-Ethylpyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50)



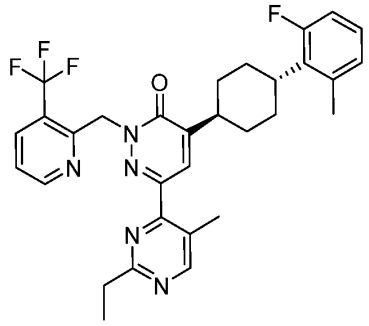
[00402] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00403] Step 2: 6-(5-chloropyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and 2-bromo-5-chloropyrazine (47.8 mg, 0.249 mmol, 1.2 equiv) as the starting materials to give 6-(5-chloropyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 51%) as a white solid. MS *m/z*: 558 [M+H]$^+$.

[00404] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinylpyrazin-2-yl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-(5-chloropyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60.0 mg, 0.108 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (18.4 mg, 0.118 mmol, 1.1 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinylpyrazin-2-yl)pyridazin-3(2*H*)-one (40 mg, 71%) as a white solid. MS *m/z*: 550 $[M+H]^+$.

[00405] Step 4: 6-(5-ethylpyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure B using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-6-(5-vinylpyrazin-2-yl)pyridazin-3(2*H*)-one (40 mg, 0.073 mmol, 1.0 equiv) as the starting material to give 6-(5-ethylpyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18.7 mg, 46.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.62 (s, 1H), 8.50 (s, 1H), 8.15 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.33 (s, 1H), 7.08 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.5, 8.4 Hz, 1H), 5.78 (s, 2H), 3.13 (t, *J* = 12.0 Hz, 1H), 3.00 – 2.85 (m, 3H), 2.36 (s, 3H), 2.15 (d, *J* = 12.1 Hz, 4H), 1.84 (s, 2H), 1.63 – 1.53 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H). MS m/z: 552.10 $[M+H]^+$.

6-(2-Ethyl-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (51)



[00406] Step 1 : (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-

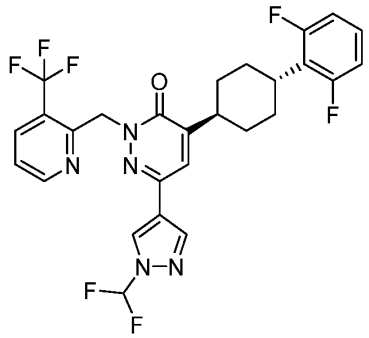
((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00407] Step 2 : 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and 2,4-dichloro-5-methylpyrimidine (37.1 mg, 0.228 mmol, 1.1 equiv) as the starting materials to give 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55 mg, 54%) as a light green oil. MS *m/z*: 572 $[M+H]^+$.

[00408] Step 3 : 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-vinylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-(2-chloro-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.070 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (21.5 mg, 0.140 mmol, 2.0 equiv) as the starting materials to give 4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-vinylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 76.1%) as a colorless oil. MS *m/z*: 564 $[M+H]^+$.

[00409] Step 4 : 6-(2-ethyl-5-methylpyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-methyl-2-vinylpyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25 mg, 0.044 mmol, 1.0 equiv) as the starting material to give 6-(2-ethyl-5-methylpyrimidin-4-yl)-4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9.5 mg, 37%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 8.53 (s, 1H), 8.12 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.09 – 7.00 (m, 1H), 6.96 – 6.80 (m, 2H), 5.76 (s, 2H), 3.16 – 3.11 (m, 3H), 2.90 (t, *J* = 12.1 Hz, 1H), 2.36 (d, *J* = 7.9 Hz, 6H), 2.16 (d, *J* = 12.3 Hz, 4H), 1.87 (d, *J* = 12.0 Hz, 2H), 1.57 (d, *J* = 12.7 Hz, 2H), 1.46 (s, 3H). MS *m/z*: 566.20 $[M+H]^+$.

6-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52)



[00410] Step 1: ethyl 2',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate: Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (2.0 g, 7.1 mmol, 1.0 equiv) and 2-bromo-1,3-difluorobenzene (1.38 g, 7.1 mmol, 1.0 equiv) as the starting materials to give ethyl 2',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.8 g, 94%) as a yellow oil. MS *m/z*: 267 $[M+H]^+$.

[00411] Step 2: ethyl 4-(2,6-difluorophenyl)cyclohexane-1-carboxylate: ollowed the general procedure B using ethyl 2',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.8 g, 6.7 mmol, 1.0 equiv) as the starting material to give the the crude product ethyl 4-(2,6-difluorophenyl)cyclohexane-1-carboxylate (1.7 g, crude) as a light yellow oil. MS *m/z*: 269 $[M+H]^+$.

[00412] Step 3: 4-(2,6-difluorophenyl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2,6-difluorophenyl)cyclohexane-1-carboxylate (1.7 g, 6.3 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2,6-difluorophenyl)cyclohexane-1-carboxylic acid (1.45 g, crude) as a white solid. MS *m/z*: 239 $[M+H]^+$.

[00413] Step 4: 3,6-dichloro-4-(4-(2,6-difluorophenyl)cyclohexyl)pyridazine: Followed the general procedure D using 4-(2,6-difluorophenyl)cyclohexane-1-carboxylic acid (1.45 g, 6.1 mmol, 1.0 equiv) and 3,6-dichloropyridazine (0.81 g, 5.4 mmol, 0.9 equiv) as the starting materials to give 3,6-dichloro-4-(4-(2,6-difluorophenyl)cyclohexyl)pyridazine (1.1 g, 53%) as a white solid. MS *m/z*: 343 $[M+H]^+$.

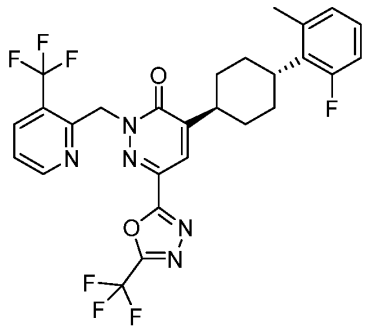
[00414] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E using 3,6-dichloro-4-(4-(2,6-difluorophenyl)cyclohexyl)pyridazine (1.1 g, 3.2 mmol, 1.0 equiv) as the starting material to

give 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (260 mg, 24%) as a white solid. MS *m/z*: 325 $[M+H]^+$.

[00415] Step 6: 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (260 mg, 0.8 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (156 mg, 0.8 mmol, 1.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 10%) as a white solid. MS *m/z*: 484 $[M+H]^+$.

[00416] Step 7: 2-(2,2-difluoropropyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-7-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.083 mmol, 1.0 equiv) and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (24.2 mg, 0.10 mmol, 1.2 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (21.1 mg, 45.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.7 Hz, 1H), 8.16 (s, 1H), 7.98 (d, *J* = 6.1 Hz, 2H), 7.32 (d, *J* = 7.1 Hz, 2H), 7.22 – 7.03 (m, 2H), 6.82 (t, *J* = 8.6 Hz, 2H), 5.71 (s, 2H), 3.16 – 3.04 (m, 2H), 2.17 – 2.05 (m, 4H), 1.94 – 1.85 (m, 2H), 1.58 – 1.43 (m, 2H). MS *m/z*: 566.05 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (53)



[00417] Step 1: ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-

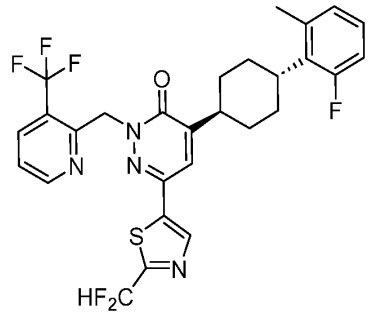
((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (150 mg, 0.313 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (120 mg, 74%) as a white solid. MS *m/z*: 518 $[M+H]^+$.

[00418] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (120 mg, 0.232 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 85%) as a white solid. MS *m/z*: 504 $[M+H]^+$.

[00419] Step 3: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-*N'*-(2,2,2-trifluoroacetyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 0.119 mmol, 1.0 equiv) and 2,2,2-trifluoroacetic anhydride (62.5 mg, 0.298 mmol, 1.5 equiv) as the starting materials to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-*N'*-(2,2,2-trifluoroacetyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (80 mg, 67%) as a white solid. MS *m/z*: 582 $[M+H]^+$.

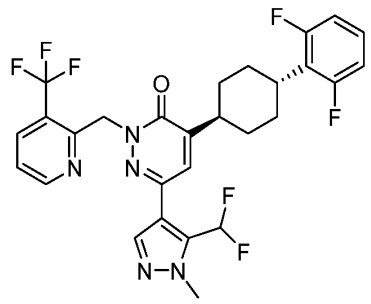
[00420] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure P using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-*N'*-(2,2,2-trifluoroacetyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (80 mg, 0.133 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40.8 mg, 52.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 8.0 Hz 1H), 7.95 (s, 1H), 7.34 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.04 (td, *J* = 7.9, 5.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.9, 8.2 Hz, 1H), 5.79 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12 Hz 1H), 2.37 (s, 3H), 2.14 (d, *J* = 11.8 Hz, 4H), 1.86 (dd, *J* = 13.6, 3.8 Hz, 2H), 1.56 – 1.47 (m, 2H). MS m/z: 582.00 $[M+H]^+$.

6-(2-(Difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (54)



[00421] Step 1: 6-(2-(difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (40 mg, 0.082 mmol, 1.0 equiv) and 5-bromo-2-(difluoromethyl)thiazole (21 mg, 0.098 mmol, 1.2 equiv) as the starting materials to give 6-(2-(difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (34.0 mg, 70.9%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.6 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.47 (s, 1H), 7.38 (t, *J* = 6.4 Hz, 1H), 7.10 – 6.60 (m, 4H), 5.72 (s, 2H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 2.37 (s, 3H), 2.15 (d, *J* = 12.3 Hz, 4H), 1.90 – 1.83 (m, 2H), 1.53 (q, *J* = 12.6 Hz, 2H). MS *m/z*: 579.05[M+H]$^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55)



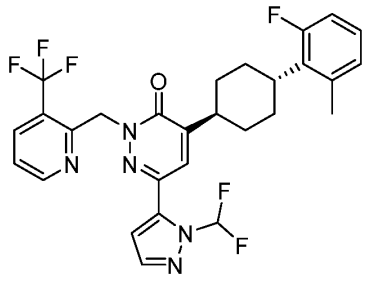
[00422] Step 1: 4-bromo-5-(difluoromethyl)-1-methyl-1H-pyrazole: Followed the general procedure I using 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (100 mg, 0.529 mmol, 1.0

equiv) as the starting material to give 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-pyrazole (38 mg, 34%) as a yellow oil. MS *m/z*: 211 $[M+H]^+$.

[00423] Step 2: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.207 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00424] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.207 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-pyrazole (52.4 mg, 0.248 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.4 mg, 18.9%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.71 (s, 1H), 7.44 – 7.33 (m, 1H), 7.29 (d, *J* = 0.9 Hz, 1H), 7.20 – 6.90 (m, 2H), 6.83 (t, *J* = 8.5 Hz, 2H), 5.70 (s, 2H), 4.06 (s, 3H), 3.10 (t, *J* = 12.2 Hz, 2H), 2.10 (d, *J* = 11.1 Hz, 4H), 1.99 – 1.89 (m, 2H), 1.60 – 1.40 (m, 2H). MS *m/z*: 580.05 $[M+H]^+$.

6-(1-(Difluoromethyl)-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (56)

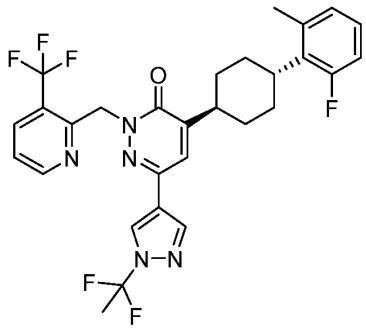


[00425] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general

procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (100 mg, 0.208 mmol, 1.0 equiv) and 5-bromo-1*H*-pyrazole (52.9 mg, 0.208 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 41%) as a white solid. MS *m/z*: 512 $[M+H]^+$.

[00426] Step 2: 6-(1-(difluoromethyl)-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.098 mmol, 1.0 equiv) and chlorodifluoromethane (gas) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5.3 mg, 9.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 3.6 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.71 (m, 2H), 7.42 – 7.35 (m, 2H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 2H), 6.69 (s, 1H), 5.72 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.87 (d, *J* = 13.1 Hz, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 12.9 Hz, 4H), 1.85 (d, *J* = 12.7 Hz, 2H), 1.50 (d, *J* = 12.6 Hz, 2H). MS *m/z*: 562.05 $[M+H]^+$.

6-(1-(1,1-Difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (57)



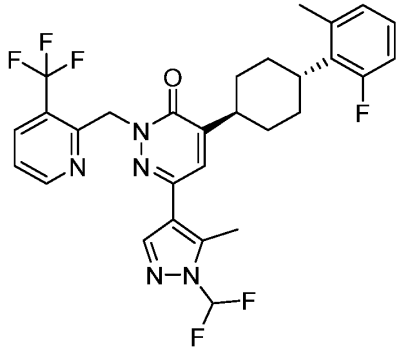
[00427] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.417 mmol, 1.0 equiv) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethan-1-one (196

mg, 0.834 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl) pyridazin-3(2*H*)-one (90 mg, 42%) as a white solid. MS *m/z*: 512 $[M+H]^+$.

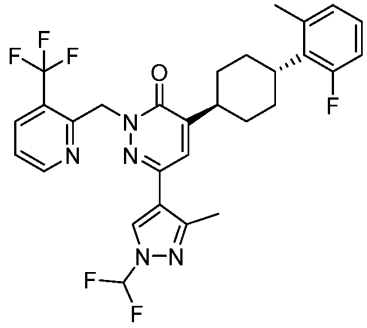
[00428] Step 2: 6-(1-(2-bromo-1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: To a stirred mixture of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (90.0 mg, 0.176 mmol, 1.0 equiv) and KOH (29.6 mg, 0.528 mmol, 3.0 equiv) in ACN (2 mL) and H_2O (0.4 mL) at room temperature. The resulting mixture was stirred for 1 h at 50 °C under 2-bromo-1,1-difluoroethene atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 3:1) to afford 6-(1-(2-bromo-1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 34%) as a light yellow solid. MS *m/z*: 654 $[M+H]^+$.

[00429] Step 3: 6-(1-(1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure B using 6-(1-(2-bromo-1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl) pyridazin-3(2*H*)-one (40 mg, 0.061 mmol, 1.0 equiv) as the starting material to give 6-(1-(1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5.2 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.7 Hz, 1H), 8.17 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.33 (d, *J* = 13.3 Hz, 2H), 7.08 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.81 (m, 1H), 5.72 (s, 2H), 3.09 (t, *J* = 12.2 Hz, 1H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.30 (t, *J* = 16.1 Hz, 3H), 2.14 (t, *J* = 11.4 Hz, 4H), 1.85 (d, *J* = 12.8 Hz, 2H), 1.54 – 1.43 (m, 2H). MS *m/z*: 576.10 $[M+H]^+$.

6-(1-(Difluoromethyl)-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (58A)



6-(1-(Difluoromethyl)-5-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (58B)

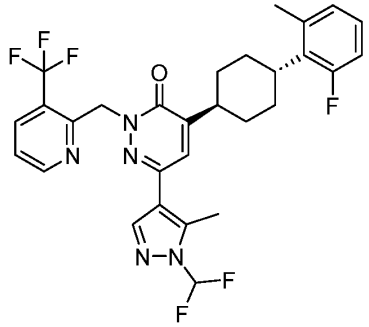


[00430] Step 1: 1-(difluoromethyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole: Followed the general procedure F using 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (200 mg, 0.961 mmol, 1.0 equiv) and chlorodifluoromethane (gas) as the starting materials to give 1-(difluoromethyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (120 mg, 48%) as a white solid. MS *m/z*: 259 $[M+H]^+$.

[00431] Step 2: 6-(1-(difluoromethyl)-5-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 1-(difluoromethyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (120 mg, 0.465 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (223 mg, 0.465 mmol, 1.0 equiv) as the starting materials to give 6-(1-(difluoromethyl)-5-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-

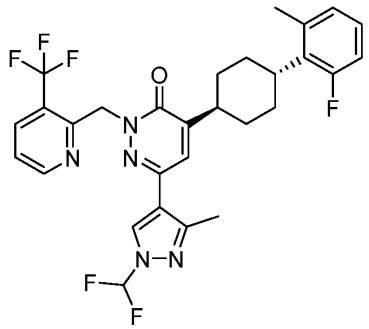
methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (21.6 mg, 8.0%) and 6-(1-(difluoromethyl)-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (46.7 mg, 17.3%) as a white solid.

6-(1-(Difluoromethyl)-3-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (58A)



[00432] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.65 (d, J = 4.2 Hz, 1H), 8.04 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 6.2 Hz, 1H), 7.27 (s, 1H), 7.14 – 6.79 (m, 4H), 5.71 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 11.7 Hz, 1H), 2.36 (s, 3H), 2.29 (s, 3H), 2.24 – 2.05 (m, 4H), 1.91 – 1.79 (m, 2H), 1.61 – 1.40 (m, 2H), 1.21 (d, *J* = 6.1 Hz, 2H). MS *m/z*: 576.10 $[M+H]^+$.

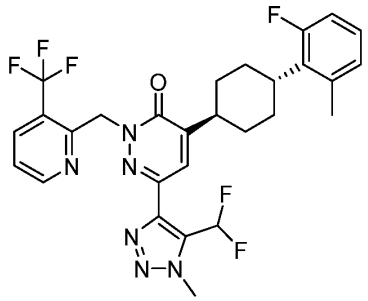
6-(1-(Difluoromethyl)-5-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (58B)



[00433] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.45 – 7.27 (m, 2H), 7.23 (s, 1H), 7.07 – 7.0 (m, 1H), 6.96 – 6.79 (m, 2H),

5.71 (s, 2H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.0 Hz, 1H), 2.52 (s, 3H), 2.37 (s, 3H), 2.26 – 2.05 (m, 4H), 1.91 – 1.78 (m, 2H), 1.59 – 1.40 (m, 2H), 1.21 (d, *J* = 6.1 Hz, 3H). MS *m/z*: 576.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (59)



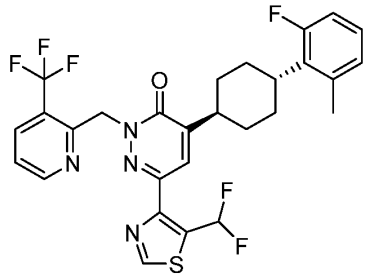
[00434] Step 1: 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole hydrochloride: Followed the general procedure I using 4-bromo-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (250 mg, 1.31 mmol, 1.0 equiv) as the starting material to give 4-bromo-5-(difluoromethyl)-1-methyl-1H-1,2,3-triazole hydrochloride (200 mg, 71%) as a white solid.MS *m/z*: 212 $[M+H]^+$.

[00435] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 $[M+H]^+$.

[00436] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole hydrochloride (43.8 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-

yl)methyl)pyridazin-3(2*H*)-one (48.0 mg, 82.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 4.7 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.41 – 7.34 (m, 1H), 7.20 (s, 1H), 7.09 – 7.00 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.7, 8.0 Hz, 1H), 5.71 (s, 2H), 4.25 (s, 3H), 3.13 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.21 – 1.99 (m, 4H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.57 (t, *J* = 12.8 Hz, 2H). MS *m/z*: 577.10 [M+H]$^+$.

6-(5-(Difluoromethyl)thiazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60)



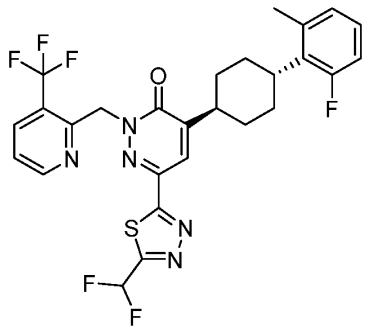
[00437] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 [M+H]$^+$.

[00438] Step 2: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-5-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and 4-chlorothiazole-5-carbaldehyde (61.4 mg, 0.416 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-5-carbaldehyde (80 mg, 70%) as a colorless oil. MS *m/z*: 557 [M+H]$^+$.

[00439] Step 3: 6-(5-(difluoromethyl)thiazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-5-carbaldehyde (80.0 mg, 0.144 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)thiazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (45.4 mg, 54.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 8.71 – 8.66 (m, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.44 – 7.37 (m, 1H), 7.25 (s, 1H), 7.12 – 7.01 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.76 (s, 2H), 3.17 – 3.05 (m, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 10.6 Hz, 4H), 1.87 (d, *J* = 3.8 Hz, 2H), 1.62 – 1.51 (m, 2H). MS *m/z*: 579.00 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (61)

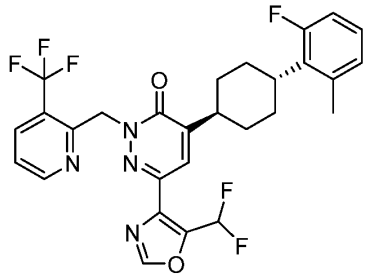


[00440] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 $[M+H]^+$.

[00441] Step 2: 6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyrid-azin-3-yl) boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-bromo-5-(difluoromethyl)-1,3,4-thiadiazole (33.1 mg, 0.156 mmol, 1.5 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cycloh-exyl)-2-((3-

(trifluoromethyl)pyridine-2-yl)methyl)pyridazin-3(2*H*)-one (25.6 mg, 42.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.34 (m, 1H), 7.16 – 6.91 (m, 3H), 6.89 – 6.82 (m, 1H), 5.75 (s, 2H), 3.11 (t, *J* = 11.9 Hz, 1H), 2.90 (s, 1H), 2.37 (s, 3H), 2.14 (d, *J* = 12.2 Hz, 4H), 1.86 (d, *J* = 12.7 Hz, 2H), 1.55 (d, *J* = 12.5 Hz, 2H). MS *m/z*: 579.95 [M+H]$^+$.

6-(5-(Difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (62)



[00442] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*) -one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)py-ridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 [M+H]$^+$.

[00443] Step 2: ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylateL Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.204 mmol, 1.0 equiv) and ethyl 4-bromooxazole-5-carboxylate (89.9 mg, 0.408 mmol, 2.0 equiv) as the starting materials to give ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylate (90 mg, 75%) as a brown oil. MS *m/z*: 585 [M+H]$^+$.

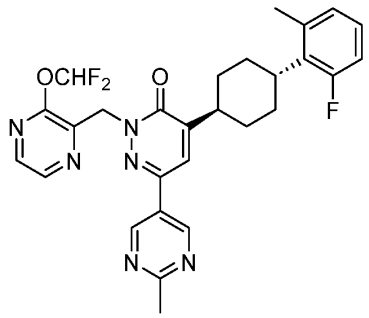
[00444] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl) oxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-

((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylate (90.0 mg, 0.154 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)oxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70 mg, 83%) as a colorless oil. MS *m/z*: 543 $[M+H]^+$.

[00445] Step 4: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-(5-(hydroxymethyl)oxazol-4-yl)-2-((3-(trifluoromethyl)pyridine-2-yl)methyl)pyridazin-3(2*H*)-one (70.0 mg, 0.129 mmol, 1.0 equiv) as the starting material to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carbaldehyde (50 mg, 71%) as a white solid. MS *m/z*: 541 $[M+H]^+$.

[00446] Step 5: 6-(5-(difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carbaldehyde (50 mg, 0.093 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.1 mg, 57.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 – 8.69 (m, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 0.9 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.07 – 6.99 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.75 (s, 2H), 3.11 (t, *J* = 12.2 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 11.6 Hz, 4H), 1.87 – 1.83 (m, 2H), 1.55 (t, *J* = 12.0 Hz, 2H). MS *m/z*: 563.00 $[M+H]^+$.

2-((3-(Difluoromethoxy)pyrazin-2-yl)methyl)-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one (63)



[00447] Step 1: 2-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazine: To a stirred solution of 3-methylpyrazin-2-ol (5.00 g, 45.4 mmol, 1.0 equiv) and DHP (11.4 g, 136 mmol, 3.0 equiv) in DCM (25 mL) was added PTSA (0.780 g, 4.54 mmol, 0.1 equiv). The reaction was stirred for overnight at room temperature. The reaction was monitored by LCMS. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:10) to afford 2-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazine (2.50 g, 28%) as a light brown oil. MS *m/z*: 195 $[M+H]^+$.

[00448] Step 2: 2-(bromomethyl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazine: Followed the general procedure T using 2-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin (2.50 g, 12.8 mmol, 1.0 equiv) as the starting material to give 2-(bromomethyl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazine (360 mg, 10%) as a light green oil. MS *m/z*: 273 $[M+H]^+$.

[00449] Step 3: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 2-(bromomethyl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazine (360 mg, 1.31 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (338 mg, 1.05 mmol, 0.8 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (380 mg, 56%) as a colorless oil. MS *m/z*: 513.

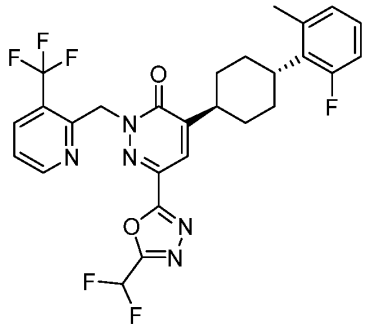
[00450] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (380 mg, 0.741 mmol, 1.0 equiv) and (2-methylpyrimidin-5-yl)boronic acid (122 mg, 0.889 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (320 mg, 75%) as a light brown oil. MS *m/z*: 571 $[M+H]^+$.

[00451] Step 5: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: A solution of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)-2-((3-((tetrahydro-2*H*-pyran-2-yl)oxy)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (320 mg, 0.561 mmol, 1.0 equiv) in DCM (2 mL) was added CF_3COOH (2 mL) at 0 °C. The reaction was stirred for 2 h at room temperature. The reaction was monitored by LCMS. The resulting

mixture was concentrated under reduced pressure to afford the crude product 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-hydroxypyrazin-2-yl)methyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one (300 mg) as a light brown oil. MS *m/z*: 487 $[M+H]^+$.

[00452] Step 6: 2-((3-(difluoromethoxy)pyrazin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one: Followed the general procedure F using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-hydroxypyrazin-2-yl)methyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one (300 mg, 0.617 mmol, 1.0 equiv) and methyl 2-chloro-2,2-difluoroacetate (106 mg, 0.740 mmol, 1.2 equiv) as the starting materials to give 2-((3-(difluoromethoxy)pyrazin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-methylpyrimidin-5-yl)pyridazin-3(2*H*)-one (5.5 mg, 1.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.09 (s, 2H), 8.27 (d, *J* = 2.7 Hz, 1H), 8.08 (d, *J* = 2.7 Hz, 1H), 7.66 – 7.45 (m, 2H), 7.08 – 7.02 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.65 (s, 2H), 3.12 (t, *J* = 12.0 Hz, 1H), 2.93 – 2.87 (m, 4H), 2.37 (s, 3H), 2.13 (d, *J* = 12.5 Hz, 4H), 1.89 (s, 2H), 1.53 (d, *J* = 12.4 Hz, 2H). MS *m/z*: 537.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (64)



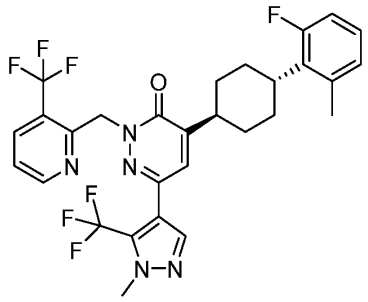
[00453] Step 1: ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (120 mg, 0.250 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 61%) as a white solid. MS *m/z*: 518 $[M+H]^+$.

[00454] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80.0 mg, 0.155 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60 mg, 77%) as a white solid. MS *m/z*: 504 $[M+H]^+$.

[00455] Step 3: *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60.0 mg, 0.119 mmol, 1.0 equiv) as the starting materials to give *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg, 57%) as a white solid. MS *m/z*: 582 $[M+H]^+$.

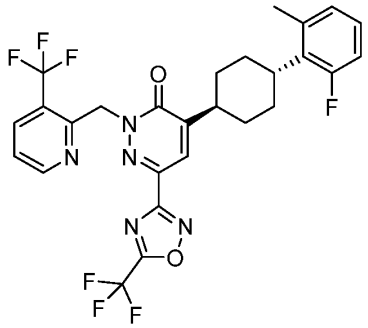
[00456] Step 4: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure P using *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg, 0.069 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.6 mg, 12.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.95 (s, 1H), 7.39 (s, 1H), 7.08 – 6.92 (m, 2H), 6.92 – 6.76 (m, 2H), 5.81 (s, 2H), 3.09 (t, *J* = 12 Hz, 1H), 2.87 (t, *J* = 12.1 Hz, 1H), 2.36 (s, 3H), 2.13 (d, *J* = 12.2 Hz, 4H), 1.86 (d, *J* = 12.6 Hz, 2H), 1.56 – 1.47 (m, 2H). MS *m/z*: 564.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (65)



[00457] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (32.0 mg, 0.114 mmol, 1.1 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (41.3 mg, 66.1%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.9 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.45-7.33 (m, 1H), 7.18 (s, 1H), 7.09-6.98 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.74 (s, 2H), 4.05 (s, 3H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.1 Hz, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 11.5 Hz, 4H), 1.88-1.76 (m, 2H), 1.58-1.38 (m, 2H). MS *m/z*: 594.00 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (66)



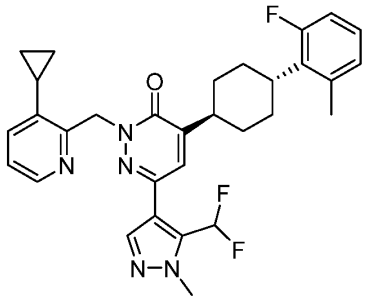
[00458] Step 1: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the

general procedure W using 6-chloro-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (80.0 mg, 0.167 mmol, 1.0 equiv) as the starting material to afford 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 61%) as a white solid. MS m/z: 471 [M+H]+.

[00459] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (50.0 mg, 0.106 mmol, 1.0 equiv) as the starting material to afford 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (35 mg, 65%) as a white solid. MS m/z: 504 [M+H]+.

[00460] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure Y using 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (30 mg, 0.06 mmol, 1.0 equiv) as the starting material to afford 4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (28.6 mg, 82.6%) as a white solid. 1H NMR (400 MHz, Chloroform-d) δ 8.58 (d, J = 4.7 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 0.9 Hz, 1H), 7.34 (dd, J = 7.8, 4.6 Hz, 1H), 7.04 (td, J = 7.9, 5.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.84 (dd, J = 11.8, 8.1 Hz, 1H), 5.84 (s, 2H), 3.09 (t, J = 12.1 Hz, 1H), 2.90 (t, J = 12.1 Hz, 1H), 2.36 (s, 3H), 2.14 (d, J = 12.1 Hz, 4H), 1.86 (d, J = 12.6 Hz, 2H), 1.55 (t, J = 12.5 Hz, 2H). MS m/z: 582.05 [M+H]+.

2-((3-Cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (67)

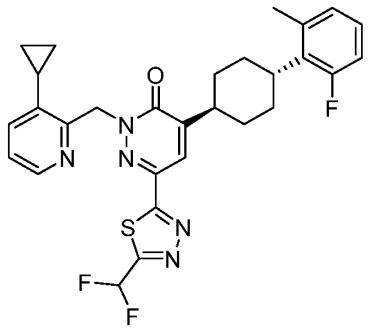


[00461] Step 1: (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) -6-oxo-1,6-dihydropyridazin-3-yl)boronic acid*:* Followed the general procedure G using 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r)*-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.111 mmol, 1.0 equiv) as the starting material to give (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 462 $[M+H]^+$.

[00462] Step 2: 4-(1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.111 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (24.8 mg, 0.133 mmol, 1.2 equiv) as the starting materials to give 4-(1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (30 mg, 52%) as a pink solid. MS *m/z*: 526 $[M+H]^+$.

[00463] Step 3: 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (30 mg, 0.057 mmol, 1.0 equiv) as the starting material to give 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (29 mg, 92%) as a white solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.29 – 8.26 (m, 1H), 7.85 (d, J = 1.1 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.22 – 7.16 (m, 1H), 7.12 – 7.02 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 6.92 – 6.86 (m, 1H), 5.66 (s, 2H), 3.98 (s, 3H), 2.98 (d, J = 22.2 Hz, 2H), 2.38 (s, 3H), 2.09 (d, J = 7.5 Hz, 2H), 2.05 – 2.01 (m, 3H), 1.85 (d, J = 12.3 Hz, 2H), 1.61 (t, J = 12.5 Hz, 2H), 0.98 – 0.92 (m, 2H), 0.69 – 0.65 (m, 2H). MS *m/z*: 548.20 $[M+H]^+$.

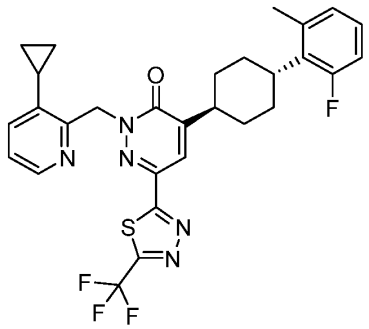
2-((3-Cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (68)



[00464] Step 1: (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) -6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.111 mmol, 1.0 equiv) as the starting material to give (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 462 $[M+H]^+$.

[00465] Step 2: 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.111 mmol, 1.0 equiv) and 2-chloro-5-(difluoromethyl)-1,3,4-thiadiazole (28.1 mg, 0.166 mmol, 1.5 equiv) as the starting materials to give 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (25.9 mg, 43.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 8.08 (s, 1H), 7.62 (s, 1H), 7.39 (s, 1H), 7.16 – 7.00 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.93 (s, 2H), 3.11 (t, *J* = 13.7 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.37 (s, 3H), 2.21 – 2.08 (m, 5H), 1.87 (d, *J* = 12.9 Hz, 2H), 1.53 – 1.49 (m, 2H), 1.11 (d, *J* = 8.0 Hz, 2H), 0.78 (d, *J* = 5.3 Hz, 2H). MS *m/z*: 552.10 $[M+H]^+$.

2-((3-Cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)pyridazin-3(2*H*)-one (69)

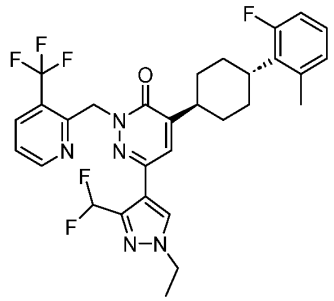


[00466] Step 1: 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (150 mg, 0.468 mmol, 1.0 equiv) and 2-(chloromethyl)-3-cyclopropylpyridine (94.0 mg, 0.562 mmol, 1.2 equiv) as the starting materials to give 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) pyridazin-3(2*H*)-one (150 mg, 70%) as a pink solid. MS *m/z*: 452 $[M+H]^+$.

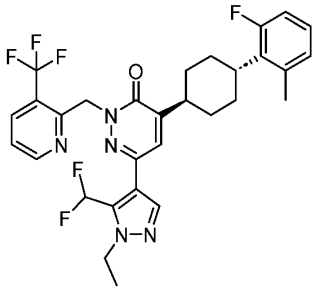
[00467] Step 2: (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl) -6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.111 mmol, 1.0 equiv) as the starting material to give (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 462 $[M+H]^+$.

[00468] Step 3: 6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.111 mmol, 1.0 equiv) and 2-chloro-5-(trifluoromethyl)-1,3,4-thiadiazole (31.3 mg, 0.166 mmol, 1.5 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl) pyridazin-3(2*H*)-one (16.1 mg, 25.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.21 (m, 1H), 8.08 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.14 – 7.08 (m, 1H), 7.01 – 6.91 (m, 2H), 5.71 (s, 2H), 3.05 – 2.85 (m, 2H), 2.37 (s, 3H), 2.12 – 2.07 (m, 1H), 1.96 (d, *J* = 11.9 Hz, 4H), 1.81 (d, *J* = 12.0 Hz, 2H), 1.66 (d, *J* = 12.3 Hz, 2H), 1.04 – 0.97 (m, 2H), 0.78 – 0.72 (m, 2H). MS *m/z*: 570.20 $[M+H]^+$.

6-(3-(Difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70A)



6-(5-(Difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70B)



[00469] Step 1: 4-bromo-5-(difluoromethyl)-1-ethyl-1*H*-pyrazole: To a stirred mixture of 4-bromo-5-(difluoromethyl)-1*H*-pyrazole (100 mg, 0.508 mmol, 1.0 equiv) and DIPEA (196 mg, 1.52 mmol, 3.0 equiv) in DMF (2 mL) was added ethyl iodide (87.1 mg, 0.559 mmol, 1.1 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. MS *m/z*: 225 $[M+H]^+$.

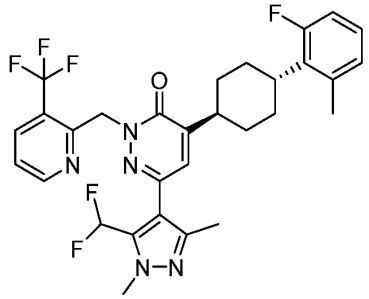
[00470] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00471] Step 3: 6-(5-(difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-ethyl-1*H*-pyrazole (46.9 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8.7 mg, 14%) as a white solid and 6-(3-(difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10 mg, 16%) as a white solid.

[00472] 6-(3-(Difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70A) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 7.13 – 6.96 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.70 (s, 2H), 4.43 – 4.33 (m, 2H), 3.10 (t, *J* = 11.9 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.37 (s, 3H), 2.23 – 2.09 (m, 4H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.49 (t, *J* = 14.4 Hz, 5H). MS *m/z*: 590.20 $[M+H]^+$.

[00473] 6-(5-(Difluoromethyl)-1-ethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70B) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.77 (s, 1H), 7.41 (s, 1H), 7.36 (s, 1H), 7.09 – 6.79 (m, 4H), 5.71 (s, 2H), 4.28 – 4.15 (m, 2H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 12 Hz, 1H), 2.35 (d, *J* = 8.1 Hz, 3H), 2.13 (s, 4H), 1.86 (s, 2H), 1.53 (t, *J* = 7.3 Hz, 5H). MS *m/z*: 590.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (71)



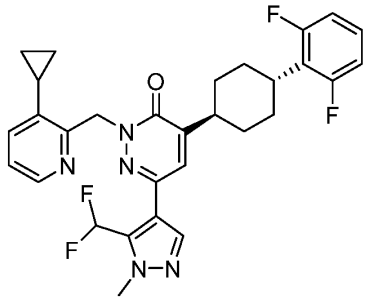
[00474] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60.0 mg, 0.125 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00475] Step 2: 6-(5-chloropyrazin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using e(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.125 mmol, 1.0 equiv) and 4-bromo-1,3-dimethyl-1*H*-pyrazole-5-carbaldehyde (50.8 mg, 0.250 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1,3-dimethyl-1*H*-pyrazole-5-carbaldehyde (40 mg, 56%) as a white solid. MS *m/z*: 568 $[M+H]^+$.

[00476] Step 3: 6-(5-(difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1,3-dimethyl-1*H*-pyrazole-5-carbaldehyde (40 mg, 0.07 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (37.8 mg, 90.9%) as a white solid. ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 8.69 (d, *J* = 4.9 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.24 (d, *J* = 0.9 Hz, 1H), 7.09 – 6.96 (m, 1H), 6.93 – 6.71 (m, 3H), 5.73 (s, 2H), 3.99 (s, 3H), 3.08 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.37 (d, *J* = 7.6 Hz, 6H), 2.14 (t, *J* = 10.8 Hz, 4H), 1.83 (s, 2H), 1.52 – 1.40 (m, 2H). MS m/z: 590.25 $[M+H]^+$.

2-((3-Cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (72)



[00477] Step 1: 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (200 mg, 0.616 mmol, 1.0 equiv) and 2-(chloromethyl)-3-cyclopropylpyridine (113 mg, 0.678 mmol, 1.1 equiv) as the starting materials to give 6-chloro-2-((3-cyclopropylpyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 35%) as a white solid. MS *m/z*: 456 $[M+H]^+$.

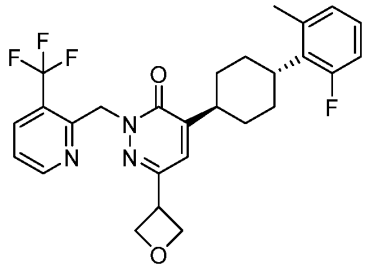
[00478] Step 2: (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.219 mmol, 1.0 equiv) as the starting material to give (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 466 $[M+H]^+$.

[00479] Step 3: 4-(1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.219 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (45.1 mg, 0.241 mmol, 1.1 equiv) as the starting materials to give 4-(1-((3-

cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (50 mg, 43%) as a white solid. MS *m/z*: 530 $[M+H]^+$.

[00480] Step 4: 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (50 mg, 0.094 mmol, 1.0 equiv) as the starting material to give 2-((3-cyclopropylpyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (23.8 mg, 43.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 – 8.39 (m, 1H), 7.68 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 1H), 7.18 – 7.06 (m, 1H), 6.96 (s, 1H), 6.83 (t, *J* = 8.6 Hz, 2H), 5.77 (s, 2H), 4.03 (s, 3H), 3.17 – 3.06 (m, 2H), 2.11 (d, *J* = 11.9 Hz, 4H), 2.04 – 1.99 (m, 1H), 1.94 – 1.87 (m, 2H), 1.55 – 1.44 (m, 2H), 1.25 (s, 1H), 1.02 – 0.93 (m, 2H), 0.71 – 0.62 (m, 2H). MS *m/z*: 552.20 $[M+H]^+$.

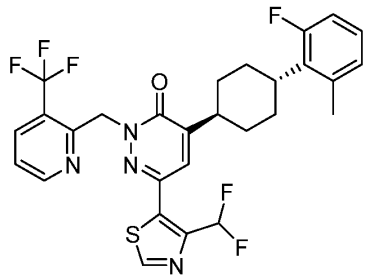
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (73)



[00481] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: A mixture of 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv), 3-iodooxetane (28.8 mg, 0.156 mmol, 1.5 equiv), 1,10-phenanthroline (1.9 mg, 0.015 mmol, 0.1 equiv), Mn (11.5 mg, 0.208 mmol, 2.0 equiv), sodium fluoroborate (5.7 mg, 0.052 mmol, 0.5 equiv) and (DME)$NiCl_2$ (2.5 mg, 0.015 mmol, 0.1 equiv) in MeOH (3 mL) was stirred for 4 h at 60 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (40 mL), extracted with EtOAc (3 x 40 mL). The combined organic layers

were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane/EA = 3/1) to afford 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.8 mg, 27.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, *J* = 4.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.54 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.41 (s, 1H), 7.10 (td, *J* = 7.9, 5.6 Hz, 1H), 7.04 – 6.89 (m, 2H), 5.53 (s, 2H), 4.84 (dd, *J* = 8.4, 5.9 Hz, 2H), 4.67 (t, *J* = 6.3 Hz, 2H), 4.23 (tt, *J* = 8.5, 6.6 Hz, 1H), 2.98 – 2.75 (m, 2H), 2.35 (s, 3H), 2.00 – 1.85 (m, 4H), 1.83 – 1.70 (m, 2H), 1.62 – 1.46 (m, 2H). MS *m/z*: 502.20 $[M+H]^+$.

6-(4-(Difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (74)



[00482] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00483] Step 2: methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and methyl 5-bromothiazole-4-carboxylate (92.3 mg, 0.416 mmol, 2.0 equiv) as the starting materials to give methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-

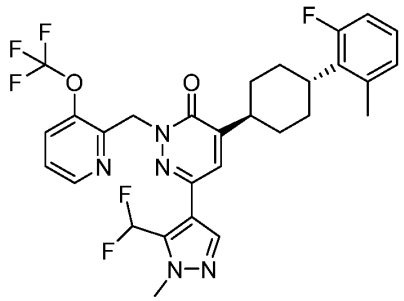
dihydropyridazin-3-yl)thiazole-4-carboxylate (90 mg, 87%) as a yellow oil. MS *m/z*: 587 $[M+H]^+$.

[00484] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)thiazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carboxylate (90.0 mg, 0.153 mmol, 1.0 equiv) and $NaBH_4$ (58.0 mg, 1.53 mmol, 10 equiv) as the starting materials to give the crude product 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)thiazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80 mg). MS *m/z*: 559 $[M+H]^+$.

[00485] Step 4: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)thiazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (115 mg, 0.206 mmol, 1.0 equiv) as the starting material, using DMP (873 mg, 2.06 mmol, 10 equiv) as the oxidant to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carbaldehyde (60 mg, 52%) as a yellow oil. MS *m/z*: 557 $[M+H]^+$.

[00486] Step 5: 6-(4-(difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)thiazole-4-carbaldehyde (50 mg, 0.09 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)thiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.3 mg, 61.7 %) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 8.03 – 8.01 (m, 1H), 7.46 (s, 1H), 7.38 – 7.35 (m, 1H), 7.11 – 6.97 (m, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.72 (s, 2H), 3.12 – 3.04 (m, 1H), 2.93 – 2.84 (m, 1H), 2.36 (s, 3H), 2.21 – 2.11 (m, 4H), 1.88 – 1.83 (m, 2H), 1.54 – 1.43 (m, 2H). MS *m/z*: 579.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (75)



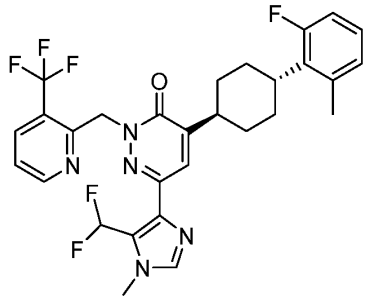
[00487] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy) pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.156 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (65.9 mg, 0.312 mmol, 2.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 64%) as a colorless oil. MS *m/z*: 496 $[M+H]^+$.

[00488] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy) pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.101 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 506 $[M+H]^+$.

[00489] Step 3: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy) pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl) boronic acid (crude, 0.101 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (37.8 mg, 0.202 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (30 mg, 53%) as a white solid. MS *m/z*: 570 $[M+H]^+$.

[00490] Step 4: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (30 mg, 0.053 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19.3 mg, 60.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.49 (s, 1H), 7.30 (d, *J* = 10.3 Hz, 1H), 7.18 (s, 1H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.81 (m, 1H), 5.71 (s, 2H), 4.06 (s, 3H), 3.08 (t, *J* = 11.9 Hz, 1H), 2.87 (d, *J* = 12.6 Hz, 1H), 2.36 (s, 3H), 2.20 – 2.09 (m, 4H), 1.85 (d, *J* = 12.6 Hz, 2H), 1.54 – 1.45 (m, 2H). MS *m/z*: 592.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (76)



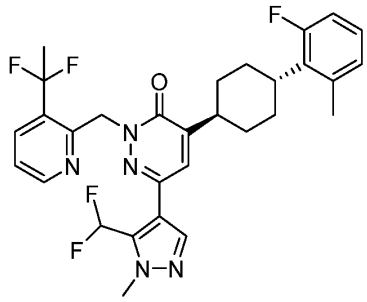
[00491] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60.0 mg, 0.125 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00492] Step 2: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde: Followed the general procedure H using e(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-

dihydropyridazin-3-yl)boronic acid (crude, 0.125 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde (47.3 mg, 0.250 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde (40 mg, 56%) as a white solid. MS *m/z*: 554 $[M+H]^+$.

[00493] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde (40 mg, 0.072 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23.9 mg, 57.5%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 8 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H), 7.92 (s, 1H), 7.59 (s, 1H), 7.38 – 7.31 (m, 1H), 7.18 (s, 1H), 7.06 – 7.00 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.69 (s, 2H), 3.85 (s, 3H), 3.17 – 3.06 (m, 1H), 2.87 (t, *J* = 12.5 Hz, 1H), 2.35 (s, 3H), 2.12 (t, *J* = 11.0 Hz, 4H), 1.83 (dd, *J* = 13.7, 3.7 Hz, 2H), 1.60 – 1.51 (m, 2H). MS m/z: 576.30 $[M+H]^+$.

2-((3-(1,1-Difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (77)



[00494] Step 1: 6-chloro-2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.156 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(1,1-difluoroethyl)pyridine (35.8 mg, 0.187 mmol, 1.2 equiv) as the starting materials to give 6-chloro-2-((3-(1,1-

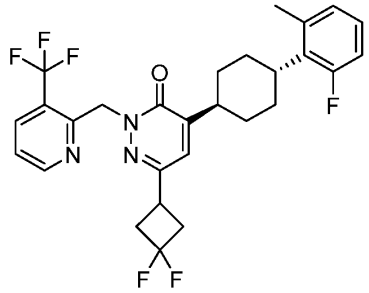
difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 53%) as a white solid. MS *m/z*: 476 $[M+H]^+$.

[00495] Step 2: (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 0.084 mmol, 1.0 equiv) as the starting material to give (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 486 $[M+H]^+$.

[00496] Step 3: 4-(1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.084 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (31.7 mg, 0.168 mmol, 2.0 equiv) as the starting materials to give 4-(1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (25 mg, 55%) as a white solid. MS *m/z*: 550 $[M+H]^+$.

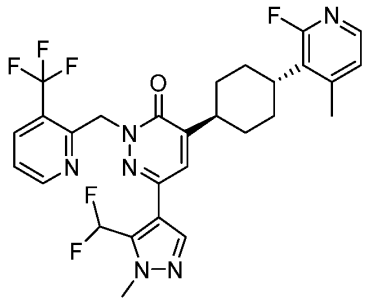
[00497] Step 4: 2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(1-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (25 mg, 0.045 mmol, 1.0 equiv) as the starting material to give 2-((3-(1,1-difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (9.5 mg, 36%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.72 (s, 1H), 7.33 – 7.28 (m, 2H), 7.17 – 6.99 (m, 2H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.81 (m, 1H), 5.63 (s, 2H), 4.07 (s, 3H), 3.13 – 3.03 (m, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.37 (s, 3H), 2.22 – 2.09 (m, 7H), 1.84 (d, *J* = 12.7 Hz, 2H), 1.51 – 1.43 (m, 2H). MS *m/z*: 572.25 $[M+H]^+$.

6-(3,3-Difluorocyclobutyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (78)



[00498] Step 1: 6-(3,3-difluorocyclobutyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: A mixture of 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv), 3-bromo-1,1-difluorocyclobutane (26.7 mg, 0.156 mmol, 1.5 equiv), 1,10-phenanthroline (1.9 mg, 0.01 mmol, 0.1 equiv), Mn (11.5 mg, 0.208 mmol, 2.0 equiv), sodium fluoroborate (5.7 mg, 0.052 mmol, 0.5 equiv) and (DME)$NiCl_2$ (2.3 mg, 0.01 mmol, 0.1 equiv) in MeOH (3 mL) was stirred for 4 h at 60 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (40 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane/EA = 3/1) to afford 6-(3,3-difluorocyclobutyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (24.9 mg, 43.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.70 (s, 2H), 3.29 (tt, *J* = 9.0, 4.5 Hz, 1H), 3.02 (t, *J* = 12.0 Hz, 1H), 2.95 – 2.75 (m, 5H), 2.35 (s, 3H), 2.20 – 2.09 (m, 4H), 1.82 (d, *J* = 12.7 Hz, 2H), 1.52 – 1.37 (m, 2H). MS *m/z*: 536.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (79)



[00499] Step 1: ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate: Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (3.54 g, 12.6 mmol, 1.2 equiv) and 3-bromo-2-fluoro-4-methylpyridine (2.00 g, 10.5 mmol, 1.0 equiv) as the starting materials to give ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate (1.7 g, 61%) as a yellow oil. MS *m/z*: 264 $[M+H]^+$.

[00500] Step 2: ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate (1.70 g, 6.45 mmol, 1.0 equiv) as the starting material to give ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (1.08 g, 63%) as a colorless oil. MS *m/z*: 266 $[M+H]^+$.

[00501] Step 3: 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (1.08 g, 4.07 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid (1.0 g). MS *m/z*: 238 $[M+H]^+$.

[00502] Step 4: 3,6-dichloro-4-(4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazine: Followed the general procedure D using 4-(2-fluoro-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid (1.00 g, 4.21 mmol, 1.0 equiv) and 3,6-dichloropyridazine (0.750 g, 5.05 mmol, 1.2 equiv) as the starting materials to give 3,6-dichloro-4-(4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazine (1.0 g, 69%) as a white solid. MS *m/z*: 340 $[M+H]^+$.

[00503] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E using 3,6-dichloro-4-(4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazine (1.00 g, 2.93 mmol, 1.0 equiv) as the starting material to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 10%) as a yellow oil. MS *m/z*: 322 $[M+H]^+$.

[00504] Step 6: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (80.0 mg, 0.249 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (115 mg, 0.498 mmol, 2.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (90 mg, 75%) as a white solid. MS *m/z*: 481 $[M+H]^+$.

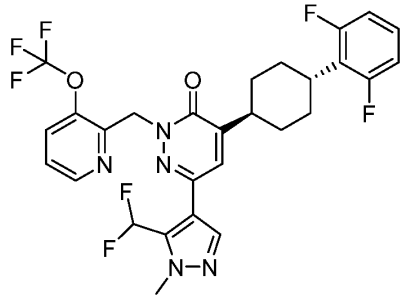
[00505] Step 7: (5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 491 $[M+H]^+$.

[00506] Step 8: 4-(5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (78.6 mg, 0.416 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (68 mg, 60%) as a yellow solid. MS *m/z*: 555 $[M+H]^+$.

[00507] Step 9: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (65.0 mg, 0.117 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.2 mg, 44.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.66 (m, 1H), 8.04 – 8.02 (m, 1H), 7.91 – 7.89 (m, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.29 (d, *J* = 0.8 Hz, 1H), 7.21 – 6.94 (m, 2H), 5.69 (s, 2H), 4.06 (s, 3H), 3.12 – 3.04 (m, 1H),

2.94 – 2.86 (m, 1H), 2.40 (s, 3H), 2.18 – 2.08 (m, 4H), 1.85 – 1.80 (m, 2H), 1.60 – 1.49 (m, 2H). MS *m/z*: 577.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80)



[00508] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.308 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (65.1 mg, 0.308 mmol, 1.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80 mg, 51%) as a white solid. MS *m/z*: 456 $[M+H]^+$.

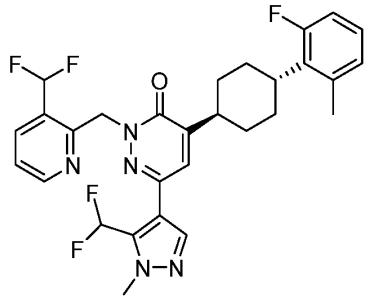
[00509] Step 2: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80.0 mg, 0.157 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 510 $[M+H]^+$.

[00510] Step 3: 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (1-((3-cyclopropylpyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.157 mmol, 1.1 equiv) and 4-bromo-1-methyl-1H-pyrazole-5-carbaldehyde (32.6 mg, 0.173 mmol, 1.1 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-

dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 22%) as a white solid. MS *m/z*: 574 $[M+H]^+$.

[00511] Step 4: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 0.035 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9.4 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 7.71 (d, *J* = 9.6 Hz, 2H), 7.41 (s, 1H), 7.27 (s, 1H), 7.18 – 7.02 (m, 2H), 6.83 (t, *J* = 8.6 Hz, 2H), 5.66 (s, 2H), 4.07 (d, *J* = 9.4 Hz, 3H), 3.09 (t, *J* = 11.7 Hz, 2H), 2.11 (d, *J* = 12.0 Hz, 4H), 1.92 (s, 2H), 1.50 (q, *J* = 12.9, 12.2 Hz, 2H). MS *m/z*: 596.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(difluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (81)



[00512] Step 1: 3-(difluoromethyl)-2-methylpyridine*:* Followed the general procedure I using 2-methylnicotinaldehyde (500 mg, 4.12 mmol, 1.0 equiv) as the starting material to give 3-(difluoromethyl)-2-methylpyridine (200 mg, 33%) as a light yellow oil. MS *m/z*: 144 $[M+H]^+$.

[00513] Step 2: 2-(bromomethyl)-3-(difluoromethyl)pyridine hydrochloride: Followed the general procedure T using 3-(difluoromethyl)-2-methylpyridine (500 mg, 3.49 mmol, 1.0 equiv) as the starting material to give 2-(bromomethyl)-3-(difluoromethyl)pyridine hydrochloride (160 mg, 20%) as a light yellow oil. MS *m/z*: 258 $[M+H]^+$.

[00514] Step 3: 6-chloro-2-((3-(difluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (100 mg,

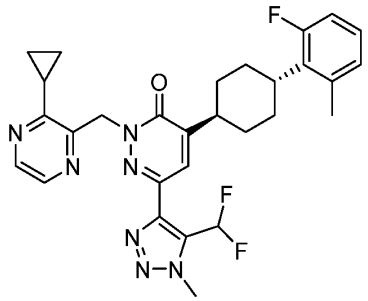
0.312 mmol, 1.0 equiv) and 2-(bromomethyl)-3-(difluoromethyl)pyridine hydrochloride (138 mg, 0.624 mmol, 2.0 equiv) as the starting materials to give 6-chloro-2-((3-(difluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 27%) as a white solid. MS *m/z*: 462 $[M+H]^+$.

[00515] Step 4: (1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(difluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 0.087 mmol, 1.0 equiv) as the starting material to give (1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 472 $[M+H]^+$.

[00516] Step 5: 4-(1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.087 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (32.8 mg, 0.174 mmol, 2.0 equiv) as the starting materials to give 4-(1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 44%) as a colorless oil. MS *m/z*: 536 $[M+H]^+$.

[00517] Step 6: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(difluoromethyl)pyridin-2-yl) methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(1-((3-(difluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 0.037 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(difluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (4.3 mg, 20%) as a white solid. 1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.71 (s, 1H), 7.42 (d, *J* = 26.0 Hz, 3H), 7.21 (s, 1H), 7.08 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.81 (m, 1H), 5.62 (s, 2H), 4.08 (s, 3H), 3.05 (t, *J* = 12.0 Hz, 1H), 2.87 (d, *J* = 12.8 Hz, 1H), 2.36 (s, 3H), 2.23 – 1.99 (m, 4H), 1.85 (d, *J* = 13.3 Hz, 2H), 1.47 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 598.05 $[M+H]^+$.

2-((3-Cyclopropylpyrazin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1r,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (82)



[00518] Step 1: (3-cyclopropylpyrazin-2-yl)methanol: Followed the general procedure A using (3-chloropyrazin-2-yl)methanol (500 mg, 3.45 mmol, 1.0 equiv) and cyclopropylboronic acid (594 mg, 6.91 mmol, 2.0 equiv) as the starting materials to give (3-cyclopropylpyrazin-2-yl)methanol (280 mg, 53%) as a light brown oil. MS *m/z*: 151.

[00519] Step 2: 2-(chloromethyl)-3-cyclopropylpyrazine: Followed the general procedure Q using (3-cyclopropylpyrazin-2-yl)methanol (220 mg, 1.46 mmol, 1.0 equiv) as the starting material to give the crude product 2-(chloromethyl)-3-cyclopropylpyrazine (180 mg) as a colorless oil. MS *m/z*: 387 $[M+H]^+$.

[00520] Step 3: 6-chloro-2-((3-cyclopropylpyrazin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 2-(chloromethyl)-3-cyclopropylpyrazine (180 mg, 1.06 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (339 mg, 1.06 mmol, 1.0 equiv) as the starting materials to give 6-chloro-2-((3-cyclopropylpyrazin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (110 mg, 22%) as a colorless oil. MS *m/z*: 453 $[M+H]^+$.

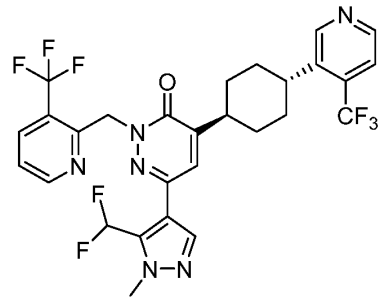
[00521] Step 4: (1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-cyclopropylpyrazin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.221 mmol, 1.0 equiv) as the starting material to give (1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 463 $[M+H]^+$.

[00522] Step 5: 4-(1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-

carbaldehyde: Followed the general procedure H using (1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.221 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (83.9 mg, 0.442 mmol, 2.0 equiv) as the starting materials to give 4-(1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (58 mg, 57%) as a light brown oil. MS *m/z*: 528 $[M+H]^+$.

[00523] Step 6: 2-((3-cyclopropylpyrazin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(1-((3-cyclopropylpyrazin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (50 mg, 0.095 mmol, 1.0 equiv) as the starting material to give 2-((3-cyclopropylpyrazin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (14.6 mg, 27.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 2.6 Hz, 1H), 8.28 (d, J = 2.6 Hz, 1H), 7.94 – 7.90 (m, 1H), 7.42 (t, J = 51.9 Hz, 1H), 7.14 – 7.08 (m, 1H), 7.02 – 6.94 (m, 2H), 5.76 (s, 2H), 4.22 (s, 3H), 2.94 (d, J = 13.8 Hz, 2H), 2.42 – 2.22 (m, 5H), 2.00 – 1.93 (m, 3H), 1.80 (d, J = 11.4 Hz, 2H), 1.62 (t, J = 12.3 Hz, 2H), 1.05 – 0.99 (m, 4H). MS *m/z*: 550.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (83)



[00524] Step 1: ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate : Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (2.00 g, 7.13 mmol, 1.0 equiv) and 3-bromo-4-(trifluoromethyl)pyridine (1.93 g, 8.56 mmol, 1.2 equiv) as the starting materials to give ethyl

4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate (760 mg, 35%) as a light brown oil. MS *m/z*: 300 $[M+H]^+$.

[00525] Step 2: ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohex-3-ene-1-carboxylate (1.85 g, 6.18 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate (890 mg) as a colorless oil. MS *m/z*: 302 $[M+H]^+$.

[00526] Step 3: 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid : Followed the general procedure C using ethyl 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylate (890 mg, 2.95 mmol, 1.0 equiv) as the starting material to give 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid (100 mg, 92%) as a colorless oil. MS *m/z*: 274 $[M+H]^+$

[00527] Step 4: 3,6-dichloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine: Followed the general procedure D using 4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexane-1-carboxylic acid (770 mg, 2.81 mmol, 1.0 equiv) and 3,6-dichloropyridazine (461 mg, 3.10 mmol, 1.1 equiv) as the starting materials to give 3,6-dichloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine (280 mg, 26%) as an off-white solid. MS *m/z*: 376 $[M+H]^+$.

[00528] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E using 3,6-dichloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazine (280 mg, 0.744 mmol, 1.0 equiv) as the starting material to give 6-chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (60 mg, 22%) as a white solid. MS *m/z*: 358 $[M+H]^+$

[00529] Step 6: 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (60.0 mg, 0.168 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (39.3 mg, 0.202 mmol, 1.2 equiv) as the starting materials to give 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (65 mg, 74%) as a white solid. MS *m/z*: 517 $[M+H]^+$.

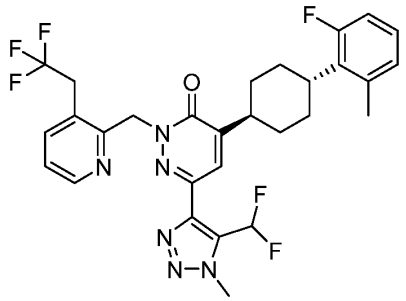
[00530] Step 7: (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-

((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (65.0 mg, 0.126 mmol, 1.0 equiv) as the starting material to give (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 527 $[M+H]^+$.

[00531] Step 8: 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure H using (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.126 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-pyrazole-5-carbaldehyde (28.4 mg, 0.151 mmol, 1.2 equiv) as the starting materials to give 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (45 mg, 61%) as a white solid. MS *m/z*: 591 $[M+H]^+$.

[00532] Step 9: 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (40 mg, 0.068 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (20.4 mg, 48.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 8.69 – 8.62 (m, 2H), 8.04 – 7.99 (m, 1H), 7.73 (s, 1H), 7.62 (d, *J* = 5.0 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 5.69 (s, 2H), 4.06 (s, 3H), 3.10 (d, *J* = 15.5 Hz, 2H), 2.20 (d, *J* = 13.0 Hz, 2H), 2.04 (s, 2H), 1.81 (d, *J* = 12.3 Hz, 2H), 1.59 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 613.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (84)



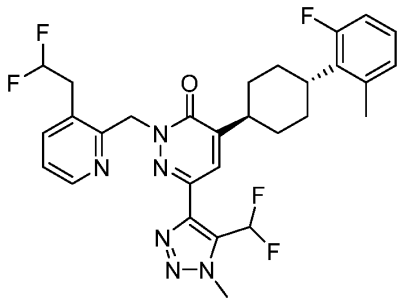
[00533] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (150 mg, 0.469 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(2,2,2-trifluoroethyl)pyridine (126 mg, 0.601 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (202 mg, 81%). MS *m/z*: 494 $[M+H]^+$.

[00534] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general Procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60.0 mg, 0.121 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 504 $[M+H]^+$.

[00535] Step 3: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general Procedure H using methyl (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.121 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (27.4 mg, 0.145 mmol, 1.2 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (55 mg, 80%). MS *m/z*: 569 $[M+H]^+$.

[00536] Step 4: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (30 mg, 0.053 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (7.0 mg, 22%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.97 (d, *J* = 0.9 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 12.0 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.08 – 6.98 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.57 (s, 2H), 4.27 (s, 3H), 3.77 (q, *J* = 10.5 Hz, 2H), 3.09 (t, *J* = 12.2 Hz, 1H), 2.87 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.24 – 2.02 (m, 4H), 1.84 (d, *J* = 13.1 Hz, 2H), 1.55-1.49 (m, 2H). MS *m/z*: 591.15 $[M+H]^+$.

2-((3-(2,2-Difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (85)



[00537] Step 1: 6-chloro-2-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general Procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*) -one (121 mg, 0.380 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(2,2-difluoroethyl)pyridine (80.0 mg, 0.418 mmol, 1.1 equiv) as the starting materials to give 6-chloro-2-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (126 mg, 69%). MS *m/z*: 476 $[M+H]^+$.

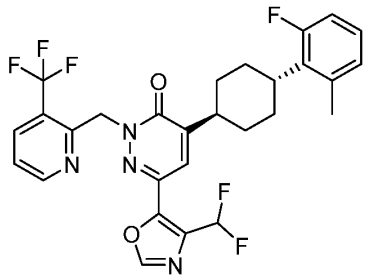
[00538] Step 2: (1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general Procedure G using 6-chloro-2-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-

4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (60.0 mg, 0.126 mmol, 1.0 equiv) as the starting material to give (1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 486 $[M+H]^+$.

[00539] Step 3: 4-(1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general Procedure H using (1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.126 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (26.0 mg, 0.139 mmol, 1.1 equiv) as the starting materials to give 4-(1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (50 mg, 72%). MS *m/z*: 551 $[M+H]^+$.

[00540] Step 4: 2-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-on: Followed the general Procedure I using 4-(1-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (30 mg, 0.054 mmol, 1.0 equiv) as the starting material to give 2-((3-(2,2-difluoroethyl)pyridin-2-yl)methyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (9.9 mg, 31%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 3.8 Hz, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.52-7.31 (m, 2H), 7.13-6.98 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 11.8, 8.2 Hz, 1H), 6.02 (tt, *J* = 56.0, 3.8 Hz, 1H), 5.62 (s, 2H), 4.26 (s, 3H), 3.45 (td, *J* = 17.7, 3.8 Hz, 2H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.24-2.04 (m, 4H), 1.94-1.80 (m, 2H), 1.55-1.50 (m, 2H). MS *m/z*: 573.2 $[M+H]^+$.

6-(4-(Difluoromethyl)oxazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (86)



[00541] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00542] Step 2: ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and ethyl 5-bromooxazole-4-carboxylate (90.2 mg, 0.416 mmol, 2.0 equiv) as the starting materials to give ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate (100 mg, 83%) as a white solid. MS *m/z*: 585 $[M+H]^+$.

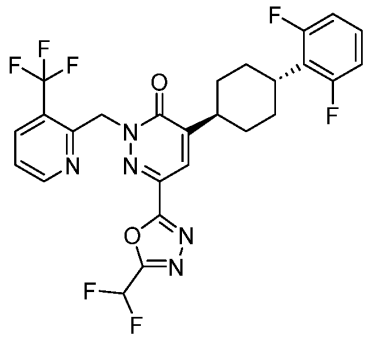
[00543] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)oxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate (100 mg, 0.171 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)oxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 43%) as a white solid. MS *m/z*: 543 $[M+H]^+$.

[00544] Step 4: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-

6-(4-(hydroxymethyl)oxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.074 mmol, 1.0 equiv) as the starting material to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde (25 mg, 62%) as a white solid. MS *m/z*: 541 $[M+H]^+$.

[00545] Step 5: 6-(4-(difluoromethyl)oxazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde (25 mg, 0.04 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)oxazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (7.8 mg, 30%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.9 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H), 7.53 (s, 1H), 7.38 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.05 (td, *J* = 7.8, 5.4 Hz, 1H), 6.94 – 6.71 (m, 3H), 5.72 (s, 2H), 3.11 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.6 Hz, 1H), 2.36 (s, 3H), 2.14 (t, *J* = 12.3 Hz, 4H), 1.86 (d, *J* = 12.3 Hz, 2H), 1.49 (s, 2H). MS m/z: 563.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (87)



[00546] Step 1: ethyl 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (90.0 mg, 0.186 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-

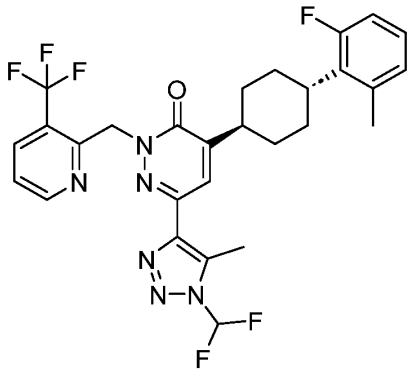
((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (58 mg, 59%) as a white solid. MS *m/z*: 522 $[M+H]^+$.

[00547] Step 2: 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide. Followed the general procedure N using ethyl 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (58.0 mg, 0.111 mmol, 1.0 equiv) as the starting material to give the crude product 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg) as a white solid. MS *m/z*: 508 $[M+H]^+$.

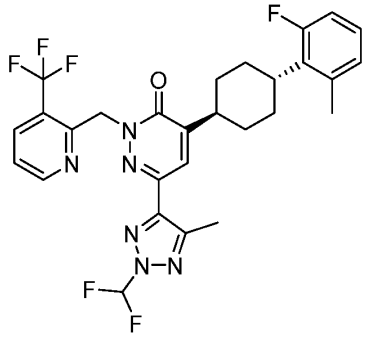
[00548] Step 3: N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 0.099 mmol, 1.0 equiv) as the starting material to give N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (30 mg, 52%) as a white solid. MS *m/z*: 586 $[M+H]^+$.

[00549] Step 4: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure P using N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (30 mg, 0.051 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.9 mg, 50.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.9 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.94 (s, 1H), 7.38 – 7.30 (m, 1H), 7.18 – 7.06 (m, 1H), 6.91 – 6.75 (m, 3H), 5.80 (s, 2H), 3.12 (t, *J* = 6.1 Hz, 1H), 3.08 (s, 1H), 2.09 (d, *J* = 14.3 Hz, 4H), 1.96 – 1.87 (m, 2H), 1.54 (d, *J* = 10.8 Hz, 2H). MS *m/z*: 568.20 $[M+H]^+$.

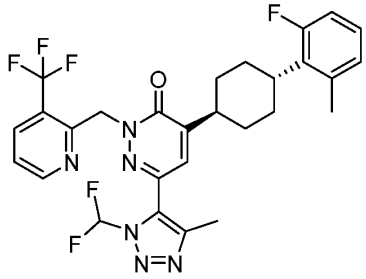
6-(1-(Difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88A)



6-(2-(Difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88B)



6-(1-(Difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88C)



[00550] Step 1: 5-bromo-1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazole: Followed the general procedure F using 5-bromo-4-methyl-1*H*-1,2,3-triazole (500 mg, 3.08 mmol, 1.0 equiv) and chlorodifluoromethane (800 mg, 9.26 mmol, 3.0 equiv) as the starting materials to give 5-bromo-1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazole (350 mg, 53%) as a colorless liquid. MS *m/z*: 212 $[M+H]^+$.

[00551] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydro- pyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

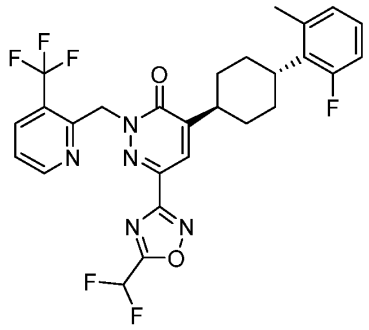
[00552] Step 3: 6-(1-(difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one : Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl) boronic acid (crude, 0.208 mmol, 1.0 equiv) and 5-bromo-1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazole (88.3 mg, 0.416 mmol, 2.0 equiv) as the starting materials to give 6-(1-(difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12.6 mg, 10.3%) as a white solid, 6-(2-(difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.7 mg, 12.1%) as a white solid and 6-(1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (7.3 mg, 6.0%) as a white solid.

[00553] 6-(1-(Difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88A) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 – 8.63 (m, 1H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 57.8 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.07 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.81 (m, 1H), 5.72 (s, 2H), 3.20 – 3.09 (m, 1H), 2.95 – 2.83 (m, 1H), 2.57 (s, 3H), 2.37 (s, 3H), 2.23 – 2.09 (m, 4H), 2.01 (s, 1H), 1.89 – 1.81 (m, 2H), 1.53 (s, 1H). MS *m/z*: 577.30 $[M+H]^+$.

[00554] 6-(2-(Difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88B) ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.65 – 8.59 (m, 1H), 8.14 – 8.08 (m, 1H), 7.79 – 7.65 (m, 1H), 7.53 – 7.37 (m, 2H), 7.13 – 7.04 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.93 – 6.85 (m, 1H), 5.68 (s, 2H), 3.04 – 2.93 (m, 2H), 2.38 (s, 3H), 2.29 (s, 3H), 2.09 (d, *J* = 12.9 Hz, 1H), 2.06 – 1.99 (m, 3H), 1.88 – 1.81 (m, 2H), 1.64 – 1.52 (m, 2H). MS *m/z*: 577.15 $[M+H]^+$.

[00555] **6-(1-(Difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (88C)** ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.64 – 8.60 (m, 1H), 8.15 – 8.10 (m, 1H), 7.72 (t, J = 57.7 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.11 – 7.05 (m, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 – 6.84 (m, 1H), 5.68 (s, 2H), 2.97 (t, J = 13.5 Hz, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 2.13 – 2.07 (m, 1H), 2.05 – 1.99 (m, 3H), 1.88 – 1.80 (m, 2H), 1.63 – 1.49 (m, 2H). MS *m/z*: 577.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (89)



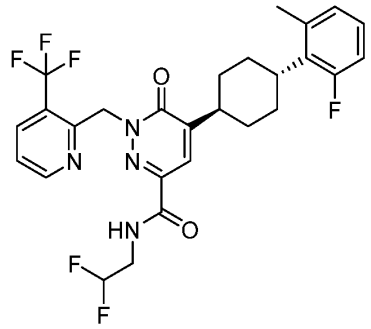
[00556] Step 1: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure W using 6-chloro-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (80.0 mg, 0.167 mmol, 1.0 equiv) as the starting material to afford 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 61%) as a white solid. MS m/z: 471 [M+H]+.

[00557] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (50.0 mg, 0.106 mmol, 1.0 equiv) as the starting material to afford 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (35 mg, 65%) as a white solid. MS m/z: 504 [M+H]+.

[00558] Step 3: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

Followed the general procedure Y using 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (30 mg, 0.060 mmol, 1.0 equiv) as the starting material to afford 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (15 mg, 44%) as a white solid. 1H NMR (400 MHz, Chloroform-d) δ 8.56 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.87 (s, 1H), 7.31 (dd, J = 7.9, 4.9 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.95 – 6.75 (m, 3H), 5.82 (s, 2H), 3.09 (t, J = 12.4 Hz, 1H), 2.89 (t, J = 12.4 Hz, 1H), 2.36 (s, 3H), 2.14 (d, J = 12.2 Hz, 4H), 1.90 – 1.82 (m, 2H), 1.54 (d, J = 12.9 Hz, 2H). MS m/z: 564.10 [M+H]+.

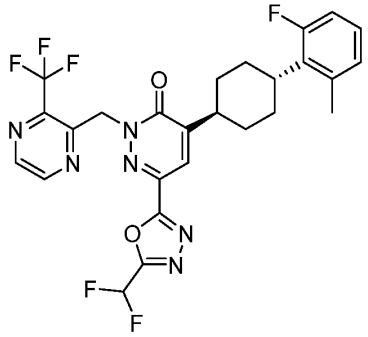
_N_-(2,2-Difluoroethyl)-5-((1_r_,4_r_)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluo-romethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (90)



[00559] Step 1: *N*-(2,2-difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide: To a stirred mixture of ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80.0 mg, 0.155 mmol, 1.0 equiv) and 2,2-difluoroethan-1-amine (25 mg, 0.31 mmol, 2.0 equiv) in EtOH (3 mL) at room temperature. The resulting mixture was stirred for 3 days at 80 °C under air atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane / EA = 2:1) to afford *N*-(2,2-difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (8.5 mg, 9.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.60 (m, 1H), 8.04 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.08 – 6.98 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.06 – 5.75 (m, 1H), 5.71 (s, 2H), 3.84 – 3.72

(m, 2H), 3.10 – 2.99 (m, 1H), 2.87 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.17 – 2.03 (m, 4H), 1.83 (d, *J* = 12.1 Hz, 2H), 1.56 – 1.44 (m, 2H).. MS *m/z*: 553.10[M+H]$^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (91)



[00560] Step 1: 2-(bromomethyl)-3-(trifluoromethyl)pyrazine: Followed the general procedure T using 2-methyl-3-(trifluoromethyl)pyrazine (500 mg, 3.07 mmol, 1.0 equiv) as the starting material to give 2-(bromomethyl)-3-(trifluoromethyl)pyrazine (220 mg, 29%) as a colorless oil. MS *m/z*: 241 [M+H]$^+$.

[00561] Step 2: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (133 mg, 0.25 mmol, 1.0 equiv) and 2-(bromomethyl)-3-(trifluoromethyl)pyrazine (100 mg, 0.415 mmol, 1.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (95 mg, 47%) as a white solid. MS *m/z*: 481 [M+H]$^+$.

[00562] Step 3: ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (95.0 mg, 0.197 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (75 mg, 73%) as a white solid. MS *m/z*: 519 [M+H]$^+$.

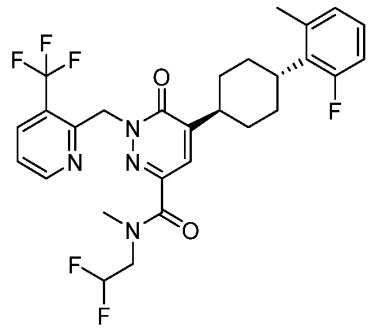
[00563] Step 4: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the

general procedure N using ethyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (75.0 mg, 0.144 mmol, 1.0 equiv) as the starting material to give the crude product 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60 mg) as a white solid. MS *m/z*: 505 $[M+H]^+$.

[00564] Step 5: *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60.0 mg, 0.118 mmol, 1.0 equiv) as the starting material to give *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 75%) as a white solid. MS *m/z*: 583 $[M+H]^+$.

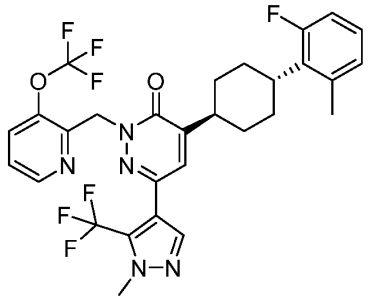
[00565] Step 6: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin -2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure P using *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 0.085 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (14.5 mg, 30.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (s, 2H), 7.96 (d, *J* = 0.9 Hz, 1H), 7.04 (td, *J* = 7.7, 5.5 Hz, 1H), 6.96 – 6.75 (m, 3H), 5.84 (d, *J* = 1.4 Hz, 2H), 3.13 – 3.03 (m, 1H), 2.94 – 2.85 (m, 1H), 2.37 (s, 3H), 2.13 (t, *J* = 11.2 Hz, 4H), 1.87 (dd, *J* = 14.1, 3.6 Hz, 2H), 1.52 (t, *J* = 12.1 Hz, 2H). MS m/z: 565.10 $[M+H]^+$.

_N_-(2,2-Difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-_N_-methyl-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (92)



[00566] Step 1: *N*-(2,2-difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-methyl-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide: Followed the general procedure F using *N*-(2,2-difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (30 mg, 0.054 mmol, 1.0 equiv) and MeI (15.4 mg, 0.108 mmol, 2.0 equiv) as the starting materials to give *N*-(2,2-difluoroethyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-methyl-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (9.1 mg, 29%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 – 8.58 (m, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 11.3 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.08 – 6.99 (m, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.21 – 5.93 (m, 1H), 5.69 (d, *J* = 10.5 Hz, 2H), 3.92 – 3.74 (m, 2H), 3.21 (d, *J* = 33.0 Hz, 3H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.86 (t, *J* = 12.3 Hz, 1H), 2.35 (s, 3H), 2.10 (t, *J* = 12.2 Hz, 4H), 1.83 (d, *J* = 13.0 Hz, 2H), 1.54 – 1.43 (m, 2H). MS *m/z*: 567.10[M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (93)

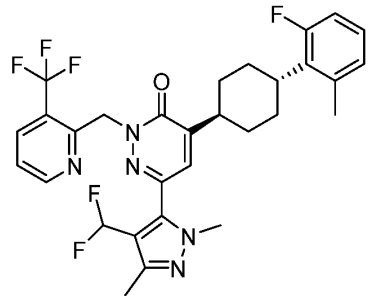


[00567] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one**:** Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (60.0 mg, 0.187 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (51.4 mg, 0.243 mmol, 1.3 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55 mg, 59%) as a brown solid. MS *m/z*: 496 [M+H]$^+$.

[00568] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one

(50.0 mg, 0.101 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (55.6 mg, 0.202 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (38.3 mg, 61.6%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (dd, J = 4.7, 8.0 Hz, 1H), 8.00 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.50 (q, J = 4.4 Hz, 2H), 7.08-7.13 (m, 1H), 7.04 – 6.90 (m, 2H), 5.50 (s, 2H), 4.01 (s, 3H), 2.88 (q, J = 12.7, 12.2 Hz, 2H), 2.35 (s, 3H), 1.94 (t, J = 11.5 Hz, 4H), 1.84 – 1.74 (m, 2H), 1.57 (q, J = 12.6 Hz, 2H). MS *m/z*: 610.25 $[M+H]^+$.

6-(4-(Difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (94)



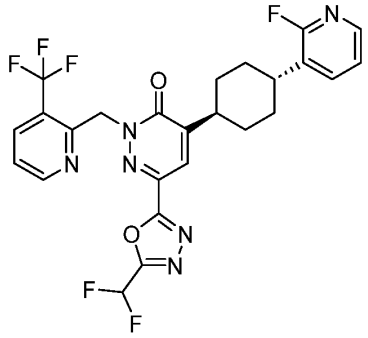
[00569] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00570] Step 2: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl) boronic acid (crude, 0.208 mmol, 1.0 equiv) and 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (39.6 mg, 0.249 mmol, 1.2 equiv) as the starting materials to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-

(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (60 mg, 51%) as a yellow oil. MS *m/z*: 568 $[M+H]^+$.

[00571] Step 3: 6-(4-(difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (60.0 mg, 0.106 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 – 8.61 (m, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.07 – 6.99 (m, 1H), 6.94 – 6.80 (m, 2H), 6.63 (t, *J* = 54.7 Hz, 1H), 5.75 (s, 2H), 3.81 (s, 3H), 3.14 – 3.03 (m, 1H), 2.87 (t, *J* = 12.4 Hz, 1H), 2.37 (d, *J* = 11.4 Hz, 6H), 2.13 (t, *J* = 9.5 Hz, 4H), 1.86 (s, 2H), 1.52 – 1.39 (m, 2H). MS *m/z*: 590.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (95)



[00572] Step 1: ethyl 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.214 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (55 mg, 50%) as a white solid. MS *m/z*: 505 $[M+H]^+$.

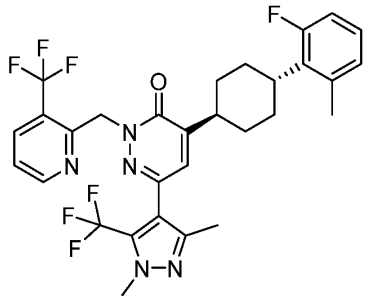
[00573] Step 2: 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the

general procedure N using ethyl 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (55.0 mg, 0.109 mmol, 1.0 equiv) as the starting material to give the crude product 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg) as a white solid. MS *m/z*: 491 $[M+H]^+$.

[00574] Step 3: N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg, 0.082 mmol, 1.0 equiv) as the starting material to give N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (30 mg, 64%) as a white solid. MS *m/z*: 569 $[M+H]^+$.

[00575] Step 4: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (30 mg, 0.053 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoropyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.8 mg, 23%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.9 Hz, 1H), 8.06 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 0.9 Hz, 1H), 7.64 (t, *J* = 8.4 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.15 (s, 1H), 6.90 (s, 1H), 5.79 (s, 2H), 3.04 (t, *J* = 11.4 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.17 (d, *J* = 12.0 Hz, 2H), 2.08 (d, *J* = 12.5 Hz, 2H), 1.71 – 1.60 (m, 4H). MS *m/z*: 551.20 $[M+H]^+$.

6-(1,3-Dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (96)

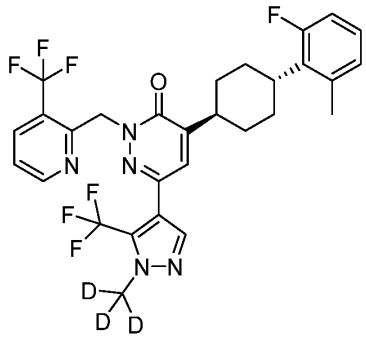


[00576] Step 1: 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole: Followed the general procedure J using 4-bromo-1-methyl-1*H*-1,2,3-triazole (1.00 g, 5.71 mmol, 1.0 equiv) and sodium trifluoromethanesulfinate (2.67 g, 17.1 mmol, 3.0 equiv) as the starting materials to give 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole (350 mg, 25%) as a yellow oil. MS *m/z*: 243 $[M+H]^+$.

[00577] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00578] Step 3: 6-(1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one Followed the general procedure H using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole (20.1 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9.2 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.7 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.07 (s, 1H), 7.04 – 7.00 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.74 (s, 2H), 3.97 (s, 3H), 3.07 (t, *J* = 12.1 Hz, 1H), 2.87 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.17 (s, 4H), 2.12 (d, *J* = 11.8 Hz, 3H), 1.83 (d, *J* = 12.4 Hz, 2H), 1.43 (q, *J* = 12.6 Hz, 2H). MS *m/z*: 608.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-(methyl-d_3)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (97)

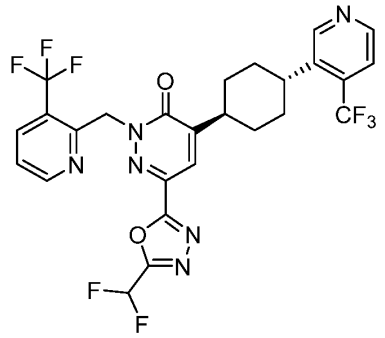


[00579] Step 1: 1-(methyl-d_3)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole: A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (100 mg, 0.382 mmol, 1.0 equiv) and NaH (30.5 mg, 0.764 mmol, 2.0 equiv, 60% in oil) in DMF (1 mL) was stirred for 30 min at 0 °C under air atmosphere. To the above mixture was added iodomethane-d_3 (55.3 mg, 0.382 mmol, 1.0 equiv) dropwise over 1 min at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by GCMS. The reaction was quenched with sat. NH_4Cl (aq.) at room temperature. The resulting mixture was diluted with water (40 mL) extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture (100 mg) was used in the next step directly without further purification. MS *m/z*: 280 $[M+H]^+$.

[00580] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(methyl-d_3)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using 1-(methyl-d_3)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (100 mg, 0.358 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (172 mg, 0.358 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(methyl-d_3)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.5 mg, 6.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.38 – 7.30 (m, 1H), 7.19 (s, 1H), 7.08 – 6.97 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.78 (m, 1H), 5.71

(s, 2H), 3.07 (t, J = 12.0 Hz, 1H), 2.87 (t, J = 12.3 Hz, 1H), 2.36 (s, 3H), 2.20 – 2.09 (m, 4H), 1.84 (d, J = 12.7 Hz, 2H), 1.46 (q, J = 12.4 Hz, 2H). MS *m/z*: 597.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (98)



[00581] Step 1: ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.193 mmol, 1.0 equiv) as the starting material to give ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate (100 mg, 93%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

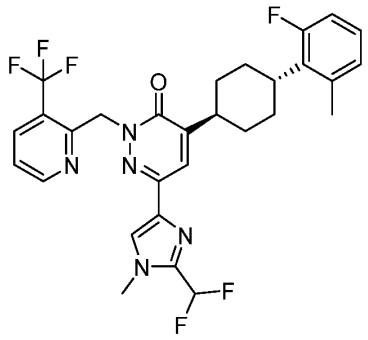
[00582] Step 2: 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate (100 mg, 0.180 mmol, 1.0 equiv) as the starting material to give 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (75 mg, 76%) as a white solid. MS *m/z*: 541 $[M+H]^+$.

[00583] Step 3: *N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (75.0 mg, 0.138 mmol, 1.0 equiv) as the starting material to give *N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-

yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 58%) as a white solid. MS *m/z*: 619 $[M+H]^+$.

[00584] Step 4: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure P using *N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 0.081 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (16.4 mg, 33.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.84 (s, 1H), 8.68 (d, *J* = 5.3 Hz, 1H), 8.58 (d, *J* = 4.8 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.34 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.04 – 6.75 (m, 1H), 5.80 (s, 2H), 3.10 (t, *J* = 12.2 Hz, 2H), 2.21 (d, *J* = 12.8 Hz, 2H), 2.08 (d, *J* = 12.6 Hz, 2H), 1.79 (d, *J* = 12.4 Hz, 2H), 1.63 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 601.05 $[M+H]^+$.

6-(2-(Difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (99)

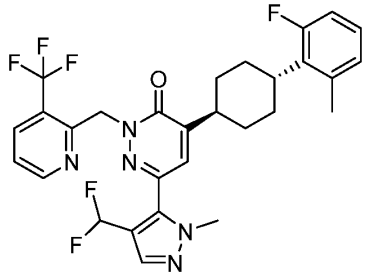


[00585] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00586] Step 2: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-2-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl) boronic acid (crude, 0.208 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-imidazole-2-carbaldehyde (47.1 mg, 0.249 mmol, 1.2 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-2-carbaldehyde (50 mg, 44%) as a light yellow solid. MS *m/z*: 554 $[M+H]^+$.

[00587] Step 3: 6-(2-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridine-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-2-carbaldehyde (50 mg, 0.090 mmol, 1.0 equiv) as the starting material to give 6-(2-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (36 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.40 (s, 1H), 7.32 – 7.27 (m, 1H), 7.07 – 6.99 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.66 (m, 2H), 5.70 (s, 2H), 3.86 (s, 3H), 3.15 – 3.04 (m, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.35 (s, 3H), 2.18 – 2.10 (m, 4H), 1.86 – 1.80 (m, 2H), 1.57 (t, *J* = 12.4 Hz, 2H). MS *m/z*: 576.15 $[M+H]^+$.

6-(4-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100)



[00588] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the

general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.214 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00589] Step 2: ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.214 mmol, 1.0 equiv) and ethyl 5-bromo-1-methyl-1*H*-pyrazole-4-carboxylate (55.1 mg, 0.235 mmol, 1.1 equiv) as the starting materials to give ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carboxylate (61 mg, 49%) as a light yellow solid. MS *m/z*: 498 $[M+H]^+$.

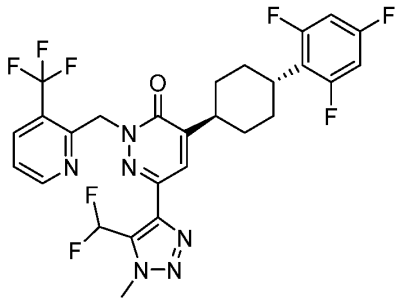
[00590] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carboxylate (61.0 mg, 0.102 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (35 mg, 61%) as a white solid. MS *m/z*: 556 $[M+H]^+$.

[00591] Step 4: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (35 mg, 0.063 mmol, 1.0 equiv) as the starting materials to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carbaldehyde (25 mg, 71%) as a white solid. MS *m/z*: 554 $[M+H]^+$.

[00592] Step 5: 6-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-

dihydropyridazin-3-yl)-1-methyl-1*H*-pyrazole-4-carbaldehyde (25 mg, 0.045 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (6.2 mg, 23%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.35 (d, *J* = 6.9 Hz, 2H), 7.08 – 6.99 (m, 1H), 6.92 – 6.85 (m, 1H), 6.84 – 6.53 (m, 2H), 5.75 (s, 2H), 3.89 (s, 3H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.86 (d, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.15 (d, *J* = 12.1 Hz, 4H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.45 (d, *J* = 12.5 Hz, 2H). MS *m/z*: 576.25 [M+H]$^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (101)



[00593] Step 1: ethyl 2',4',6'-trifluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate: Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (5.00 g, 17.8 mmol, 1.0 equiv) and 2-bromo-1,3,5-trifluorobenzene (4.51 g, 21.3 mmol, 1.2 equiv) as the starting materials to give 2-bromo-1,3,5-trifluorobenzene (4.0 g, 78%) as a light brown oil. MS *m/z*: 285 [M+H]$^+$.

[00594] Step 2: ethyl 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylate: Followed the general procedure B using 2-bromo-1,3,5-trifluorobenzene (4.00 g, 14.1 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylate (3.6 g) as a colorless oil. MS *m/z*: 287 [M+H]$^+$.

[00595] Step 3: 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylate (3.60 g, 12.5 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylic acid (3.2 g) as a colorless oil. MS *m/z*: 259 [M+H]$^+$.

[00596] Step 4: 3,6-dichloro-4-(4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazine: Followed the general procedure D using 4-(2,4,6-trifluorophenyl)cyclohexane-1-carboxylic acid (3.20

g, 12.3 mmol, 1.0 equiv) and 3,6-dichloropyridazine (2.03 g, 13.6 mmol, 1.1 equiv) as the starting materials to give 3,6-dichloro-4-(4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazine (4.0 g, 89%) as an off-white solid. MS *m/z*: 361 $[M+H]^+$.

[00597] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E using 3,6-dichloro-4-(4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazine (4.00 g, 11.1 mmol, 1.0 equiv) as the starting material to give 6-chloro-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (1.0 g, 26%) as a white solid. MS *m/z*: 344 $[M+H]^+$.

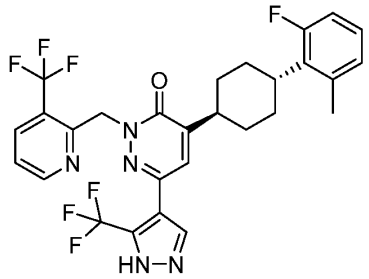
[00598] Step 6: 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (200 mg, 0.581 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (137 mg, 0.698 mmol, 1.2 equiv) as the starting materials to give 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (220 mg, 75%) as a white solid. MS *m/z*: 502 $[M+H]^+$.

[00599] Step 7: (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (70.0 mg, 0.139 mmol, 1.0 equiv) as the starting material to give (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 512 $[M+H]^+$.

[00600] Step 8 : 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.139 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (35.2 mg, 0.166 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (41.8 mg, 51.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 4.7 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 7.44 – 7.35 (m, 1H), 7.16 (d, *J* = 52.7 Hz, 1H), 6.61 (t, *J* = 8.8 Hz, 2H), 5.72 (s, 2H), 4.25 (s,

3H), 3.14 – 2.98 (m, 2H), 2.08 (dd, *J* = 30.0, 13.3 Hz, 4H), 1.88 – 1.83 (m, 2H), 1.61 – 1.47 (m, 2H). MS *m/z*: 599.05 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (102)



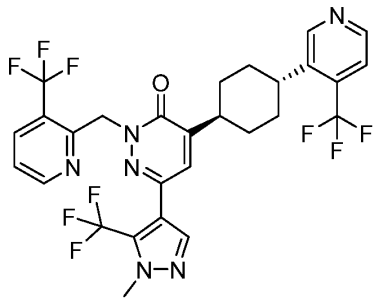
[00601] Step 1: 1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole: A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (100 mg, 0.382 mmol, 1.0 equiv), 3,4-dihydro-2*H*-pyran (96.3 mg, 1.15 mmol, 3.0 equiv) and TsOH (6.6 mg, 0.038 mmol, 0.1 equiv) in DCM (2 mL) was stirred for 3 h at room temperature. The reaction was monitored by GCMS. The resulting mixture was diluted with water (30 mL) extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture (90 mg) was used in the next step directly without further purification. MS *m/z*: 347 $[M+H]^+$.

[00602] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (90.0 mg, 0.260 mmol, 1.0 equiv) and 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (125 mg, 0.260 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 86%) as a light yellow oil. MS *m/z*: 664 $[M+H]^+$.

[00603] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: A solution of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-

(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (140 mg, 0.211 mmol, 1.0 equiv) in HCl (gas) in 1,4-dioxane (3 mL) was stirred for overnight at room temperature. The reaction was monitored by LCMS. The mixture was neutralized to pH ~ 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 5% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (65.0 mg, 52.6%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.84 (s, 1H), 8.70 (d, *J* = 4.5 Hz, 1H), 8.62 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.62 (s, 1H), 7.54 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.17 – 7.07 (m, 1H), 7.05 – 6.89 (m, 2H), 5.54 (s, 2H), 2.89 (t, *J* = 10.7 Hz, 2H), 2.36 (s, 3H), 1.97 (d, *J* = 11.5 Hz, 4H), 1.81 (d, *J* = 10.0 Hz, 2H), 1.59 (q, *J* = 12.8, 12.3 Hz, 2H). MS *m/z*: 580.15 $[M+H]^+$.

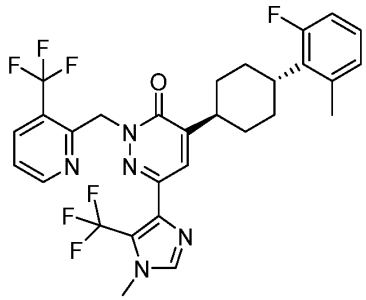
6-(1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (103)



[00604] Step 1: 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (25 mg, 0.048 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (16 mg, 0.058 mmol, 1.2 equiv) as the starting materials to give 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-

yl)cyclohexyl)pyridazin-3(2*H*)-one (27 mg, 86%) as an off-white solid.[1]H NMR (400 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 8.66 – 8.56 (m, 2H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.65 (s, 2H), 7.31 (t, *J* = 5.5 Hz, 1H), 7.19 (s, 1H), 5.71 (s, 2H), 4.05 (s, 3H), 3.22 – 3.00 (m, 2H), 2.20 (s, 2H), 2.07 (s, 2H), 1.83 (s, 2H), 1.55 (s, 2H). MS *m/z*: 631.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (104)



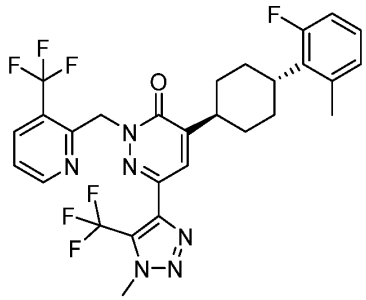
[00605] Step 1: 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-imidazole: Followed the general procedure J using 4-bromo-1-methyl-1*H*-imidazole (1.00 g, 6.21 mmol, 1.0 equiv) as the starting material to give 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-imidazole (300 mg, 21%) as a colorless oil. MS *m/z*: 229 $[M+H]^+$.

[00606] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00607] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-imidazole (57.1 mg, 0.249 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (27.3 mg, 21.6%) as a white solid. [1]H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 4.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz,

1H), 7.87 – 7.68 (m, 1H), 7.47 (s, 1H), 7.38 (t, *J* = 6.3 Hz, 1H), 7.10 – 6.99 (m, 1H), 6.94 – 6.89 (m, 1H), 6.86 – 6.81 (m, 1H), 5.73 (s, 2H), 3.88 – 3.82 (m, 3H), 3.09 (t, *J* = 12.0 Hz, 1H), 2.89 (t, *J* = 12.1 Hz, 1H), 2.36 (s, 3H), 2.11 (t, *J* = 11.4 Hz, 4H), 1.83 (d, *J* = 11.2 Hz, 2H), 1.63 – 1.51 (m, 2H). MS *m/z*: 594.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (105)



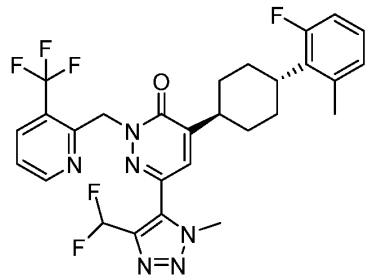
[00608] Step 1: 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole: Followed the general procedure J using 4-bromo-1-methyl-1*H*-1,2,3-triazole (1.00 g, 6.17 mmol, 1.0 equiv) and sodium trifluoromethanesulfinate (2.89 g, 18.5 mmol, 3.0 equiv) as the starting materials to give 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (150 mg, 10%) as a light yellow oil. MS *m/z*: 230 $[M+H]^+$.

[00609] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. MS *m/z*: 490 $[M+H]^+$.

[00610] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (54.9 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12.2

mg, 19.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.83 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.87 – 6.82 (m, 1H), 5.74 (s, 2H), 4.24 (d, *J* = 1.6 Hz, 3H), 3.16 – 3.08 (m, 1H), 2.92 – 2.84 (m, 1H), 2.36 (s, 3H), 2.15 (d, *J* = 12.0 Hz, 4H), 1.83 (s, 1H), 1.54 (q, *J* = 12.6 Hz, 3H). MS *m/z*: 595.20 $[M+H]^+$.

6-(4-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (106)



[00611] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.313 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00612] Step 2: methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.313 mmol, 1.0 equiv) and methyl 5-bromo-1-methyl-1*H*-1,2,3-triazole-4-carboxylate (135 mg, 0.626 mmol, 2.0 equiv) as the starting materials to give methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carboxylate (80 mg, 44%) as a colorless oil. MS *m/z*: 585 $[M+H]^+$.

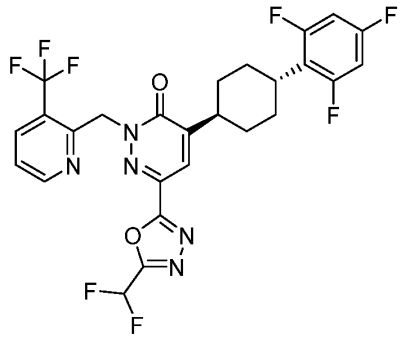
[00613] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-

one: Followed the general procedure L using methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carboxylate (75.0 mg, 0.128 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (45 mg, 63%) as a white solid. MS *m/z*: 557 $[M+H]^+$.

[00614] Step 4: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.072 mmol, 1.0 equiv) as the starting material to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde (30 mg, 75%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

[00615] Step 5: 6-(4-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde (30 mg, 0.054 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18 mg, 57%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 4.9 Hz, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.74 (s, 1H), 7.49 – 7.42 (m, 1H), 7.07 – 7.01 (m, 1H), 6.95 – 6.75 (m, 3H), 5.77 (s, 2H), 4.26 (s, 3H), 3.17 – 3.07 (m, 1H), 2.95 – 2.84 (m, 1H), 2.36 (s, 3H), 2.13 (d, *J* = 12.1 Hz, 4H), 1.91 – 1.82 (m, 2H), 1.55 (t, *J* = 12.2 Hz, 2H). MS *m/z*: 577.15 $[M+H]^+$

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (107)



[00616] Step 1: ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (120 mg, 0.239 mmol, 1.0 equiv) as the starting material to give ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate (120 mg, 92%) as a white solid. MS *m/z*: 540 $[M+H]^+$.

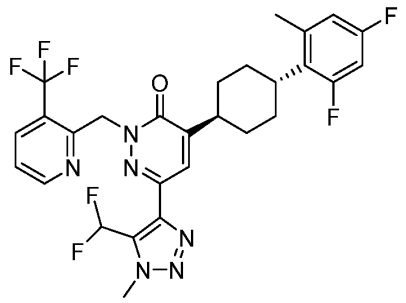
[00617] Step 2: 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using ethyl 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboxylate (120 mg, 0.222 mmol, 1.0 equiv) as the starting material to give 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 85%) as a white solid. MS *m/z*: 526 $[M+H]^+$.

[00618] Step 3: *N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (120 mg, 0.190 mmol, 1.0 equiv) as the starting material to give *N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (110 mg, 95.7%) as a white solid. MS *m/z*: 604 $[M+H]^+$.

[00619] Step 4: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed

the general Procedure P using *N*'-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbohydrazide (110 mg, 0.182 mmol, 1.00 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (49.7 mg, 46.5%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.9 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.93 (s, 1H), 7.35 (dd, *J* = 7.9, 5.0 Hz, 1H), 6.90 (t, *J* = 51.6 Hz, 1H), 6.61 (t, *J* = 8.7 Hz, 2H), 5.79 (s, 2H), 3.11 – 2.99 (m, 2H), 2.15 – 2.00 (m, 4H), 1.93 – 1.85 (m, 2H), 1.53 (d, *J* = 12.3 Hz, 2H). MS m/z: 586.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (108)



[00620] Step 1: ethyl 2',4'-difluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate: Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (1.00 g, 3.56 mmol, 1.0 equiv) and 2-bromo-1,5-difluoro-3-methylbenzene (0.890 g, 4.28 mmol, 1.2 equiv) as the starting materials to give ethyl 2',4'-difluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (800 mg, 79%) as a brown oil. MS *m/z*: 281 $[M+H]^+$.

[00621] Step 2: ethyl 4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 2',4'-difluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (800 mg, 2.85 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylate (730 mg) as a colorless oil. MS *m/z*: 283 $[M+H]^+$.

[00622] Step 3: 4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylate (730 mg, 2.59 mmol, 1.0 equiv) as the starting material to give the crude product

4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylic acid (700 mg) as a white solid. MS *m/z*: 253 $[M-H]^+$.

[00623] Step 4: 3,6-dichloro-4-(4-(2,4-difluoro-6-methylphenyl)cyclohexyl)pyridazine*:* Followed the general procedure D using 4-(2,4-difluoro-6-methylphenyl)cyclohexane-1-carboxylic acid (700 mg, 2.75 mmol, 1.0 equiv) as the starting material to give 3,6-dichloro-4-(4-(2,4-difluoro-6-methylphenyl)cyclohexyl)pyridazine (800 mg, 81%) as a white solid. MS *m/z*: 357 $[M+H]^+$.

[00624] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E useing 3,6-dichloro-4-(4-(2,4-difluoro-6-methylphenyl) cyclohexyl)pyridazine (800 mg, 2.24 mmol, 1.0 equiv) as the starting material to give 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (150 mg, 19%) as a white solid. MS *m/z*: 339 $[M+H]^+$.

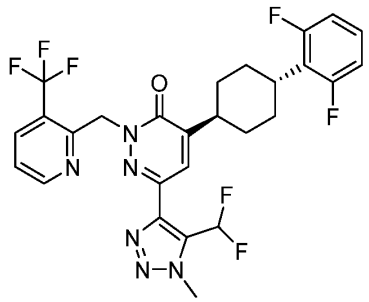
[00625] Step 6: 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl) pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl) cyclohexyl)pyridazin-3(2*H*)-one (150 mg, 0.443 mmol, 1.0 equiv) as the starting material to give 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 90%) as a white solid. MS *m/z*:498 $[M+H]^+$.

[00626] Step 7: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.201 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 508 $[M+H]^+$.

[00627] Step 8: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl) boronic acid (crude, 0.201 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (51.2 mg, 0.241 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-

yl)methyl)pyridazin-3(2*H*)-one (39.2 mg, 33%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 8.00 (s, 1H), 7.47 – 7.34 (m, 1H), 7.16 (d, *J* = 52.6 Hz, 1H), 6.71 – 6.55 (m, 2H), 5.73 (s, 2H), 4.25 (s, 3H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.84 (t, *J* = 12.5 Hz, 1H), 2.34 (s, 3H), 2.11 (t, *J* = 10.5 Hz, 4H), 1.82 (d, *J* = 12.7 Hz, 2H), 1.61 – 1.48 (m, 2H). MS *m/z*: 595.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (109)

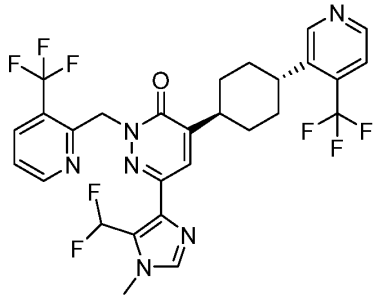


[00628] Step 1: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.103 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00629] Step 2: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.103 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (21.6 mg, 0.103 mmol, 1.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.8 mg, 37.0%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.6 Hz, 1H), 8.10 – 7.96 (m, 2H), 7.38 (s, 1H), 7.19 – 7.00 (m, 2H), 6.82 (t, *J* = 8.5 Hz, 2H), 5.71 (d, *J* = 6.1 Hz, 2H), 4.24 (s, 3H), 3.18

– 3.03 (m, 2H), 2.12 (t, J = 11.8 Hz, 4H), 1.94 – 1.86 (m, 2H), 1.58 (t, J = 11.7 Hz, 2H). MS m/z: 581.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (110)



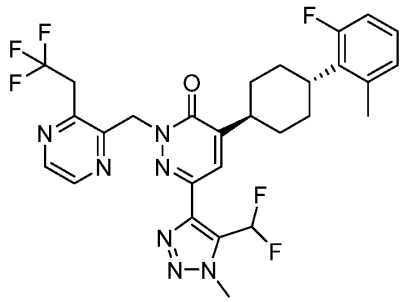
[00630] Step 1: (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (40 mg, 0.077 mmol, 1.0 equiv) as the starting material to give (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS m/z: 527 $[M+H]^+$.

[00631] Step 2: 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde: Followed the general procedure H using (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.077 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde (17.4 mg, 0.092 mmol, 1.2 equiv) as the starting materials to give 1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde (30 mg, 77%) as a light yellow solid. MS m/z: 591 $[M+H]^+$.

[00632] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one:Followed the general procedure I using1-methyl-4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde (40 mg, 0.068

mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(4-(trifluoromethyl)pyridin-3-yl)cyclohexyl)pyridazin-3(2*H*)-one (7.1 mg, 16%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.84 (s, 1H), 8.67 (d, *J* = 5.1 Hz, 2H), 8.05 – 7.98 (m, 2H), 7.79 – 7.69 (m, 2H), 7.41 – 7.34 (m, 1H), 7.17 (s, 1H), 5.70 (s, 2H), 3.88 (s, 3H), 3.10 (d, *J* = 12.6 Hz, 2H), 2.20 (d, *J* = 12.6 Hz, 2H), 2.05 (d, *J* = 12.4 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.67 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 327.75 [M+H]$^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (111)



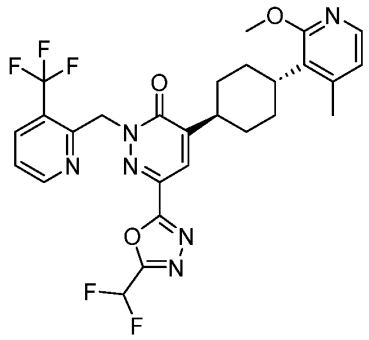
[00633] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.156 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(2,2,2-trifluoroethyl)pyrazine (49.0 mg, 0.234 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (45 mg, 58%). MS *m/z*: 495 [M+H]$^+$.

[00634] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general Procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (45 mg, 0.091 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 505 [M+H]$^+$.

[00635] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-

yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.091 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (23.0 mg, 0.107 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(2,2,2-trifluoroethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (14 mg, 26%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.00 (s, 1H), 7.57 (t, *J* = 52.6 Hz, 1H), 7.13-6.98 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 11.9, 8.1 Hz, 1H), 5.55 (s, 2H), 4.29 (s, 3H), 4.05 (q, *J* = 10.4 Hz, 2H), 3.19-2.98 (m, 1H), 2.96-2.78 (m, 1H), 2.36 (s, 3H), 2.24-2.01 (m, 4H), 1.92-1.77 (m, 2H), 1.58-1.44 (m, 2H). MS *m/z*: 592.2 [M+H]$^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (112)



[00636] Step 1: ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate*:* Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (1.00 g, 3.56 mmol, 1.0 equiv) and 3-bromo-2-methoxy-4-methylpyridine (0.870 g, 4.23 mmol, 1.2 equiv) as the starting materials to give ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate(800 mg, 81%) as a brown oil. MS *m/z*: 276 [M+H]$^+$.

[00637] Step 2: ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohex-3-ene-1-carboxylate (800 mg, 2.90 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (750 mg) as a colorless oil. MS *m/z*: 278 [M+H]$^+$.

[00638] Step 3: 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (750 mg, 2.70 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid (700 mg) as a white solid. MS *m/z*: 250 $[M+H]^+$.

[00639] Step 4: 1,3-dioxoisoindolin-2-yl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate*:* Followed the general procedure R using 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylic acid (700 mg, 2.80 mmol, 1.0 equiv) and 2-hydroxyisoindoline-1,3-dione (503 mg, 3.08 mmol, 1.1 equiv) as the starting materials to give 1,3-dioxoisoindolin-2-yl 4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate(800 mg, 72%) as a white solid. MS *m/z*: 395 $[M+H]^+$.

[00640] Step 5: methyl 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure S using methyl 5-bromo-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (300 mg, 0.765 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl4-(2-methoxy-4-methylpyridin-3-yl)cyclohexane-1-carboxylate (441 mg, 1.14 mmol, 1.5 equiv) as the starting materials to give methyl 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (200 mg, 50%) as a light yellow solid . MS *m/z*: 517 $[M+H]^+$.

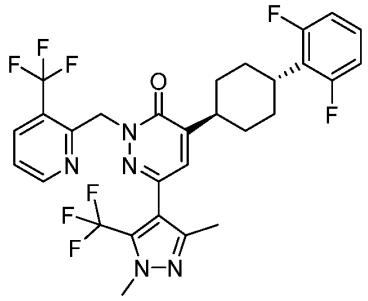
[00641] Step 6: 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using methyl 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (200 mg, 0.387 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (150 mg, 75%) as a white solid. MS *m/z*: 517 $[M+H]^+$.

[00642] Step 7: *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (150 mg, 0.290 mmol, 1.0 equiv) as the starting material to give *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-

oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 57%) as a white solid. MS *m/z*: 595 $[M+H]^+$.

[00643] Step 8: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure P using *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 0.168 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-methoxy-4-methylpyridin-3-yl) cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.2 mg, 20.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.9 Hz, 1H), 8.11 – 7.85 (m, 3H), 7.38 – 7.30 (m, 1H), 7.04 – 6.76 (m, 2H), 5.79 (s, 2H), 4.16 (s, 3H), 3.11 – 2.82 (m, 2H), 2.42 (s, 3H), 2.34 – 2.19 (m, 2H), 2.12 (d, *J* = 12.6 Hz, 2H), 1.74 – 1.72 (m, 2H), 1.58 – 1.46 (m, 2H). MS *m/z*: 577.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-6-(1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (113)

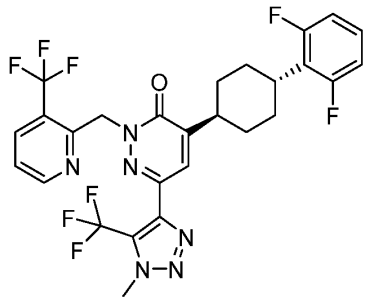


[00644] Step 1: 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole: Followed the general procedure J using 4-bromo-1,3-dimethyl-1*H*-pyrazole (100 mg, 0.571 mmol, 1.0 equiv) as the starting material to give 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole (30 mg, 21%) as a yellow oil. MS *m/z*: 243 $[M+H]^+$.

[00645] Step 2: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.103 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00646] Step 3: 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.103 mmol, 1.0 equiv) and 4-bromo-1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazole (30.3 mg, 0.123 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1,3-dimethyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.4 mg, 20.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.5 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.16 – 7.04 (m, 2H), 6.82 (t, *J* = 8.6 Hz, 2H), 5.74 (s, 2H), 3.97 (d, *J* = 1.4 Hz, 3H), 3.13 – 3.02 (m, 2H), 2.14 (d, *J* = 22.6 Hz, 7H), 1.93 – 1.85 (m, 2H), 1.50 – 1.34 (m, 2H). MS *m/z*: 612.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (114)

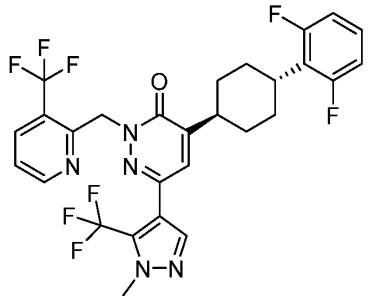


[00647] Step 1: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.103 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00648] Step 2: 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.103 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-

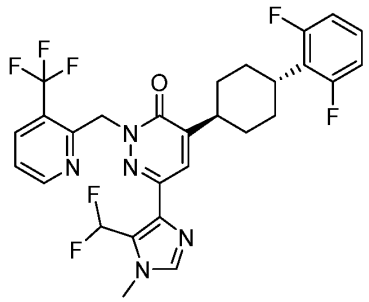
(trifluoromethyl)-1*H*-1,2,3-triazole (23.7 mg, 0.103 mmol, 1.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12.2 mg, 18.3%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.38 – 7.28 (m, 1H), 7.18 – 7.03 (m, 1H), 6.82 (t, *J* = 8.6 Hz, 2H), 5.70 (d, *J* = 8.7 Hz, 2H), 4.24 (q, *J* = 1.5 Hz, 3H), 3.18 – 3.03 (m, 2H), 2.12 (t, *J* = 12.8 Hz, 4H), 1.90 (d, *J* = 11.7 Hz, 2H), 1.60 – 1.46 (m, 2H). MS *m/z*: 599.20 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (115)



[00649] Step 1: 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (43 mg, 0.16 mmol, 1.5 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25.2 mg, 40.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.62 (m, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.65 (s, 1H), 7.34 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.17 (s, 1H), 7.11 (tt, *J* = 8.2, 6.3 Hz, 1H), 6.82 (t, *J* = 8.6 Hz, 2H), 5.72 (s, 2H), 4.05 (d, *J* = 1.6 Hz, 3H), 3.07 (td, *J* = 12.2, 6.2 Hz, 2H), 2.18 – 2.03 (m, 4H), 1.89 (dd, *J* = 12.7, 4.9 Hz, 2H), 1.53 – 1.36 (m, 2H). MS *m/z*: 598.20 [M+H]$^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (116)

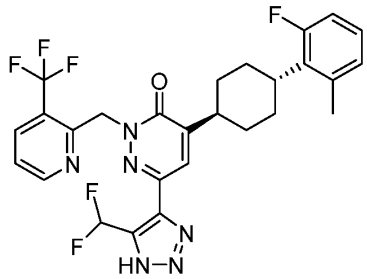


[00650] Step 1: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00651] Step 2: 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde (39.2 mg, 0.208 mmol, 2.0 equiv) as the starting materials to give 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde (43 mg, 76%) as a light yellow solid.

[00652] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-imidazole-5-carbaldehyde (43 mg, 0.077 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (21.4 mg, 47.5%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 – 8.66 (m, 1H), 8.02 – 8.00 (m, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.37 – 7.31 (m, 1H), 7.18 – 7.03 (m, 2H), 6.81 (t, *J* = 8.6 Hz, 2H), 5.69 (s, 2H), 3.88 (s, 3H), 3.14 – 3.05 (m, 2H), 2.14 – 2.03 (m, 4H), 1.92 – 1.87 (m, 2H), 1.62 – 1.51 (m, 2H). MS *m/z*: 580.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (117)



[00653] Step 1: methyl 4-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate: To a stirred mixture of methyl 4-bromo-1*H*-1,2,3-triazole-5-carboxylate (1.00 g, 6.75 mmol, 1.0 equiv) and DHP (1.71 g, 20.2 mmol, 3.0 equiv) in DCM (10 mL) was added TsOH (116 mg, 0.676 mmol, 0.1 equiv) at 0 °C. The resulting mixture was stirred for 3 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was diluted with water (150 mL), extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10% to 50% gradient in 15 min) to afford methyl 4-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (710 mg, 45%) as a light yellow oil. MS *m/z*: 290 $[M+H]^+$.

[00654] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using ethyl 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.313 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

Step 3: methyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.313 mmol, 1.0 equiv) and methyl 4-bromo-1-

(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (180 mg, 0.626 mmol, 2.0 equiv) as the starting materials to give methyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (170 mg, 84%) as a light yellow solid. MS *m/z*: 655 $[M+H]^+$.

[00655] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using methyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (170 mg, 0.26 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 92%) as a white solid. MS *m/z*: 627 $[M+H]^+$.

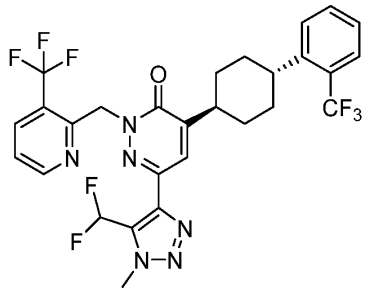
[00656] Step 5: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (75 mg, 0.12 mmol, 1.0 equiv) as the starting material to give the crude product 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (70 mg). MS *m/z*: 625 $[M+H]^+$.

[00657] Step 6: 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (70.0 mg, 0.112 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 83%). MS *m/z*: 647 $[M+H]^+$.

[00658] Step 7: 6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

To a stirred mixture of 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 0.093 mmol, 1.0 equiv) in DCM (3 mL) were added TFA (3 mL) dropwise at 0 °C. The resulting mixture was stirred for 6h at room temperature. The reaction was monitored by LCMS. The mixture was basified to pH ~ 8 with saturated $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 50% to 90% gradient in 15 min; detector, UV 254 nm, to afford 6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (24.1 mg, 43.9%) as an off-white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 7.71 (s, 1H), 7.46 (s, 1H), 7.13 – 6.99 (m, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.86 – 6.81 (m, 1H), 5.76 (s, 2H), 3.09 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.0 Hz, 1H), 2.34 (s, 3H), 2.13 (d, *J* = 12.0 Hz, 4H), 1.84 (d, *J* = 11.2 Hz, 2H), 1.52 (q, *J* = 12.4 Hz, 2H). MS *m/z*: 563.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (118)



[00659] Step 1: ethyl 2'-(trifluoromethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate*:* Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (2.00 g, 7.13 mmol, 1.0 equiv) and 1-bromo-2-(trifluoromethyl)benzene (1.77 g, 7.85 mmol, 1.1 equiv) as the starting material to give ethyl 2'-(trifluoromethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.5 g, 70%) as a yellow oil. MS *m/z*: 299 $[M+H]^+$.

[00660] Step 2: ethyl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 2'-(trifluoromethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.50 g, 5.02 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate (1.0 g) as a light yellow oil. MS *m/z*: 301 $[M+H]^+$.

[00661] Step 3: 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylat (1.00 g, 3.33 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylic acid (800 mg) as a white solid. MS *m/z*: 273 $[M+H]^+$.

[00662] Step 4: 1,3-dioxoisoindolin-2-yl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate: Followed the general procedure R using 4-(2,6-difluorophenyl)cyclohexane-1-carboxylic acid (800 mg, 2.93 mmol, 1.0 equiv) and 2-hydroxyisoindoline-1,3-dione (719 mg, 4.40 mmol, 1.5 equiv) as the starting materials to give 1,3-dioxoisoindolin-2-yl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate (470 mg, 38%) as a white solid. MS *m/z*: 418 $[M+H]^+$.

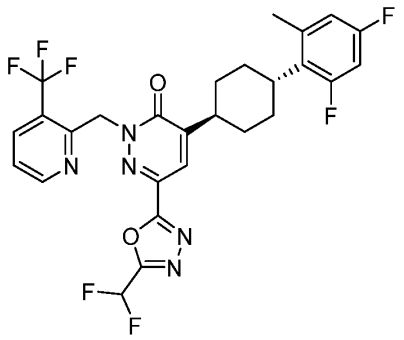
[00663] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate (470 mg, 1.12 mmol, 1.0 equiv) and 4-bromo-6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (332 mg, 0.901 mmol, 0.8 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80 mg, 13%) as a white solid. MS m/z: 516 [M+H]+.

[00664] Step 6: (6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80.0 mg, 0.155 mmol, 1.0 equiv) as the starting materials to give (6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 526 $[M+H]^+$.

[00665] Step 7: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-

3(2*H*)-one: Followed the general procedure H using (6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.155 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (39.6 mg, 0.186 mmol, 1.2 equiv) as the starting materials to give the product 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5.8 mg, 6.1%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.9 Hz, 1H), 8.08 – 7.98 (m, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.33 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 52.7 Hz, 1H), 5.71 (s, 2H), 4.24 (s, 3H), 3.19 – 2.98 (m, 2H), 2.15 (d, *J* = 12.1 Hz, 2H), 2.00 (d, *J* = 12.4 Hz, 2H), 1.77 – 1.55 (m, 4H). MS *m/z*: 613.20 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (119)



[00666] Step 1: ethyl 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure U using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.301 mmol, 1.0 equiv) as the starting material to give ethyl 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (110 mg, 68%) as a white solid. MS *m/z*: 536 [M+H]$^+$.

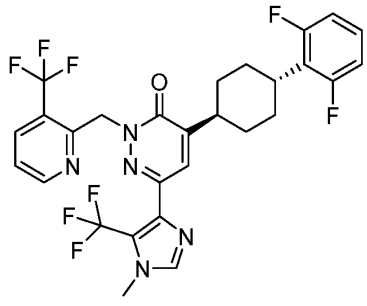
[00667] Step 2: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl) pyridine-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using ethyl 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (110 mg, 0.205 mmol, 1.0 equiv) as the starting material to give the crude product 5-((1*r*,4*r*)-4-

(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (80 mg,) as a white solid. MS *m/z*: 522 $[M+H]^+$.

[00668] Step 3: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (80.0 mg, 0.153 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl) pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60 mg, 65%) as a white solid. MS *m/z*: 600 $[M+H]^+$.

[00669] Step 4: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure P using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl) cyclohexyl)-*N'*-(2,2-difluoroacetyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (60.0 mg, 0.100 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (39 mg, 67%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.8 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.94 (s, 1H), 7.40 – 7.33 (m, 1H), 6.90 (t, *J* = 51.7 Hz, 1H), 6.70 – 6.56 (m, 2H), 5.79 (s, 2H), 3.12 – 3.02 (m, 1H), 2.89 – 2.78 (m, 1H), 2.34 (s, 3H), 2.16 – 2.05 (m, 4H), 1.89 – 1.79 (m, 2H), 1.60 – 1.47 (m, 2H). MS *m/z*: 582.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,6-Difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120)

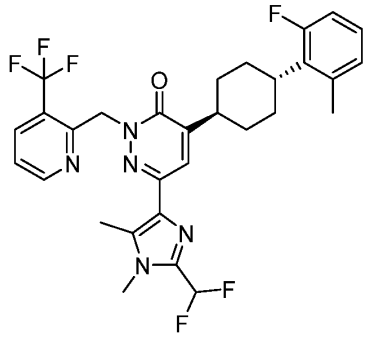


[00670] Step 1: (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.103 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 494 $[M+H]^+$.

[00671] Step 2: 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.103 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (33.3 mg, 0.123 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-imidazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8.8 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.85 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.16 – 7.04 (m, 1H), 6.81 (t, *J* = 8.6 Hz, 2H), 5.72 (s, 2H), 3.83 (s, 3H), 3.14 – 3.04 (m, 2H), 2.09 (t, *J* = 12.4 Hz, 4H), 1.90 (s, 1H), 1.87 (s, 1H), 1.59 (t, *J* = 12.4 Hz, 2H). MS *m/z*: 598.20 $[M+H]^+$.

6-(2-(Difluoromethyl)-1,5-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (121)

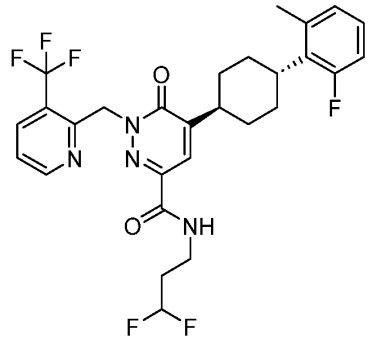


[00672] Step 1: 4-bromo-2-(difluoromethyl)-1,5-dimethyl-1*H*-imidazole: Followed the general procedure J using 4-bromo-1,5-dimethyl-1*H*-imidazole (500 mg, 2.85 mmol, 1.0 equiv) and sodium difluoromethanesulfinate (1.18 g, 8.57 mmol, 3.0 equiv) as the starting materials to give 4-bromo-2-(difluoromethyl)-1,5-dimethyl-1*H*-imidazole (271 mg, 36.2%) as a light grey oil. MS *m/z*: 225 $[M+H]^+$.

[00673] Step 2: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00674] Step 3: 6-(2-(difluoromethyl)-1,5-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-2-(difluoromethyl)-1,5-dimethyl-1*H*-imidazole (32.0 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(2-(difluoromethyl)-1,5-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (24.4 mg, 46.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.91 (s, 1H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.02 (q, *J* = 7.4 Hz, 1H), 6.93 – 6.75 (m, 3H), 5.70 (s, 2H), 3.72 (s, 3H), 3.11 (t, *J* = 12.0 Hz, 1H), 2.90 (t, *J* = 12.0 Hz, 1H), 2.35 (d, *J* = 3.0 Hz, 6H), 2.13 (s, 4H), 1.84 (d, *J* = 12.7 Hz, 2H), 1.58 (d, *J* = 12.9 Hz, 2H). MS *m/z*: 590.20 $[M+H]^+$.

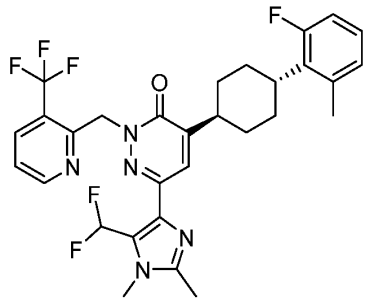
_N_-(3,3-Difluoropropyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (122)



[00675] Step 1: *N*-(3,3-difluoropropyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide: A mixture of methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-

(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (35 mg, 0.070 mmol, 1.0 equiv), 3,3-difluoropropan-1-amine hydrochloride (18 mg, 0.140 mmol, 2.0 equiv) and TEA (14 mg, 0.140 mmol, 2.0 equiv) in MeOH (2 mL) was stirred for overnight at 80 °C. The reaction was monitored by LCMS. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (Hexane / EA 1:1) to afford *N*-(3,3-difluoropropyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxamide (22.7 mg, 55.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.39 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.32 (t, *J* = 6.2 Hz, 1H), 7.08-6.98 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 11.6, 8.3 Hz, 1H), 5.94 (tt, *J* = 56.1, 4.2 Hz, 1H), 5.71 (s, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.12-2.97 (m, 1H), 2.95-2.79 (m, 1H), 2.36 (s, 3H), 2.24-2.03 (m, 6H), 1.89-1.78 (m, 2H), 1.59-1.42 (m, 2H). MS *m/z*: 567.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (123)



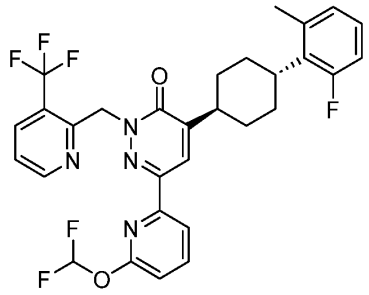
[00676] Step 1: 4-bromo-5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazole: Followed the general procedure J using 4-bromo-5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazole (1.00 g, 5.75 mmol, 1.0 equiv) and bis(((difluoromethyl)sulfinyl)oxy)zinc (3.70 g, 12.5 mmol, 2.2 equiv) as the starting materials to give 4-bromo-5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazole (200 mg, 40%) as a yellow oil. MS *m/z*: 225 $[M+H]^+$.

[00677] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) as the starting materials give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00678] Step 3: 6-(5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazole (67.5 mg, 0.30 mmol, 3.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,2-dimethyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.5 mg, 19%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.85 (s, 1H), 7.34 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.12 (s, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.68 (s, 2H), 3.70 (s, 3H), 3.18 – 3.04 (m, 1H), 2.95 – 2.79 (m, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.20 – 2.13 (m, 4H), 1.90 – 1.77 (m, 2H), 1.62 – 1.52 (m, 2H). MS *m/z*: 590.25 $[M+H]^+$.

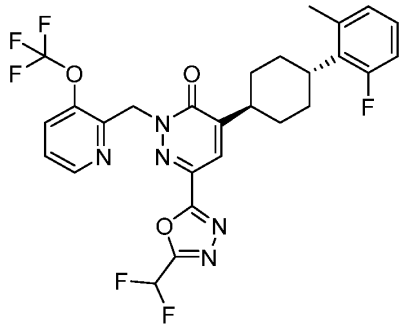
6-(6-(Difluoromethoxy)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (124)



[00679] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid without further purification which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00680] Step 2: 6-(6-(difluoromethoxy)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-bromo-6-(difluoromethoxy)pyridine (28.2 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(6-(difluoromethoxy)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40.8 mg, 77.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 – 8.60 (m, 1H), 8.04 (d, *J* = 0.9 Hz, 1H), 8.03 – 7.99 (m, 1H), 7.90 – 7.86 (m, 1H), 7.81 – 7.75 (m, 1H), 7.58 (s, 1H), 7.41 – 7.31 (m, 1H), 7.07 – 7.00 (m, 1H), 6.94 – 6.90 (m, 2H), 6.88 – 6.82 (m, 1H), 5.77 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 12.0 Hz, 1H), 2.39 (s, 3H), 2.22 – 2.10 (m, 4H), 1.90 – 1.83 (m, 2H), 1.62 – 1.49 (m, 2H). MS *m/z*: 589.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (125)



[00681] Step 1: methyl 5-bromo-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure F using methyl 5-bromo-6-oxo-1,6-dihydropyridazine-3-carboxylate (500 mg, 2.14 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (544 mg, 2.57 mmol, 1.2 equiv) as the starting materials to give methyl 5-bromo-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (650 mg, 74%) as a yellow oil. MS *m/z*: 408 $[M+H]^+$.

[00682] Step 2: methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate: Followed the general procedure S using methyl 5-bromo-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (650 mg, 1.59 mmol, 1.0 equiv) and 1,3-

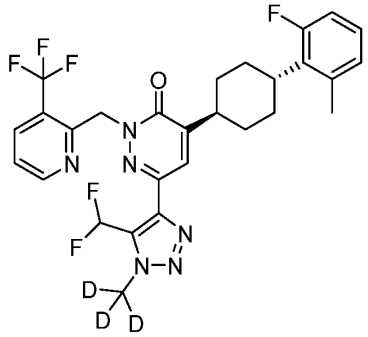
dioxoisoindolin-2-yl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (911 mg, 2.38 mmol, 1.5 equiv) as the starting materials to give methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (450 mg, 54%) as a light yellow solid. MS *m/z*: 520 $[M+H]^+$.

[00683] Step 3: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure N using methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (100 mg, 0.192 mmol, 1.0 equiv) and hydrazine hydrate (29.5 mg, 0.576 mmol, 3.0 equiv, 98%) as the starting materials to give the crude product 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg). MS *m/z*: 520 $[M+H]^+$.

[00684] Step 4: N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 0.192 mmol, 1.0 equiv) and 2,2-difluoroacetic anhydride (100 mg, 0.576 mmol, 3.0 equiv) as the starting materials to give N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 86%) as a light yellow solid. MS *m/z*: 598 $[M+H]^+$.

[00685] Step 5: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure P using N'-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (55 mg, 0.092 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.9 mg, 27.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 – 8.40 (m, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.31 – 7.28 (m, 1H), 7.07 – 7.01 (m, 1H), 6.93 – 6.77 (m, 3H), 5.69 (s, 2H), 3.13 – 3.05 (m, 1H), 2.92 – 2.84 (m, 1H), 2.36 (s, 3H), 2.19 – 2.10 (m, 4H), 1.88 – 1.83 (m, 2H), 1.47 (s, 2H). MS *m/z*: 580.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-(methyl-d3)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (126)



[00686] Step 1: 4,5-dibromo-1-(methyl-d_3)-1*H*-1,2,3-triazole: Followed the general procedure F using 4,5-dibromo-1*H*-1,2,3-triazole (1.00 g, 4.40 mmol, 1.0 equiv) and iodomethane-d_3 (0.960 g, 6.61 mmol, 1.5 equiv) as the starting materials to give 4,5-dibromo-1-(methyl-d_3)-1*H*-1,2,3-triazole (350 mg, 30%) as a white solid. MS *m/z*: 243 $[M+H]^+$.

[00687] Step 2: 4-bromo-1-(methyl-d_3)-1*H*-1,2,3-triazole-5-carbaldehyde: To a stirred mixture of 4,5-dibromo-1-(methyl-d3)-1*H*-1,2,3-triazole (340 mg, 1.39 mmol, 1.0 equiv) and DMF (509 mg, 6.97 mmol, 5.0 equiv) in THF (5 mL) were added iPrMgCl.LiCl (3.49 mL, 6.97 mmol, 5.0 equiv, 2 mol/L) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 4-bromo-1-(methyl-d_3)-1*H*-1,2,3-triazole-5-carbaldehyde (100 mg, 34%) as a white solid. MS *m/z*: 193 $[M+H]^+$.

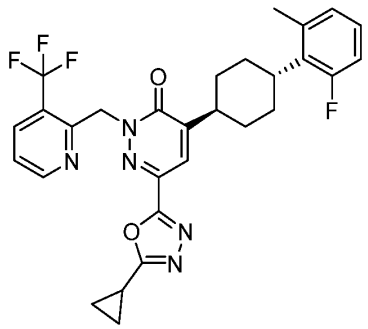
[00688] Step 3: 4-bromo-5-(difluoromethyl)-1-(methyl-d_3)-1*H*-1,2,3-triazole: Followed the general procedure I using 4-bromo-1-(methyl-d_3)-1*H*-1,2,3-triazole-5-carbaldehyde (90.0 mg, 0.466 mmol, 1.0 equiv) as the starting material to give 4-bromo-5-(difluoromethyl)-1-(methyl-d_3)-1*H*-1,2,3-triazole (30 mg, 27%) as a white solid. MS *m/z*: 215 $[M+H]^+$.

[00689] Step 4: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv)

as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00690] Step 5: 6-(5-(difluoromethyl)-1-(methyl-d_3)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-(methyl-d_3)-1*H*-1,2,3-triazole (26.4 mg, 0.135 mmol, 1.3 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-(methyl-d_3)-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5.6 mg, 11%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.74 – 8.57 (m, 1H), 8.08 – 7.95 (m, 2H), 7.42 – 7.33 (m, 1H), 7.18 (s, 1H), 7.09 – 6.98 (m, 1H), 6.97 – 6.75 (m, 2H), 5.70 (s, 2H), 3.13 (t, *J* = 12.1 Hz, 1H), 2.87 (t, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.14 (d, *J* = 12.7 Hz, 4H), 1.91 – 1.78 (m, 2H), 1.61 (s, 1H), 1.49 (s, 1H). MS *m/z*: 580.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (127)

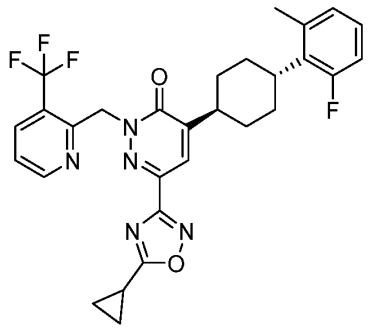


[00691] Step 1: *N'*-(cyclopropanecarbonyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide: Followed the general Procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (120 mg, 0.238 mmol, 1.0 equiv) and cyclopropanecarboxylic anhydride (53.9 mg, 0.357 mmol, 1.5 equiv) as the starting materials to give *N'*-(cyclopropanecarbonyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-

1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (115 mg, 84%). MS *m/z*: 572 $[M+H]^+$.

[00692] Step 2: 6-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure P using *N'*-(cyclopropanecarbonyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (115 mg, 0.201 mmol, 1.0 equiv) as the starting material to give 6-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.7 mg, 27.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (d, *J* = 3.3 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.92 (d, J = 0.9 Hz, 1H), 7.35 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.09 – 6.98 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.79 (m, 1H), 5.77 (s, 2H), 3.07 (t, *J* = 12.2 Hz, 1H), 2.86 (t, *J* = 12.6 1H), 2.36 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 2.04 (m, 4H), 1.90 – 1.79 (m, 2H), 1.59 – 1.44 (m, 2H), 1.30 – 1.15 (m, 4H). MS *m/z*: 554.15 $[M+H]^+$.

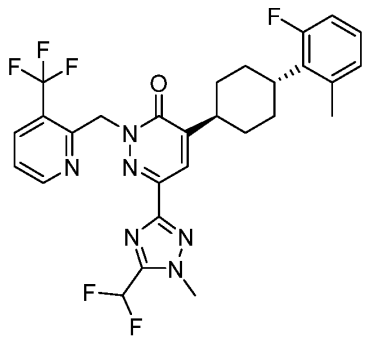
6-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (128)



[00693] Step 1: 6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure Y using 5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (60.0 mg, 0.119 mmol, 1.0 equiv) as the starting material to afford 6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.2 mg, 33.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.55 (d, J = 4.8 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H), 7.32-7.27 (m, 1H), 7.08-6.99 (m, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.88-6.79 (m, 1H),

5.81 (s, 2H), 3.07 (tt, J = 12.3, 3.0 Hz, 1H), 2.87 (t, J = 12.3 Hz, 1H), 2.36 (s, 3H), 2.33-2.27 (m, 1H), 2.20-2.07 (m, 4H), 1.91-1.79 (m, 2H), 1.60-1.46 (m, 2H), 1.40-1.32 (m, 2H), 1.31-1.25 (m, 2H). MS m/z: 554.2 [M+H]+ .

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (129)



[00694] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general Procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*) -one (150 mg, 0.313 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00695] Step 2: methyl 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate: Followed the general Procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl) cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.313 mmol, 1.0 equiv) and methyl 3-bromo-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (137 mg, 0.626 mmol, 2.0 equiv) as the starting materials to give methyl 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (170 mg, 93%) as a white solid. MS *m/z*: 585 $[M+H]^+$.

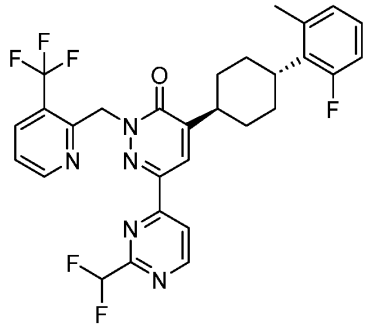
[00696] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure L using methyl 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (170 mg, 0.291 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (130 mg, 80%). MS *m/z*: 557 $[M+H]^+$.

[00697] Step 4: 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde: Followed the general Procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (130 mg, 0.234 mmol, 1.0 equiv) as the starting material to give the crude product 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde (50 mg). MS *m/z*: 555 $[M+H]^+$.

[00698] Step 5: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general Procedure I using 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde (50 mg, 0.090 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18.1 mg, 33.8%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 4.4 Hz, 1H), 8.02-7.87 (m, 2H), 7.31-7.27 (m, 1H), 7.13-6.97 (m, 1H), 6.96-6.75 (m, 3H), 5.83 (s, 2H), 4.13 (s, 3H), 3.09 (tt, *J* = 12.2, 2.9 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.23-2.05 (m, 4H), 1.91-1.79 (m, 2H), 1.64-1.47 (m, 2H). MS *m/z*: 577.20 $[M+H]^+$.

6-(2-(Difluoromethyl)pyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (130)



[00699] Step 1: ethyl 2'-fluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate*:* Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (2.00 g, 7.13 mmol, 1.0 equiv) and 2-bromo-1-fluoro-3-methylbenzene (1.35 g, 7.13 mmol, 1.0 equiv) as the starting materials to give ethyl 2'-fluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.78 g, 95%) as a yellow oil. MS *m/z*: 263 $[M+H]^+$.

[00700] Step 2: ethyl 4-(2,6-difluorophenyl)cyclohexane-1-carboxylate: Followed the general procedure B using ethyl 2'-fluoro-6'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (1.78 g, 6.78 mmol, 1.0 equiv) as the starting material to give the crude product ethyl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (1.6 g) as a light yellow oil. MS *m/z*: 265 $[M+H]^+$.

[00701] Step 3: 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylic acid: Followed the general procedure C using ethyl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (1.60 g, 6.05 mmol, 1.0 equiv) as the starting material to give the crude product 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylic acid (1.55 g) as a white solid. MS *m/z*: 235 $[M+H]^+$.

[00702] Step 4: 3,6-dichloro-4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine:Followed the general procedure D using 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylic acid (1.55 g, 6.56 mmol, 1.0 equiv) and 3,6-dichloropyridazine (0.88 g, 5.9 mmol, 0.9 equiv) as the starting materials to give 3,6-dichloro-4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine (1.2 g, 53%) as a white solid. MS *m/z*: 339 $[M+H]^+$.

[00703] Step 5: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure E using 3,6-dichloro-4-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine (1.20 g, 3.53 mmol, 1.0 equiv) as the starting material to

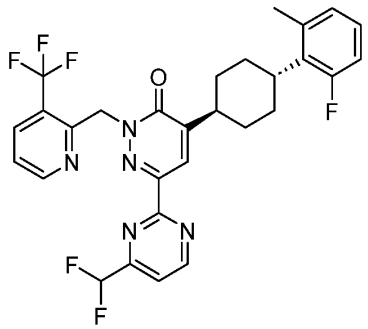
give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (310 mg, 27%) as a white solid. MS *m/z*: 321 $[M+H]^+$.

[00704] Step 6: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (310 mg, 0.966 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (207 mg, 1.06 mmol, 1.1 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (300 mg, 64%) as a white solid. MS *m/z*: 480 $[M+H]^+$.

[00705] Step 7: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS *m/z*: 490 $[M+H]^+$.

[00706] Step 8: 6-(2-(difluoromethyl)pyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 4-chloro-2-(difluoromethyl)pyrimidine (17.0 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give 6-(2-(difluoromethyl)pyrimidin-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (38.8 mg, 61.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (d, *J* = 5.3 Hz, 1H), 8.63 – 8.57 (m, 1H), 8.28 (d, *J* = 0.9 Hz, 1H), 8.14 – 8.08 (m, 1H), 8.05 – 7.95 (m, 1H), 7.38 – 7.30 (m, 1H), 7.09 – 6.99 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.60 (m, 2H), 5.79 (s, 2H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.93 (t, *J* = 12.4 Hz, 1H), 2.38 (s, 3H), 2.15 (t, *J* = 11.3 Hz, 4H), 1.91 – 1.83 (m, 2H), 1.60 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 574.25 $[M+H]^+$.

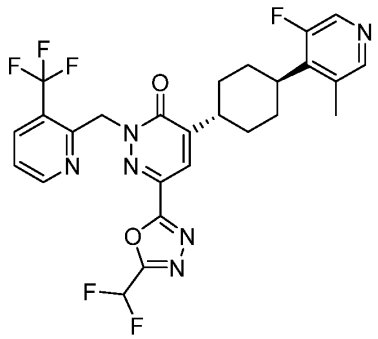
6-(4-(Difluoromethyl)pyrimidin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (131)



[00707] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80.0 mg, 0.104 mmol, 1.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in next step. MS m/*z*: 490 $[M+H]^+$.

[00708] Step 2: 6-(4-(difluoromethyl)pyrimidin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.104 mmol, 1.0 equiv) and 2-chloro-4-(difluoromethyl)pyrimidine (20.4 mg, 0.124 mmol, 1.2 equiv) as the starting materials to give 6-(4-(difluoromethyl)pyrimidin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (57.0 mg, 58.0%) as an off-white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.12 (d, *J* = 5.0 Hz, 1H), 8.58 (d, *J* = 4.9 Hz, 1H), 8.33 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 5.0 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.11 – 7.00 (m, 1H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.88 (dd, *J* = 7.8, 3.9 Hz, 1H), 6.85 – 6.50 (m, 1H), 5.91 (s, 2H), 3.18 – 3.06 (m, 1H), 2.93 (d, *J* = 12.5 Hz, 1H), 2.39 (s, 3H), 2.17 (d, *J* = 12.0 Hz, 4H), 1.88 (d, *J* = 11.3 Hz, 2H), 1.69 – 1.55 (m, 2H). MS *m/z*: 574.20 $[M+H]^+$.

6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(3-fluoro-5-methylpyridin-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (132)



[00709] Step 1: ethyl 4-(3-chloro-5-fluoropyridin-4-yl)cyclohex-3-ene-1-carboxylate. Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (751 mg, 3.56 mmol, 1.0 equiv) and ethyl 4-bromo-3-chloro-5-fluoropyridine (1.0 g, 3.5 mmol, 1.0 equiv) as the starting materials to give ethyl 4-(3-chloro-5-fluoropyridin-4-yl)cyclohex-3-ene-1-carboxylate (800 mg, 75%) as a colorless liquid. MS *m/z*: 284 $[M+H]^+$.

[00710] Step 2: ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohex-3-ene-1-carboxylate. Followed the general procedure A using ethyl 4-(3-chloro-5-fluoropyridin-4-yl)cyclohex-3-ene-1-carboxylate (780 mg, 2.75 mmol, 1.0 equiv) and methylboronic acid (246 mg, 4.12 mmol, 1.5 equiv) as the starting materials to give ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohex-3-ene-1-carboxylate (600 mg, 76%) as a colorless liquid. MS *m/z*: 264 $[M+H]^+$.

[00711] Step 3: ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate. Followed the general procedure B using ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohex-3-ene-1-carboxylate (580 mg, 2.20 mmol, 1.0 equiv) as the starting material to give ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate (500 mg, 77%) as a white solid. MS *m/z*: 266 $[M+H]^+$.

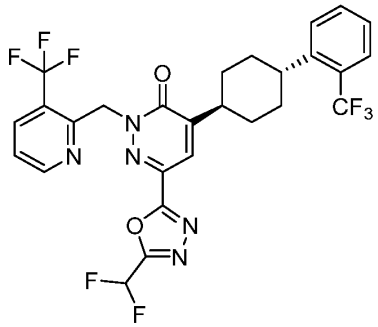
[00712] Step 4: 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylic acid. Followed the general procedure C using ethyl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate (500 mg, 1.88 mmol, 1.0 equiv) as the starting materials to give 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylic acid (400 mg, 80%) as a white solid. MS *m/z*: 238 $[M+H]^+$.

[00713] Step 5: 1,3-dioxoisoindolin-2-yl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate. Followed the general procedure R using 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylic acid (400 mg, 1.68 mmol, 1.0 equiv) and *N*-hydroxyphthalimide (302 mg, 1.85 mmol, 1.1 equiv) as the starting materials to give 1,3-dioxoisoindolin-2-yl 4-

(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate (400 mg, 57%) as a white soild. MS *m/z*: 383 $[M+H]^+$.

[00714] Step 6: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(3-fluoro-5-methylpyridin-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 4-(3-fluoro-5-methylpyridin-4-yl)cyclohexane-1-carboxylate (80 mg, 0.21 mmol, 1.0 equiv) and 4-bromo-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (75 mg, 0.16 mmol, 0.8 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(3-fluoro-5-methylpyridin-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52.5 mg, 42.3%) as white soild. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.9 Hz, 1H), 8.20 (s, 2H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 1.0 Hz, 1H), 7.34 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.09 – 6.71 (m, 1H), 5.79 (s, 2H), 3.10 (t, *J* = 12.0 Hz, 1H), 2.89 (t, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.28 – 2.04 (m, 4H), 1.88 (d, *J* = 13.2 Hz, 2H), 1.55 (d, *J* = 12.4 Hz, 2H). MS *m/z*: 565.20 $[M+H]^+$.

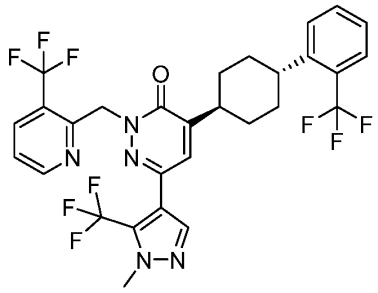
6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (133)



[00715] Step 1: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure S using 4-bromo-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.11 mmol, 1 equiv) and 1,3-dioxoisoindolin-2-yl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate (69.2 mg, 0.167 mmol, 1.5 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.5 mg, 47.3%). ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.54-7.47 (m, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 6.90 (t, *J* = 51.7 Hz, 1H), 5.80 (s, 2H), 3.21 -2.97 (m, 2H), 2.22-2.11 (m, 2H), 2.06-1.98 (m, 2H), 1.77-1.53 (m, 4H). MS *m/z*: 600.10 $[M+H]^+$.

6-(1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (134)

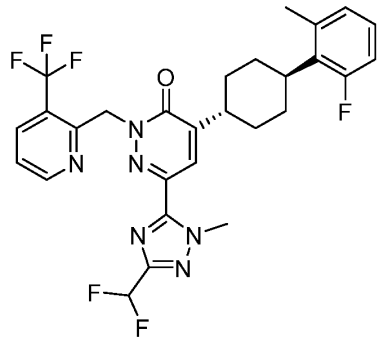


[00716] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure S using 4-bromo-6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.543 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl 4-(2-(trifluoromethyl)phenyl)cyclohexane-1-carboxylate (339 mg, 0.815 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (210 mg, 75%) as a white solid. MS *m/z*: 516 $[M+H]^+$.

[00717] Step 2: 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure H using 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.097 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (40 mg, 0.15 mmol, 1.5 equiv) as the starting materials to give 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (17.9 mg, 28.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.36-7.27 (m, 2H), 7.20 (s, 1H), 5.72 (s, 2H), 4.06 (s, 3H),

3.19-2.95 (m, 2H), 2.22-2.06 (m, 2H), 2.06-1.94 (m, 2H), 1.72-1.65 (m, 2H), 1.56-1.42 (m, 2H). MS *m/z*: 630.05 $[M+H]^+$.

6-(3-(Difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (135)



[00718] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg, 1.04 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00719] Step 2: methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.208 mmol, 1.0 equiv) and methyl 5-bromo-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (113 mg, 0.520 mmol, 2.5 equiv) as the starting materials to give methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (100 mg, 83.7%) as a yellow oil. MS *m/z*: 585 $[M+H]^+$.

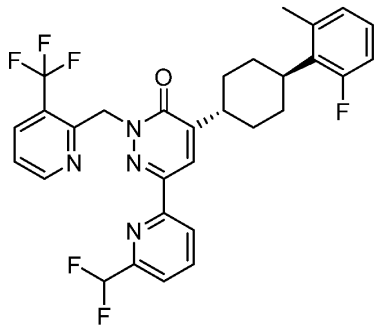
[00720] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(3-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure L using methyl 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (100 mg, 0.171 mmol, 1.0 equiv) and $NaBH_4$ (64.7 mg, 1.71 mmol, 10.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(3-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (68 mg, 71%) as a white solid. MS *m/z*: 557 $[M+H]^+$.

[00721] Step 4: 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carbaldehyde. Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(3-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (68 mg, 0.12 mmol, 1.0 equiv) as the starting material to give 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carbaldehyde (55 mg, 81%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

[00722] Step 5: 6-(3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-methyl-1*H*-1,2,4-triazole-3-carbaldehyde (55 mg, 0.099 mmol, 1.0 equiv) as the starting material to give 6-(3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.1 mg, 51.2%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.6 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 0.9 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.06 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.57 (m, 2H), 5.75 (s, 2H), 4.03 (s, 3H), 3.12 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.19 – 2.09 (m, 4H), 1.87 – 1.83 (m, 2H), 1.62 – 1.51 (m, 2H). MS *m/z*: 577.20 $[M+H]^+$.

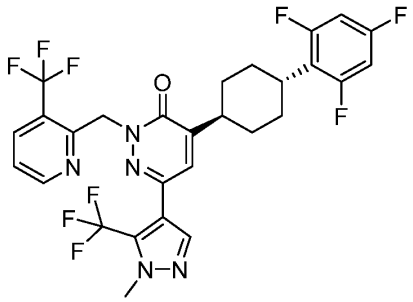
6-(6-(Difluoromethyl)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (136)



[00723] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55.0 mg, 0.114 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg, 0.570 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

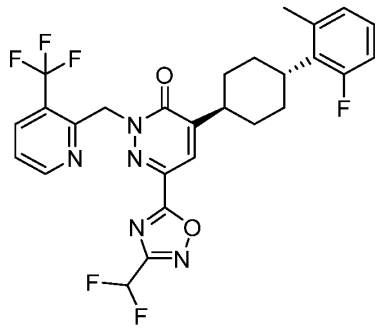
[00724] Step 2: 6-(6-(difluoromethyl)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.114 mmol, 1.0 equiv) and methyl 5-bromothiazole-4-carboxylate (47.1 mg, 0.228 mmol, 2.0 equiv) as the starting materials to give 6-(6-(difluoromethyl)pyridin-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.3 mg, 77.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.8 Hz, 1H), 8.26 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.06 – 7.01 (m, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.87 – 6.59 (m, 2H), 5.78 (s, 2H), 3.11 (t, *J* = 12.0 Hz, 1H), 2.93 (t, *J* = 12.4 Hz, 1H), 2.38 (s, 3H), 2.22 – 2.11 (m, 4H), 1.89 – 1.84 (m, 2H), 1.65 – 1.58 (m, 2H). MS *m/z*: 573.20 $[M+H]^+$.

6-(1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (137)



[00725] Step 1: 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure H using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (52.0 mg, 0.104 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (85.8 mg, 0.312 mmol, 3.0 equiv) as the starting materials to give 6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (28.3 mg, 44.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.33 – 7.30 (m, 1H), 7.16 (s, 1H), 6.60 (t, *J* = 8.8 Hz, 2H), 5.70 (s, 2H), 4.05 (d, *J* = 1.2 Hz, 3H), 3.09 – 2.97 (m, 2H), 2.12 – 2.02 (m, 4H), 1.88 – 1.84 (m, 2H), 1.49 – 1.40 (m, 2H). MS *m/z*: 616.15 $[M+H]^+$.

6-(3-(Difluoromethyl)-1,2,4-oxadiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (138)

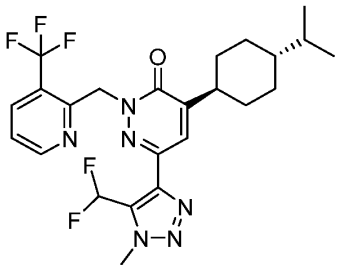


[00726] Step 1: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylic acid. Followed the general procedure C using methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-

1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (300 mg, 0.595 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylic acid (290 mg, 99.4%) as a white solid. MS *m/z*: 490 $[M+H]^+$.

[00727] Step 2: 6-(3-(difluoromethyl)-1,2,4-oxadiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred solution of 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylic acid (100 mg, 0.204 mmol, 1.0 equiv) and DMF (2 mg, 0.02 mmol, 0.1 equiv) in $CHCl_3$ (3 mL) was added oxalyl chloride (259 mg, 2.04 mmol, 10.0 equiv) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred for overnight at room temperature, then concentrated under reduced pressure. The residue was dissolved in acetone (3 mL). To the above mixture was added 2,2-difluoro-N-hydroxyacetimidamide (45.0 mg, 0.408 mmol, 2.0 equiv) and TEA (62.0 mg, 0.612 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in DMSO (3 mL). To the above mixture was added KOH (17.2 mg, 0.306 mmol, 1.5 equiv.) at room temperature. The resulting mixture was stirred for additional 2 h at 80 °C and monitored by LCMS. The resulting mixture was diluted with water (50 mL), extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane/ EtOAc = 1:1) to afford 6-(3-(difluoromethyl)-1,2,4-oxadiazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12.6 mg, 10.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.8 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.95 – 7.90 (m, 1H), 7.35 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.04 (td, *J* = 7.9, 5.5 Hz, 1H), 6.98 – 6.70 (m, 3H), 5.83 (s, 2H), 3.15 – 3.03 (m, 1H), 2.96 – 2.82 (m, 1H), 2.36 (s, 3H), 2.18 – 2.07 (m, 4H), 1.86 (dd, *J* = 13.7, 3.8 Hz, 2H), 1.54 (d, *J* = 12.0 Hz, 2H). MS *m/z*: 564.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (139)



[00728] Step 1: ethyl 4-(prop-1-en-2-yl)cyclohex-3-ene-1-carboxylate. Followed the general procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (6.0 g, 21 mmol, 1.0 equiv) and 1-propene, 2-bromoprop-1-ene (3.89 g, 32.1 mmol, 1.5 equiv) as the starting materials to give ethyl 4-(prop-1-en-2-yl)cyclohex-3-ene-1-carboxylate (2.0 g, 48%) as a brown solid. MS *m/z*: 195 $[M+H]^+$.

[00729] Step 2: ethyl 4-isopropylcyclohexane-1-carboxylate. Followed the general procedure B using ethyl 4-(prop-1-en-2-yl)cyclohex-3-ene-1-carboxylate (2.00 g, 10.3 mmol, 1.0 equiv) as the starting material to give ethyl 4-isopropylcyclohexane-1-carboxylate (1.2 g, 59%) as a brown solid. MS *m/z*: 199 $[M+H]^+$.

[00730] Step 3: 4-isopropylcyclohexane-1-carboxylic acid. Followed the general procedure C using ethyl 4-isopropylcyclohexane-1-carboxylate (0.70 g, 3.5 mmol, 1.0 equiv) as the starting material to give 4-isopropylcyclohexane-1-carboxylic acid (450 mg, 75%) as a brown solid. MS *m/z*: 171 $[M+H]^+$.

[00731] Step 4: 1,3-dioxoisoindolin-2-yl 4-isopropylcyclohexane-1-carboxylate. Followed the general procedure R using 4-isopropylcyclohexane-1-carboxylic acid (410 mg, 2.41 mmol, 1.0 equiv) as the starting material to give 1,3-dioxoisoindolin-2-yl 4-isopropylcyclohexane-1-carboxylate (470 mg, 62%) as a white solid. MS *m/z*: 316 $[M+H]^+$

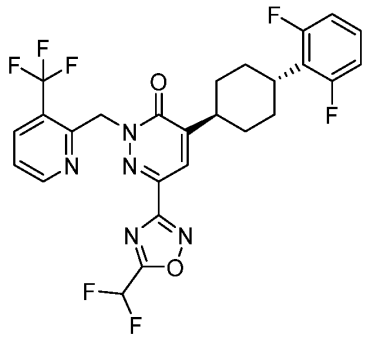
[00732] Step 5: 6-chloro-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 4-isopropylcyclohexane-1-carboxylate (420 mg, 1.33 mmol, 1.0 equiv.) and 4-bromo-6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (489 mg, 1.33 mmol, 1.0 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (170 mg, 31%) as a white solid. MS *m/z* : 414 $[M+H]^+$.

[00733] Step 6: (5-((1*r*,4*r*)-4-isopropylcyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.242 mmol, 1.0 equiv.) as the starting materials to

give (5-((1r,4r)-4-isopropylcyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 424 $[M+H]^+$

[00734] Step 7: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-isopropylcyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.242 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (61.3 mg, 0.290 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (33.1 mg, 26.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 4.7 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 0.9 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.25 – 7.01 (m, 1H), 5.68 (s, 2H), 4.23 (s, 3H), 3.01 – 2.76 (m, 1H), 2.11 – 1.93 (m, 2H), 1.91 – 1.74 (m, 2H), 1.53 – 1.27 (m, 3H), 1.27 – 1.06 (m, 3H), 0.88 (d, *J* = 6.8 Hz, 6H). MS *m/z*: 511.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (140)

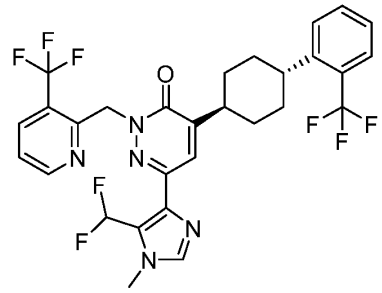


[00735] Step 1: 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.413 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (160 mg, 81.5%) as a white solid. MS *m/z*: 475 $[M+H]^+$

[00736] Step 2: 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide . Followed the general procedure X using 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (160 mg, 0.337 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (140 mg) as a white solid. MS *m/z*: 508 $[M+H]^+$.

[00737] Step 3: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (60.0 mg, 0.118 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52.7 mg, 74.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.36 – 7.30 (m, 1H), 7.19 – 7.01 (m, 1H), 6.92 – 6.74 (m, 3H), 5.83 (s, 2H), 3.16 – 3.02 (m, 2H), 2.18 – 2.03 (m, 4H), 1.92 (s, 2H), 1.61 – 1.48 (m, 2H). MS *m/z*: 568.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (141)



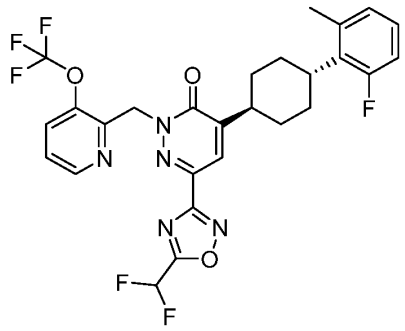
[00738] Step 1: (6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general Procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.097 mmol, 1.0 equiv) as the starting material to give (6-oxo-5-((1*r*,4*r*)-4-(2-

(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 526 $[M+H]^+$.

[00739] Step 2: 1-methyl-4-(6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde. Followed the general Procedure H using (6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.097 mmol, 1.0 equiv) and 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde as the starting materials to give 1-methyl-4-(6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde (45 mg, 79%) as a white solid. MS *m/z*: 590 [M+H].

[00740] Step 3: 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure I using 1-methyl-4-(6-oxo-5-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-imidazole-5-carbaldehyde (45 mg, 0.076 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-methyl-1*H*-imidazol-4-yl)-4-((1*r*,4*r*)-4-(2-(trifluoromethyl)phenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.8 mg, 48.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.91 (s, 1H), 7.67-7.56 (m, 2H), 7.55-7.43 (m, 2H), 7.40-7.33 (m, 1H), 7.31-7.27 (m, 1H), 7.10 (t, *J* = 52.8 Hz, 1H), 5.70 (s, 2H), 3.84 (s, 3H), 3.12 (tt, *J* = 11.6, 3.2 Hz, 1H), 3.02 (t, *J* = 11.9 Hz, 1H), 2.23-2.08 (m, 2H), 2.03-1.94 (m, 2H), 1.77-1.54 (m, 4H). MS *m/z*: 612.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (142)

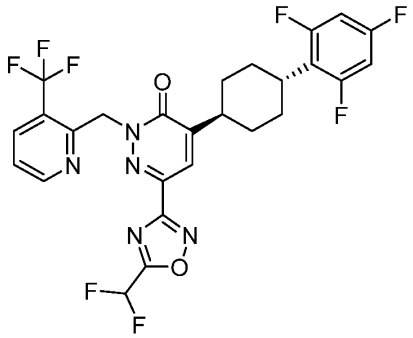


[00741] Step 1: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.202 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (60 mg, 61%) as a white solid. MS *m/z*: 487 $[M+H]^+$.

[00742] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (50.0 mg, 0.103 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg) as a white solid. MS *m/z*: 520 $[M+H]^+$.

[00743] Step 3: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg, 0.096 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (27.6 mg, 49.2%) as a white solid. ^{1}H NMR(400 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 4.6 Hz, 1H), 7.84 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.09 – 6.97 (m, 1H), 6.96 – 6.74 (m, 3H), 5.73 (s, 2H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.1 Hz, 1H), 2.36 (s, 3H), 2.22 – 2.11 (m, 2H), 1.92 – 1.79 (m, 2H), 1.68 – 1.46 (m, 4H). MS *m/z*: 580.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (143)



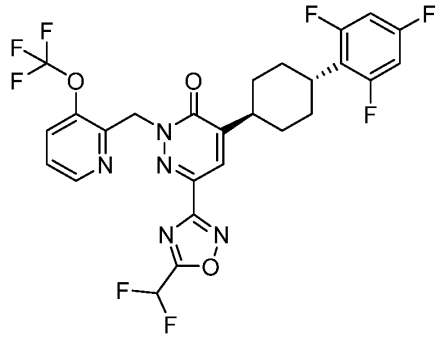
[00744] Step 1: 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile (60 mg, 58%) as a yellow solid. MS *m/z*: 493 $[M+H]^+$.

[00745] Step 2: *N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile (60.0 mg, 0.122 mmol, 1.0 equiv) as the starting material to give *N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboximidamide (crude), which was used in the next step directly without further purification. MS *m/z*: 526 $[M+H]^+$

[00746] Step 3: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using *N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboximidamide (crude, 0.122 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (23.8 mg, 33.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 1.2 Hz, 1H), 7.31 (t, *J* = 6.4 Hz, 1H), 6.89 (t, *J* = 52 Hz, 1H), 6.60 (t, *J* = 8.8 Hz, 2H), 5.83 (s, 2H), 3.05 –

3.00 (m, 2H), 2.13 (d, *J* = 13.1 Hz, 2H), 2.02 (t, *J* = 12.8 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.59 – 1.48 (m, 2H). MS *m/z*: 586.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (144)



[00747] Step 1: 6-chloro-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (200 mg, 0.584 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine hydrochloride (217 mg, 0.876 mmol, 1.5 equiv) as the starting materials to give 6-chloro-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (230 mg, 76.1%) as a white solid. MS *m/z*: 518 $[M+H]^+$.

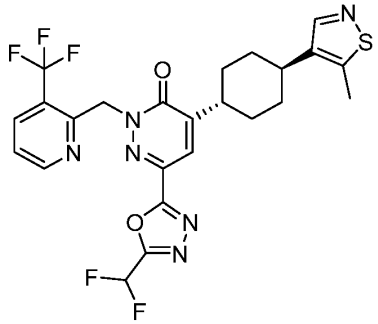
[00748] Step 2: 6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (230 mg, 0.444 mmol, 1.0 equiv) as the starting material to give 6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile (186 mg, 82.3%) as a white solid. MS *m/z*: 509 $[M+H]^+$.

[00749] Step 3: *N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carbonitrile (90.0 mg, 0.177 mmol, 1.0 equiv) as the starting material to give the crude product *N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-

dihydropyridazine-3-carboximidamide (crude) which was used in the next step directly without further purification. MS *m/z*: 542 $[M+H]^+$.

[00750] Step 4: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using *N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazine-3-carboximidamide (crude, 0.177 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (43.1 mg, 40.4%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 4.8 Hz, 1H), 7.83 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.28 (m, 1H), 6.88 (t, *J* = 52.0 Hz, 1H), 6.60 (t, *J* = 8.8 Hz, 2H)), 5.73 (s, 2H), 3.10 – 3.00 (m, 2H), 2.15 – 2.09 (m, 2H), 2.02 (t, *J* = 12.8 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.56 – 1.47 (m, 2H). MS *m/z*: 602.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(5-methylisothiazol-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (145)



[00751] Step 1: 4-bromo-5-methylisothiazole. To a stirred mixture of 4-bromo-1,2-thiazole (1.0 g, 6.1 mmol, 1.0 equiv) and methyl iodide (1.3 g, 9.1 mmol, 1.5 equiv) in THF (15 mL) was added n-BuLi (0.43 g, 6.7 mmol, 1.1 equiv) in portions was stirred for 2 h at -78 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (100 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA = 5:1) to afford 4-bromo-5-methylisothiazole (600 mg, 51%) as a colorless liquid. MS *m/z*: 178 $[M+H]^+$

[00752] Step 2: ethyl 4-(5-methylisothiazol-4-yl)cyclohex-3-ene-1-carboxylate. Followed the general procedure A using 4-bromo-5-methylisothiazole (580 mg, 3.25 mmol, 1.0 equiv) and ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (1.37 g, 4.88 mmol, 1.5 equiv) as the starting materials to give ethyl 4-(5-methylisothiazol-4-yl)cyclohex-3-ene-1-carboxylate3(400 mg, 81%) as a colorless liquid. MS *m/z*: 252 $[M+H]^+$.

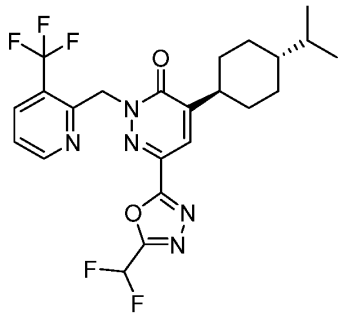
[00753] Step 3: ethyl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylate. Followed the general procedure B using 4-(5-methylisothiazol-4-yl)cyclohex-3-ene-1-carboxylate (400 mg, 1.59 mmol, 1.0 equiv) as the starting material to give ethyl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylate (300 mg, 68%) as a white solid. MS *m/z*: 254 $[M+H]^+$.

[00754] Step 4: 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylic acid. Followed the general procedure C using ethyl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carbo (300 mg, 1.18 mmol, 1.0 equiv) and LiOH (141 mg, 5.92 mmol, 5.0 equiv) as the starting materials to give 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylic acid (200 mg, 71%) as a white solid. MS *m/z*: 226 $[M+H]^+$.

[00755] Step 5: 1,3-dioxoisoindolin-2-yl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylate. Followed the general procedure R using 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylic acid (200 mg, 1.28 mmol, 1.0 equiv) and *N*-hydroxyphthalimide (272 mg, 1.67 mmol, 1.3 equiv) as the starting materials to give 1,3-dioxoisoindolin-2-yl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylate (300 mg, 59%) as a colorless liquid. MS *m/z*: 371 $[M+H]^+$.

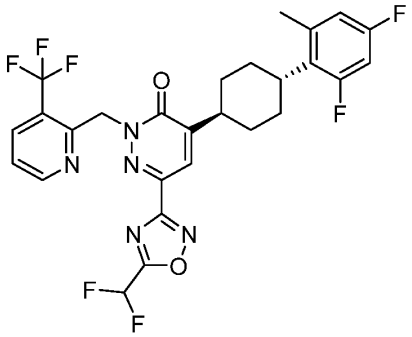
[00756] Step 6: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(5-methylisothiazol-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 4-(5-methylisothiazol-4-yl)cyclohexane-1-carboxylate (80 mg, 0.21 mmol, 1.0 equiv) and 4-bromo-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (78 mg, 0.17 mmol, 0.8 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(5-methylisothiazol-4-yl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.2 mg, 8.9%) as a white soild. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 – 8.53 (m, 1H), 8.29 (s, 1H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.95 (d, *J* = 0.9 Hz, 1H), 7.34 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.90 (t, *J* = 51.6 Hz, 1H), 5.79 (s, 2H), 3.11 – 3.00 (m, 1H), 2.73 – 2.64 (m, 1H), 2.47 (s, 3H), 2.19 – 2.08 (m, 2H), 2.06 – 1.96 (m, 2H), 1.73 (dd, *J* = 12.9, 3.1 Hz, 1H), 1.65 (dd, *J* = 11.5, 9.1 Hz, 1H), 1.62 – 1.51 (m, 2H). MS *m/z*: 553.10 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (146)



[00757] Step 1: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 4-bromo-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.11 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl 4-isopropylcyclohexane-1-carboxylate (52.3 mg, 0.167 mmol, 1.5 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-isopropylcyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.5 mg, 23%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.7 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.38 – 7.29 (m, 1H), 6.89 (t, *J* = 51.7 Hz, 1H), 5.78 (s, 2H), 2.97 – 2.77 (m, 1H), 2.08 – 1.96 (m, 2H), 1.89 – 1.82 (m, 2H), 1.51 – 1.40 (m, 1H), 1.41 – 1.27 (m, 2H), 1.27 – 1.09 (m, 3H), 0.91 – 0.85 (m, 6H). MS *m/z*: 498.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (147)

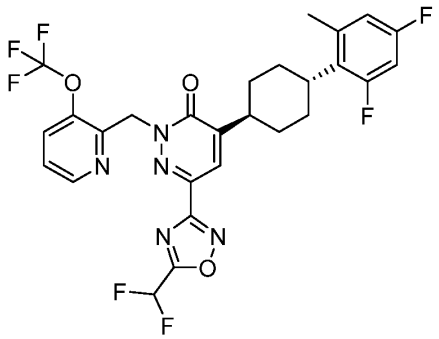


[00758] Step 1: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.201 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (70 mg, 71%) as a white solid. MS *m/z*: 498 $[M+H]^+$

[00759] Step 2: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (70 mg, 0.13 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg, 67%) as a white solid. MS *m/z*: 522 $[M+H]^+$.

[00760] Step 3: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg, 0.09 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (32.3 mg, 57%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.36 – 7.29 (m, 1H), 6.89 (t, *J* = 52.0, 1H), 6.71 – 6.64 (m, 1H), 6.65 – 6.56 (m, 1H), 5.83 (s, 2H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.90 – 2.78 (m, 1H), 2.34 (s, 3H), 2.17 – 2.04 (m, 4H), 1.88 – 1.79 (m, 2H), 1.53 (dd, *J* = 12.4 Hz, 2H). MS *m/z*: 582.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (148)



[00761] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.295 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (68.4 mg, 0.354 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 95%) as a white solid. MS *m/z*: 514 $[M+H]^+$

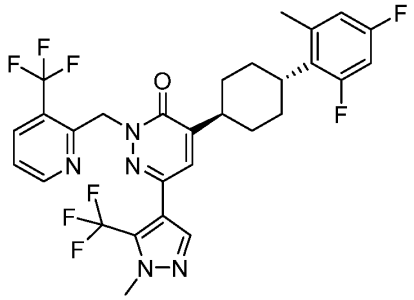
[00762] Step 2: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one(100 mg, 0.195 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (90 mg, 91%) as a white solid. MS *m/z*: 505 $[M+H]^+$.

[00763] Step 3: 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (90 mg, 0.17 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (70 mg, 73%) as a white solid. MS *m/z*: 538 $[M+H]^+$.

[00764] Step 4: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-

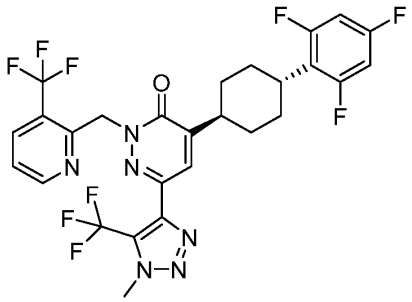
yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (70 mg, 0.13 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52.3 mg, 67.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 – 8.35 (m, 1H), 7.84 (s, 1H), 7.66 – 7.58 (m, 1H), 7.32 – 7.28 (m, 1H), 6.95 (t, *J* = 52.0 Hz, 1H), 6.70 – 6.65 (m, 1H), 6.64 – 6.57 (m, 1H), 5.73 (s, 2H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.83 (t, *J* = 12.0 Hz, 1H), 2.34 (s, 3H), 2.17 – 2.01 (m, 4H), 1.90 – 1.83 (m, 2H), 1.58 – 1.46 (m, 2H). MS *m/z*: 598.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (149)



[00765] Step 1: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (33 mg, 0.12 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18.2 mg, 29%) as white soild. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.36 – 7.29 (m, 1H), 7.17 (s, 1H), 6.70 – 6.55 (m, 2H), 5.71 (s, 2H), 4.12 – 3.95 (m, 3H), 3.06 (t, *J* = 12.4 Hz, 1H), 2.81 (d, *J* = 12.9 Hz, 1H), 2.33 (d, *J* = 7.1 Hz, 3H), 2.10 (d, *J* = 11.8 Hz, 4H), 1.80 (d, *J* = 12.9 Hz, 2H), 1.52 – 1.39 (m, 2H). MS *m/z*: 612.25 $[M+H]^+$.

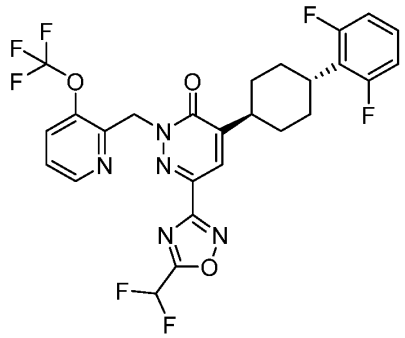
6-(1-Methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (150)



[00766] Step 1: (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (70 mg, 0.139 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (212 mg, 0.834 mmol, 6.0 equiv) as the starting materials to give (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 512 $[M+H]^+$.

[00767] Step 2: 6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure H using 6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.139 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole hydrochloride (73.6 mg, 0.278 mmol, 2.0 equiv) as the starting materials to give 6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (29.5 mg, 34.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.8 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.81 (s, 1H), 7.38 – 7.35 (m, 1H), 6.60 (t, *J* = 8.8 Hz, 2H), 5.74 (s, 2H), 4.23 (s, 3H), 3.13 – 2.98 (m, 2H), 2.14 (d, *J* = 13.2 Hz, 2H), 2.07 – 2.01 (m, 2H), 1.90 – 1.85 (m, 2H), 1.58 – 1.48 (m, 2H). MS *m/z*: 617.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (151)



[00768] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 4-bromo-6-chloropyridazin-3(2*H*)-one (200 mg, 0.955 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl 4-(2,6-difluorophenyl)cyclohexane-1-carboxylate (552 mg, 1.43 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (130 mg, 41.9%) as a white solid. MS *m/z*: 325 $[M+H]^+$.

[00769] Step 2: 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure F using 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (130 mg, 0.400 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethoxy)pyridine (93.2 mg, 0.440 mmol, 1.1 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (160 mg, 79.9%) as a white solid. MS *m/z*: 500 $[M+H]^+$

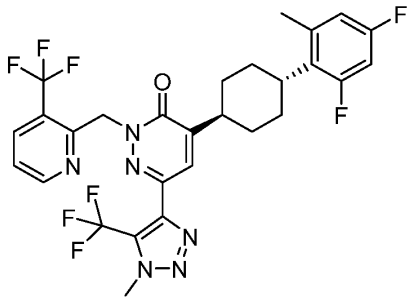
[00770] Step 3: 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile. To a stirred solution of 6-chloro-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.30 mmol, 1.0 equiv) and $K_4[Fe(CN)_6]$ (55.2 mg, 0.15 mmol, 0.5 equiv) in 1.4-dioxane (2 mL) and H_2O (2 mL) were added KOAc (14.7 mg, 0.15 mmol, 0.5 equiv), *t*BuXPhos Pd G3 (47.6 mg, 0.06 mmol, 0.2 equiv) and Me*4*tBuXPhos (28.0 mg, 0.06 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 100°C. The reaction was monitored by LCMS. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified

by silica gel column chromatography, eluted with EtOAc/PE = 1/1 to afford 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (80 mg, 54%) as a white solid. MS *m/z*: 491 $[M+H]^+$.

[00771] Step 4: 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide. Followed the general procedure X using 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (70.0 mg, 0.143 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-N-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg, 66%) as a white solid. MS *m/z*: 524 $[M+H]^+$

[00772] Step 5: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (50 mg, 0.096 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.1 mg, 53.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 – 8.36 (m, 1H), 7.83 (d, *J* = 0.9 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.30 – 7.27 (m, 1H), 7.16 – 7.00 (m, 1H), 6.89 – 6.75 (m, 3H), 5.73 (s, 2H), 3.18 – 3.01 (m, 2H), 2.19 – 2.00 (m, 4H), 1.95 – 1.88 (m, 2H), 1.60 – 1.47 (m, 2H). MS *m/z*: 584.20 $[M+H]^+$.

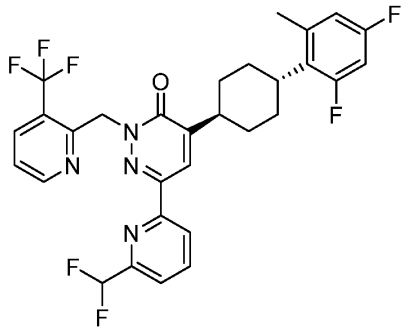
4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (152)



[00773] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg, 1.04 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$

[00774] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (45 mg, 0.20 mmol, 2.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.5 mg, 22%) as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.7 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.82 (s, 1H), 7.39 – 7.29 (m, 1H), 6.74 – 6.52 (m, 2H), 5.71 (s, 2H), 4.24 (d, *J* = 2.1 Hz, 3H), 3.11 (t, *J* = 12.1 Hz, 1H), 2.83 (t, *J* = 12.4 Hz, 1H), 2.34 (s, 3H), 2.24 – 1.99 (m, 4H), 1.88 – 1.76 (m, 2H), 1.53 (d, *J* = 12.2 Hz, 2H). MS *m/z*: 613.30 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(6-(difluoromethyl)pyridin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (153)

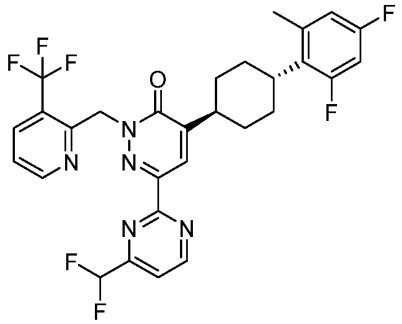


[00775] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the

general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg, 1.04 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$.

[00776] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(6-(difluoromethyl)pyridin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv) and 2-bromo-6-(difluoromethyl)pyridine (25 mg, 0.12 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(6-(difluoromethyl)pyridin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.7 mg, 19.8%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 – 8.62 (m, 1H), 8.26 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.19 – 8.06 (m, 3H), 7.78 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.56 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.18 (d, *J* = 54.9 Hz, 1H), 7.03 – 6.84 (m, 2H), 5.69 (s, 2H), 3.05 – 2.77 (m, 2H), 2.37 (s, 3H), 1.88 (dt, *J* = 39.9, 12.4 Hz, 6H), 1.59 (t, *J* = 12.1 Hz, 2H). MS *m/z*: 591.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)pyrimidin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (154)

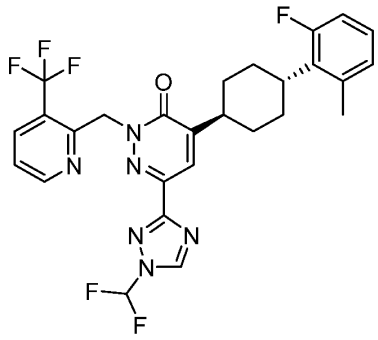


[00777] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg, 1.04 mmol, 5.0

equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$.

[00778] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)pyrimidin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv) and 2-chloro-4-(difluoromethyl)pyrimidine (20 mg, 0.12 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)pyrimidin-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (8.9 mg, 15%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (d, *J* = 5.0 Hz, 1H), 8.66 (d, *J* = 4.6 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.22 (s, 1H), 7.86 (d, J = 5.1 Hz, 1H), 7.55 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.19 (d, *J* = 54.0 Hz, 1H), 7.01 – 6.90 (m, 2H), 5.70 (s, 2H), 3.01 – 2.79 (m, 2H), 2.37 (s, 3H), 1.88 (dt, *J* = 40.6, 12.4 Hz, 6H), 1.60 (t, *J* = 12.2 Hz, 2H). MS *m/z*: 592.30 $[M+H]^+$.

6-(1-(Difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (155)



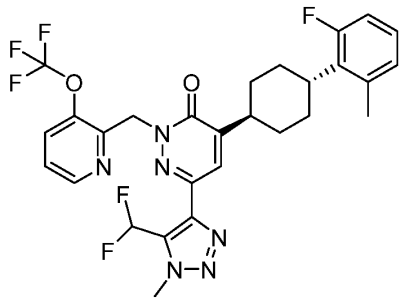
[00779] Step 1: 3-bromo-1-(difluoromethyl)-1*H*-1,2,4-triazole. Followed the general Procedure F using 3-bromo-1*H*-1,2,4-triazole (1.00 g, 6.76 mmol, 1.0 equiv) and CHF_2Cl (gas) as the starting materials to give 3-bromo-1-(difluoromethyl)-1*H*-1,2,4-triazole (0.94 g, 70%) as a colorless liquid. MS *m/z*: 198 $[M+H]^+$

[00780] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the

general Procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00781] Step 3: 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.204 mmol, 1.0 equiv) and 3-bromo-1-(difluoromethyl)-1*H*-1,2,4-triazole (48.5 mg, 0.245 mmol, 1.2 equiv) as the starting materials to give 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19.6 mg, 17.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 7.96 (d, *J* = 4.4 Hz, 2H), 7.42 (d, *J* = 60.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.09 – 6.99 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.80 (m, 1H), 5.83 (s, 2H), 3.10 (tt, *J* = 12.1, 3.0 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.29 – 2.06 (m, 4H), 1.94 – 1.82 (m, 2H), 1.62 – 1.49 (m, 2H). MS *m/z*: 563.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (156)

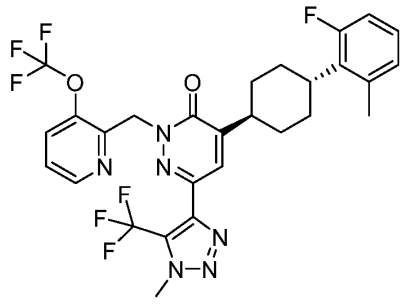


[00782] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (72 mg, 0.50 mmol, 5.0 equiv)

as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 506 $[M+H]^+$.

[00783] Step 2: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (25 mg, 0.12 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (35.5 mg, 60%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 4.7 Hz, 1H), 7.99 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.16 (d, *J* = 52.6 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.64 (s, 2H), 4.25 (s, 3H), 3.12 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.13 (t, *J* = 12.7 Hz, 4H), 1.90 – 1.82 (m, 2H), 1.61 – 1.48 (m, 2H). MS *m/z*: 593.25 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (157)



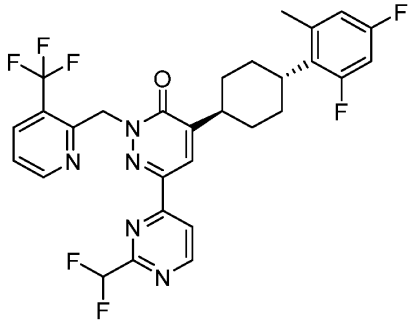
[00784] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure S using 4-bromo-6-chloro-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (600 mg, 1.56 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (892 mg, 2.34 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (400 mg, 66%) as a white solid. MS *m/z*: 596 $[M+H]^+$.

[00785] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (72 mg, 0.50 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 506 $[M+H]^+$

[00786] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethoxy)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.10 mmol, 1.0 equiv.) and 4-bromo-1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazole (27.3 mg, 0.12 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethoxy)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.5 mg, 37%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 4.7 Hz, 1H), 7.82 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.06 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.82 (m, 1H), 5.66 (s, 2H), 4.30 – 4.17 (m, 3H), 3.12 (t, *J* = 12.1 Hz, 1H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.22 – 2.08 (m, 4H), 1.89 – 1.82 (m, 2H), 1.61 – 1.48 (m, 2H). MS *m/z*: 611.25 $[M+H]^+$.

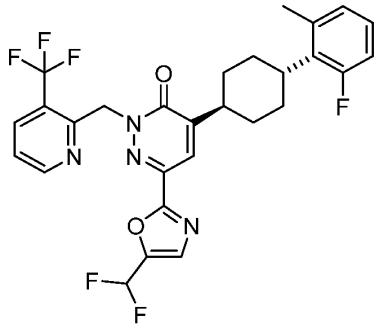
4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (158)



[00787] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60.0 mg, 0.121 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$

[00788] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((1r,4r)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.118 mmol, 1.0 equiv) and 4-chloro-2-(difluoromethyl)pyrimidine (23.3 mg, 0.142 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (12.5 mg, 17.9%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (d, J = 5.3 Hz, 1H), 8.68 (d, J = 4.8 Hz, 1H), 8.31 – 8.22 (m, 1H), 8.20 – 8.10 (m, 2H), 7.56 (dd, J = 7.9, 4.9 Hz, 1H), 7.17 (d, J = 54.0 Hz, 1H), 7.02 – 6.87 (m, 2H), 5.72 (s, 2H), 3.05 – 2.80 (m, 2H), 2.37 (s, 3H), 1.88 (dt, J = 39.5, 12.2 Hz, 6H), 1.61 (t, J = 12.3 Hz, 2H). MS *m/z*: 592.25 $[M+H]^+$.

6-(5-(Difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (159)



[00789] **Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid.** Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.313 mmol, 1.0

equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (396 mg, 1.56 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00790] Step 2: ethyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylate. Followed the general procedure H using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.313 mmol, 1.0 equiv) and ethyl 2-bromooxazole-5-carboxylate (137 mg, 0.626 mmol, 2.0 equiv) as the starting materials to give ethyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylate (160 mg, 89%) as a yellow oil. MS *m/z*: 585 $[M+H]^+$.

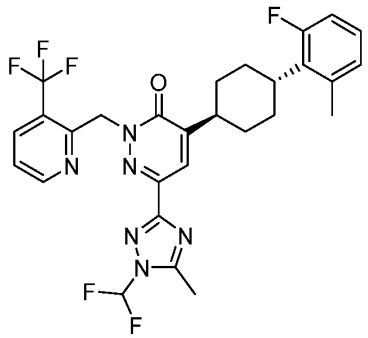
[00791] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)oxazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure L using ethyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carboxylate (150 mg, 0.257 mmol, 1.0 equiv) and $NaBH_4$ (97.0 mg, 2.57 mmol, 10.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)oxazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 43%) as a white solid. MS *m/z*: 543 $[M+H]^+$.

[00792] Step 4: 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carbaldehyde. Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(3-(hydroxymethyl)-1-methyl-1*H*-1,2,4-triazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (68 mg, 0.122 mmol, 1.0 equiv) and Dess-Martin periodinane (136 mg, 0.321 mmol, 3.0 equiv) as the starting materials to give 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-5-carbaldehyde (55 mg, 83%) as a white solid. MS *m/z*: 541 $[M+H]^+$.

[00793] Step 5: 6-(5-(difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure I using 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-

dihydropyridazin-3-yl)oxazole-5-carbaldehyde (55.0 mg, 0.102 mmol, 1.0 equiv) and DAST (164 mg, 1.02 mmol, 10.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.9 mg, 24.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.90 (s, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.33 –7.30 (m, 1H), 7.06 – 7.01 (m, 1H), 6.93 – 6.64 (m, 3H), 5.79 (s, 2H), 3.08 (tt, *J* = 12.0, 2.9 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.36 (s, 3H), 2.18 – 2.09 (m, 4H), 1.88 – 1.83 (m, 2H), 1.59 – 1.49 (m, 2H). MS *m/z*: 563.20 [M+H]$^+$.

6-(1-(Difluoromethyl)-5-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (160)



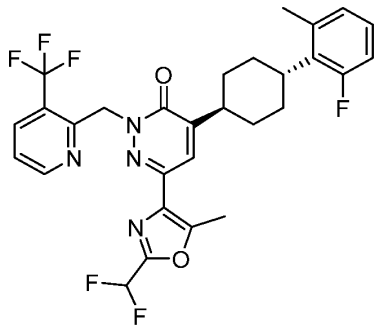
[00794] Step 1: 3-bromo-1-(difluoromethyl)-5-methyl-1*H*-1,2,4-triazole. To a stirred mixture of 3-bromo-5-methyl-1*H*-1,2,4-triazole (1.0 g, 6.2 mmol, 1.0 equiv) in DMF (5 mL) was added K_2CO_3 (2.56 g, 18.5 mmol, 3.0 equiv) in portions at room temperature. The resulting mixture was stirred for overnight at room temperature under CHF_2Cl atmosphere. The reaction was monitored by LCMS. After complete disappearance of the starting material, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford 3-bromo-1-(difluoromethyl)-5-methyl-1*H*-1,2,4-triazole (900 mg, 68%) as a colorless semi-solid. MS *m/z*: 212 [M+H]$^+$.

[00795] Step 2: (5-((*1r,4r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-

(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.209 mmol, 1.0 equiv) as the starting material to give (5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00796] Step 3: 6-(1-(difluoromethyl)-5-methyl-1H-1,2,4-triazol-3-yl)-4-((*1r,4r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure H using (5-((*1r,4r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.209 mmol, 1 equiv) and 3-bromo-1-(difluoromethyl)-5-methyl-1*H*-1,2,4-triazole (53.2 mg, 0.250 mmol, 1.2 equiv) as the starting materials to give 6-(1-(difluoromethyl)-5-methyl-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (52.7 mg, 45%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.8 Hz, 1H), 8.25 (dd, J = 8.0, 1.5 Hz, 1H), 8.06 (t, J = 56.9 Hz, 1H), 7.86 (s, 1H), 7.59 – 7.51 (m, 1H), 7.16 – 7.05 (m, 1H), 7.04 – 6.89 (m, 2H), 5.65 (s, 2H), 3.04 – 2.80 (m, 2H), 2.65 (s, 3H), 2.36 (s, 3H), 2.04 – 1.86 (m, 4H), 1.84 – 1.74 (m, 2H), 1.68 – 1.49 (m, 2H). MS *m/z*: 577.25 $[M+H]^+$.

6-(2-(Difluoromethyl)-5-methyloxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (161)



[00797] Step 1: ethyl 4-bromo-5-methyloxazole-2-carboxylate. A mixture of ethyl 5-methyloxazole-2-carboxylate (500 mg, 3.23 mmol, 1 equiv) and NBS (1.14 g, 6.46 mmol, 2 equiv) in AcOH (5 mL) was stirred at 80 °C for overnight under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate

was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford ethyl 4-bromo-5-methyloxazole-2-carboxylate as a colorless liquid (300 mg, 40%) as a colorless liquid. MS *m/z*: 234 $[M+H]^+$.

[00798] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid. Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.416 mmol, 1.0 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (288 mg, 2.08 mmol, 5.0 equiv) as the starting materials to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00799] Step 3: ethyl 4-(5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carboxylate. Followed the general Procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.416 mmol, 1.0 equiv) and ethyl 4-bromo-5-methyloxazole-2-carboxylate (194 mg, 0.832 mmol, 2.0 equiv) as the starting materials to give ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carboxylate (170 mg, 68%) as a white solid. MS *m/z*: 599 $[M+H]^+$.

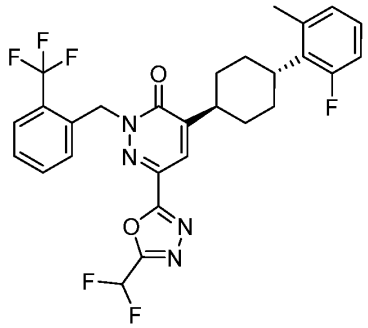
[00800] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-5-methyloxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure L using ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carboxylate (170 mg, 0.289 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-5-methyloxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 94%) as a white solid. MS *m/z*: 557 $[M+H]^+$.

[00801] Step 5: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carbaldehyde. Followed the general Procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-5-methyloxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.270 mmol, 1.0 equiv) as the starting material to give 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-

1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carbaldehyde (85 mg, 57%) as a white solid. MS *m/z*: 555 $[M+H]^+$

[00802] Step 6: 6-(2-(difluoromethyl)-5-methyloxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general Procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methyloxazole-2-carbaldehyde (85 mg, 0.15 mmol, 1.0 equiv) as the starting material to give 6-(2-(difluoromethyl)-5-methyloxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (23.6 mg, 26.8%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.10 – 6.97 (m, 1H), 6.96 – 6.81 (m, 2H), 6.63 (t, *J* = 52.6 Hz, 1H), 5.71 (s, 2H), 3.12 (t, *J* = 12.1 Hz, 1H), 2.87 (t, *J* = 12.6 Hz, 1H), 2.46 (s, 3H), 2.36 (s, 3H), 2.25-2.07 (m, 4H), 1.91 – 1.77 (m, 2H), 1.57 – 1.43 (m, 2H). MS *m/z*: 577.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (162)



[00803] Step 1: methyl 5-bromo-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate. Followed the general procedure F using methyl 5-bromo-6-oxo-1,6-dihydropyridazine-3-carboxylate (1.00 g, 4.29 mmol, 1.0 equiv) and 1-(chloromethyl)-2-(trifluoromethyl)benzene (0.920 g, 4.72 mmol, 1.1 equiv) as the starting materials to give methyl 5-bromo-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate (1.2 g, 71%) as a light yellow solid. MS *m/z*: 391 $[M+H]^+$.

[00804] Step 2: methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate. Followed the general procedure S using methyl 5-bromo-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate (300 mg, 0.767 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-

2-yl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (438 mg, 1.15 mmol, 1.5 equiv) as the starting materials to give methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate (280 mg, 72%) as a white solid. MS *m/z*: 503 $[M+H]^+$.

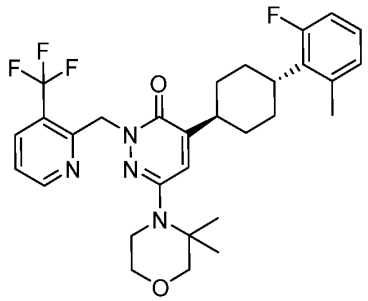
[00805] Step 3: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide. Followed the general procedure N using methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboxylate (100 mg, 0.199 mmol, 1.0 equiv) and hydrazine hydrate (30.5 mg, 0.597 mmol, 3.0 equiv) as the starting materials to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide which was used directly in the next step. MS *m/z*: 503 $[M+H]^+$.

[00806] Step 4: *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide. Followed the general procedure O using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide (crude, 0.199 mmol, 1.0 equiv) and 2,2-difluoroacetic anhydride (69.2 mg, 0.398 mmol, 2.0 equiv) as the starting materials to give *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide (100 mg, 86%) as a white solid. MS *m/z*: 581 $[M+H]^+$.

[00807] Step 5: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one. To a stirred mixture of *N'*-(2,2-difluoroacetyl)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbohydrazide (50 mg, 0.086 mmol, 1.0 equiv) in acetonitrile (1.5 mL) were added DIEA (33.4 mg, 0.258 mmol, 3.0 equiv) and 4-methylbenzenesulfonyl chloride (41.0 mg, 0.215 mmol, 2.5 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature and monitored by LCMS. After complete disappearance of the starting material, the resulting mixture was diluted with water (60 mL), extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane / EA 3:1) to afford 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (16.4 mg, 33.8%) as an off-white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93

(s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.95 – 6.76 (m, 3H), 5.71 (s, 2H), 3.13 (t, *J* = 12.0 Hz, 1H), 2.89 (t, *J* = 12.4 Hz, 1H), 2.37 (s, 3H), 2.21 – 2.11 (m, 4H), 1.87 (d, *J* = 12.8 Hz, 2H), 1.59 – 1.47 (m, 2H). MS *m/z*: 563.10 $[M+H]^+$.

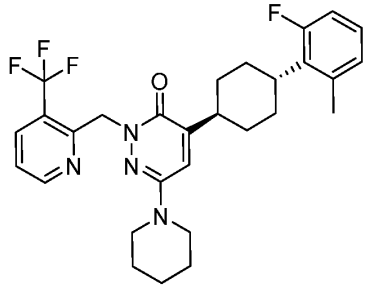
6-(3,3-Dimethylmorpholino)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (163)



[00808] Step 1: 6-(3,3-dimethylmorpholino)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one (200 mg, 0.42 mmol, 1.0 equiv) and 3,3-dimethylmorpholine (72.3 mg, 0.63 mmol, 1.5 equiv) as the starting materials to give 6-(3,3-dimethylmorpholino)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (130 mg, 56%) as a white solid. MS *m/z*: 557 $[M+H]^+$

[00809] Step 2: 6-(3,3-dimethylmorpholino)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure B using ethyl 6-(3,3-dimethylmorpholino)-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (131 mg, 0.235 mmol, 1.0 equiv) as the starting material to give 6-(3,3-dimethylmorpholino)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.8 mg, 9.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.6 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.31 – 7.28 (m, 1H), 7.08 – 6.98 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.86 – 6.76 (m, 1H), 5.60 (s, 2H), 3.82 (s, 2H), 3.40 (s, 2H), 3.15 (s, 2H), 3.05 (t, *J* = 12.2 Hz, 1H), 2.88 (t, *J* = 12.2 Hz, 1H), 2.36 (s, 3H), 2.24 (d, *J* = 13.9 Hz, 2H), 2.08 – 1.99 (m, 2H), 1.91 (d, *J* = 13.4 Hz, 2H), 1.63 (d, *J* = 13.0 Hz, 2H), 1.14 (s, 6H). MS *m/z*: 559.25 $[M+H]^+$.

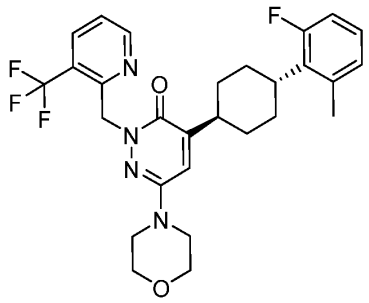
4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (164)



[00810] Step 1: 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (110 mg, 0.230 mmol, 1.0 equiv) and piperidine (29.4 mg, 0.345 mmol, 1.5 equiv) as the starting materials, $Pd_2(dba)_3$ (42 mg, 0.046 mmol, 0.2 equiv) as the catalyst, XPhos (22 mg, 0.046 mmol, 0.2 equiv) as the ligand and Cs_2CO_3 (224 mg, 0.69 mmol, 3.0 equiv) as the base to give 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (108 mg, 89%) as a white solid. MS *m/z*: 527 $[M+H]^+$.

[00811] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure B using 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.190 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(piperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.1 mg, 9.9%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.64 (d, J = 4.8 Hz, 1H), 8.17 – 8.11 (m, 1H), 7.50 – 7.46 (m, 1H), 7.25 (s, 1H), 7.08 – 7.00 (m, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.87 – 6.80 (m, 1H), 5.52 (s, 2H), 3.22 (d, J = 4.4 Hz, 4H), 3.00 – 2.92 (m, 2H), 2.37 (s, 3H), 2.17 – 1.99 (m, 4H), 1.87 – 1.79 (m, 2H), 1.58 (s, 8H). MS *m/z*: 529.25 $[M+H]^+$.

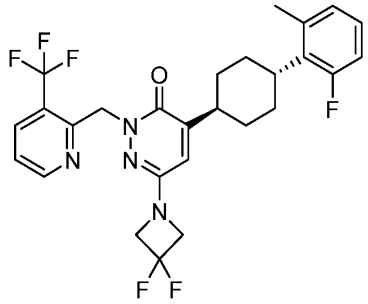
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (165)



[00812] Step 1: 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-on. Followed the general procedure Z using 6-chloro-4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.314 mmol, 1.0 equiv) and morpholine (54.6 mg, 0.628 mmol, 2.0 equiv) as the starting materials to give 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120 mg, 72%) as a yellow oil. MS *m/z*: 529 $[M+H]^+$.

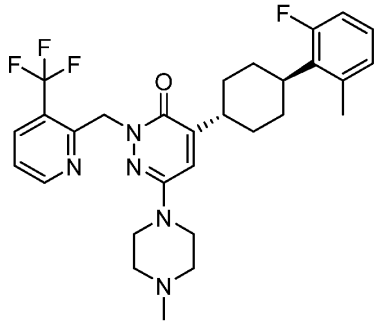
[00813] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure B using 4-(2'-fluoro-6'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (120 mg, 0.227 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (21.6 mg, 17.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.05 – 7.01 (m, 1H), 7.00 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.86 – 6.81 (m, 1H), 5.56 (s, 2H), 3.79 (t, *J* = 4.8 Hz, 4H), 3.21 (t, *J* = 4.8 Hz, 4H), 3.06 (t, *J* = 12.0 Hz, 1H), 2.86 (t, *J* = 12.2 Hz, 1H), 2.35 (s, 3H), 2.18 – 2.08 (m, 4H), 1.82 (d, *J* = 12.4 Hz, 2H), 1.44 (q, *J* = 12.2 Hz, 2H). MS *m/z*: 531.15 $[M+H]^+$.

6-(3,3-Difluoroazetidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (166)



[00814] Step 1: 6-(3,3-difluoroazetidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55.0 mg, 0.114 mmol, 1.0 equiv) and 3,3-difluoroazetidine hydrochloride (29.8 mg, 0.229 mmol, 2.0 equiv) as the starting materials, Xphos (10.9 mg, 0.023 mmol, 0.2 equiv) as the ligand to give 6-(3,3-difluoroazetidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.1 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.79 (m, 1H), 6.63 (d, *J* = 0.9 Hz, 1H), 5.54 (s, 2H), 4.26 (t, *J* = 11.9 Hz, 4H), 3.05 (t, *J* = 12.1 Hz, 1H), 2.85 (t, *J* = 12.1 Hz, 1H), 2.35 (s, 3H), 2.22 – 2.05 (m, 4H), 1.86 – 1.77 (m, 2H), 1.51 – 1.36 (m, 2H). MS *m/z*: 537.10 $[M+H]^+$.

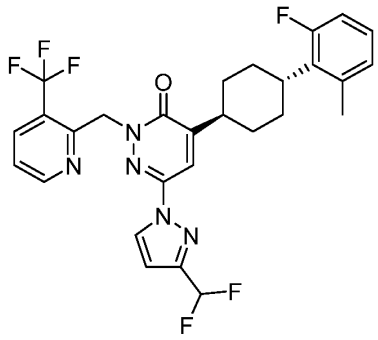
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (167)



[00815] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general

procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (70.0 mg, 0.146 mmol, 1.0 equiv) and 1-methylpiperazine (43.8 mg, 0.438 mmol, 3.0 equiv) as the starting materials, RuPhos Pd G3 (24 mg, 0.029 mmol, 0.2 equiv) as the catalyst, RuPhos (13 mg, 0.029 mmol, 0.2 equiv) as the ligand to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (61 mg, 76 %) as a light yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.28 (m, 1H), 7.05 – 7.00 (m, 1H), 6.97 (s, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.86 – 6.81 (m, 1H), 5.54 (s, 2H), 3.32 (t, *J* = 5.2 Hz, 4H), 3.05 (tt, *J* = 12.0, 3.0 Hz, 1H), 2.86 (t, *J* = 12.2 Hz, 1H), 2.59 (s, 4H), 2.40 (s, 3H), 2.35 (s, 3H), 2.18 – 2.06 (m, 4H), 1.83 – 1.79 (m, 2H), 1.49 – 1.39 (m, 2H). MS *m/z*: 544.30 [M+H]$^+$.

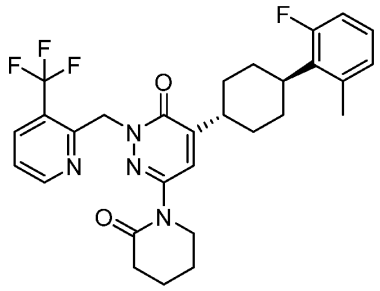
6-(3-(Difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (168)



[00816] Step 1: 6-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 3-(difluoromethyl)-1*H*-pyrazole (36.9 mg, 0.312 mmol, 3.0 equiv) as the starting materials, GPhos Pd G6 TES (19 mg, 0.021 mmol, 0.2 equiv) as the catalyst, GPhos (11 mg, 0.021 mmol, 0.2 equiv) as the ligand to give 6-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.6 mg, 19.7%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.19 (s, 1H), 8.12 – 7.88 (m, 2H), 7.33 (s, 2H), 7.09 – 6.99 (m, 1H), 6.96 – 6.80 (m, 2H), 6.69 – 6.54 (m, 1H), 5.68 (s, 2H), 3.18 – 3.09

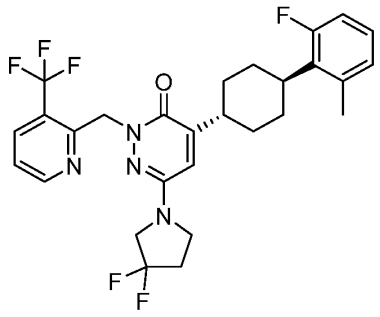
(s, 1H), 2.94 – 2.87 (s, 1H), 2.36 (s, 3H), 2.15 (d, *J* = 11.7 Hz, 4H), 1.88 – 1.69 (m, 4H). MS *m/z*: 562.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopiperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (169)



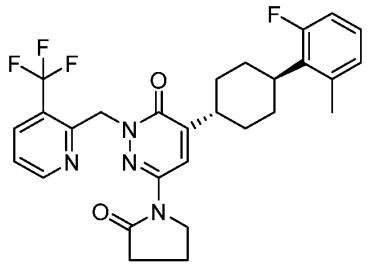
[00817] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopiperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.10 mmol, 1.0 equiv) and piperidin-2-one (15 mg, 0.16 mmol, 1.5 equiv) as the starting materials, XPhos Pd G4 (17 mg, 0.021 mmol, 0.2 equiv) as the catalyst, XPhos (9.9 mg, 0.021 mmol, 0.2 equiv) as the ligand to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopiperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (7.1 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.08 – 6.97 (m, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.60 (s, 2H), 3.71 (d, *J* = 5.7 Hz, 2H), 3.03 (t, *J* = 12.4 Hz, 1H), 2.84 (t, *J* = 12.4 Hz, 1H), 2.57 (d, *J* = 6.2 Hz, 2H), 2.34 (s, 3H), 2.11 (dd, *J* = 10.7, 5.1 Hz, 4H), 1.97 – 1.85 (m, 4H), 1.85 – 1.75 (m, 2H), 1.48 (dd, *J* = 12.1, 3.3 Hz, 2H). MS *m/z*: 543.10 $[M+H]^+$.

6-(3,3-Difluoropyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (170)



[00818] Step 1: 6-(3,3-difluoropyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.20 mmol, 1.0 equiv) and 3,3-difluoropyrrolidine (44.6 mg, 0.416 mmol, 2.0 equiv) as the starting materials, XPhos Pd G3 (35.2 mg, 0.042 mmol, 0.2 equiv) as the catalyst, XPhos (20 mg, 0.042 mmol, 0.2 equiv) as the ligand to give 6-(3,3-difluoropyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (58.9 mg, 50%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (d, *J* = 4.9 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.32 (m, 1H), 7.06 – 6.99 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.87 – 6.73 (m, 2H), 5.57 (s, 2H), 3.68 (t, *J* = 13.1 Hz, 2H), 3.57 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.91 – 2.82 (m, 1H), 2.51 – 2.39 (m, 2H), 2.35 (s, 3H), 2.20 – 2.05 (m, 4H), 1.89 – 1.78 (m, 2H), 1.44 (q, *J* = 5.6 Hz, 2H). MS *m/z*: 551.10 $[M+H]^+$.

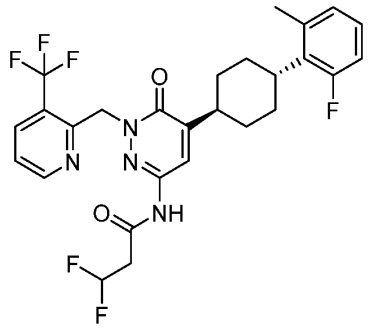
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopyrrolidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (171)



[00819] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopyrrolidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (55.0 mg, 0.114 mmol, 1.0 equiv)

and pyrrolidin-2-one (10.9 mg, 0.126 mmol, 1.1 equiv) as the starting materials, Xphos Pd G4 (9.6 mg, 0.012 mmol, 0.1 equiv) as the catalyst, Xphos (5.5 mg, 0.012 mmol, 0.1 equiv) as the ligand to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-oxopyrrolidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (37.4 mg, 61%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.8 Hz, 1H), 8.43 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 11.8, 8.1 Hz, 1H), 5.60 (s, 2H), 3.80 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.2 Hz, 1H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.35 (s, 3H), 2.19 – 2.03 (m, 6H), 1.86 – 1.77 (m, 2H), 1.57 – 1.46 (m, 2H). MS *m/z*: 529.05 [M+H]$^+$.

3,3-Difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)propanamide (172)



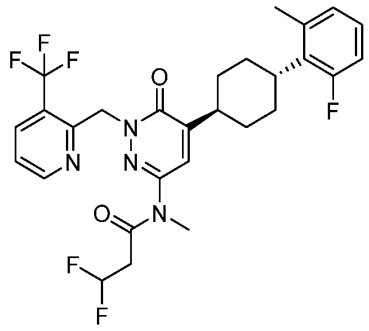
[00820] Step 1: *tert*-butyl (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)carbamate. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.417 mmol, 1.0 equiv) and *tert*-butyl carbamate (97.6 mg, 0.834 mmol, 2.0 equiv) as the starting materials, RuPhos Pd G4 (35.4 mg, 0.042 mmol, 0.1 equiv) as the catalyst, RuPhos (19.5 mg, 0.042 mmol, 0.1 equiv) as the ligand to give *tert*-butyl (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)carbamate (210 mg, 90%) as a light yellow solid. MS *m/z*: 561 [M+H]$^+$

[00821] Step 2: 6-amino-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. A solution of *tert*-butyl (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)carbamate (210 mg, 0.374 mmol, 1.0 equiv.) and CF_3COOH (2 mL) in DCM (2 mL) was stirred for 2 h at room temperature and monitored by LCMS. After complete disappearance of the starting material, the mixture was acidified to

pH ~ 8 with saturated $NaHCO_3$ (aq.), extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE = 1 / 1 to afford 6-amino-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 87%) as a light yellow solid. MS *m/z*: 461 $[M+H]^+$.

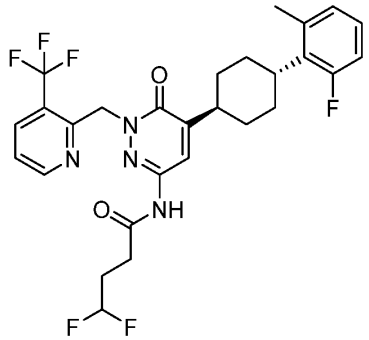
[00822] Step 3: 3,3-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)propanamide. To a stirred mixture of 6-amino-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.109 mmol, 1.0 equiv) and 3,3-difluoropropanoic acid (14.3 mg, 0.131 mmol, 1.2 equiv) in DCM (2 mL) were added DMAP (1.3 mg, 0.011 mmol, 0.1 equiv) and DCC (33.6 mg, 0.164 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature and monitored by LCMS. The resulting mixture was diluted with water (30 mL), extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (n-hexane / EA = 1:1) to afford 3,3-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)propanamide (24.0 mg, 39.8%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.9 Hz, 1H), 8.10 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.34 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.03 (td, *J* = 7.9, 5.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.83 (dd, *J* = 11.9, 8.1 Hz, 1H), 6.26 (tt, *J* = 55.5, 4.6 Hz, 1H), 5.56 (s, 2H), 3.07 (t, *J* = 12.0, Hz, 1H), 2.96 (td, *J* = 15.8, 4.5 Hz, 2H), 2.84 (t, *J* = 12.0 Hz, 1H), 2.35 (s, 3H), 2.17 – 2.05 (m, 4H), 1.85 – 1.79 (m, 2H), 1.57 – 1.40 (m, 2H). MS *m/z*: 553.15 $[M+H]^+$.

3,3-Difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylpropanamide (173)



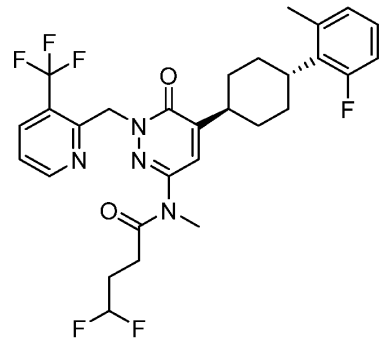
[00823] Step 1: 3,3-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylpropanamide. Followed the general procedure F using 3,3-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)propanamide (45.0 mg, 0.081 mmol, 1.0 equiv) and CH_3I (12.7 mg, 0.089 mmol, 1.1 equiv) as the starting materials to give 3,3-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylpropanamide (8.6 mg, 18%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.33 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.04 (td, *J* = 7.9, 5.5 Hz, 2H), 6.95 – 6.80 (m, 2H), 6.21 (t, *J* = 55.9 Hz, 1H), 5.64 (s, 2H), 3.27 (s, 3H), 3.06 (t, *J* = 12.2 Hz, 1H), 2.96 – 2.80 (m, 3H), 2.35 (s, 3H), 2.13 (t, *J* = 11.0 Hz, 4H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.46 (q, *J* = 12.4 Hz, 2H). MS *m/z*: 567.20 $[M+H]^+$.

4,4-Difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)butanamide (174)



[00824] Step 1: 4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)butanamide. To a stirred mixture of 6-amino-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (25 mg, 0.054 mmol, 1.0 equiv) and 4,4-difluorobutanoic acid (8.1 mg, 0.065 mmol, 1.2 equiv) in DCM (1 mL) were added DCC (16 mg, 0.081 mmol, 1.5 equiv) and DMAP (1 mg, 0.005 mmol, 0.1 equiv) in portions at 0 °C. The resulting mixture was stirred for 2 h at room temperature and monitored by LCMS.. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 3:1) to afford 4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)butanamide (9.9 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 4.9 Hz, 1H), 8.13 (s, 1H), 7.99 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.64 (s, 1H), 7.33 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.09-6.96 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.83 (dd, *J* = 11.8, 8.1 Hz, 1H), 6.00 (tt, *J* = 56.6, 4.0 Hz, 1H), 5.56 (s, 2H), 3.07 (tt, *J* = 11.9, 2.9 Hz, 1H), 2.86 (t, *J* = 11.5 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 2.32-2.20 (m, 2H), 2.19-2.04 (m, 4H), 1.84 -1.80 (m, 2H), 1.57-1.42 (m, 2H). MS *m/z*: 567.15 $[M+H]^+$.

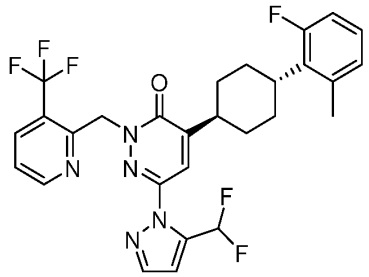
4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylbutanamide (175)



[00825] Step 1: 4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylbutanamide. Followed the general procedure F using 4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-

dihydropyridazin-3-yl)butanamide (54 mg, 0.095 mmol, 1.0 equiv) and CH_3I (27 mg, 0.19 mmol, 2.0 equiv) as the starting materials to give 4,4-difluoro-*N*-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-*N*-methylbutanamide (13.5 mg, 23.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 7.3 Hz, 1H), 7.35 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.15-6.98 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.88-6.76 (m, 1H), 5.90 (t, *J* = 56.8 Hz, 1H), 5.64 (s, 2H), 3.27 (s, 3H), 3.05 (t, *J* = 12.0 Hz, 1H), 2.87 (t, *J* = 12.3 Hz, 1H), 2.60-2.40 (m, 2H), 2.35 (s, 3H), 2.26-2.04 (m, 6H), 1.86-1.82 (m, 2H), 1.56-1.39 (m, 2H). MS *m/z*: 581.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (176)



[00826] Step 1: *tert*-butyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate. Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.417 mmol, 1.0 equiv) and *tert*-butyl hydrazinecarboxylate (124 mg, 0.942 mmol, 2.0 equiv) as the starting materials, XPhos Pd G4 (80 mg, 0.094 mmol, 0.2 equiv) as the catalyst, XPhos (44 mg, 0.094 mmol, 0.2 equiv) as the ligand to give *tert*-butyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate (200 mg, 83%) as a brown oil. MS *m/z*: 576 $[M+H]^+$.

[00827] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-hydrazineyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred mixture of *tert*-butyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate (200 mg, 0.374 mmol, 1.0

equiv) in DCM (2 mL) was added TFA (2 mL) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature and monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. MS *m/z*: 476 $[M+H]^+$.

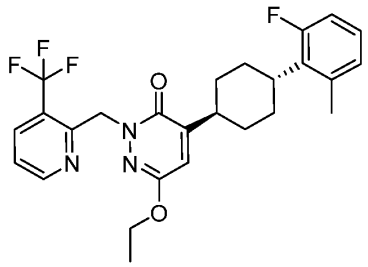
[00828] Step 3: ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carboxylate. To a stirred mixture of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-hydrazineyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (crude, 0.374 mmol, 1.0 equiv) and ethyl (*E*)-4-(dimethylamino)-2-oxobut-3-enoate (191 mg, 1.12 mmol, 3.0 equiv) in EtOH (2 mL) were added conc.HCl (7.5 mg, 0.075 mmol, 0.2 equiv, 36.5%) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 80 °C and monitored by LCMS. The resulting mixture was diluted with water (60 mL). The mixture was basified to pH ~ 8 with saturated $NaHCO_3$ (aq.) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 2:1) to afford ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carboxylate (120 mg, 54.8%) as a yellow oil. MS *m/z*: 584 $[M+H]^+$.

[00829] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1H-pyrazol-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure L using ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carboxylate (95.0 mg, 0.163 mmol, 1.0 equiv) and $NaBH_4$ (36.9 mg, 0.978 mmol, 6.0 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1*H*-pyrazol-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 68%) as an off-white solid. MS *m/z*: 542 $[M+H]^+$.

[00830] Step 5: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde. Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1*H*-pyrazol-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 0.111 mmol, 1.0 equiv) as the starting material to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde which was used directly in the next step. MS *m/z*: 540 $[M+H]^+$.

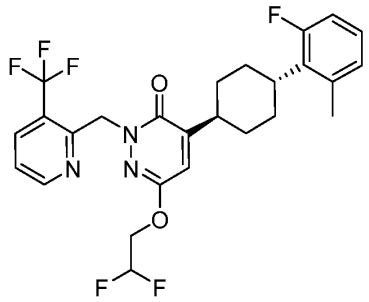
[00831] Step 6: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde. Followed the general procedure I using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (crude, 0.111 mmol, 1.0 equiv) and DAST (178 mg, 1.11 mmol, 10.0 equiv) as the starting materials to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1*H*-pyrazole-5-carbaldehyde (24.4 mg, 38.7%) as a white solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.66 – 8.60 (m, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.46 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.22 – 6.95 (m, 3H), 6.88 (dd, *J* = 12.2, 8.0 Hz, 1H), 6.80 (s, 1H), 5.62 (s, 2H), 3.03 – 2.94 (m, 2H), 2.37 (s, 3H), 2.08 – 2.01 (m, 4H), 1.87 – 1.82 (m, 2H), 1.64 – 1.53 (m, 2H). MS *m/z*: 562.10 $[M+H]^+$.

6-Ethoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (177)



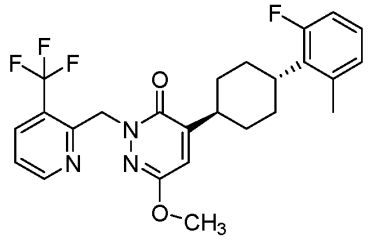
[00832] Step 1: 6-ethoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (35.0 mg, 0.075 mmol, 1.0 equiv) and ethanol (1 mL) as the starting materials to give 6-ethoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.2 mg, 36.0%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.09 – 6.98 (m, 1H), 6.95 – 6.78 (m, 3H), 5.55 (s, 2H), 4.15 – 4.02 (m, 2H), 3.03 (t, *J* = 12.0 Hz, 1H), 2.94 – 2.78 (m, 1H), 2.35 (s, 3H), 2.10 (t, *J* = 12.0 Hz, 4H), 1.81 (d, *J* = 12.9 Hz, 2H), 1.42 (t, *J* = 12.6 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H). MS *m/z*: 490.20 $[M+H]^+$.

6-(2,2-Difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (178)



[00833] Step 1: 6-(2,2-difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 2,2-difluoroethan-1-ol (25.6 mg, 0.312 mmol, 3.0 equiv) as the starting materials, DMF (2 mL) as the solvent to give 6-(2,2-difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (15.4 mg, 26.9%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.07 – 7.00 (m, 1H), 6.94 – 6.83 (m, 3H), 6.17 – 5.85 (m, 1H), 5.55 (s, 2H), 4.32 – 4.20 (m, 2H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.85 (t, *J* = 12.1 Hz, 1H), 2.35 (s, 3H), 2.11 (t, *J* = 13.6 Hz, 4H), 1.86 – 1.79 (m, 2H), 1.41 (q, *J* = 12.4 Hz, 2H). MS *m/z*: 526.20 $[M+H]^+$.

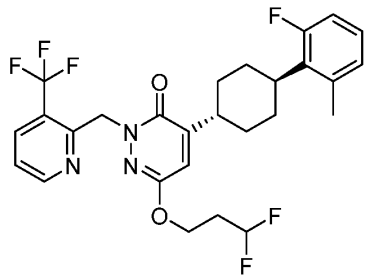
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (179)



[00834] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.06 mmol, 1.0 equiv) and MeOH (1 mL) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-

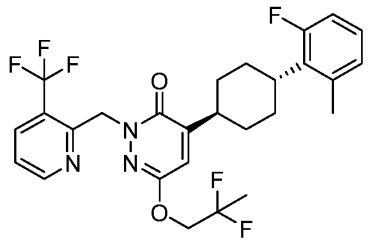
methylphenyl)cyclohexyl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.1 mg, 65.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.06 – 6.99 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.80 (m, 2H), 5.59 (s, 2H), 3.74 (s, 3H), 3.01 (t, *J* = 12.1 Hz, 1H), 2.85 (t, *J* = 12.4 Hz, 1H), 2.35 (s, 3H), 2.10 (t, *J* = 13.8 Hz, 4H), 1.86 – 1.81 (m, 2H), 1.40 (q, *J* = 12.4 Hz, 2H). MS *m/z*: 476.20 [M+H]$^+$.

6-(3,3-Difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (180)



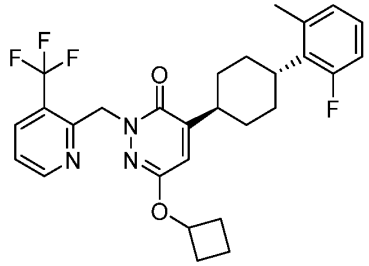
[00835] Step 1: 6-(3,3-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.06 mmol, 1 equiv) and 3,3-difluoropropan-1-ol (1 mL) as the starting materials to give 6-(3,3-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (14.4 mg, 36.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.9 Hz, 1H), 8.00 – 7.94 (m, 1H), 7.35 – 7.27 (m, 1H), 7.03 (td, *J* = 7.9, 5.5 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.13 – 5.83 (m, 1H), 5.54 (s, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.85 (t, *J* = 12.0 Hz, 1H), 2.35 (s, 3H), 2.28 – 2.05 (m, 6H), 1.86 – 1.77 (m, 2H), 1.48 – 1.34 (m, 2H). MS *m/z*: 540.10 [M+H]$^+$.

6-(2,2-Difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (181)



[00836] Step 1: 6-(2,2-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.06 mmol, 1 equiv) and 2,2-difluoropropan-1-ol (1 mL) as the starting materials to give 6-(2,2-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (18 mg, 51%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 4.9 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.37 (m, 1H), 7.07 – 7.00 (m, 1H), 6.93 – 6.89 (m, 2H), 6.87 – 6.81 (m, 1H), 5.56 (s, 2H), 4.20 (t, *J* = 11.9 Hz, 2H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.85 (t, *J* = 12.2 Hz, 1H), 2.35 (s, 3H), 2.11 (t, *J* = 12.5 Hz, 4H), 1.82 (d, *J* = 13.0 Hz, 2H), 1.70 (t, *J* = 20.0 Hz, 3H), 1.42 (q, *J* = 12.6 Hz, 2H). MS *m/z*: 540.10 $[M+H]^+$.

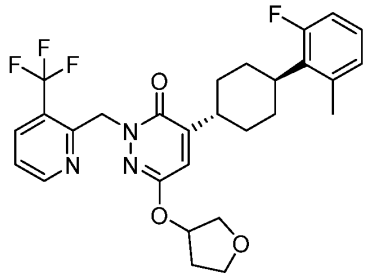
6-Cyclobutoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (182)



[00837] Step 1: 6-cyclobutoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.06 mmol, 1 equiv) and cyclobutanol (1 mL) as the starting materials to give 6-cyclobutoxy-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.3 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.8 Hz,

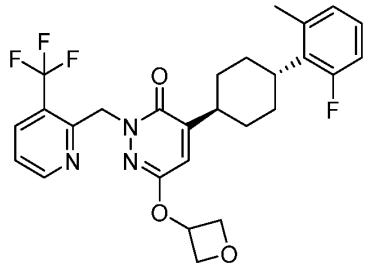
1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.08 – 6.99 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 11.9, 8.1 Hz, 1H), 6.76 (s, 1H), 5.54 (s, 2H), 4.83 – 4.71 (m, 1H), 3.02 (t, *J* = 11.9 Hz, 1H), 2.85 (t, *J* = 12.3 Hz, 1H), 2.35 (s, 3H), 2.26 – 2.18 (m, 2H), 2.10 (t, *J* = 14.0 Hz, 4H), 2.05 – 1.99 (m, 2H), 1.85 – 1.77 (m, 3H), 1.60 – 1.49 (m, 1H), 1.62 – 1.43 (m, 2H). MS *m/z*: 516.10 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-((tetrahydrofuran-3-yl)oxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (183)



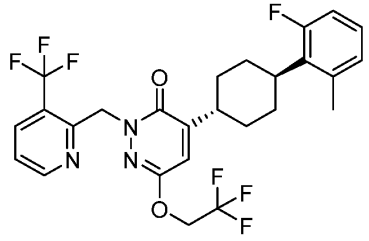
[00838] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-((tetrahydrofuran-3-yl)oxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 0.063 mmol, 1.0 equiv) and tetrahydrofuran-3-ol (1.0 mL) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-((tetrahydrofuran-3-yl)oxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19.2 mg, 57.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 4.9 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.03 (td, *J* = 7.9, 5.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.78 (m, 2H), 5.66 – 5.50 (m, 2H), 5.12 (d, *J* = 4.3 Hz, 1H), 3.93 (q, *J* = 7.9 Hz, 1H), 3.85 – 3.71 (m, 3H), 3.03 (t, *J* = 12.1 Hz, 1H), 2.84 (t, *J* = 12.4 Hz, 1H), 2.35 (s, 3H), 2.08 (dd, *J* = 10.5, 5.4 Hz, 6H), 1.86 – 1.82 (m, 2H), 1.40 (q, *J* = 12.5 Hz, 2H). MS *m/z*: 532.40 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yloxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (184)



[00839] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yloxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 0.063 mmol, 1.0 equiv) and oxetan-3-ol (1 mL) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(oxetan-3-yloxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.3 mg, 19%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.81 (m, 2H), 5.49 (s, 2H), 5.29 – 5.19 (m, 1H), 4.69 (t, *J* = 6.9 Hz, 2H), 4.63 – 4.55 (m, 2H), 3.05 (t, *J* = 12.1 Hz, 1H), 2.86 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.12 (t, *J* = 13.5 Hz, 4H), 1.83 (d, *J* = 12.7 Hz, 2H), 1.48 – 1.36 (m, 2H). MS *m/z*: 518.10 $[M+H]^+$.

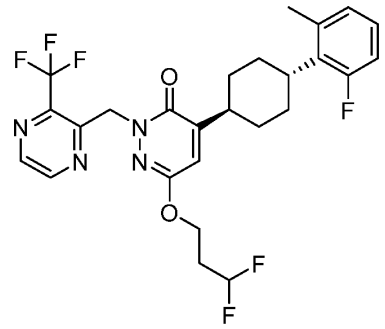
4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-(2,2,2-trifluoroethoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (185)



[00840] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2,2,2-trifluoroethoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.1 mmol, 1 equiv) and 2,2,2-trifluoroethan-1-ol (1 mL) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-

methylphenyl)cyclohexyl)-6-(2,2,2-trifluoroethoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (22.6 mg, 39.8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 4.9 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.08 – 6.98 (m, 1H), 6.94 – 6.89 (m, 2H), 6.89 – 6.79 (m, 1H), 5.54 (s, 2H), 4.43 (q, *J* = 8.3 Hz, 2H), 3.05 (t, *J* = 12.1 Hz, 1H), 2.85 (t, *J* = 12.2 Hz, 1H), 2.35 (s, 3H), 2.11 (t, *J* = 12.6 Hz, 4H), 1.83 (d, *J* = 13.1 Hz, 2H), 1.42 (q, *J* = 12.7 Hz, 2H). MS *m/z*: 544.00 [M+H]$^+$.

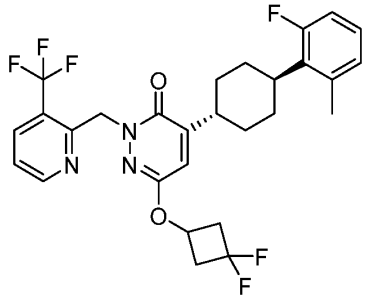
6-(3,3-Difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (186)



[00841] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.320 mmol, 1.0 equiv) and 2-(bromomethyl)-3-(trifluoromethyl)pyrazine (90 mg, 0.38 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 42%) as a white soild. MS *m/z*: 481 [M+H]+.

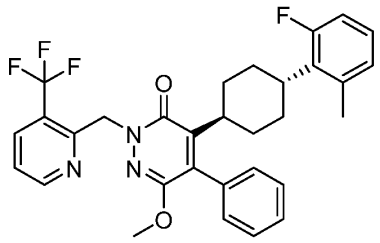
[00842] Step 2: 6-(3,3-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (35 mg, 0.073 mmol, 1.0 equiv) and 3,3-difluoropropan-1-ol (0.3 mL) as the starting materials to give 6-(3,3-difluoropropoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (6.0 mg, 14%) as colorless semi-solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 26.7 Hz, 2H), 7.11 – 6.98 (m, 1H), 6.95 – 6.79 (m, 3H), 5.59 (s, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 3.02 (t, *J* = 12.3 Hz, 1H), 2.85 (t, *J* = 12.3 Hz, 1H), 2.35 (s, 3H), 2.26 – 2.15 (m, 2H), 2.08 (d, *J* = 13.0 Hz, 4H), 1.82 (d, *J* = 13.0 Hz, 2H), 1.41 (q, *J* = 12.5 Hz, 2H). MS *m/z*: 541.20 [M+H]$^+$.

(6-(3,3-Difluorocyclobutoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (187)



[00843] Step 1: (6-(3,3-difluorocyclobutoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. To a stirred solution of 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.104 mmol, 1.0 equiv) and 3,3-difluorocyclobutan-1-ol (113 mg, 1.04 mmol, 10.0 equiv.) in dioxane (1 mL) was added *t*BuOK (35.1 mg, 0.312 mmol, 3.0 equiv). The resulting mixture was stirred for 2 h at 100 °C under argon atmosphere. The reaction was monitored by LCMS. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 30 min; detector, UV 254 nm. The resulting mixture was concentrated under reduced pressure. This resulted in 6-(3,3-difluorocyclobutoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (4.7 mg, 8%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 – 8.62 (m, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.07 – 6.98 (m, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.81 (m, 1H), 6.79 (s, 1H), 5.52 (s, 2H), 4.72 (s, 1H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.92 – 2.79 (m, 3H), 2.70 – 2.54 (m, 2H), 2.35 (s, 3H), 2.11 (t, *J* = 14.1 Hz, 4H), 1.82 (d, *J* = 12.7 Hz, 2H), 1.46 – 1.35 (m, 2H). MS *m/z*: 552.20 $[M+H]^+$

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-6-methoxy-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (188)



[00844] Step 1: 6-chloro-5-phenylpyridazin-3(2*H*)-one. Followed the general procedure A using 5,6-dichloropyridazin-3(2*H*)-one (2.0 g, 12 mmol, 1.0 equiv) and phenylboronic acid (1.9 g, 15 mmol, 1.3 equiv) as the starting materials to give 6-chloro-5-phenylpyridazin-3(2*H*)-one (1.5 g, 55%) as a colorless oil. MS *m/z*: 207 $[M+H]^+$.

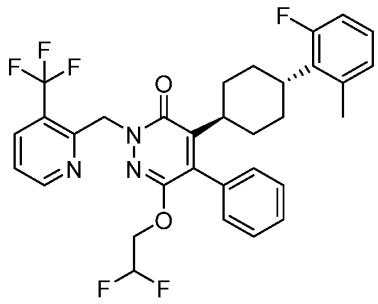
[00845] Step 2: 4-bromo-6-chloro-5-phenylpyridazin-3(2*H*)-one. To a stirred mixture of 6-chloro-5-phenylpyridazin-3(2*H*)-one (1.01 g, 4.84 mmol, 1.0 equiv) and Br_2 (2.32 g, 14.4 mmol, 3.0 equiv) in H_2O (12 mL) were added KBr (1.7 g, 7.2 mmol, 3.0 equiv) and AcOK (702 mg, 3.63 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (200 mL), extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 5:1) to afford 4-bromo-6-chloro-5-phenylpyridazin-3(2*H*)-one (400 mg, 24%) as a white soild. MS *m/z*: 285 $[M+H]^+$.

[00846] Step 3: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one**.** Followed the general procedure S using 4-bromo-6-chloro-5-phenylpyridazin-3(2*H*)-one (400 mg, 1.40 mmol, 1.0 equiv) and 1,3-dioxoisoindolin-2-yl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (801 mg, 2.10 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one (140 mg, 23%) as a white solid. MS *m/z*: 397 $[M+H]^+$.

[00847] Step 4: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure V using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one (140 mg, 0.353 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (89 mg, 0.46 mmol, 1.3 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 20%) as a white solid. MS *m/z*: 556 $[M+H]^+$.

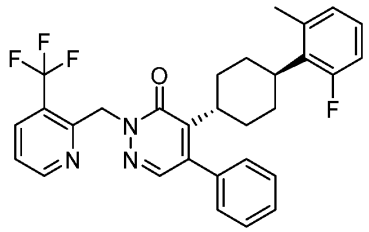
[00848] Step 5: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-methoxy-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.054 mmol, 1.0 equiv) and methanol (1 mL) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-methoxy-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (4.9 mg, 16%) as white soild. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.71 (d, *J* = 4.7 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.66 – 7.40 (m, 3H), 7.25 – 7.21 (m, 2H),7.34 (d, *J* = 8.4 Hz, 1H), 7.05 – 6.92 (m, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.77 (d, *J* = 10.8 Hz, 1H), 5.60 (s, 2H), 3.60 (d, *J* = 2.6 Hz, 3H), 2.82 (s, 1H), 2.59 (d, *J* = 10.6 Hz, 1H), 2.43 (s, 2H), 2.26 (d, *J* = 2.6 Hz, 3H), 1.57 (s, 6H). MS *m/z*: 552.20 [M+H]$^+$.

6-(2,2-Difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (189)



[00849] Step 1: 6-(2,2-difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.054 mmol, 1.0 equiv) and 2,2-difluoroethan-1-ol (8.8 mg, 0.11 mmol, 2.0 equiv) as the starting materials, DMF (1 mL) as the solvent to give 6-(2,2-difluoroethoxy)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (5.0 mg, 15%) as a white soild. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 7.8, 3.2 Hz, 3H), 7.36 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.02 – 6.94 (m, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 12.0, 8.1 Hz, 1H), 5.96 – 5.65 (m, 1H), 5.59 (s, 2H), 4.20 – 4.06 (m, 2H), 2.84 (d, *J* = 11.3 Hz, 1H), 2.64 (d, *J* = 12.0 Hz, 1H), 2.42 (d, *J* = 16.8 Hz, 2H), 2.27 (s, 3H), 1.79 – 1.65 (m, 4H), 1.63 (d, *J* = 3.3 Hz, 2H). MS *m/z*: 602.15 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (190)



[00850] Step 1: 4-bromo-3,6-dichloro-5-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine. Followed the general procedure D using 4-bromo-3,6-dichloropyridazine (1.0 g, 4.3 mmol, 1.0 equiv) and 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylic acid (1.24 g, 5.26 mmol, 1.2 equiv) as the starting materials to give 4-bromo-3,6-dichloro-5-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine (960 mg, 52%) as a colorless oil. MS *m/z*: 417[M+H]$^+$.

[00851] Step 2: 5-bromo-6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one. Followed the general procedure E using 4-bromo-3,6-dichloro-5-(4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazine (840 mg, 2.00 mmol, 1.0 equiv) as the starting material to give 5-bromo-6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (280 mg, 34.8%) as a colorless oil.MS *m/z*: 399 [M+H]$^+$.

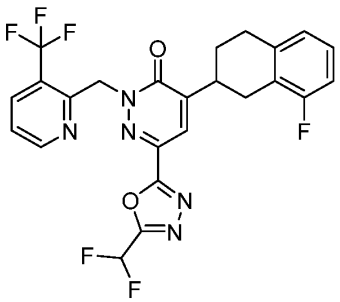
[00852] Step 3: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one. Followed the general procedure H using 5-bromo-6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)pyridazin-3(2*H*)-one (290 mg, 0.726 mmol, 1.0 equiv) and phenylboronic acid (79.6 mg, 0.653 mmol, 0.9 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one (120 mg, 41%) as a colorless oil. MS *m/z*: 397[M+H]$^+$.

[00853] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one. Followed the general procedure B using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one (110 mg, 0.277 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one(65 mg, 64%). MS *m/z*: 463 [M+H]$^+$.

[00854] Step 5: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure F using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenylpyridazin-3(2*H*)-one (60

mg, 0.16 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (38.8 mg, 0.199 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-5-phenyl-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9.4 mg, 10%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.70 (m, 2H), 7.58 (s, 1H), 7.53 – 7.35 (m, 4H), 7.06 – 7.00 (m, 1H), 6.94 – 6.80 (m, 2H), 5.82 (s, 2H), 3.11 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.30 – 2.10 (m, 4H), 1.83 (s, 2H), 1.60 – 1.48 (m, 2H). MS *m/z*: 522.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (191)



[00855] **Step 1: 8-fluoro-1,2,3,4-tetrahydronaphthalen-2-ol.** Followed the general procedure L using 8-fluoro-3,4-dihydronaphthalen-2(1*H*)-one (500 mg, 1.10 mmol, 1.0 equiv) as the starting material to give 8-fluoro-1,2,3,4-tetrahydronaphthalen-2-ol (350 mg, 68%) as a colorless oil. MS *m/z*: 167 $[M+H]^+$.

[00856] Step 2: 8-fluoro-2-iodo-1,2,3,4-tetrahydronaphthalene. A mixture of PPh_3 (828 mg, 3.16 mmol, 1.5 equiv) and 1*H*-imidazole (215 mg, 3.16 mmol, 1.5 equiv) in DCM (5 mL) was stirred for 2 h at room temperature under argon atmosphere. To the above mixture was added 8-fluoro-1,2,3,4-tetrahydronaphthalen-2-ol (350 mg, 2.10 mmol, 1.0 equiv). The resulting mixture was stirred for additional overnight at room temperature and monitored by TLC. The residue was purified by silica gel column chromatography, eluted with PE / EA (0% to 100%) to afford 8-fluoro-2-iodo-1,2,3,4-tetrahydronaphthalene (300 mg, 85%) as a white solid. MS *m/z*: 276 $[M+H]^+$.

[00857] Step 3: methyl 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate. To a stirred mixture of methyl 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (200 mg, 0.543

mmol, 1.0 equiv) and 8-fluoro-2-iodo-1,2,3,4-tetrahydronaphthalene (224 mg, 0.814 mmol, 1.5 equiv) in DMA (5 mL) were added NaI (35.5 mg, 0.237 mmol, 0.25 equiv), pyridine-2,6-dicarboximidamide dihydrochloride (22.4 mg, 0.095 mmol, 0.1 equiv), $NiBr_2DME$ (29.3 mg, 0.095 mmol, 0.1 equiv), TFA (10.8 mg, 0.095 mmol, 0.1 equiv), Zn (124 mg, 1.90 mmol, 2.0 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for overnight at 30°C under argon atmosphere and monitored by LCMS. The resulting mixture was diluted with water (100 mL), extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 3:1) to afford methyl 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 40%) as a white solid. MS *m/z*: 462 $[M+H]^+$

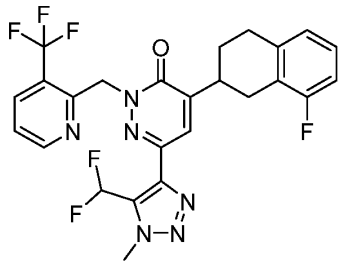
[00858] Step 4: 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide. Followed the general procedure N using methyl 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (80 mg, 0.17 mmol, 1.0 equiv) as the starting material to give 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (2*H*)-one (50 mg, 62%) as a white solid. MS *m/z*: 462 $[M+H]^+$.

[00859] Step 5: *N'*-(2,2-difluoroacetyl)-5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide. Followed the general procedure O using methyl 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide(50.0 mg, 0.108 mmol, 1.0 equiv) as the starting material to give *N'*-(2,2-difluoroacetyl)-5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg, 80%) as a white solid. MS *m/z*: 540 $[M+H]^+$.

[00860] Step 6: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one. Followed the general procedure P using *N'*-(2,2-difluoroacetyl)-5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbohydrazide (40 mg, 0.07 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (16.2 mg, 40%) as

a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.14 – 7.06 (m, 1H), 7.00 – 6.77 (m, 3H), 5.86 (s, 2H), 3.37 (t, *J* = 12.2 Hz, 1H), 3.28 (d, *J* = 17.5 Hz, 1H), 3.05 – 2.90 (m, 2H), 2.75 – 2.65 (m, 1H), 2.22 (d, *J* = 12.7 Hz, 1H), 1.92 – 1.79 (m, 1H).MS *m/z*: 522.05 $[M+H]^+$.

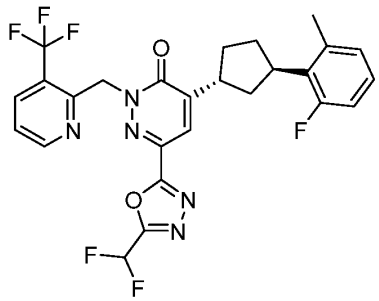
6-(5-(Difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (192)



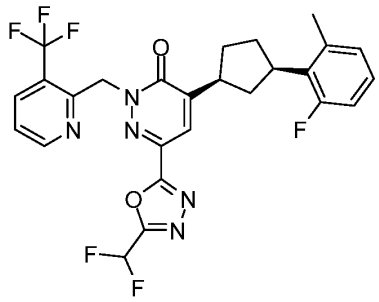
[00861] Step 1: (5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50.0 mg, 0.114 mmol, 1.0 equiv) as the starting material to give (5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 438 $[M+H]^+$.

[00862] Step 2: 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.112 mmol, 1.0 equiv) and 4-bromo-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole (28.4 mg, 0.134 mmol, 1.2 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (28.3 mg, 46%) as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.06 – 7.98 (m, 2H), 7.41 – 7.28 (m, 1H), 7.18 – 6.99 (m, 2H), 6.95 – 6.82 (m, 2H), 5.78 – 5.67 (m, 2H), 4.24 (s, 3H), 3.43 – 3.34 (m, 1H), 3.32 – 3.23 (m, 1H), 3.04 – 2.90 (m, 2H), 2.75 – 2.65 (m, 1H), 2.26 – 2.16 (m, 1H), 1.93 – 1.78 (m, 1H). MS *m/z*: 535.10 $[M+H]^+$.

6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (193A)



6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (193B)



[00863] Step 1: methyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-ene-1-carboxylate: To a stirred solution of methyl methyl 3-oxocyclopentane-1-carboxylate (1.0 g, 7.0 mmol, 1 equiv) and 2,6-dimethylpyridine (2.26 g, 21.1 mmol, 3.0 equiv) in DCM (10 mL) was added Tf_2O (5.95 g, 21.1 mmol, 3.0 equiv) dropwise at 0°C. The resulting mixture was stirred for overnight at room temperature. The reaction was monitored by TLC. The mixture was acidified to pH ~ 5 with conc. HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to dry. The crude product was used in the next step directly without further purification. MS *m/z*: 275 $[M+H]^+$.

[00864] Step 2: methyl 3-(2-fluoro-6-methylphenyl)cyclopent-3-ene-1-carboxylate: Followed the general procedure A using methyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-ene-1-carboxylate (1.1 g, 4.0 mmol, 1.0 equiv) and (2-fluoro-6-methylphenyl)boronic acid (0.74 g, 4.8 mmol, 1.2 equiv) as the starting materials to give methyl 3-(2-fluoro-6-

methylphenyl)cyclopent-3-ene-1-carboxylate (600 mg, 63%) as an off-white oil. MS *m/z*: 235 $[M+H]^+$.

[00865] Step 3: methyl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate: Followed the general procedure B using methyl 3-(2-fluoro-6-methylphenyl)cyclopent-3-ene-1-carboxylate (600 mg, 2.56 mmol, 1.0 equiv) as the starting material to give methyl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate (580 mg, 95%) as an off-white oil. MS *m/z*: 237 $[M+H]^+$.

[00866] Step 4: 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylic acid: Followed the general procedure C using methyl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate (580 mg, 2.45 mmol, 1.0 equiv) as the starting material to give 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylic acid (420 mg, 76%) as an off-white oil. MS *m/z*: 223 $[M+H]^+$.

[00867] Step 5: 1,3-dioxoisoindolin-2-yl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate: Followed the general procedure R using 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylic acid (390 mg, 0.863 mmol, 1.0 equiv) and 2-hydroxyisoindoline-1,3-dione (475 mg, 1.29 mmol, 1.5 equiv) as the starting materials to give 1,3-dioxoisoindolin-2-yl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate (380 mg, 80%) as an off-white oil. MS *m/z*: 368 $[M+H]^+$.

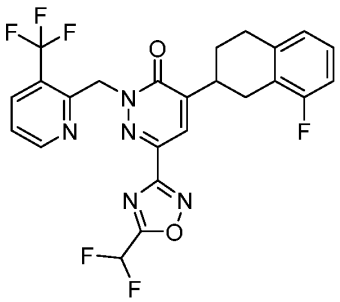
[00868] Step 6: 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one and 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate (70 mg, 0.19 mmol, 1.0 equiv) and 4-bromo-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (86 mg, 0.19 mmol, 1.0 equiv) as the starting materials to give 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (11.5 mg, 10.9%) as a white solid and 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.4 mg, 9.8%) as a white solid.

[00869] 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (193A): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 – 8.55 (m, 1H), 8.07 – 7.97 (m, 2H),

7.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.08 – 6.76 (m, 4H), 5.85 – 5.74 (m, 2H), 3.56 – 3.38 (m, 2H), 2.36 (s, 5H), 2.19 – 2.04 (m, 3H), 2.02 – 1.97 (m, 1H).MS *m/z*: 550.15 $[M+H]^+$.

[00870] 6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (193B): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.7 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.37 – 7.31 (m, 1H), 7.08 – 7.00 (m, 1H), 6.94 – 6.75 (m, 3H), 5.80 (s, 2H), 3.79 – 3.68 (m, 1H), 3.64 – 3.50 (m, 1H), 2.36 (s, 4H), 2.13 (d, *J* = 9.5 Hz, 1H), 2.11 – 2.02 (m, 2H), 1.95 – 1.79 (m, 2H). MS *m/z*: 550.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (194)



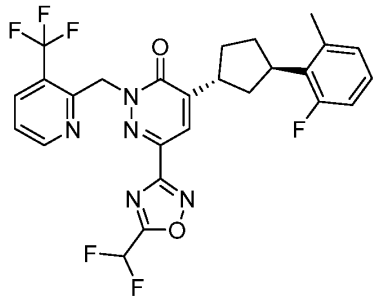
[00871] Step 1: 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile: Followed the general procedure W using 6-chloro-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.228 mmol, 1.0 equiv) as the starting material to give 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (60 mg, 60%) as a white solid. MS *m/z*: 429 $[M+H]^+$.

[00872] Step 2: 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (60 mg, 0.14 mmol, 1.0 equiv) as the starting material to give 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-N-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (40 mg, 66%) as a white solid. MS *m/z*: 462 $[M+H]^+$.

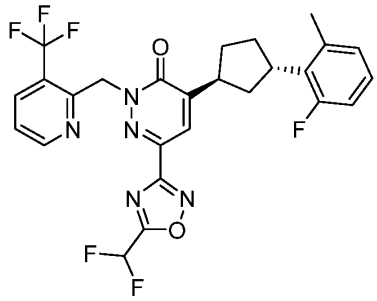
[00873] Step 3: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one:

Followed the general procedure Y using 5-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (40.0 mg, 0.087 mmol, 1.0 equiv) as the starting material to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-(8-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.8 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.89 (s, 1H), 7.32 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.15 – 7.00 (m, 1H), 6.93 – 6.74 (m, 3H), 5.85 (d, *J* = 3.1 Hz, 2H), 3.42 – 3.22 (m, 2H), 3.06 – 2.89 (m, 2H), 2.70 (dd, *J* = 16.7, 11.2 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.93 – 1.76 (m, 1H). MS *m/z*: 522.05 $[M+H]^+$.

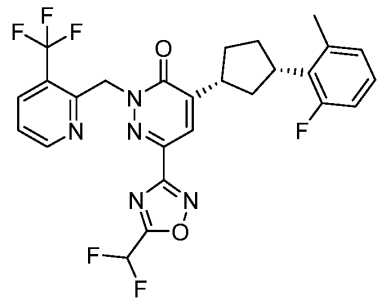
6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195A)



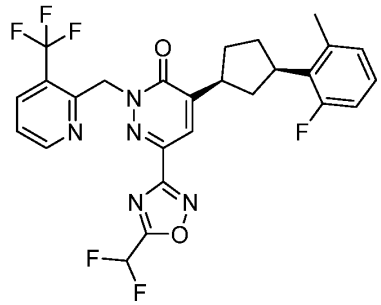
6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195B)



6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*S*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195C)



6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195D)



[00874] Step 1: 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)pyridazin-3(2H)-one: Followed the general procedure S using 1,3-dioxoisoindolin-2-yl 3-(2-fluoro-6-methylphenyl)cyclopentane-1-carboxylate (400 mg, 1.08 mmol, 1 equiv) and 4-bromo-6-chloropyridazin-3(2*H*)-one (159 mg, 0.762 mmol, 0.7 equiv) as the starting materials to give 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)pyridazin-3(2*H*)-one (300 mg, 90%) as a white solid. MS *m/z*: 307 $[M+H]^+$.

[00875] Step 2: 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)pyridazin-3(2*H*)-one (360 mg, 1.17 mmol, 1.0 equiv) and 2-(chloromethyl)-3-(trifluoromethyl)pyridine (275 mg, 1.40 mmol, 1.2 equiv) as the starting materials to give 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (270 mg, 49%) as a white solid. MS *m/z*: 466 $[M+H]^+$.

[00876] Step 3: 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile: To a stirred solution of 6-chloro-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (270 mg, 0.580 mmol, 1.0 equiv),

$K_4Fe(CN)_6.3H_2O$ (122 mg, 0.290 mmol, 0.5 equiv) and KOAc (28.4 mg, 0.290 mmol, 0.5 equiv) in 1.4-dioxane (3 mL) and H_2O(0.6 mL) were added *t*BuXPhos (49.2 mg, 0.116 mmol, 0.2 equiv) and *t*BuXPhos Pd G3 (92 mg, 0.11 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 100 °C. The reaction was monitored by LCMS. The resulting mixture was diluted with water (200 mL), extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE = 1/1 to afford 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (230 mg, 87%) as a white solid. MS *m/z*: 466 $[M+H]^+$.

[00877] Step 4: 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (230 mg, 0.50 mmol, 1.0 equiv) as the starting material to give 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (200 mg, crude) as a white solid. MS *m/z*: 490 $[M+H]^+$.

[00878] Step 5: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure Y using 5-(3-(2-fluoro-6-methylphenyl)cyclopentyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (200 mg, 0.409 mmol, 1.0 equiv) as the starting material to give the racemate. The racemate was purified by HPLC with the following conditions (Column: Lux 5u Cellulose-2, 30*250 mm, 5.0 um; Mobile Phase A: Hex(10mM NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wave Length: 216/264 nm; RT1(min): 6.147; RT2(min): 9.185; Sample Solvent: MeOH: EtOH=1: 1--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 4) to afford 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (45.7 mg, 20.4%) as a white solid and 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*S*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (46 mg, 20.5%) as a white solid. The rest was further purified by another HPLC with the following conditions (Column: CHIRALPAK IG, 3*25 cm, 5 μm; Mobile Phase A: Hex(10mM NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 10; Wave Length: 220/230 nm;

RT1(min): 13.175; RT2(min): 16.610; Sample Solvent: ACN; Injection Volume: 0.5 mL; Number Of Runs: 12) to afford 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*S*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (33.2 mg, 14.8%) as a white solid and 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (29.7 mg, 13.2%) as a white solid.

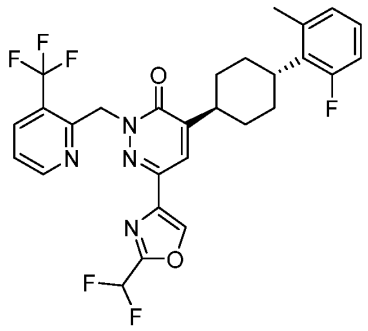
[00879] 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195A) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 4.9 Hz, 1H), 8.01 – 7.92 (m, 2H), 7.34 – 7.29 (m, 1H), 7.10 – 6.99 (m, 1H), 6.94 – 6.75 (m, 3H), 5.83 (s, 2H), 3.77 – 3.67 (m, 1H), 3.64 – 3.52 (m, 1H), 2.47 – 2.38 (m, 1H), 2.36 (s, 3H), 2.34 – 2.26 (m, 1H), 2.16 – 2.03 (m, 3H), 1.97 – 1.87 (m, 1H). MS *m/z*: 550.10 $[M+H]^+$.

[00880] 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*S*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195B) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 – 8.51 (m, 1H), 8.00 – 7.91 (m, 2H), 7.34 – 7.27 (m, 1H), 7.08 – 6.99 (m, 1H), 6.94 – 6.75 (m, 3H), 5.83 (s, 2H), 3.77 – 3.68 (m, 1H), 3.64 – 3.51 (m, 1H), 2.47 – 2.38 (m, 1H), 2.36 (s, 3H), 2.34 – 2.26 (m, 1H), 2.16 – 2.04 (m, 3H), 1.94 – 1.87 (m, 1H). MS *m/z*: 550.10 $[M+H]^+$.

[00881] 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*R*,3*S*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195C) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 4.8 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.32 – 7.27 (m, 1H), 7.09 – 7.00 (m, 1H), 6.94 – 6.75 (m, 3H), 5.88 – 5.77 (m, 2H), 3.56 – 3.39 (m, 2H), 2.36 (s, 4H), 2.31 – 2.24 (m, 1H), 2.18 – 2.10 (m, 2H), 2.07 – 1.97 (m, 2H). MS *m/z*: 550.10 $[M+H]^+$.

[00882] 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*S*,3*R*)-3-(2-fluoro-6-methylphenyl)cyclopentyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (195D) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 4.8 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.33 – 7.27 (m, 1H), 7.09 – 6.99 (m, 1H), 6.94 – 6.74 (m, 3H), 5.89 – 5.77 (m, 2H), 3.57 – 3.39 (m, 2H), 2.36 (s, 4H), 2.32 – 2.24 (m, 1H), 2.19 – 2.10 (m, 2H), 2.08 – 1.94 (m, 2H). MS *m/z*: 550.10 $[M+H]^+$.

6-(2-(Difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (196)



[00883] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.208 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00884] Step 2: ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.204 mmol, 1.0 equiv) and ethyl 4-bromooxazole-2-carboxylate (44.8 mg, 0.204 mmol, 1 equiv) as the starting materials to give ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carboxylate (60 mg, 51%) as white solid. MS *m/z*: 585 $[M+H]^+$.

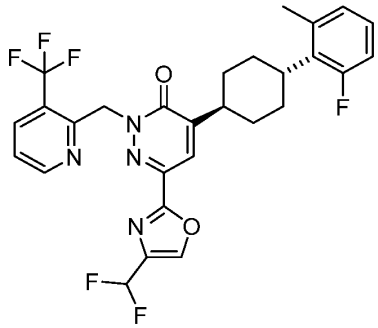
[00885] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)oxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carboxylate (60.0 mg, 0.103 mmol, 1.0 equiv) as the starting material to 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)oxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 89%) as white solid. MS *m/z*: 543 $[M+H]^+$.

[00886] Step 4: 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carbaldehyde: Followed the general procedure N using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-

6-(2-(hydroxymethyl)oxazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 0.11 mmol, 1.0 equiv) as the starting material to 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carbaldehyde (30 mg, 50%) as white solid. MS *m/z*: 541 $[M+H]^+$.

[00887] Step 5: 6-(2-(difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-2-carbaldehyde (30 mg, 0.056 mmol, 1.0 equiv) as the starting material to give 6-(2-(difluoromethyl)oxazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (13.8 mg, 44%) as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 0.9 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.73 (s, 1H), 7.37 – 7.30 (m, 1H), 7.08 – 6.99 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 – 6.79 (m, 1H), 6.64 (d, *J* = 52.5 Hz, 1H), 5.72 (s, 2H), 3.10 (t, *J* = 12.1 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.22 – 1.99 (m, 4H), 1.84 (d, *J* = 12.8 Hz, 2H), 1.54 (d, *J* = 12.6 Hz, 2H). MS *m/z*: 563.25 $[M+H]^+$.

6-(4-(Difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (197)



[00888] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (300 mg, 0.625 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 490 $[M+H]^+$.

[00889] Step 2: ethyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.613 mmol, 1.0 equiv) and ethyl 2-bromooxazole-4-carboxylate (161 mg, 0.736 mmol, 1.2 equiv) as the starting materials to give ethyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate (320 mg, 89%) as a white solid. MS *m/z*: 585 $[M+H]^+$.

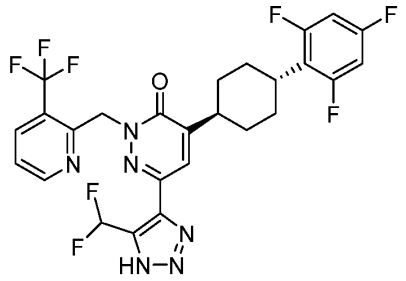
[00890] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)oxazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 2-(5-((1r,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carboxylate (200 mg, 0.342 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)oxazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80 mg, 43%) as a white solid. MS *m/z*: 543 $[M+H]^+$.

[00891] Step 4: 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)oxazol-2-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (80.0 mg, 0.147 mmol, 1.0 equiv) as the starting material to give 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde (65 mg, 81%) as a white solid. MS *m/z*: 541 $[M+H]^+$.

[00892] Step 5: 6-(4-(difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)oxazole-4-carbaldehyde (60.0 mg, 0.111 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)oxazol-2-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (31.4 mg, 50.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.91 (d, *J* = 0.9 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.07 – 7.00

(m, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.88 – 6.57 (m, 2H), 5.78 (s, 2H), 3.09 (t, J = 12.2 Hz, 1H), 2.88 (t, J = 12.4 Hz, 1H), 2.36 (s, 3H), 2.21 – 2.06 (m, 4H), 1.85 (d, J = 12.8 Hz, 2H), 1.54 (q, J = 12.1 Hz, 2H). MS *m/z*: 563.15 $[M+H]^+$.

6-(5-(Difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (198)



[00893] Step 1: (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.199 mmol, 1 equiv.) as the starting material to give the crude product (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 512 $[M+H]^+$.

[00894] Step 2: methyl 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate: Followed the general procedure H using (6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.199 mmol, 1 equiv.) and methyl 4-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (69.2 mg, 0.239 mmol, 1.2 equiv.) as the starting materials to give methyl 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (120 mg, 90%) as a colorless oil. MS *m/z*: 677 $[M+H]^+$.

[00895] Step 3: 6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure L using methyl 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-

trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (120 mg, 0.177 mmol, 1 equiv) as the starting material to give 6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (110 mg, 95%) as a white solid. MS *m/z*: 649 $[M+H]^+$.

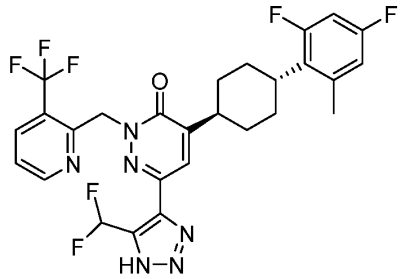
[00896] Step 4: 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general procedure M using 6-(5-(hydroxymethyl)-1-(tetrahydro-2H-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (110 mg, 0.168 mmol, 1 equiv) as the starting material to give 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (100 mg, 92%) as a white solid. MS *m/z*: 647 $[M+H]^+$.

[00897] Step 5: 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-5-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (100 mg, 0.155 mmol, 1 equiv) as the starting material to give 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 96%) as an off-white solid. MS *m/z*: 669 $[M+H]^+$.

[00898] Step 6: 6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one: Followed the general procedure AB using 6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (100 mg, 0.150 mmol, 1 equiv) as the starting material to give 6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-4-((1*r*,4*r*)-4-(2,4,6-trifluorophenyl)cyclohexyl)pyridazin-3(2*H*)-one (18.4 mg, 21%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.90 (s, 1H), 8.71 (dd, J = 5.2, 1.6 Hz, 1H), 8.25 (dd, J = 8.0, 1.6

Hz, 1H), 7.81 (s, 1H), 7.57 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.41 – 7.01 (m, 3H), 5.66 (s, 2H), 3.12 – 2.95 (m, 1H), 2.95 – 2.78 (m, 1H), 2.13 – 1.79 (m, 6H), 1.68 – 1.52 (m, 2H). MS *m/z*: 585.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (199)



[00899] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.200 mmol, 1 equiv.) as the starting material to give the crude product (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$.

[00900] Step 2: methyl 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.200 mmol, 1 equiv.) and methyl 4-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (69.8 mg, 0.241 mmol, 1.2 equiv.) as the starting materials to give methyl 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (80 mg, 60%) as a colorless oil. MS *m/z*: 673 $[M+H]^+$.

[00901] Step 3: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L

using 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carboxylate (80 mg, 0.119 mmol, 1 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 78%) as a white solid. MS *m/z*: 645 $[M+H]^+$.

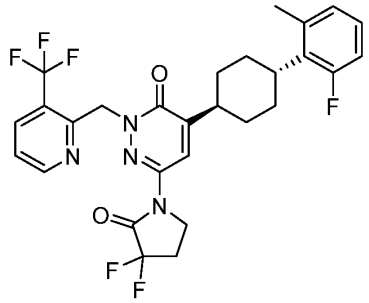
[00902] Step 4: 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (60 mg, 0.093 mmol, 1 equiv) as the starting material to give 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (50 mg, 84%) as a white solid. MS *m/z*: 643 $[M+H]^+$.

[00903] Step 5: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 4-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazole-5-carbaldehyde (50 mg, 0.077 mmol, 1 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 60%) as an off-white solid. MS *m/z*: 665 $[M+H]^+$.

[00904] Step 6: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure AB using 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 0.045 mmol, 1 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (19 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.93 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.59 (dd, J = 8.0, 4.9 Hz, 1H), 7.18 (d, J = 53.6 Hz, 1H), 7.04 – 6.95 (m,

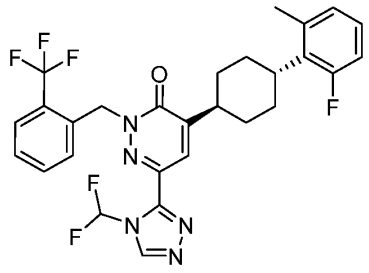
2H), 5.69 (s, 2H), 2.98 – 2.87 (m, 2H), 2.39 (s, 3H), 1.98 – 1.92 (m, 4H), 1.84 – 1.76 (m, 2H), 1.62 – 1.59 (m, 2H). MS *m/z*: 581.20 $[M+H]^+$.

6-(3,3-Difluoro-2-oxopyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200)

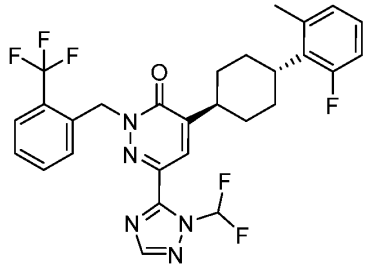


[00905] Step 1: 6-(3,3-difluoro-2-oxopyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.104 mmol, 1 equiv.) as the starting material, XPhos (5 mg, 0.01 mmol, 0.1 equiv.) and XPhos Pd G4 (9.0 mg, 0.01 mmol, 0.1 equiv.) as the catalyst, K_2CO_3 (40 mg, 0.312 mmol, 3equiv.) as the base to give the product 6-(3,3-difluoro-2-oxopyrrolidin-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (31 mg, 52.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 4.8 Hz, 1H), 8.24 (d, J = 5.8 Hz, 2H), 7.56 (dd, J = 8.0, 4.8 Hz, 1H), 7.15 – 7.08 (m, 1H), 7.03 – 6.91 (m, 2H), 5.53 (s, 2H), 3.77 (t, J = 6.4 Hz, 2H), 2.87 (dd, J = 28.4, 14.1 Hz, 2H), 2.75 – 2.61 (m, 2H), 2.36 (s, 3H), 2.08 – 1.85 (m, 4H), 1.80 (d, J = 12.0 Hz, 2H), 1.48 (q, J = 12.4 Hz, 2H). MS *m/z*: 565.20 $[M+H]^+$.

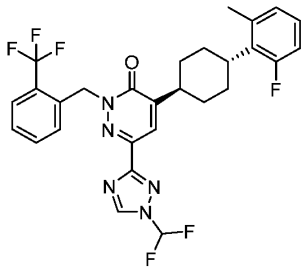
6-(4-(Difluoromethyl)-4*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201A)



6-(1-(Difluoromethyl)-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201B)



6-(1-(Difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201C)



[00906] Step 1: 3-bromo-4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazole: Followed the general procedure AA using 3-bromo-4*H*-1,2,4-triazole (500 mg, 3.37 mmol, 1 equiv) and DHP (426 mg, 5.06 mmol, 1.5 equiv) as the starting materials to give3-bromo-4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazole (500 mg, 63%) as a white solid. MS *m/z*: 232 $[M+H]^+$.

[00907] Step 2: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (100 mg, 0.209 mmol, 1.0 equiv) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 489 $[M+H]^+$.

[00908] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazol-3-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.209 mmol, 1.0 equiv) and 3-bromo-4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazole (58 mg, 0.251 mmol, 1.2 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazol-3-yl)-2-(2-

(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (70 mg, 56%) as a yellow oil. MS *m/z*: 596 $[M+H]^+$.

[00909] Step 4: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4*H*-1,2,4-triazol-3-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure AB using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(tetrahydro-2*H*-pyran-2-yl)-4*H*-1,2,4-triazol-3-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (60 mg, 0.101 mmol, 1 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4*H*-1,2,4-triazol-3-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (50 mg, 97%) as a white solid. MS *m/z*: 512 $[M+H]^+$.

[00910] Step 5: 6-(4-(difluoromethyl)-4*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one, 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one and 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4*H*-1,2,4-triazol-3-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (50 mg, 0.084 mmol, 1.0 equiv) and chlorodifluoromethane (gas) as the starting materials to give 6-(4-(difluoromethyl)-4*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (6.7 mg, 14.3%) as a white solid, 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (8.4 mg, 17.8%) as a white solid and 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (7.7 mg, 16.4%) as a white solid.

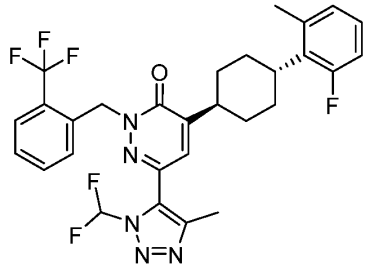
[00911] **6-(4-(difluoromethyl)-4*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201A)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.94 (d, *J* = 0.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 1H), 7.14 – 7.04 (m, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.63 (s, 2H), 3.16 (t, *J* = 12.0 Hz, 1H), 2.88 (d, *J* = 13.2 Hz, 1H), 2.37 (s, 3H), 2.21 – 2.10 (m, 4H), 1.90 – 1.84 (m, 2H), 1.63 – 1.48 (m, 2H). MS *m/z*: 562.30 $[M+H]^+$.

[00912] **6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201B)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.94 (d, *J* = 0.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz,

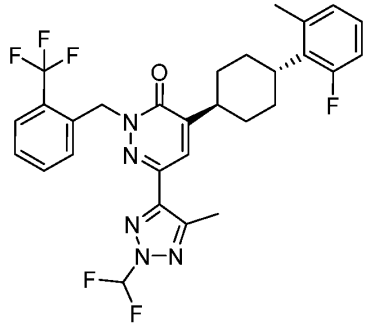
1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 1H), 7.14 – 7.04 (m, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.63 (s, 2H), 3.16 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 13.2 Hz, 1H), 2.37 (s, 3H), 2.21 – 2.10 (m, 4H), 1.90 – 1.84 (m, 2H), 1.62 – 1.50 (m, 2H). MS *m/z*: 562.30 $[M+H]^+$.

[00913] 6-(1-(difluoromethyl)-1*H*-1,2,4-triazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (201C): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.94 (d, *J* = 0.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 1H), 7.14 – 7.04 (m, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.63 (s, 2H), 3.16 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 13.2 Hz, 1H), 2.37 (s, 3H), 2.21 – 2.10 (m, 4H), 1.90 – 1.84 (m, 2H), 1.58 – 1.51 (m, 2H). MS *m/z*: 562.20 $[M+H]^+$.

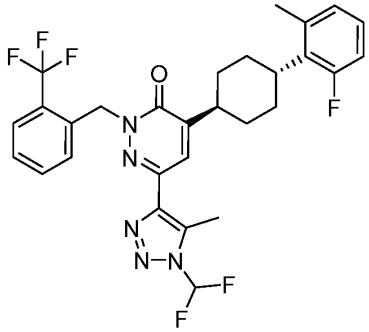
6-(1-(Difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202A)



6-(2-(Difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202B)



6-(1-(Difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202C)



[00914] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2H)-one (100 mg, 0.21 mmol, 1.0 equiv.) as the starting material to give the crude product (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 489 $[M+H]^+$.

[00915] Step 2: 6-(1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one, 6-(2-(difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one and 6-(1-(difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 0.21 mmol, 1.0 equiv.) and 5-bromo-1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazole (89 mg, 0.42 mmol, 2.0 equiv.) as the starting materials to give 6-(1-(difluoromethyl)-4-methyl-1*H*-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one(9.1 mg, 7.5%) as a white solid, 6-(2-(difluoromethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one(7.1 mg, 5.9%) as a white solid and 6-(1-(difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one(6.3 mg, 5.2%) as a white solid.

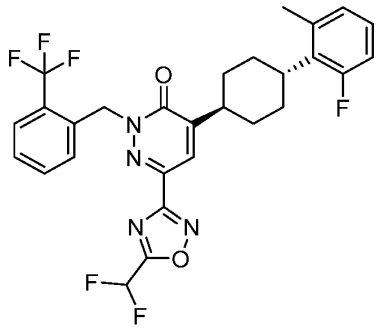
[00916] **6-(1-(difluoromethyl)-4-methyl-1H-1,2,3-triazol-5-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202A)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.32 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.04 (q, *J* = 7.2 Hz, 1H), 6.97 – 6.81 (m, 2H), 5.66 (s, 2H), 3.36 – 2.82 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H), 2.21 – 1.08 (m, 4H), 1.87 (d, *J* = 12.6 Hz, 2H), 1.57 – 1.45 (m, 2H).MS *m/z*: 576.20 $[M+H]^+$.

[00917] **6-(2-(difluoromethyl)-5-methyl-2H-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202B)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 16.4, 8.6 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.32 (s, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.10 – 6.97 (m, 1H), 6.95 – 6.81 (m, 2H), 5.64 (s, 2H), 3.14 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 12.2 Hz, 1H), 2.38 (d, *J* = 13.0 Hz, 6H), 2.22 – 1.09 (m, 4H), 1.87 (d, *J* = 12.7 Hz, 2H), 1.57 – 1.39 (m, 2H). MS *m/z*: 576.25 $[M+H]^+$.

[00918] **6-(1-(difluoromethyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (202C)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.96 (m, 1H), 7.76 – 7.55 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.04 (td, *J* = 8.0, 5.6 Hz, 1H), 6.93 (d,

J = 7.4 Hz, 1H), 6.86 (dd, *J* = 11.8, 8.0 Hz, 1H), 5.64 (s, 2H), 3.16 (t, *J* = 12.4 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 2.48 (s, 3H), 2.37 (s, 3H), 2.22 – 1.09 (m, 4H), 1.93 – 1.82 (m, 2H), 1.68 – 1.52 (m, 2H). MS *m/z*: 576.25 $[M+H]^+$.

6-(5-(Difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (203)



[00919] Step 1: 4-bromo-6-chloro-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure V using 4-bromo-6-chloropyridazin-3(2*H*)-one (2.00 g, 9.62 mmol, 1.0 equiv.) and 1-(bromomethyl)-2-(trifluoromethyl)benzene (2.73 g, 11.5 mmol, 1.2 equiv.) as the starting materials to give 4-bromo-6-chloro-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (1.6 g, 45%) as a white solid. MS *m/z*: 367 $[M+H]^+$.

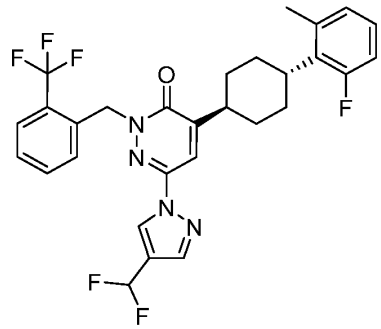
[00920] Step 2: 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure S using 4-bromo-6-chloro-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (1.70 g, 1.63 mmol, 1.0 equiv.) and 1,3-dioxoisoindolin-2-yl 4-(2-fluoro-6-methylphenyl)cyclohexane-1-carboxylate (2.65 g, 6.95 mmol, 2.0 equiv.) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (830 mg, 37%) as a white solid. MS *m/z*: 479 $[M+H]^+$.

[00921] Step 3: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbonitrile: Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (100 mg, 1.63 mmol, 1.0 equiv.) and dicyanozinc (2.65 g, 6.95 mmol, 2.0 equiv.) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carbonitrile (830 mg, 37%) as a white solid. MS *m/z*: 479 $[M+H]^+$.

[00922] Step 4: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (100 mg, 0.21 mmol, 1.0 equiv.) and hydroxylamine hydrochloride (16 mg, 0.26 mmol, 1.2 equiv.) as the starting materials to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboximidamide (36 mg, 35%) as a white solid. MS *m/z*: 503 $[M+H]^+$.

[00923] Step 5: 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazine-3-carboximidamide (36 mg, 0.07 mmol, 1.0 equiv.) and 2,2-difluoroacetic acid (9.0 mg, 0.09 mmol, 1.2 equiv.) as the starting materials to give 6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (33.6 mg, 77.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.10 – 6.98 (m, 2H), 5.74 (s, 3H), 6.96 – 6.80 (m, 3H), 3.12 (tt, *J* = 11.9, 2.9 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.36 (s, 3H), 2.25 – 2.05 (m, 4H), 1.92 – 1.80 (m, 2H), 1.65 – 1.48 (m, 2H). MS *m/z*: 563.20 $[M+H]^+$.

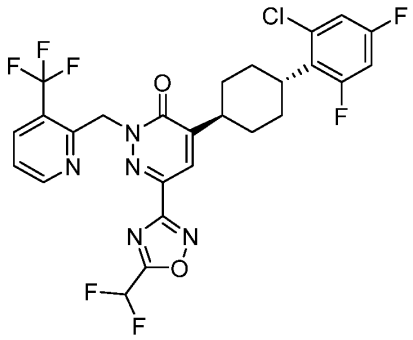
6-(4-(Difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (204)



[00924] Step 1: 6-(4-(difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (50.0 mg, 0.10 mmol, 1.0 equiv.) and 4-(difluoromethyl)-1*H*-pyrazole (14.7 mg, 0.12 mmol, 1.2 equiv.) as the starting materials,

Gphos Pd G6 TES (9.8 mg, 0.01 mmol, 0.1 equiv) and Gphos (5.6 mg, 0.01 mmol, 0.1 equiv) as the catalyst to give 6-(4-(difluoromethyl)-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (3.9 mg, 6.6%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 2.8 Hz, 1H), 7.95 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 7.08 – 6.99 (m, 1H), 6.94 – 6.83 (m, 2H), 6.75 – 6.61 (m, 2H), 5.60 (s, 2H), 3.17 (t, *J* = 12.0 Hz, 1H), 2.91 (t, *J* = 12.4 Hz, 1H), 2.37 (s, 3H), 2.25 – 2.05 (m, 4H), 1.92 – 1.80 (m, 2H), 1.65 – 1.48 (m, 2H). MS *m/z*: 561.20 [M+H]$^+$.

4-((1*r*,4*r*)-4-(2-Chloro-4,6-difluorophenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (205)



[00925] Step 1: ethyl 2'-amino-4',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate:_Followed the general Procedure A using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (6.00 g, 21.4 mmol, 1 equiv) and 2-bromo-3,5-difluoroaniline (4.43 g, 21.4 mmol, 1 equiv) as the starting materials to give ethyl 2'-amino-4',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (2.8 g, 46%) as a colourless oil. MS *m/z*: 282 [M+H]$^+$.

[00926] Step 2: ethyl 4-(2-amino-4,6-difluorophenyl)cyclohexane-1-carboxylate:_Followed the general Procedure B using ethyl 2'-amino-4',6'-difluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (2.80 g, 9.96 mmol, 1 equiv) as the starting material to give ethyl 4-(2-amino-4,6-difluorophenyl)cyclohexane-1-carboxylate as a colourless oil (2.6 g, 92%). MS *m/z*: 284 [M+H]$^+$.

[00927] Step 3: ethyl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate: To a stirred mixture of ethyl 4-(2-amino-4,6-difluorophenyl)cyclohexane-1-carboxylate (2.60 g, 9.19 mmol, 1 equiv) and *tert*-butylnitrite (1.42 g, 13.8 mmol, 1.5 equiv) in acetone (20 mL) was added $CuCl_2 \cdot H_2O$ (2.80 g in 5 mL EtOH, 18.4 mmol, 2 equiv) dropwise at 0 °C. The

resulting mixture was stirred at 0 °C for 2 h and monitored by LCMS. The resulting mixture was diluted with water (200 mL), extracted with EtOAc (3x300 mL). The combined organic layers were washed with water (400 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford ethyl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate as a colorless oil (1.87 g, 67%). MS *m/z*: 303 $[M+H]^+$.

[00928] Step 4: 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylic acid:_Followed the general Procedure C using ethyl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate (2.30 g, 7.61 mmol, 1 equiv) as the starting material to give 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylic acid (2.1 g, crude) as a white solid. MS *m/z*: 273 $[M-H]^-$.

[00929] Step 5: 1,3-dioxoisoindolin-2-yl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate: Followed the general procedure R using 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylic acid (500 mg, 1.82 mmol, 1.0 equiv.) and 2-hydroxyisoindoline-1,3-dione (327 mg, 2.01 mmol, 1.1 equiv.) as the starting materials to give 1,3-dioxoisoindolin-2-yl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate (620 mg, 81%) as an off-white solid. MS *m/z*: 420 $[M+H]^+$.

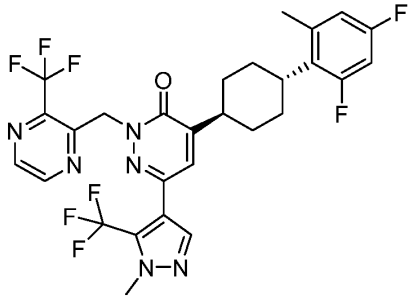
[00930] Step 6: 6-chloro-4-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure S using 4-bromo-6-chloro-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (410 mg, 1.12 mmol, 1.0 equiv.) and 1,3-dioxoisoindolin-2-yl 4-(2-chloro-4,6-difluorophenyl)cyclohexane-1-carboxylate (516 mg, 1.23 mmol, 1.1 equiv.) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 17%) as a off-white solid. MS *m/z*: 518 $[M+H]^+$.

[00931] Step 7: 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile: Followed the general procedure W using 6-chloro-4-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (100 mg, 0.19 mmol, 1.0 equiv.) as the starting material to give 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (70 mg, 72%) as a white oil. MS *m/z*: 509 $[M+H]^+$.

[00932] Step 8: 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbonitrile (70 mg, 0.14 mmol, 1.0 equiv.) as the starting material to give 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (45 mg, 59%) as a white solid. MS *m/z*: 542 $[M+H]^+$.

[00933] Step 9: 4-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure Y using 5-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (40 mg, 0.07 mmol, 1.0 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2-chloro-4,6-difluorophenyl)cyclohexyl)-6-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (10.6 mg, 23.7%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 0.8 Hz, 1H), 7.33 (m, 1H), 7.01 – 6.69 (m, 3H), 5.83 (s, 2H), 3.25 (t, *J* = 12.4 Hz, 1H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.23 – 2.01 (m, 4H), 1.94 – 1.83 (m, 2H), 1.65 – 1.48 (m, 2H). MS *m/z*: 602.15 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (206)

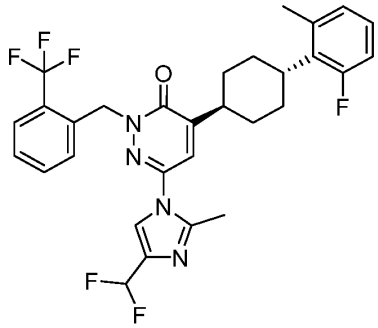


[00934] Step 1: 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure F using 6-chloro-4-[(1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl]-2*H*-pyridazin-3-one (40.0 mg, 0.118 mmol, 1.0 equiv) and 2-(bromomethyl)-3-(trifluoromethyl)pyrazine (42.7 mg, 0.177 mmol, 1.5 equiv) as the starting materials to give 6-chloro-4-((1*r*,4*r*)-4-(2,4-

difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (35 mg, 59%) as a white solid. MS *m/z*: 499 $[M+H]^+$.

[00935] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (30.0 mg, 0.06 mmol, 1.0 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (18.3 mg, 0.066 mmol, 1.1 equiv) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyrazin-2-yl)methyl)pyridazin-3(2*H*)-one (5 mg, 14%) as a white solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.61 (d, *J* = 22.2 Hz, 2H), 7.64 (s, 1H), 7.18 (s, 1H), 6.68 – 6.59 (m, 2H), 5.75 (s, 2H), 4.06 (s, 3H), 3.04 (s, 1H), 2.82 (s, 1H), 2.34 (s, 3H), 2.10 (d, *J* = 12.0 Hz, 4H), 1.83 (s, 2H), 1.45 (d, *J* = 10.8 Hz, 2H). MS *m/z*: 613.25 $[M+H]^+$.

6-(4-(Difluoromethyl)-2-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (207)

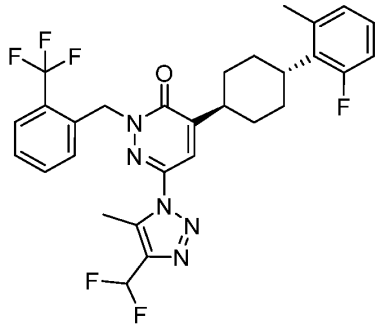


[00936] Step 1: ethyl 1-(5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carboxylate: Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (200 mg, 0.42 mmol, 1.0 equiv) and ethyl 2-methyl-1H-imidazole-4-carboxylate (77.3 mg, 0.50 mmol, 1.2 equiv) as the starting materials, $Me_4{}^{t\text{-}Bu}$XPhos (20.1 mg, 0.04 mmol, 0.1 equiv) as the ligand, K_3PO_4 (177.3 mg, 0.84 mmol, 2.0 equiv) as the base, toluene (5 mL) as the solvent to give ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carboxylate (100 mg, 40%) as a white solid. MS *m/z*: 597 $[M+H]^+$.

[00937] Step 2: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carbaldehyde: Followed the general procedure Z using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carboxylate (100 mg, 0.172 mmol, 1 equiv) as the starting material to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carbaldehyde (80 mg, 84%) as a white solid. MS *m/z*: 553 $[M+H]^+$.

[00938] Step 3: 6-(4-(difluoromethyl)-2-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2H)-one: Followed the general procedure I using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-2-methyl-1*H*-imidazole-4-carbaldehyde (70.0 mg, 0.127 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-2-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (10.8 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.08 – 7.03 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.89 – 6.55 (m, 2H), 5.59 (s, 2H), 3.16 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 2.24 – 2.14 (m, 4H), 1.89 (d, *J* = 12.8 Hz, 2H), 1.47 (q, *J* = 12.0 Hz, 2H). MS *m/z*: 575.20 $[M+H]^+$.

6-(4-(Difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (208)



[00939] Step 1: ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylate: Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (200 mg, 0.418

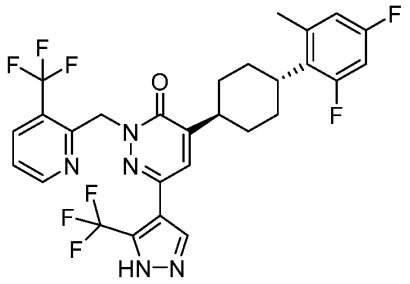
mmol, 1 equiv.) and ethyl 4-methyl-1*H*-1,2,3-triazole-5-carboxylate (97.2 mg, 0.627 mmol, 1.5 equiv.) as the starting materials, Me_4t-BuXPhos (20.0 mg, 0.042 mmol, 0.1 equiv.) as the ligand, K_3PO_4 (177 mg, 0.836 mmol, 2 equiv.) as the base to give ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylate (215 mg, 51%) as a light yellow oil. MS *m/z*: 598 $[M+H]^+$.

[00940] Step 2: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-1,2,3-triazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylate (200 mg, 3.35 mmol, 1.0 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-1,2,3-triazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (133 mg, 71%) as a white solid. MS *m/z*: 556 $[M+H]^+$.

[00941] Step 3: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-1,2,3-triazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (130 mg, 3.35 mmol, 1.0 equiv.) as the starting material to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (111 mg, 85%) as a white solid. MS *m/z*: 554 $[M+H]^+$.

[00942] Step 4: 6-(4-(difluoromethyl)-5-methyl-1H-1,2,3-triazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2H)-one: Followed the general procedure I using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-1,2,3-triazole-5-carbaldehyde (100 mg, 1.81 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (54.1 mg, 52.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.52 – 7.31 (m, 2H), 7.10 – 6.73 (m, 5H), 5.69 (s, 2H), 3.15 (t, J = 12.0 Hz, 1H), 2.90 (t, J = 12.0 Hz, 1H), 2.54 (s, 3H), 2.36 (s, 3H), 2.16 (d, J = 12.1 Hz, 4H), 1.95 – 1.79 (m, 2H), 1.59 – 1.48 (m, 2H). MS *m/z*: 576.30 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (209)



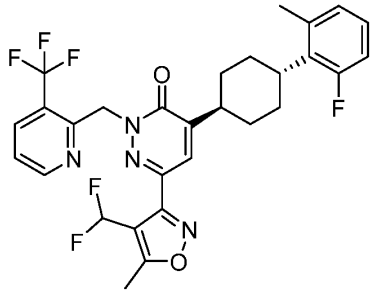
[00943] Step 1: 1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole: Followed the general procedure AA using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (500 mg, 1.91 mmol, 1 equiv) and DHP (481 mg, 5.73 mmol, 3 equiv) as the starting materials to give 1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole(500 mg, 75%) as a white solid. MS *m/z*: 347 $[M+H]^+$.

[00944] Step 2: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure A using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (200 mg, 0.402 mmol, 1 equiv.) and 1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole (417 mg, 1.20 mmol, 3 equiv.) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 54%) as a white solid. MS *m/z*: 682 $[M+H]^+$.

[00945] Step 3: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2H)-one: Followed the general procedure AB using 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (150 mg, 0.220 mmol, 1 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (94.3 mg, 71%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, J = 4.8 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.47 – 7.37 (m, 1H), 7.28 (s, 1H), 6.73 – 6.51 (m, 2H), 5.74 (s, 2H), 3.05 (t, J = 12.0 Hz, 1H), 2.82 (t, J = 12.4 Hz, 1H), 2.34 (s, 3H), 2.09 (q, J = 13.8, 12.4 Hz, 4H), 1.81 (d, J = 12.4 Hz, 2H), 1.45 (q, J = 12.4 Hz, 2H). MS *m/z*: 598.15 $[M+H]^+$.

6-(4-(Difluoromethyl)-5-methylisoxazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (210)



[00946] Step 1: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(hydroxymethyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using methyl 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (1.00 g, 1.98 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(hydroxymethyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (750 mg, 79%) as a white solid. MS *m/z*: 476 $[M+H]^+$.

[00947] Step 2: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(hydroxymethyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (750 mg, 1.57 mmol, 1.0 equiv) as the starting material to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde (590 mg, 78%) as a white solid. MS *m/z*: 474 $[M+H]^+$.

[00948] Step 3: (*Z*)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde oxime: To a stirred solution of 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde (600 mg, 1.26 mmol, 1 equiv) in EtOH (10 mL) was added hydroxylamine hydrochloride (176 mg, 2.53

mmol, 2 equiv) at room temperature. The resulting mixture was stirred at room temperature for 1h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (0% to 100% gradient in 25min) to afford (*Z*)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde oxime (500 mg, 82%) as a white solid.

[00949] Step 4: (*E*)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbimidoyl chloride: To a stirred solution of (*Z*)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbaldehyde oxime (350 mg, 0.716 mmol, 1 equiv) in DMF (8 mL) were added NCS (191 mg, 1.43 mmol, 2 equiv) in portions at room temperature. The resulting mixture was stirred at room temperature for 2h. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00950] Step 5: methyl 3-(5-((1*r*,4*r*)-4-(2-fluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methylisoxazole-4-carboxylate: To a stirred solution of (*E*)-5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carbimidoyl chloride (300 mg, 0.574 mmol, 1 equiv) in EtOH (5 mL) were added methyl 3-oxobutanoate (73.2 mg, 0.631 mmol, 1.1 equiv) and Et_3N (87.0 mg, 0.861 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred at room temperature for 2h. The resulting mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (0% to 80% gradient in 20 min) to afford methyl 3-(5-((1*r*,4*r*)-4-(2-fluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methylisoxazole-4-carboxylate (110 mg, 32%) as a white solid. MS *m/z*: 585 $[M+H]^+$.

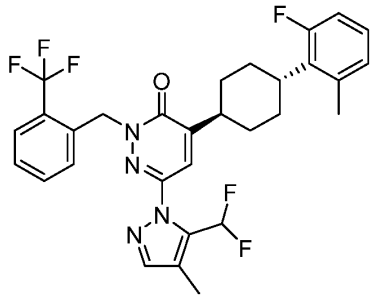
[00951] Step 6: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-5-methylisoxazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure L using methyl 3-(5-((1*r*,4*r*)-4-(2-fluorophenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-

methylisoxazole-4-carboxylate (110 mg, 0.188 mmol, 1.0 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-5-methylisoxazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (30 mg, 28%) as a white solid. MS *m/z*: 557 $[M+H]^+$.

[00952] Step 7: 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methylisoxazole-4-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(4-(hydroxymethyl)-5-methylisoxazol-3-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (40 mg, 0.072 mmol, 1.0 equiv) as the starting material to give 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methylisoxazole-4-carbaldehyde (30 mg, 75%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

[00953] Step 8: 6-(4-(difluoromethyl)-5-methylisoxazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 3-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-5-methylisoxazole-4-carbaldehyde (30 mg, 0.054 mmol, 1.0 equiv) as the starting material to give 6-(4-(difluoromethyl)-5-methylisoxazol-3-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (20.7 mg, 66.5%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 – 8.63 (m, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.38 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.08 – 6.96 (m, 1H), 6.95 – 6.64 (m, 3H), 5.71 (s, 2H), 3.10 (t, *J* = 12.0 Hz, 1H), 2.88 (t, *J* = 12.6 Hz, 1H), 2.60 (t, *J* = 2.1 Hz, 3H), 2.36 (s, 3H), 2.23 – 2.01 (m, 4H), 1.93 – 1.77 (m, 2H), 1.55 – 1.40 (m, 2H). MS *m/z*: 577.20 $[M+H]^+$.

6-(5-(Difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (211)



[00954] Step 1: ethyl (3*E*)-4-(dimethylamino)-3-methyl-2-oxobut-3-enoate: A solution of ethyl 2-oxobutanoate (700 mg, 5.38 mmol, 1 equiv) and (dimethoxymethyl)dimethylamine (961 mg, 8.07 mmol, 1.5 equiv) in THF (10 mL) was stirred at 80°C for 2h. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:10) to afford ethyl (3*E*)-4-(dimethylamino)-3-methyl-2-oxobut-3-enoate (480 mg, 48.18%) as a light yellow oil. MS *m/z*: 186 $[M+H]^+$.

[00955] Step 2: *tert*-butyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate: Followed the general procedure Z using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (300 mg, 0.63 mmol, 1.0 equiv.) and *tert*-butyl hydrazinecarboxylate (166 mg, 1.26 mmol, 2.0 equiv.) as the starting materials to give *tert*-butyl 2-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate (310 mg, 86%) as a light yellow solid. MS *m/z*: 575 $[M+H]^+$.

[00956] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-hydrazineyl-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure AD using *tert*-butyl 2-(5-((1r,4r)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)hydrazine-1-carboxylate (300 mg, 0.487 mmol, 1 equiv) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-hydrazineyl-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (287 mg, crude) as a light yellow solid. The crude product was used in the next step directly without further purification. MS *m/z*: 475 $[M+H]^+$.

[00957] Step 4: ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carboxylate: To a stirred solution of 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-hydrazineyl-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (280 mg, 0.591 mmol, 1 equiv) and ethyl (*E*)-4-(dimethylamino)-3-methyl-2-oxobut-3-enoate (218 mg, 1.181 mmol, 2.0 equiv) in EtOH (3 mL) was added *conc.* HCl (10 uL, 0.118 mmol, 0.2 equiv) dropwise at room temperature. The resulting mixture was stirred at 80°C for 2h and monitored by LCMS. The mixture was basified to pH 9 with NaOH. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:10) to afford ethyl 1-(5-

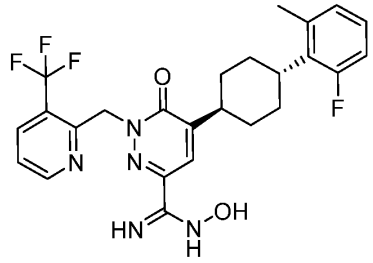
((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carboxylate (266 mg, 75%) as an off-white solid. MS *m/z*: 597 $[M+H]^+$.

[00958] Step 5: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-pyrazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carboxylate (200 mg, 0.335 mmol, 1.0 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-pyrazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (25 mg, 13%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

[00959] Step 6: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(5-(hydroxymethyl)-4-methyl-1*H*-pyrazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (25 mg, 0.045 mmol, 1.0 equiv.) as the starting material to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 80%) as a white solid. MS *m/z*: 553 $[M+H]^+$.

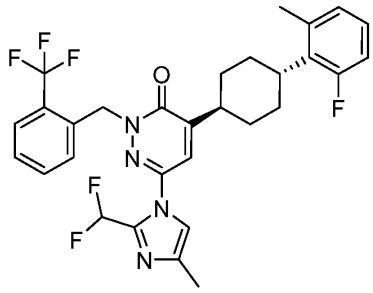
[00960] Step 7: 6-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-pyrazole-5-carbaldehyde (20 mg, 0.036 mmol, 1.0 equiv.) as the starting material to give 6-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (12.9 mg, 62.0%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 0.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.41 (m, 3H), 7.24 (s, 1H), 7.08 – 6.98 (m, 1H), 6.96 – 6.71 (m, 3H), 5.56 (s, 2H), 3.25 – 3.09 (m, 1H), 2.95 – 2.81 (m, 1H), 2.36 (s, 3H), 2.24 – 2.17 (m, 4H), 2.18 – 2.11 (m, 3H), 1.91 – 1.83 (m, 2H), 1.55 – 1.48 (m, 2H). MS *m/z*: 575.30 $[M+H]^+$.

5-((1*r*,4*r*)-4-(2-Fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (212)



[00961] Step 1: 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide: Followed the general procedure X using 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboxylate (200 mg, 0.425 mmol, 1 equiv.) and hydroxylamine hydrochloride (35.5 mg, 0.510 mmol, 1.2 equiv.) as the starting materials to give 5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-*N*-hydroxy-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazine-3-carboximidamide (63.6 mg, 29.7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H), 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 7.63 (s, 1H), 7.55 (dd, J = 8.0, 4.8 Hz, 1H), 7.15 – 7.05 (m, 1H), 7.02 – 6.89 (m, 2H), 5.63 (m, 4H), 2.90 (t, J = 12.0 Hz, 1H), 2.79 (t, J = 12.0 Hz, 1H), 2.35 (s, 3H), 2.01 – 1.85 (m, 4H), 1.83 – 1.71 (m, 2H), 1.54 – 1.40 (m, 2H). MS *m/z*: 504.30 $[M+H]^+$.

6-(2-(Difluoromethyl)-4-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (213)



[00962] Step 1: (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (250 mg, 0.522 mmol, 1 equiv.) as the starting material to give (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid (200 mg, crude) which was used in the next step directly without further purification. MS *m/z*: 489 $[M+H]^+$.

[00963] Step 2: ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carboxylate: Followed the general procedure AE using (5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)boronic acid (250 mg, 0.511 mmol, 1 equiv.) and ethyl 4-methyl-1*H*-imidazole-2-carboxylate (95.1 mg, 0.613 mmol, 1.2 equiv.) as the starting materials to give ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carboxylate (160 mg, 52%) as a white solid. MS *m/z*: 597 $[M+H]^+$.

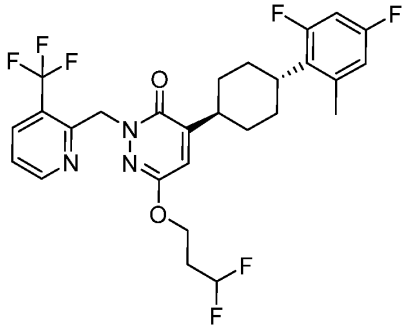
[00964] Step 3: 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-4-methyl-1*H*-imidazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure L using ethyl 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carboxylate (160 mg, 0.268 mmol, 1 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-4-methyl-1*H*-imidazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (80 mg, 53%) as a white solid. MS *m/z*: 555 $[M+H]^+$.

[00965] Step 4: 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carbaldehyde: Followed the general procedure M using 4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-(2-(hydroxymethyl)-4-methyl-1*H*-imidazol-1-yl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (80 mg, 0.144 mmol, 1 equiv.) as the starting material to give 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carbaldehyde (40 mg, 50%) as a white solid. MS *m/z*: 553 $[M+H]^+$.

[00966] Step 5: 6-(2-(difluoromethyl)-4-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 1-(5-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-(2-(trifluoromethyl)benzyl)-1,6-dihydropyridazin-3-yl)-4-methyl-1*H*-imidazole-2-carbaldehyde (40 mg, 0.072 mmol, 1 equiv.) as the starting material to give 6-(2-(difluoromethyl)-4-methyl-1*H*-imidazol-1-yl)-4-((1*r*,4*r*)-4-(2-fluoro-6-methylphenyl)cyclohexyl)-2-(2-(trifluoromethyl)benzyl)pyridazin-3(2*H*)-one (8.8 mg, 21.2%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.33 (s, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 7.04 (dd, *J* = 8.0, 5.6 Hz, 1H), 6.96

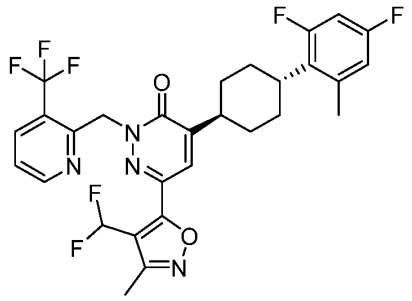
(d, J = 16.6 Hz, 1H), 6.90 (d, J = 12.8 Hz, 1H), 6.87 – 6.83 (m, 1H), 5.59 (s, 2H), 3.13 (t, J = 12.0 Hz, 1H), 2.87 (t, J = 12.0 Hz, 1H), 2.38 (s, 3H), 2.36 (s, 3H), 2.19 – 2.11 (m, 4H), 1.90 – 1.87 (m, 2H), 1.51 – 1.38 (m, 2H). MS *m/z*: 575.30 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(3,3-difluoropropoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (214)



[00967] Step 1: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(3,3-difluoropropoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure K using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (50 mg, 0.100 mmol, 1.0 equiv.) and 3,3-difluoropropan-1-ol (30 mg, 0.301 mmol, 3.0 equiv.) as the starting materials to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(3,3-difluoropropoxy)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (9.6 mg, 17.1%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.38 (s, 1H), 6.81 (s, 1H), 6.71 – 6.53 (m, 2H), 5.98 (tt, J = 56.4, 4.8 Hz, 1H), 5.56 (s, 2H), 4.21 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 12.0 Hz, 1H), 2.80 (t, J = 12.4 Hz, 1H), 2.33 (s, 3H), 2.31 – 2.14 (m, 2H), 2.15 – 2.01 (m, 4H), 1.83 – 1.71 (m, 2H), 1.50 – 1.31 (m, 2H). MS *m/z*: 558.20 $[M+H]^+$.

4-((1*r*,4*r*)-4-(2,4-Difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)-3-methylisoxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (215)



[00968] Step 1: (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid: Followed the general procedure G using 6-chloro-4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (1 g, 2.01 mmol, 1 equiv.) as the starting material, Xphos Pd G3 (170 mg, 0.201 mmol, 0.1 equiv.) as the catalyst to give (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid which was used directly in the next step. MS *m/z*: 508 $[M+H]^+$.

[00969] Step 2: ethyl 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carboxylate: Followed the general procedure H using (5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)boronic acid (crude, 1.97 mmol, 1 equiv.) and ethyl 5-chloro-3-methylisoxazole-4-carboxylate (411 mg, 2.17 mmol, 1.1 equiv.) as the starting material Xphos Pd G3 (167 mg, 0.197 mmol, 0.1 equiv.) as the catalyst to give ethyl 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carboxylate (200 mg, 16%) as a white solid. MS *m/z*: 617 $[M+H]^+$.

[00970] Step 3: 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carbaldehyde: Followed the general procedure AC using ethyl 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carboxylate (200 mg, 0.324 mmol, 1 equiv) as the catalyst to give 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carbaldehyde (50 mg, 26%) as a light yellow solid. MS *m/z*: 573 $[M+H]^+$.

[00971] Step 4: 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)-3-methylisoxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one: Followed the general procedure I using 5-(5-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-oxo-1-((3-(trifluoromethyl)pyridin-2-yl)methyl)-1,6-dihydropyridazin-3-yl)-3-methylisoxazole-4-carbaldehyde (50 mg, 0.087 mmol, 1 equiv.) as the starting material to give 4-((1*r*,4*r*)-4-(2,4-difluoro-6-methylphenyl)cyclohexyl)-6-(4-(difluoromethyl)-3-methylisoxazol-5-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)pyridazin-3(2*H*)-one (41.2 mg, 79.3%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 4.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.43 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.98 (t, *J* = 54.0 Hz, 1H), 6.71 – 6.57 (m, 2H), 5.74 (s, 2H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.82 (t, *J* = 12.0 Hz, 1H), 2.46 (s, 3H), 2.35 (s, 3H), 2.18 – 2.05 (m, 4H), 1.83 (dd, *J* = 13.8, 4.2 Hz, 2H), 1.57 – 1.44 (m, 2H). MS *m/z*: 595.20 $[M+H]^+$.

Example 2: Biological assay data and procedures

[00972] Exemplary compounds were evaluated for classical GPCR β-arrestin recruitment via complement C5a receptor 1 (C5aR1) activation in live CHO-K1 cells. This cell line expresses two fragments of the β-galactosidase protein coupled to β-arrestin and C5aR1. Complementation of the two fragments allows for the assessment of both C5aR1 agonism and antagonism. Recombinant hC5a (EC_{90}) was used as the competing natural agonist against disclosed compounds (more information on the expanded protocol and cell line can be found on the manufacturer's website: PathHunter® CHO-K1 C5aR1 β-arrestin cell line, DiscoverX, Catalog No. 93-0557C2). The results in Table 1 demonstrate that compounds of the disclosure are potent antagonists of C5aR1. IC_{50} ranges: A: $IC_{50} \leq 500$ nM; B: 500 nM < $IC_{50} \leq 5$ μM; C: 5 μM < $IC_{50} \leq 100$ μM; D: $IC_{50} > 100$ μM.

[00973] Table 1. *In vitro* cellular IC_{50} values for exemplary compounds

No.	[Antagonist] B-arrestin2 recruitment: Average IC_{50} (nM)	[Agonist] B-arrestin2 recruitment: Average EC_{50} (nM)
1	A	Non-active at 10 μM
2	A	Non-active at 10 μM
3	A	Non-active at 10 μM
4	B	Non-active at 10 μM
5	A	Non-active at 10 μM
6	B	Non-active at 10 μM
7	B	Non-active at 10 μM
8	B	Non-active at 10 μM
9	B	Non-active at 10 μM
10	A	Non-active at 10 μM
11	B	Non-active at 10 μM

12	A	Non-active at 10 μM
13	A	Non-active at 10 μM
14	A	Non-active at 10 μM
15	A	Non-active at 10 μM
16	A	Non-active at 10 μM
17	A	Non-active at 10 μM
18	A	Non-active at 10 μM
19	A	Non-active at 10 μM
20	B	Non-active at 10 μM
21	A	Non-active at 10 μM
22	A	Non-active at 10 μM
23	A	Non-active at 10 μM
24	B	Non-active at 10 μM
25	A	Non-active at 10 μM
26	A	Non-active at 10 μM
27	B	Non-active at 10 μM
28	B	Non-active at 10 μM
29	A	Non-active at 10 μM
30	A	Non-active
31	A	Non-active at 10 μM
32	A	Non-active
33	A	Non-active at 10 μM
34	A	Non-active
35	A	Non-active
36	A	Non-active
37	A	Non-active
38	A	Non-active
39	A	Non-active
40	A	Non-active
41	A	Non-active
42	A	Non-active
43	A	Non-active
44	A	Non-active at 10 μM
45	A	Non-active
46	A	Non-active
47	A	Non-active
48	A	Non-active
49	A	Non-active
50	A	Non-active at 10 μM
51	A	Non-active at 10 μM
52	A	Non-active
53	A	Non-active at 10 μM
54	A	Non-active
55	A	Non-active
56	A	Non-active at 10 μM
57	A	Non-active
58A	A	Non-active
58B	A	Non-active
59	A	Non-active
60	A	Non-active
61	A	Non-active
62	A	Non-active

63	C	Non-active
64	A	Non-active
65	A	Non-active
66	A	Non-active
67	A	Non-active
68	A	Non-active
69	A	Non-active
70A	A	Non-active at 10 μM
70B	A	Non-active
71	A	Non-active
72	A	Non-active
73	A	Non-active at 10 μM
74	A	Non-active at 10 μM
75	A	Non-active at 10 μM
76	A	Non-active at 10 μM
77	A	Non-active at 10 μM
78	A	Non-active at 10 μM
79	A	Non-active at 10 μM
80	A	Non-active at 10 μM
81	A	Non-active at 10 μM
82	A	Non-active at 10 μM
83	A	Non-active at 10 μM
84	A	Non-active
85	A	Non-active at 10 μM
86	A	Non-active
87	A	Non-active
88A	A	Non-active
88B	A	Non-active at 10 μM
88C	A	Non-active at 10 μM
89	A	Non-active
90	A	Non-active
91	A	Non-active
92	A	Non-active
93	A	Non-active
94	A	Non-active at 10 μM
95	A	Non-active at 10 μM
96	A	Non-active
97	A	Non-active at 10 μM
98	A	Non-active
99	A	Non-active
100	B	Non-active at 10 μM
101	A	Non-active
102	A	Non-active at 10 μM
103	A	Non-active
104	A	Non-active
105	A	Non-active at 10 μM
106	A	Non-active at 10 μM
107	A	Non-active at 10 μM
108	A	Non-active at 10 μM
109	A	Non-active at 10 μM
110	A	Non-active at 10 μM
111	A	Non-active at 10 μM

112	A	Non-active at 10 μM
113	A	Non-active at 10 μM
114	A	Non-active at 10 μM
115	A	Non-active at 10 μM
116	A	Non-active at 10 μM
117	C	Non-active at 10 μM
118	A	Non-active at 10 μM
119	A	Non-active at 10 μM
120	A	Non-active at 10 μM
121	A	Non-active at 10 μM
122	A	Non-active at 10 μM
123	A	Non-active at 10 μM
124	A	Non-active at 10 μM
125	A	Non-active at 10 μM
126	NT	NT
127	A	Non-active at 10 μM
128	A	Non-active at 10 μM
129	A	Non-active at 10 μM
130	A	Non-active at 10 μM
131	A	Non-active at 10 μM
132	A	Non-active at 10 μM
133	A	Non-active at 10 μM
134	A	Non-active at 10 μM
135	B	Non-active at 10 μM
136	A	Non-active at 10 μM
137	A	Non-active at 10 μM
138	A	Non-active at 10 μM
139	A	Non-active at 10 μM
140	A	Non-active at 10 μM
141	A	Non-active at 10 μM
142	A	Non-active at 10 μM
143	A	Non-active at 10 μM
144	A	Non-active at 10 μM
145	A	Non-active at 10 μM
146	A	Non-active at 10 μM
147	A	Non-active at 10 μM
148	A	Non-active at 10 μM
149	A	Non-active at 10 μM
150	A	Non-active at 10 μM
151	A	Non-active at 10 μM
152	A	Non-active at 10 μM
153	A	Non-active at 10 μM
154	A	Non-active at 10 μM
155	A	Non-active at 10 μM
156	A	Non-active
157	A	Non-active
158	A	Non-active
159	A	Non-active
160	A	Non-active
161	A	Non-active
162	A	Non-active
163	A	Non-active

164	A	Non-active
165	A	Non-active
166	A	Non-active
167	A	Non-active
168	A	Non-active
169	A	Non-active
170	A	Non-active
171	A	Non-active
172	A	Non-active
173	A	Non-active
174	A	Non-active
175	A	Non-active
176	A	Non-active
177	A	Non-active
178	A	Non-active
179	A	Non-active
180	A	Non-active
181	A	Non-active
182	A	Non-active
183	A	Non-active
184	A	Non-active
185	A	Non-active
186	A	Non-active
187	A	Non-active
188	C	Non-active
189	A	Non-active
190	A	Non-active
191	B	Non-active
192	A	Non-active
193A	A	Non-active
193B	A	Non-active
194	A	Non-active
195A	A	Non-active
195B	A	Non-active
195C	A	Non-active
195D	A	Non-active
196	A	Non-active
197	A	Non-active
198	B	Non-active
199	C	Non-active
200	A	Non-active
201A	B	Non-active
201B	A	Non-active
201C	A	Non-active
202A	B	Non-active
202B	B	Non-active
202C	A	Non-active
203	A	Non-active
204	C	Non-active
205	A	Non-active
206	A	Non-active
207	B	Non-active

208	A	Non-active
209	A	Non-active
210	A	Non-active
211	A	Non-active
212	B	Non-active
213	A	Non-active
214	A	Non-active
215	A	Non-active

NT: not tested

EQUIVALENTS AND SCOPE

[00974] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The present disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The present disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00975] Furthermore, the present disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the present disclosure, or aspects of the present disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the present disclosure or aspects of the present disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of

the present disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

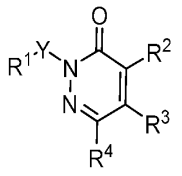
[00976] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the present disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00977] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 is optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^3 is hydrogen, halogen, optionally substituted alkyl, or optionally substituted aryl;

R^4 is hydrogen, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,$–OR^A$, $–N(R^A)_2$, $–C(=O)N(R^A)_2$, $–C(=NR^A)NR^AOR^A$, or $–NR^AC(=O)R^A$;

Y is $–C(R^5)_2–$ or a bond;

each R^5 is independently hydrogen, halogen, or optionally substituted alkyl; and

each R^A is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is $–C(R^5)_2–$.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently hydrogen or optionally substituted alkyl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein Y is $–CH_2–$.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is a bond.

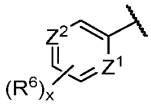
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted carbocyclyl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted aryl or optionally substituted heteroaryl.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted aryl.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted heteroaryl.

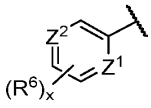
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^1 is



,

wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and x is 0, 1, 2, 3, or 4.

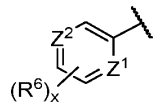
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^1 is



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wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently haloalkyl or $–OR^A$; and x is 0, 1, 2, 3, or 4.

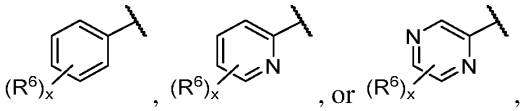
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^1 is



,

wherein Z^1 and Z^2 are each independently CH, CR^6, or N; each R^6 is independently cyclopropyl, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–OCF_3$, or $–OCHF_2$; and x is 0, 1, 2, 3, or 4.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^1 is

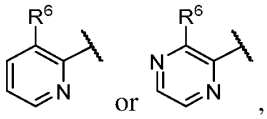


, or

,

wherein each R^6 is independently cyclopropyl, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–OCF_3$, or $–OCHF_2$; and x is 0, 1, 2, 3, or 4.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^1 is

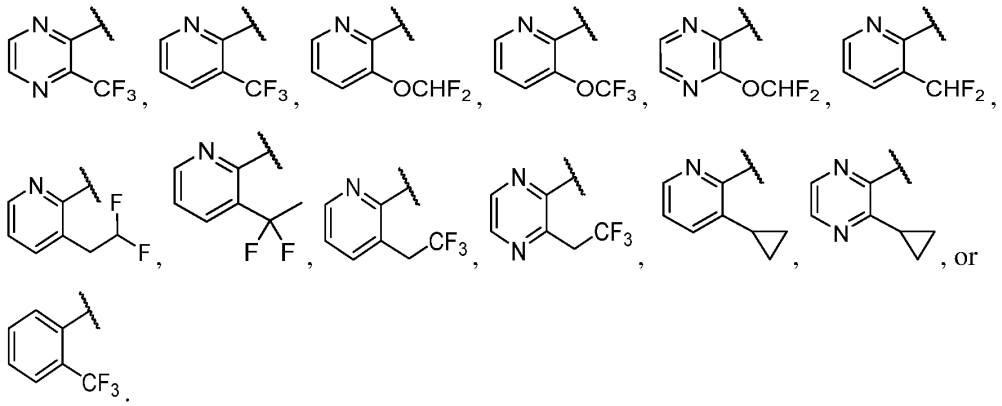


or

,

wherein R^6 is cyclopropyl, $-CF_3$, $-CHF_2$, $–CF_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–OCF_3$, or $–OCHF_2$.

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^1 is



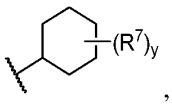
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted carbocyclyl.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted C_{3-12} cycloalkyl.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted C_{3-8} cycloalkyl.

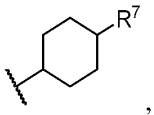
19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted cyclohexyl.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^2 is



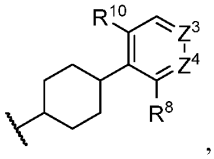
wherein each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted aryl; and y is 0, 1, or 2.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R^2 is



wherein R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

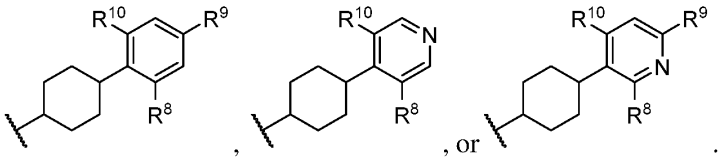
22. The compound of any one of claims 1-21, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is



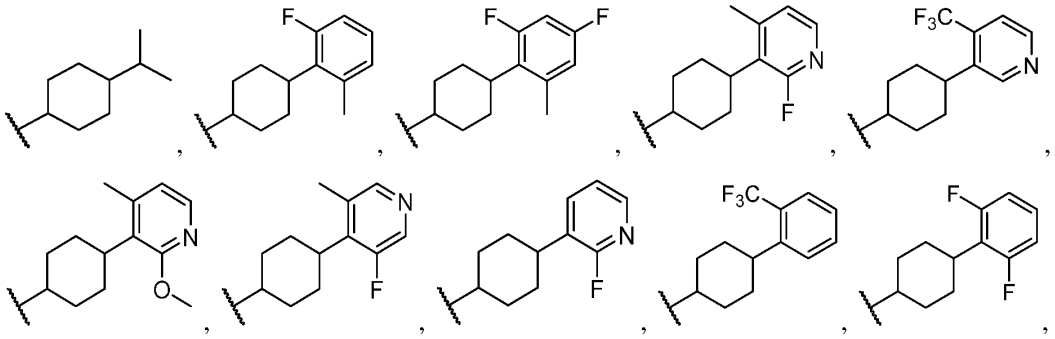
wherein Z^3 and Z^4 are each independently -N- or -CR^9-; and

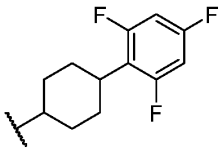
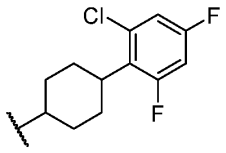
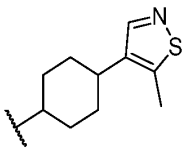
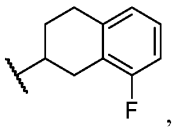
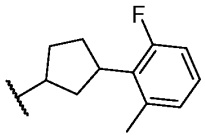
R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

23. The compound of any one of claims 1-22, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is

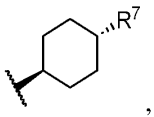


24. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^2 is



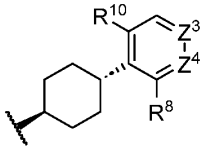




, or

.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R^2 is


,

wherein R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

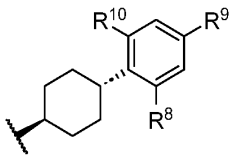
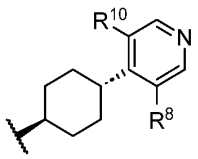
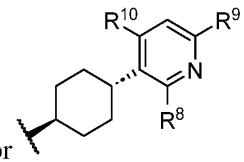
26. The compound of any one of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is


,

wherein Z^3 and Z^4 are each independently -N- or -CR^9-; and

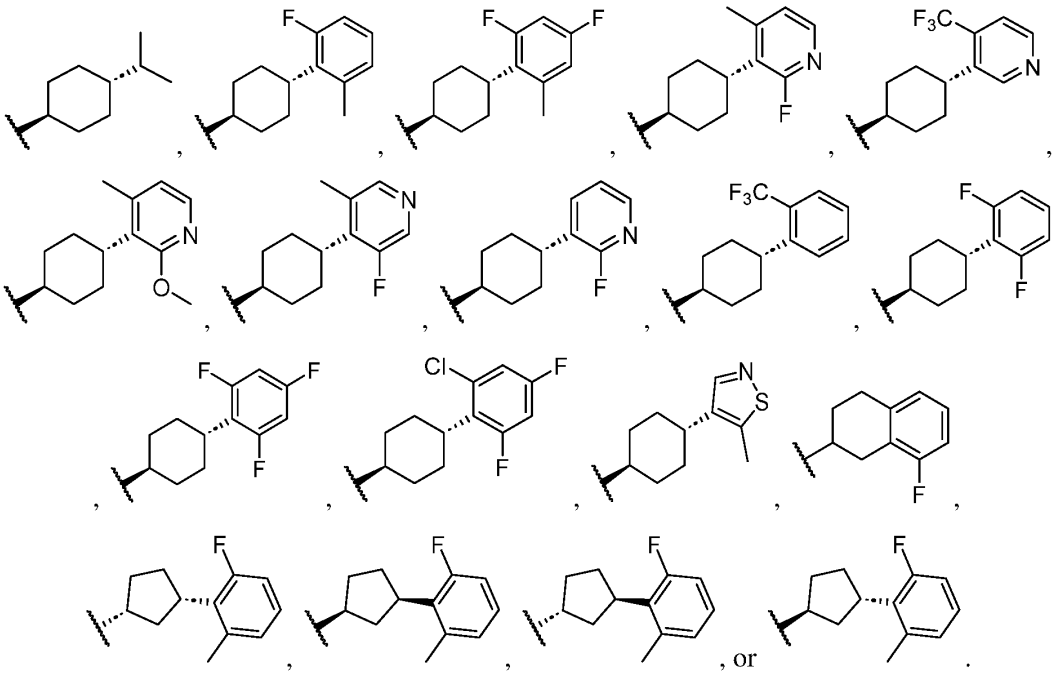
R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

27. The compound of any one of claims 1-26, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is

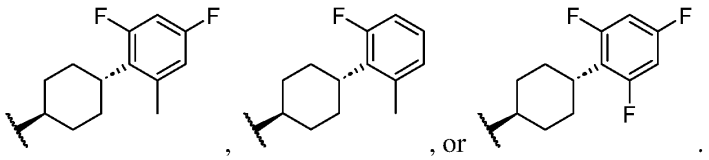

,

, or

,

wherein R^8, R^9, and R^{10} are each independently hydrogen, halogen, optionally substituted alkyl, or -OR^A.

28. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein R^2 is



29. The compound of any one of claims 1-28, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is



30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or optionally substituted aryl.

31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or optionally substituted phenyl.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $–OR^A$, $–N(R^A)_2$, $–C(=O)N(R^A)_2$, $–C(=NR^A)NR^AOR^A$, or $–NR^AC(=O)R^A$.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_{4-6} cycloalkyl, optionally substituted 4-6-membered heterocyclyl, optionally substituted 5-6-membered heteroaryl, $–OR^A$, $–N(R^A)_2$, $–C(=O)N(R^A)_2$, $–C(=NR^A)NR^AOR^A$, or $–NR^AC(=O)R^A$; and

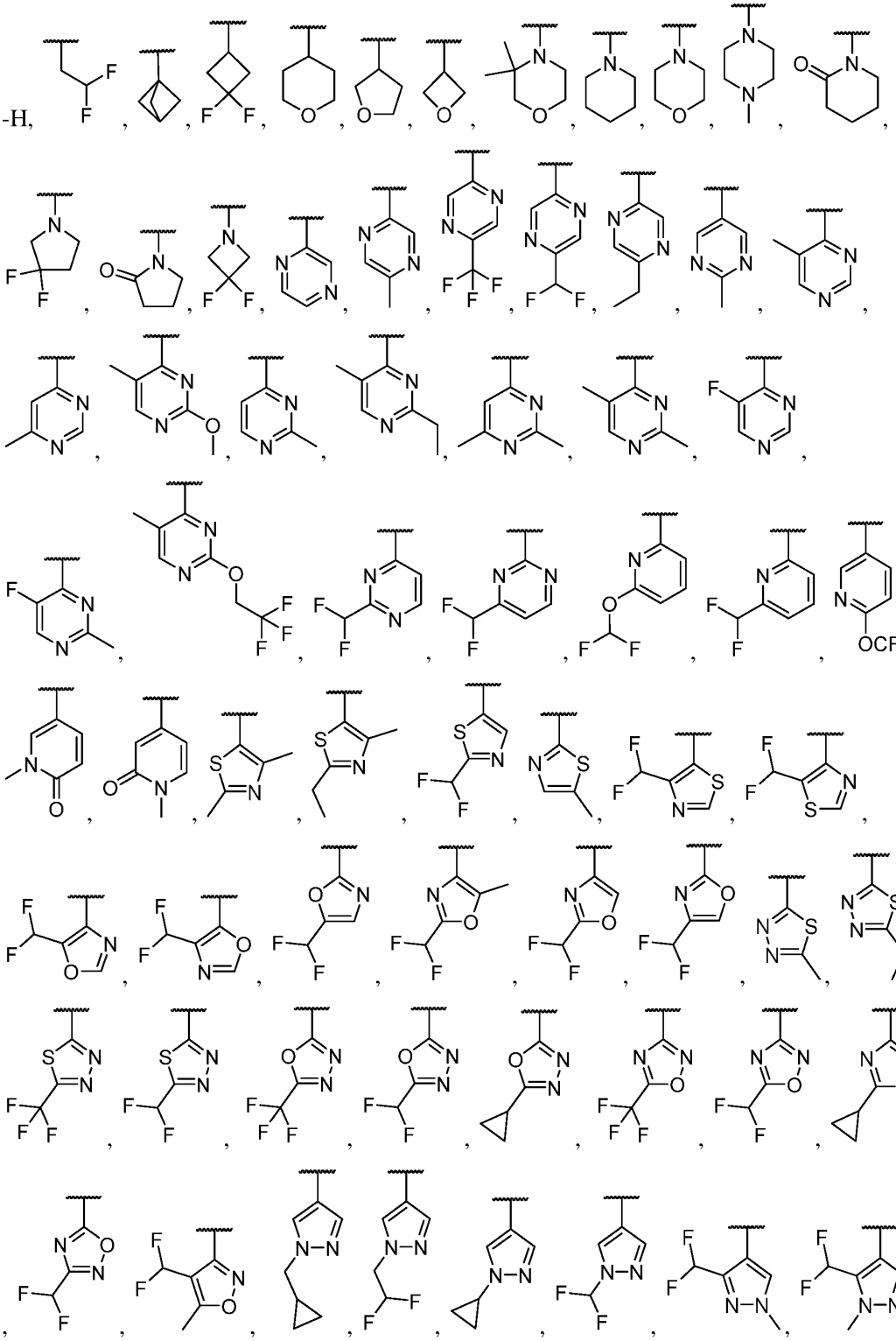
each R^A is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl, or two instances of R^A together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

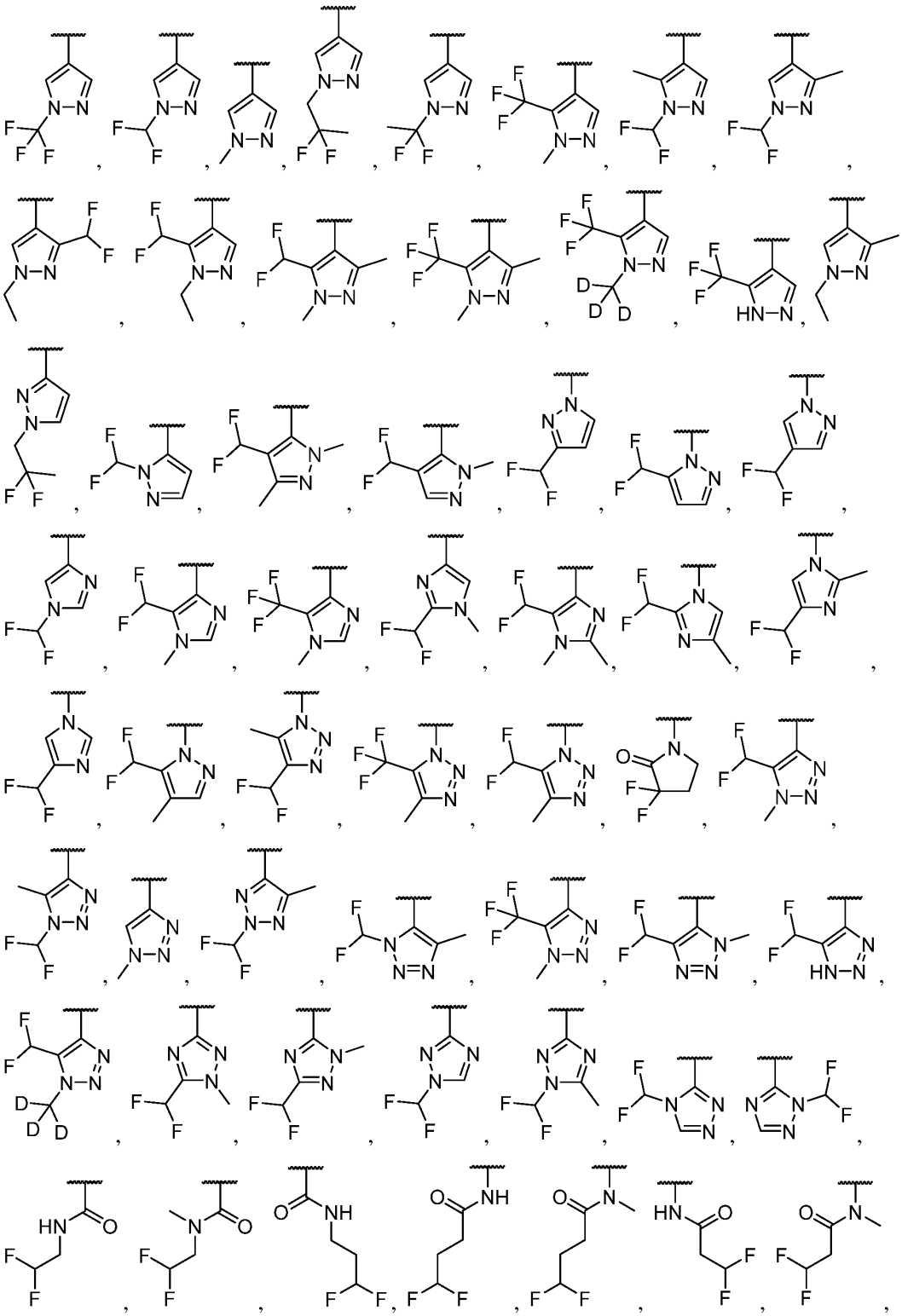
35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^4 is optionally substituted 5-6-membered heteroaryl.

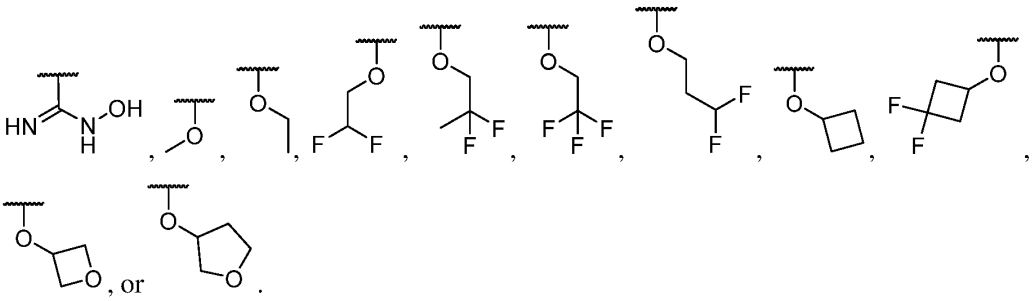
36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein R^4 is optionally substituted 5-membered heteroaryl.

37. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein R^4 is optionally substituted thiazole, optionally substituted pyrazole, optionally substituted triazole, optionally substituted dithiazole, optionally substituted imidazole, optionally substituted oxadiazole, or optionally substituted oxazole.

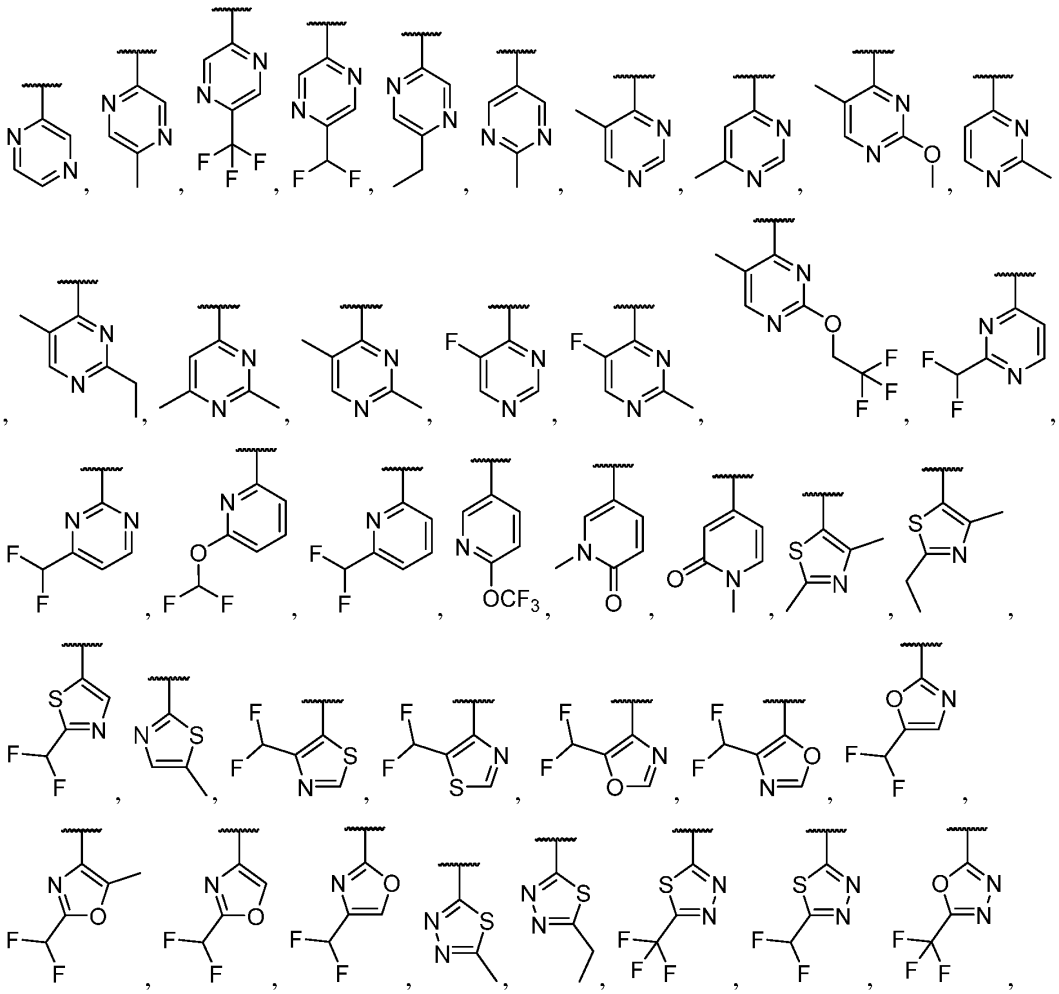
38. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

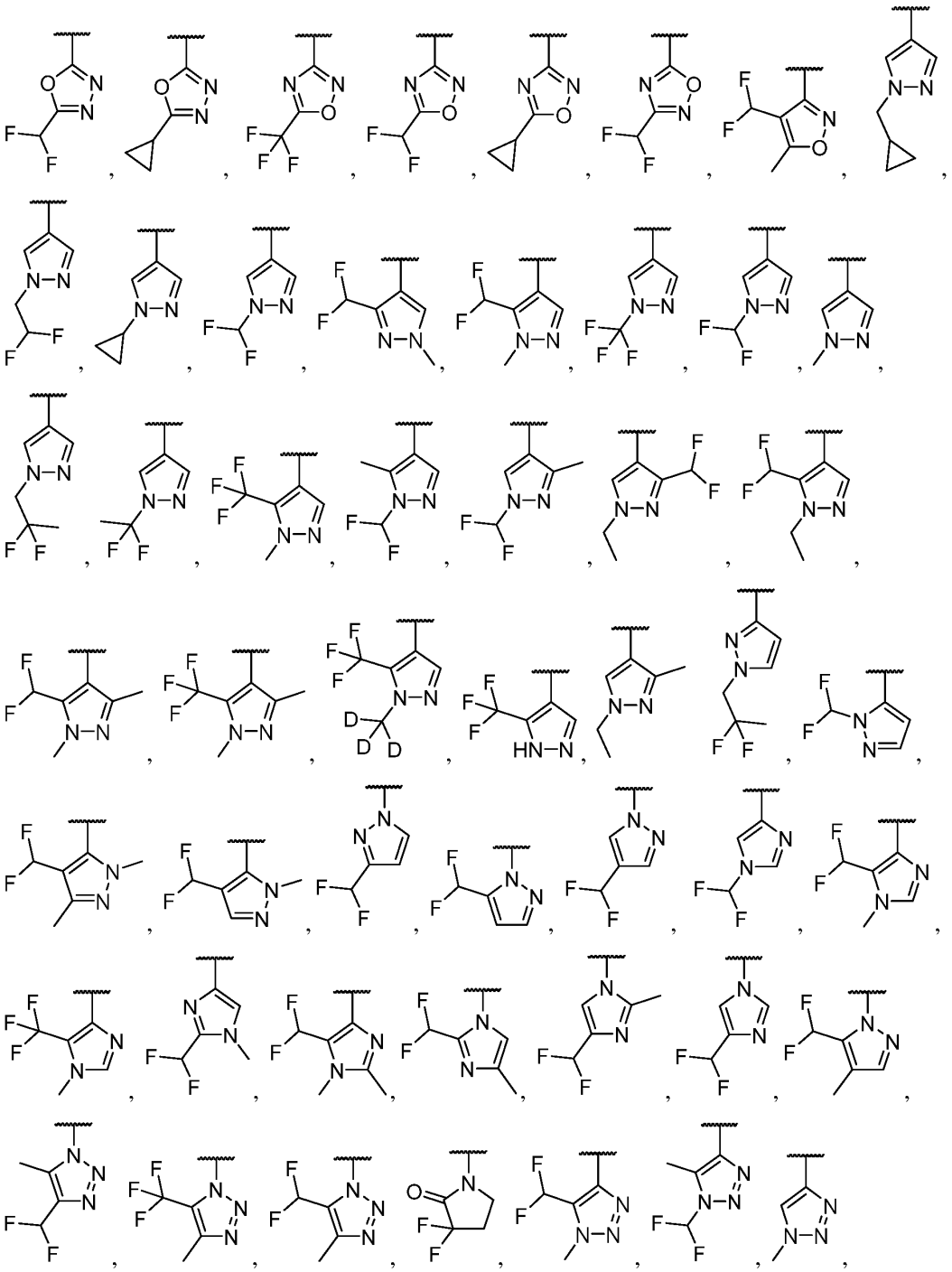
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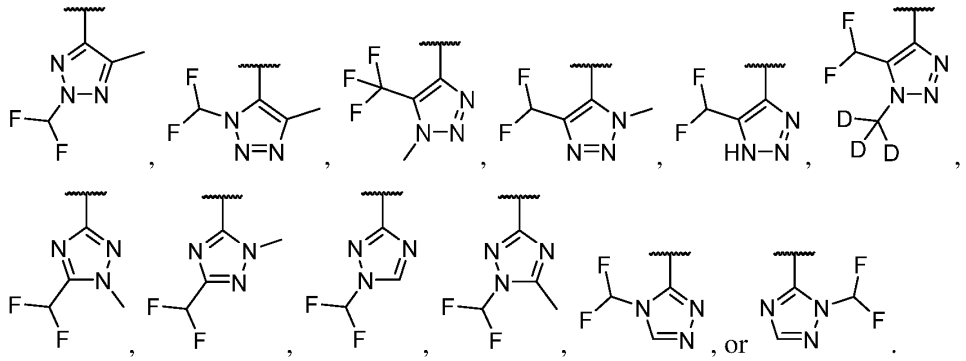




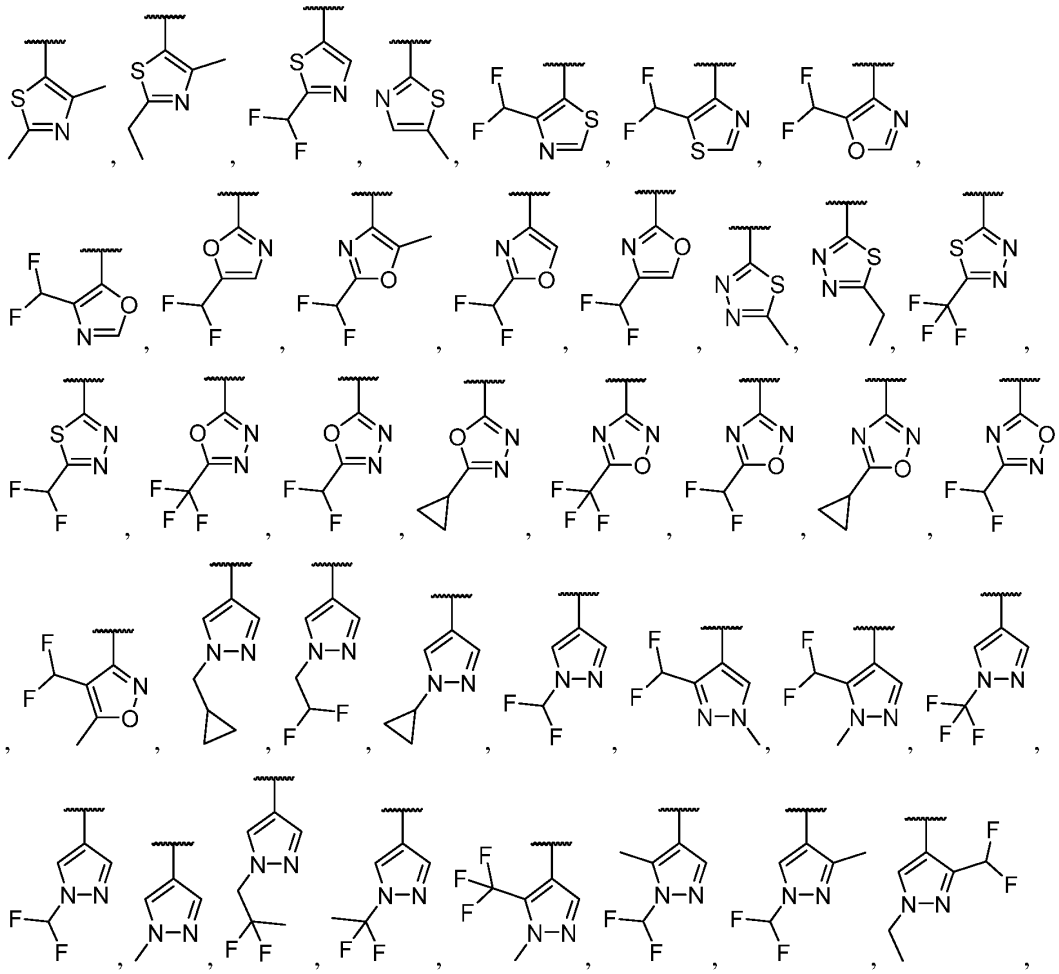
39. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein R^4 is

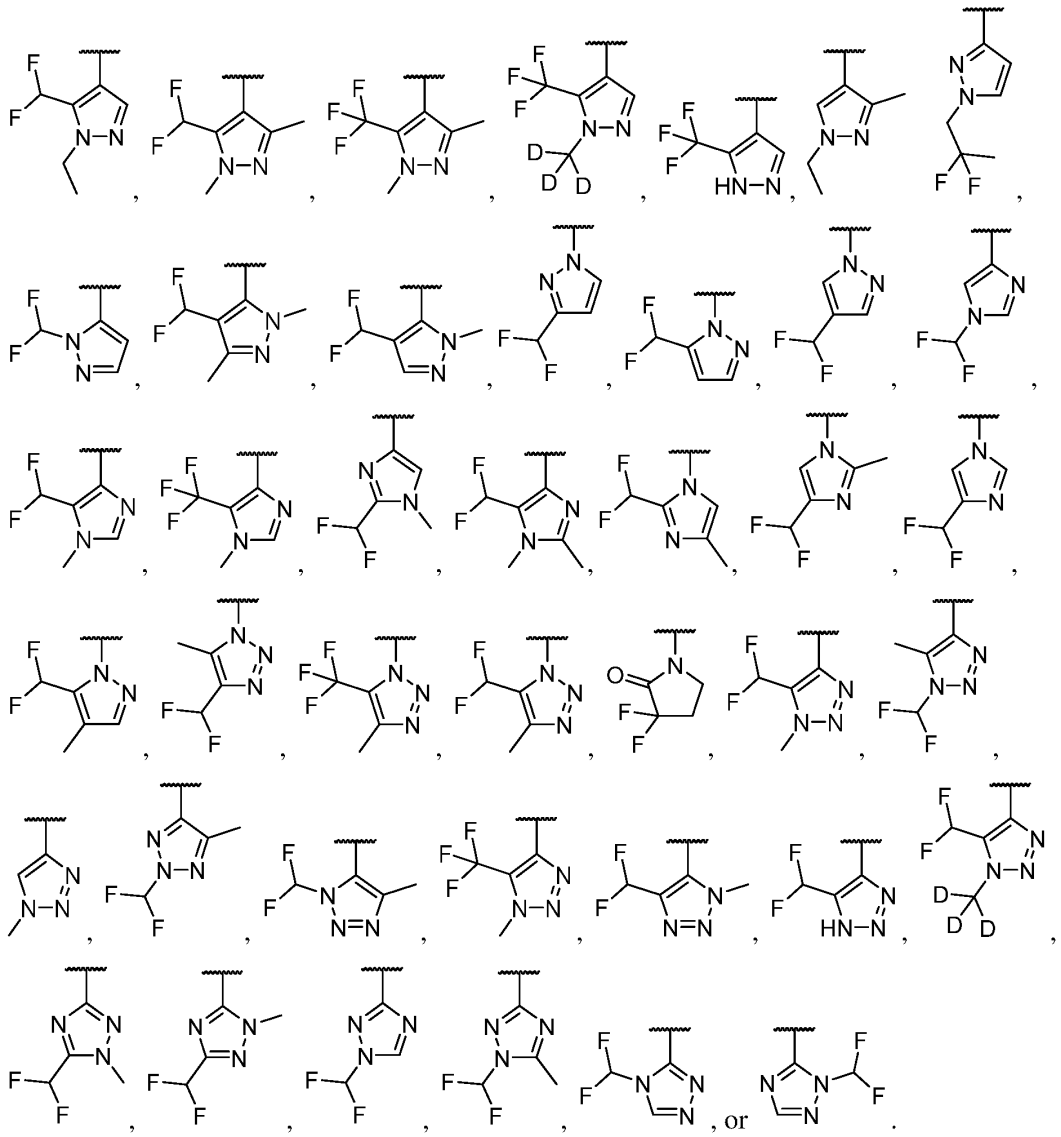




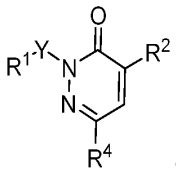


40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, wherein R^4 is





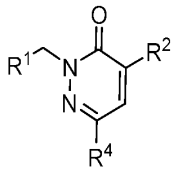
41. The compound of claim 1, wherein the compound is of Formula (**I-a**):



(**I-a**),

or a pharmaceutically acceptable salt thereof.

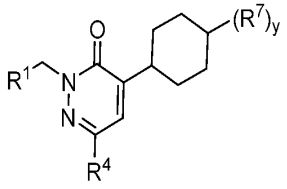
42. The compound of claim 1, wherein the compound is of Formula (**I-b**):



(**I-b**),

or a pharmaceutically acceptable salt thereof.

43. The compound of claim 1, wherein the compound is of Formula (**I-c**):

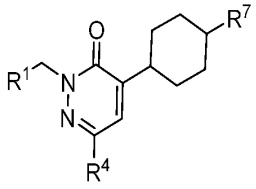


(**I-c**),

or a pharmaceutically acceptable salt thereof, wherein:

each R^7 is independently halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two instances of R^7 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl; and y is 0, 1, or 2.

44. The compound of claim 1, wherein the compound is of Formula (**I-d**):

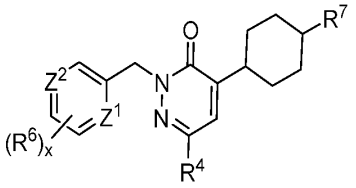


(**I-d**),

or a pharmaceutically acceptable salt thereof, wherein:

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

45. The compound of claim 1, wherein the compound is of Formula (**I-e**):



(**I-e**),

or a pharmaceutically acceptable salt thereof, wherein:

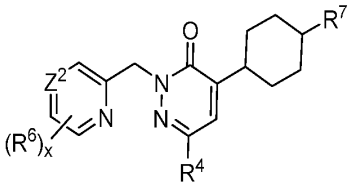
Z^1 and Z^2 are each independently CH, CR^6, or N;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl; and

x is 0, 1, or 2.

46. The compound of claim 1, wherein the compound is of Formula (**I-f**):



(**I-f**),

or a pharmaceutically acceptable salt thereof, wherein:

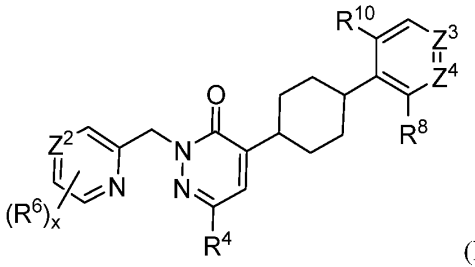
Z^2 is CH, CR^6, or N;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl; and

x is 0, 1, or 2.

47. The compound of claim 1, wherein the compound is of Formula (**I-f-1**):



(**I-f-1**),

or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is CH, CR^6, or N;

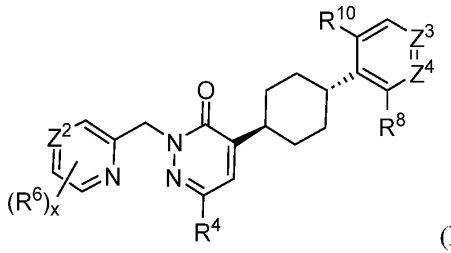
Z^3 and Z^4 are each independently -N- or $-CR^9-$;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$;

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $-OR^A$; and

x is 0, 1, or 2.

48. The compound of claim 1, wherein the compound is of Formula (**I-f-2**):



(**I-f-2**),

or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is CH, CR^6, or N;

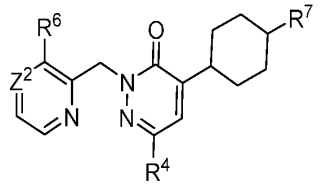
Z^3 and Z^4 are each independently -N- or $-CR^9-$;

each R^6 is independently halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $-OR^A$;

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $-OR^A$; and

x is 0, 1, or 2.

49. The compound of claim 1, wherein the compound is of Formula (**I-g**):



(**I-g**),

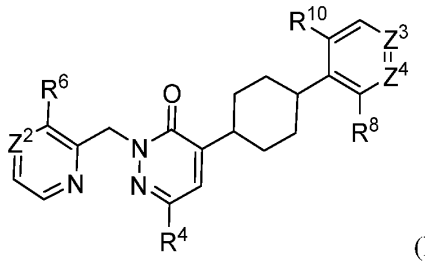
or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is CH or N;

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $-OR^A$; and

R^7 is optionally substituted alkyl, optionally substituted heteroaryl, or optionally substituted aryl.

50. The compound of claim 1, wherein the compound is of Formula (**I-g-1**):



(**I-g-1**),

or a pharmaceutically acceptable salt thereof, wherein:

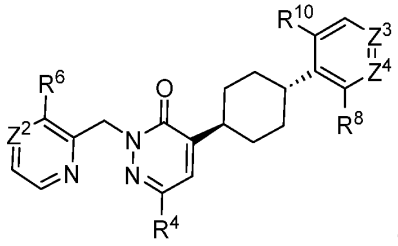
Z^2 is CH or N;

Z^3 and Z^4 are each independently -N- or -CR^9-; and

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or –OR^A.

51. The compound of claim 1, wherein the compound is of Formula (**I-g-2**):



(**I-g-2**),

or a pharmaceutically acceptable salt thereof, wherein:

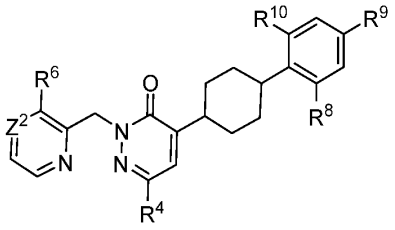
Z^2 is CH or N;

Z^3 and Z^4 are each independently -N- or -CR^9-; and

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or –OR^A; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or –OR^A.

52. The compound of claim 1, wherein the compound is of Formula (**I-g-3**):



(**I-g-3**),

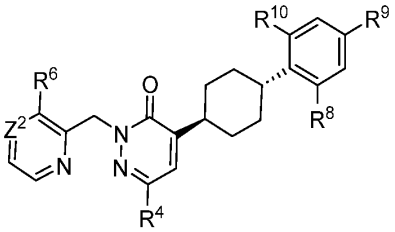
or a tautomer or pharmaceutically acceptable salt thereof, wherein:

Z^2 is CH or N; and

R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and

each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $–OR^A$.

53. The compound of claim 1, wherein the compound is of Formula (**I-g-4**):



(**I-g-4**),

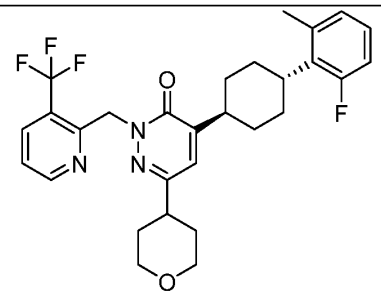
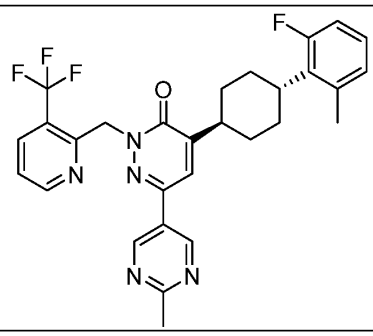
or a tautomer or pharmaceutically acceptable salt thereof, wherein:

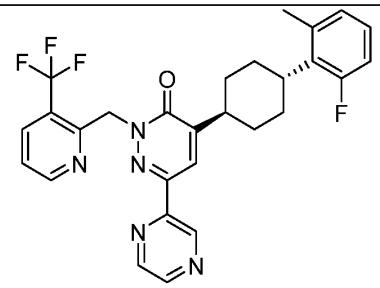
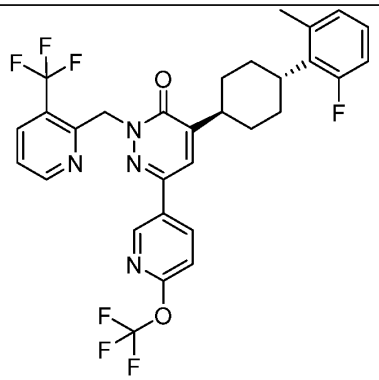
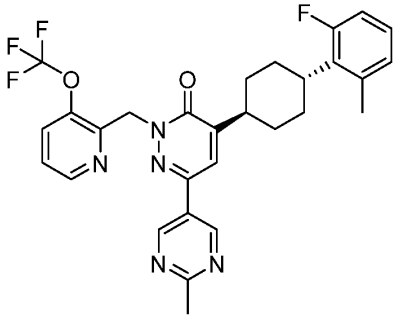
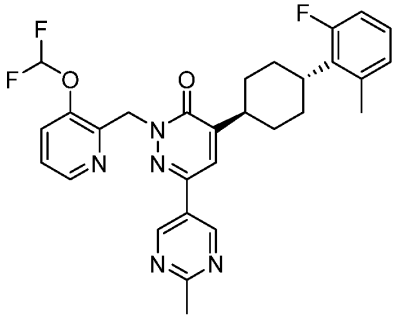
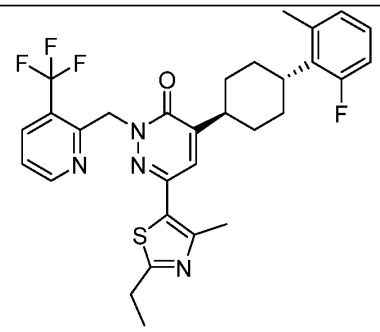
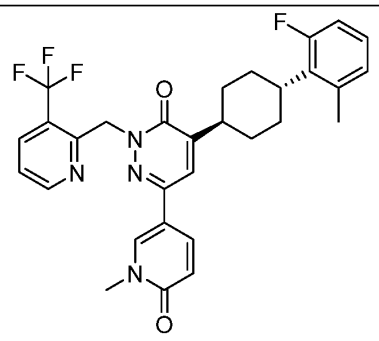
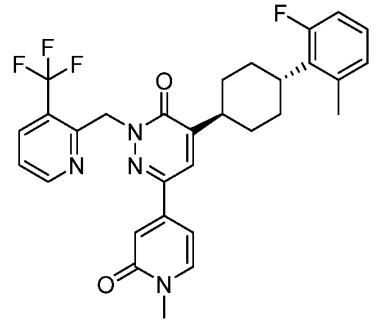
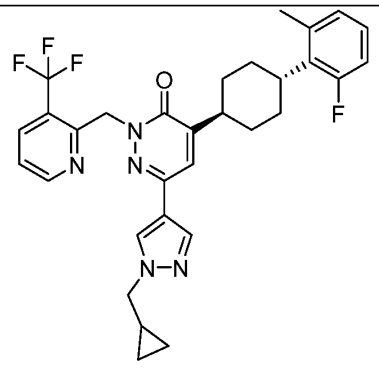
Z^2 is CH or N; and

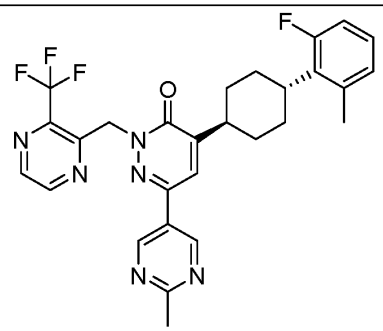
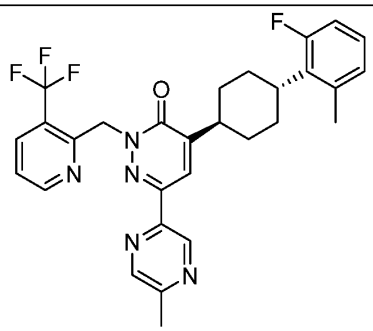
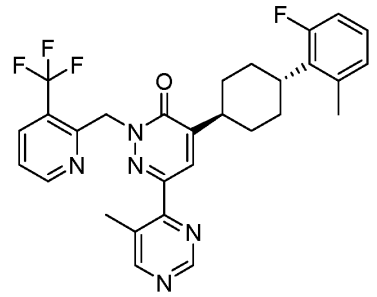
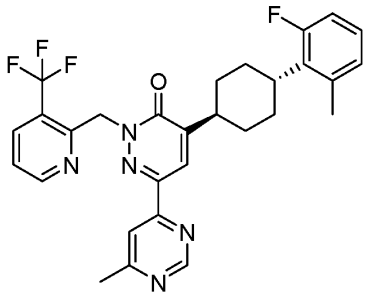
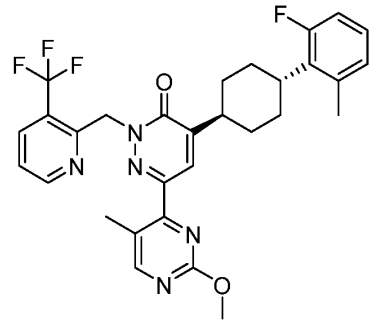
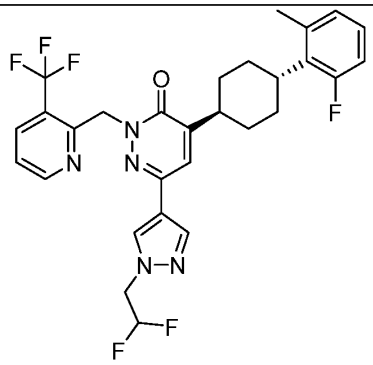
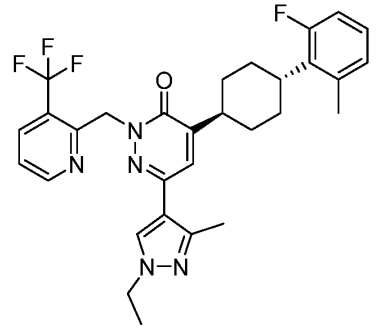
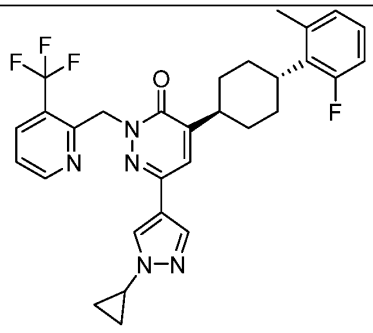
R^6 is halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or $–OR^A$; and

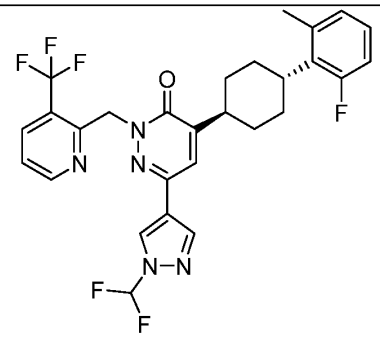
each R^8, R^9, and R^{10} is independently hydrogen, halogen, optionally substituted alkyl, or $–OR^A$.

54. The compound of claim 1, wherein the compound is:

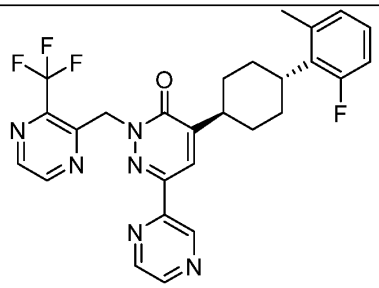
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	2
 3	 4
 5	 6
 7	 8
 9	 10

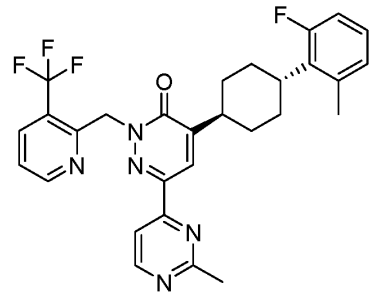
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 **17**	 **18**



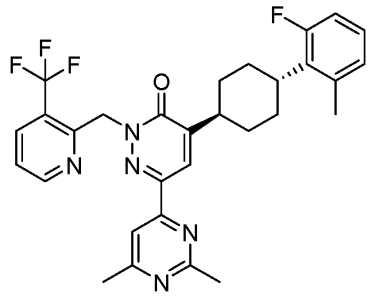
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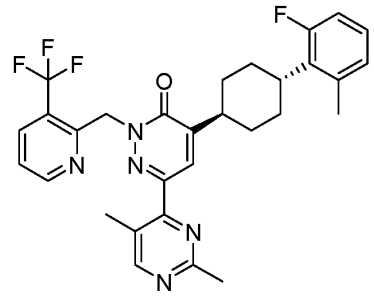
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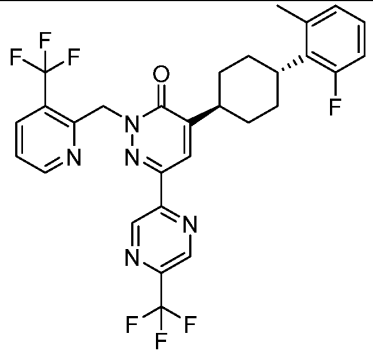
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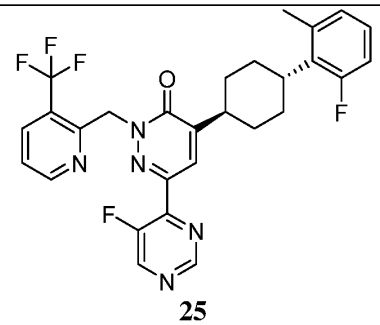
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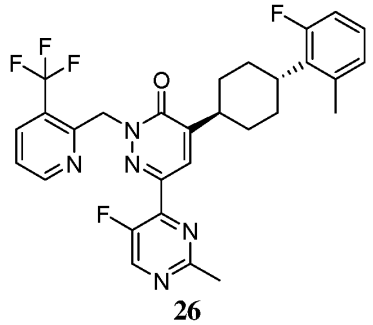
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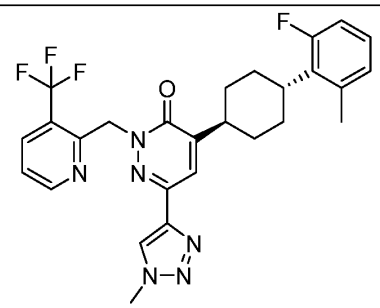
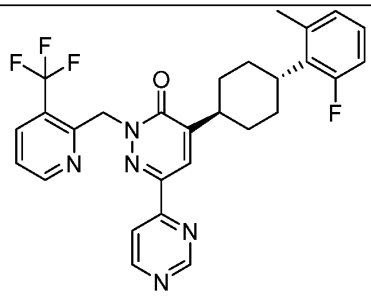
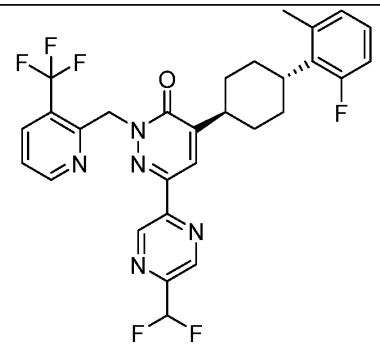
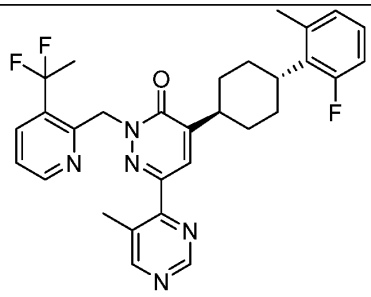
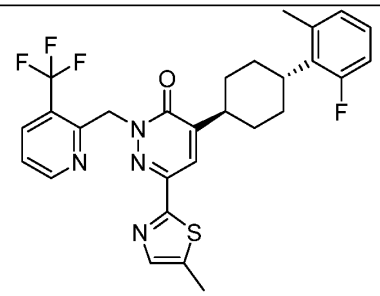
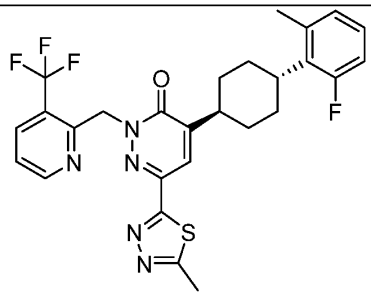
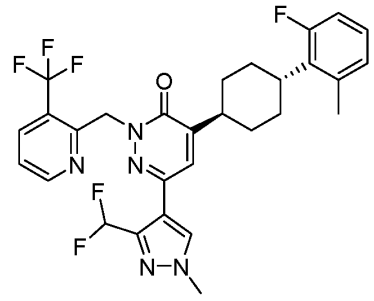
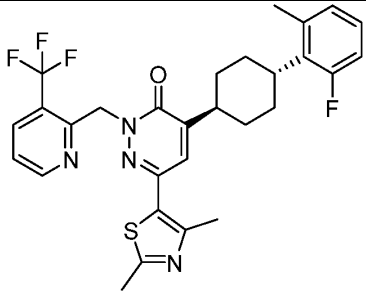
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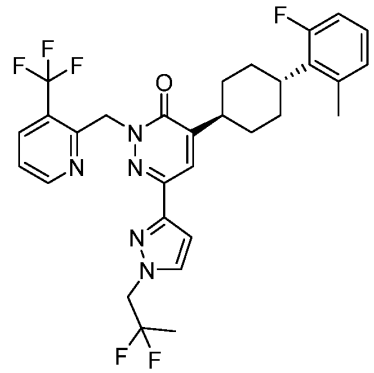


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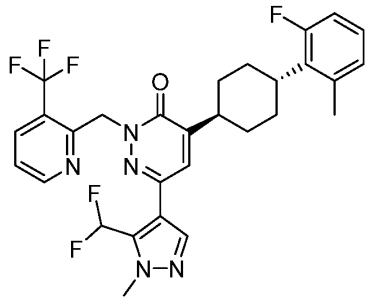


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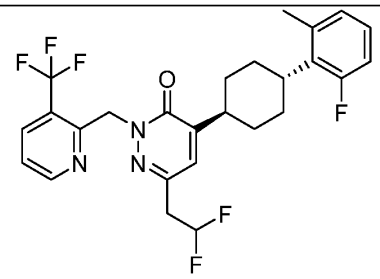
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 **33**	 **34**



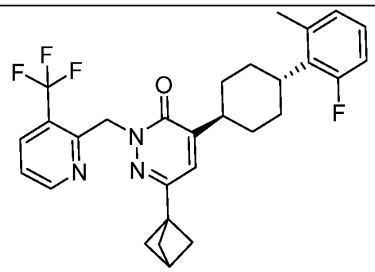
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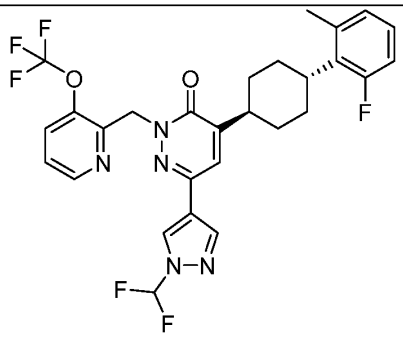
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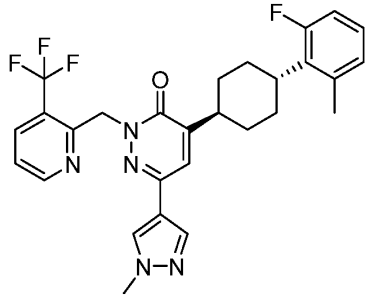
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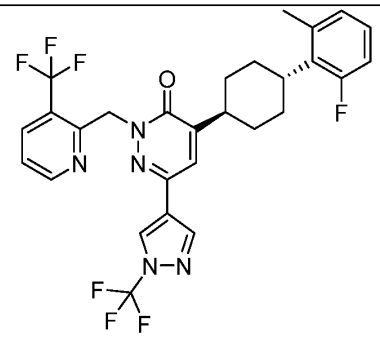
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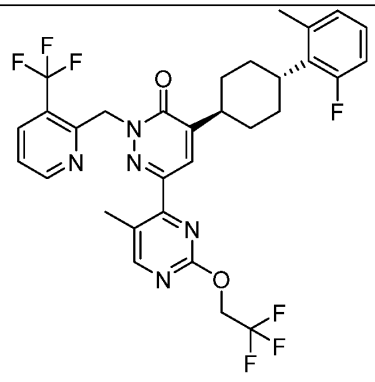
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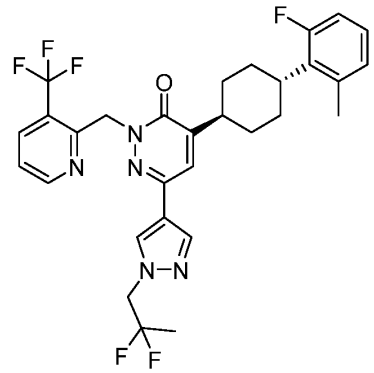
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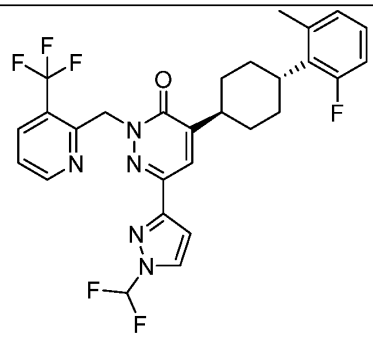
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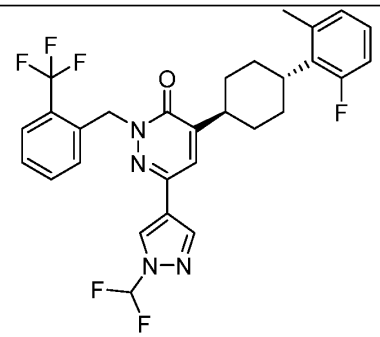
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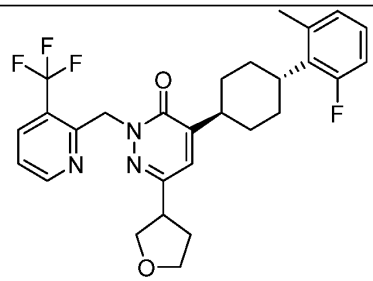
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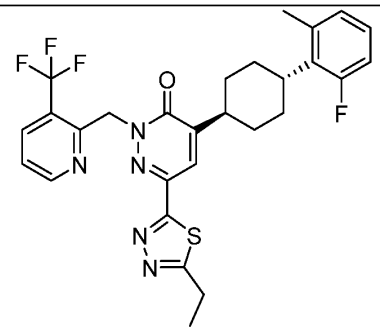
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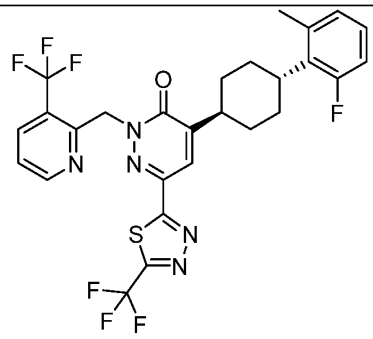
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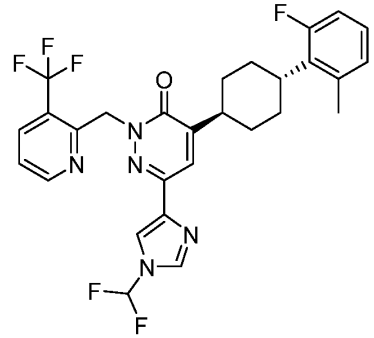
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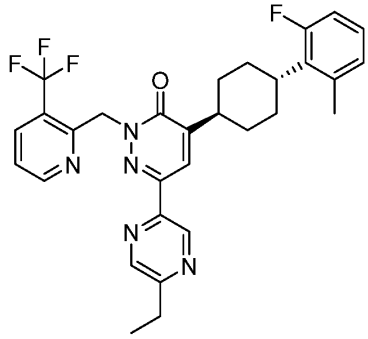
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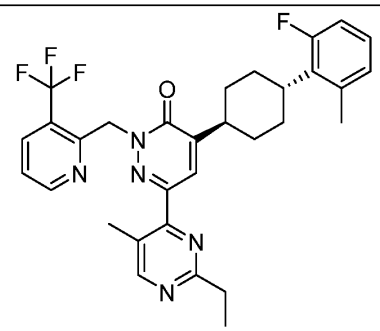
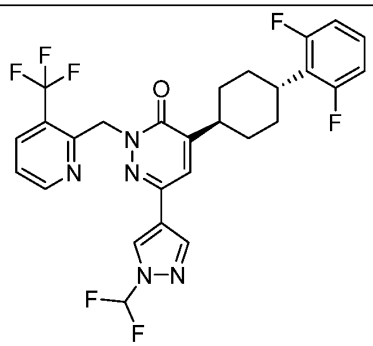
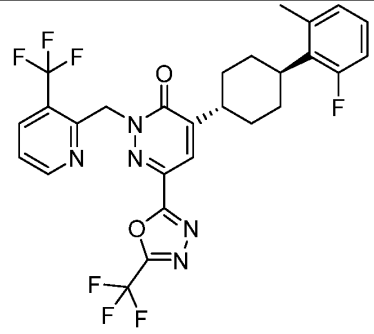
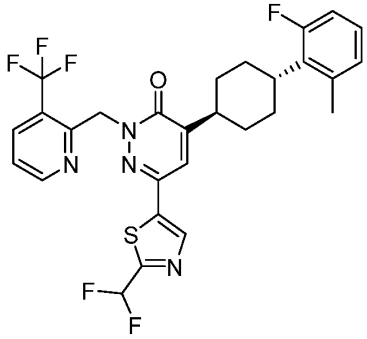
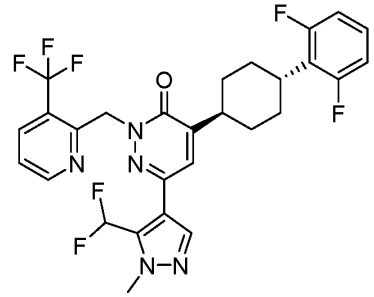
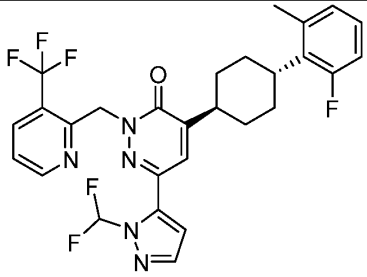
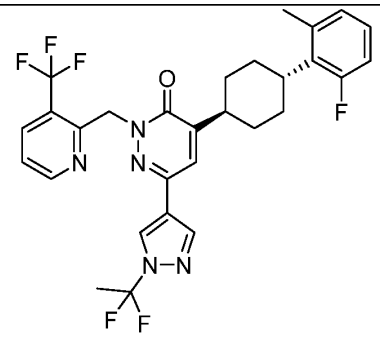
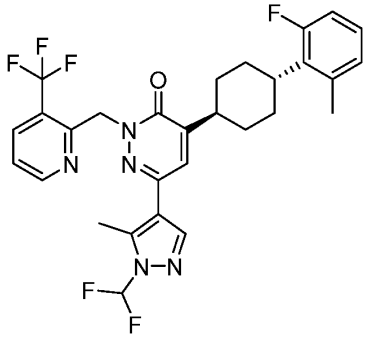
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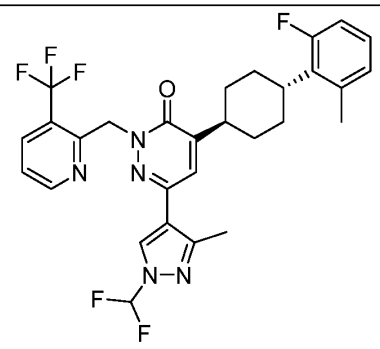
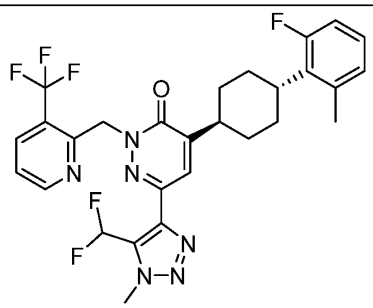
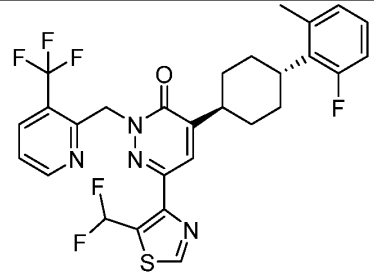
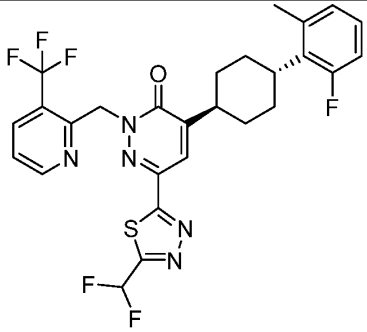
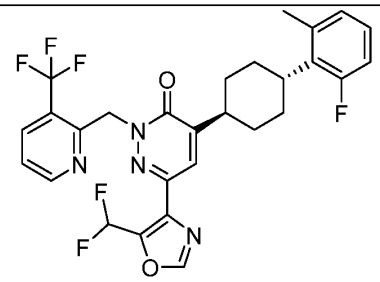
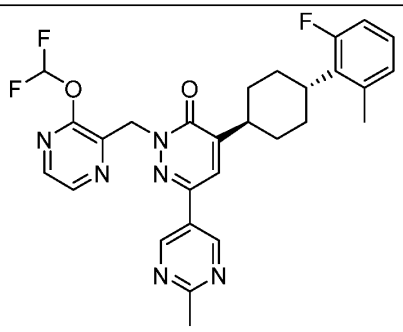
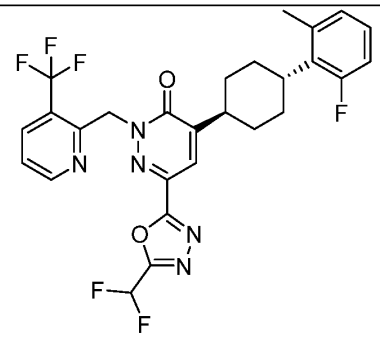
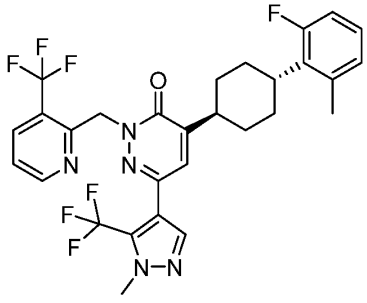


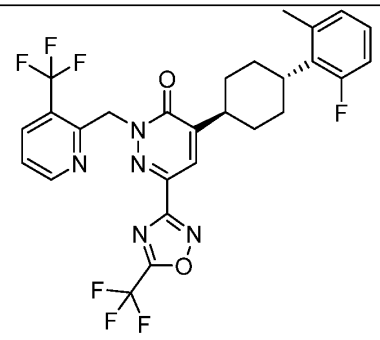
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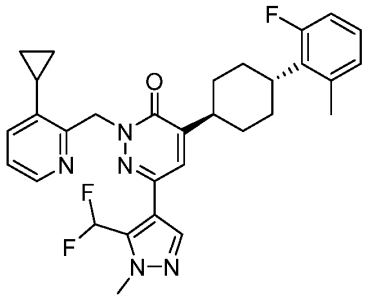
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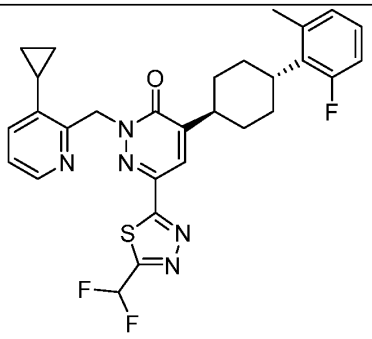
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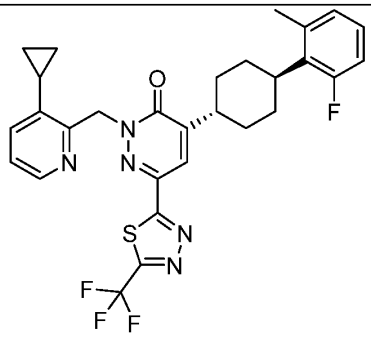
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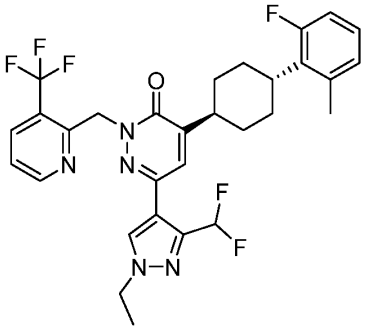
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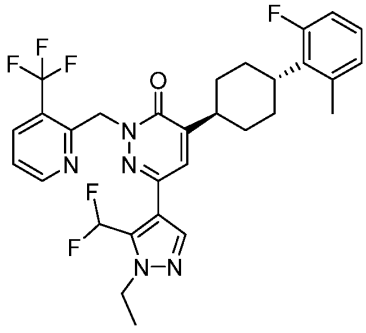
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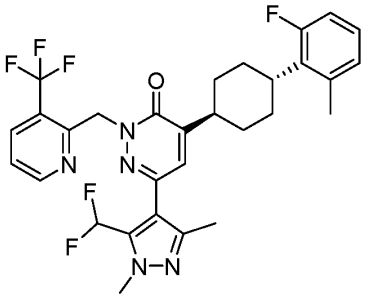
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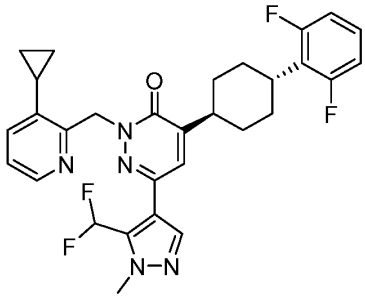
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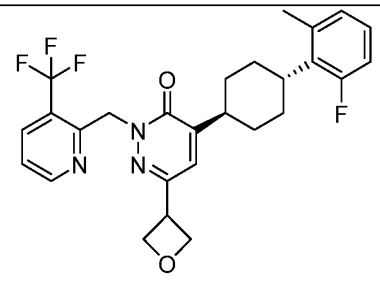
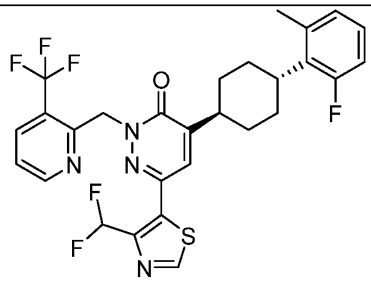
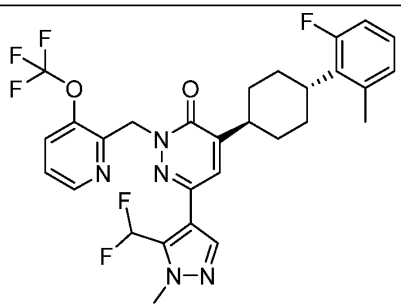
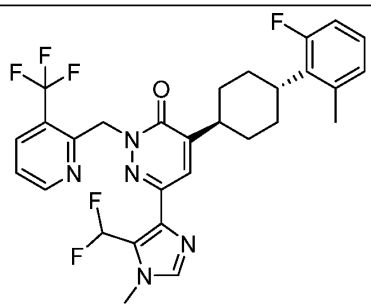
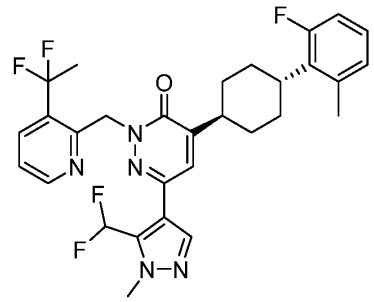
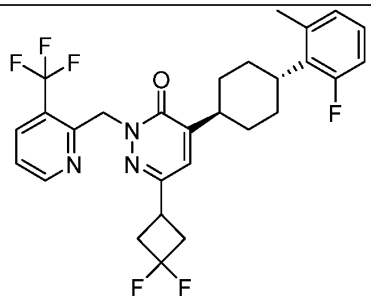
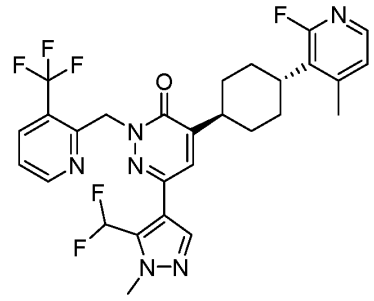
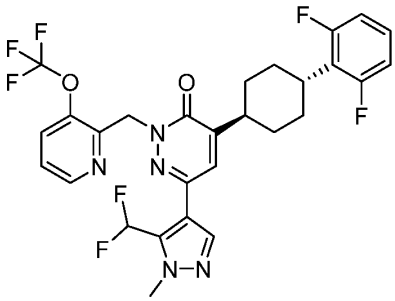
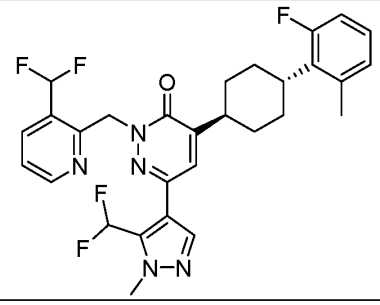
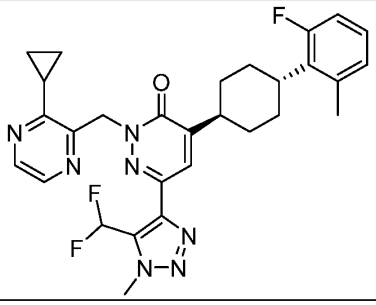
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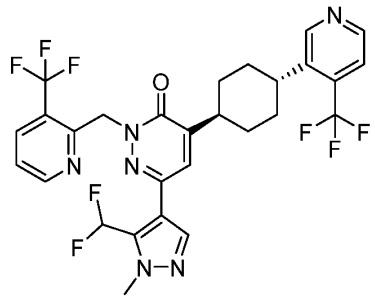
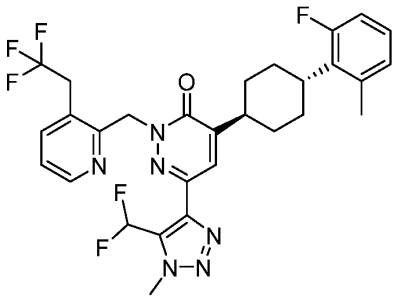
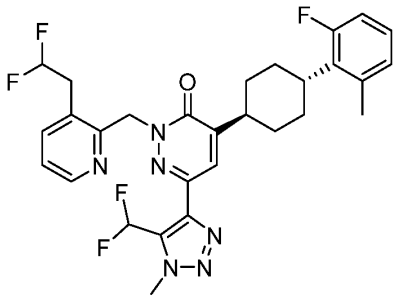
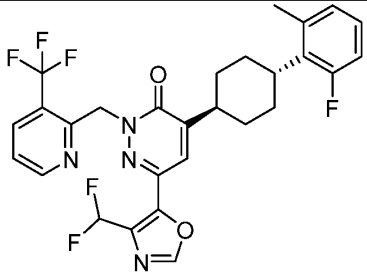
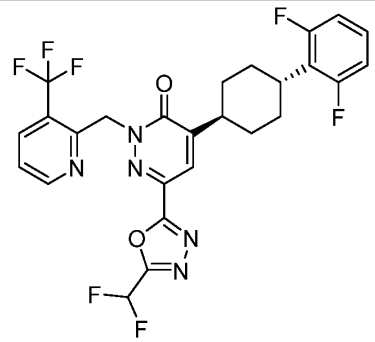
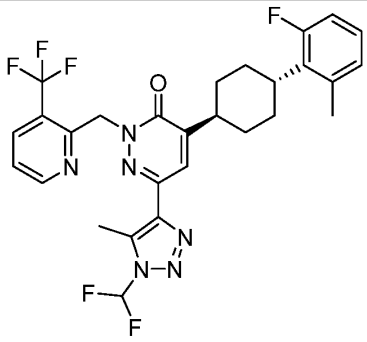
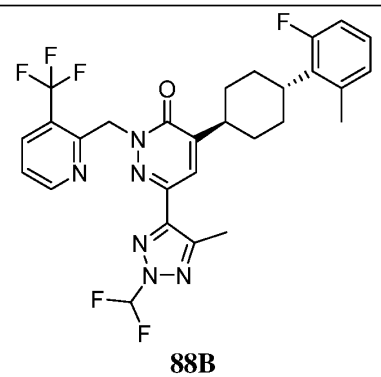
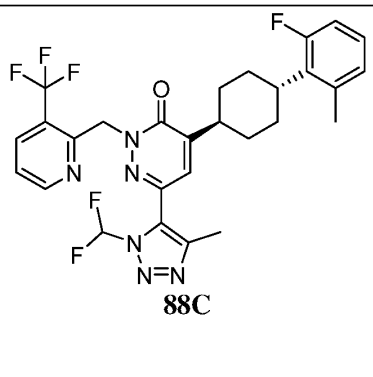


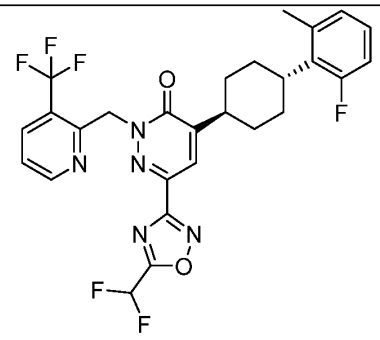
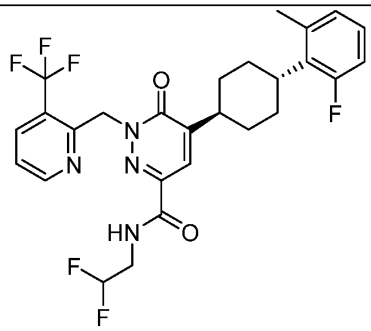
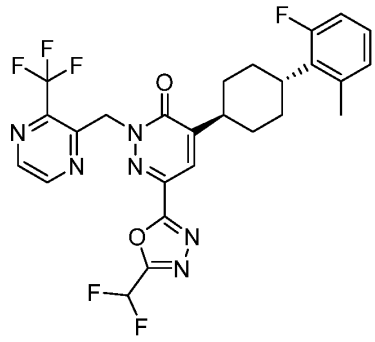
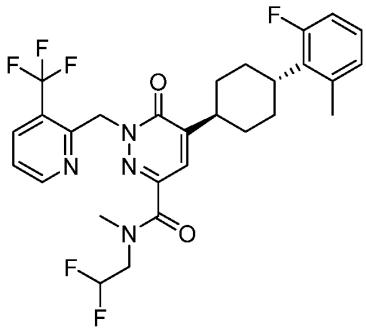
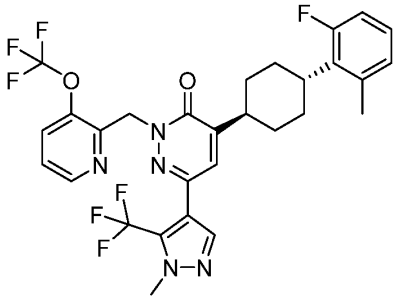
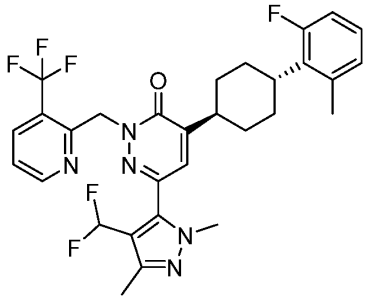
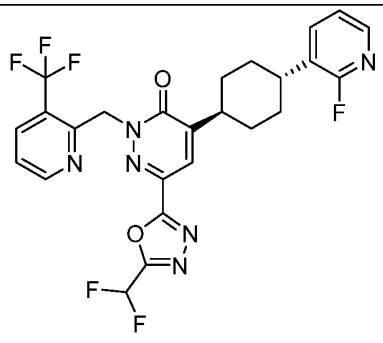
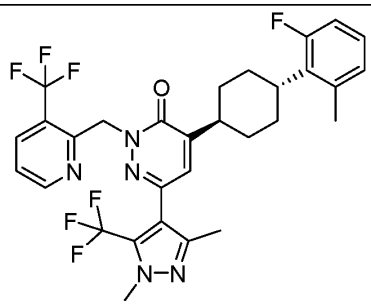
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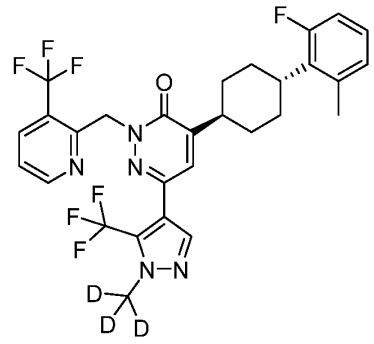
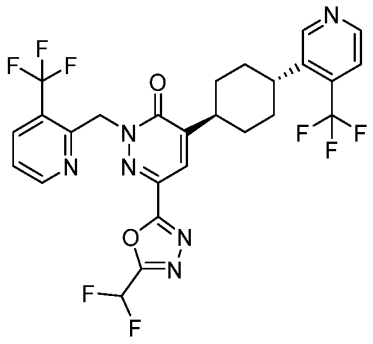
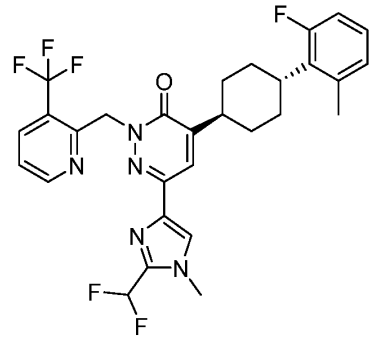
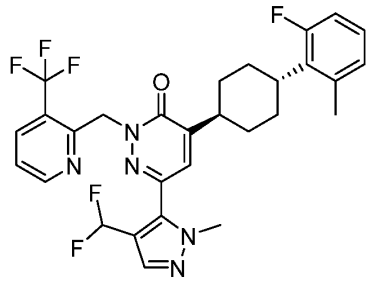
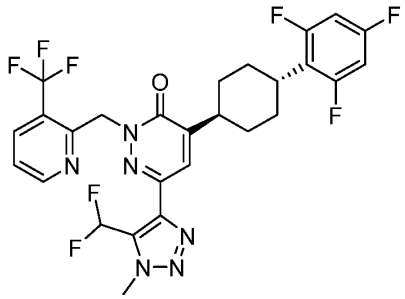
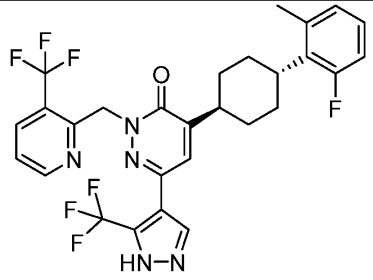
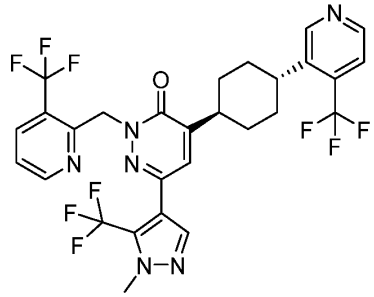
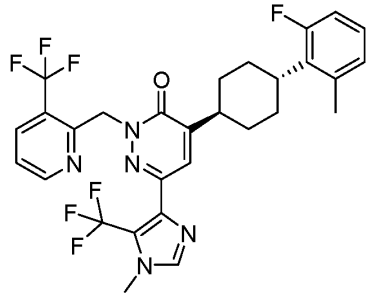


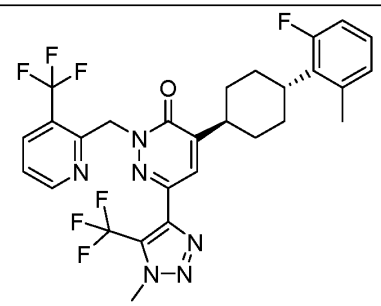
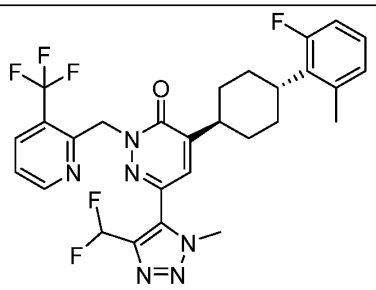
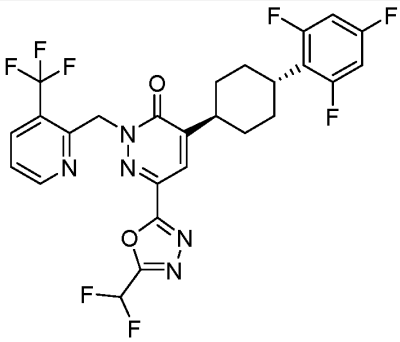
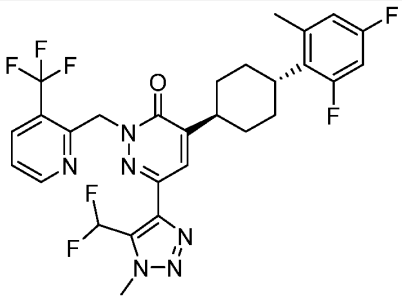
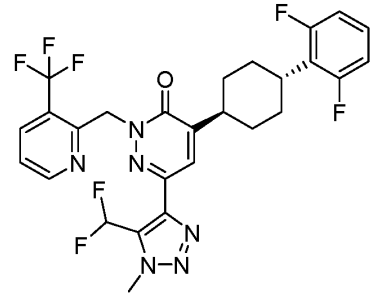
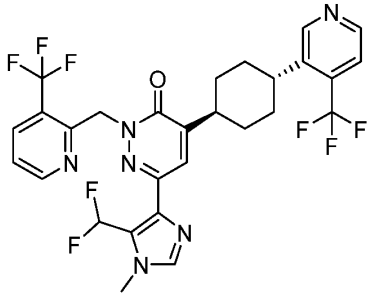
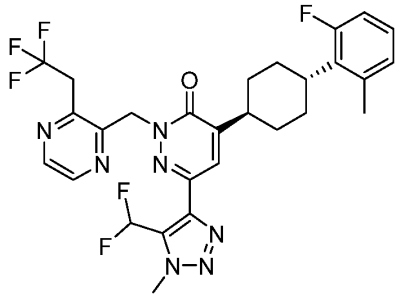
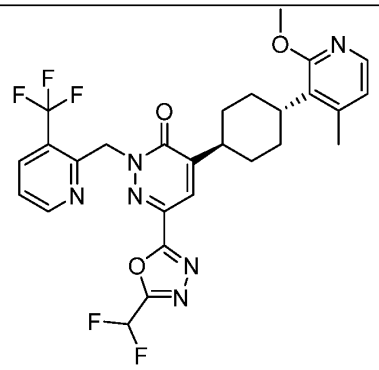
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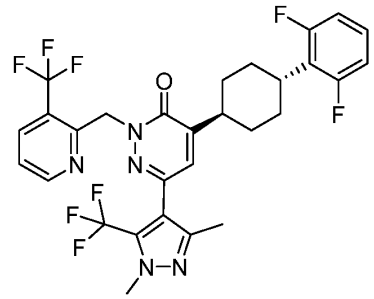
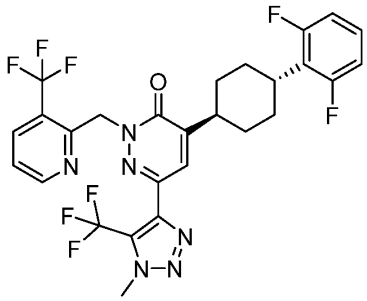
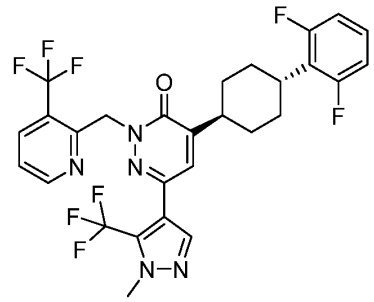
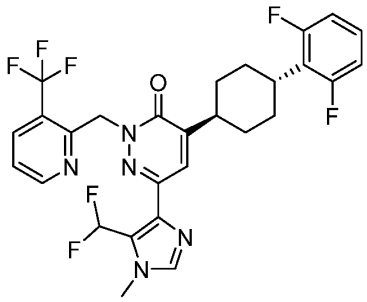
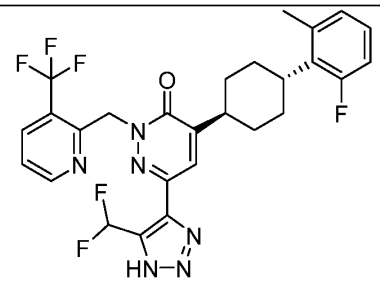
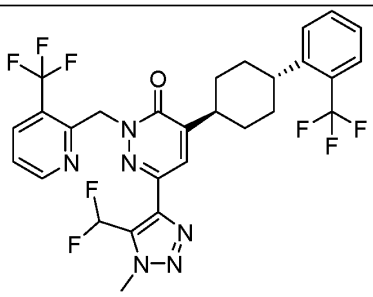
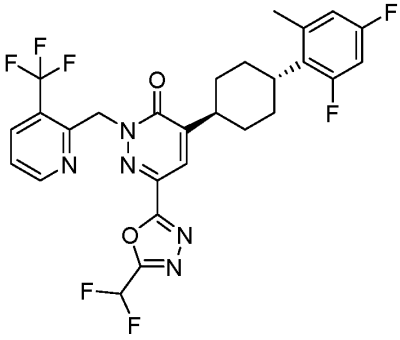
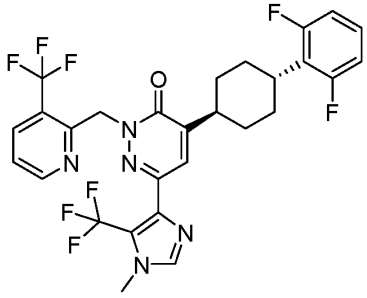
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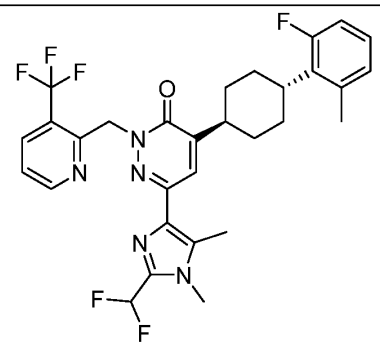
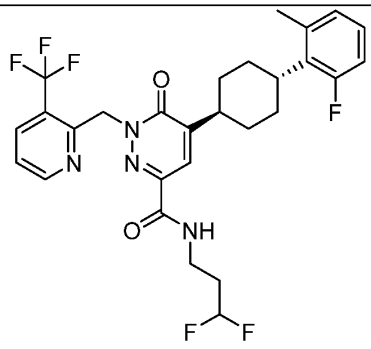
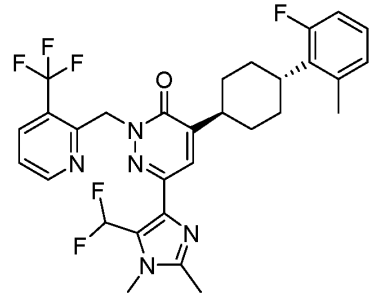
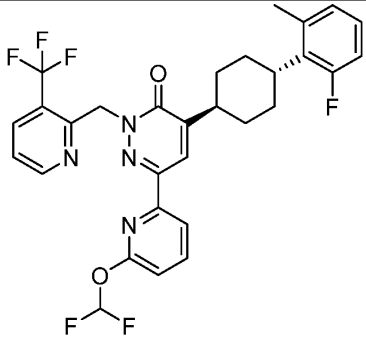
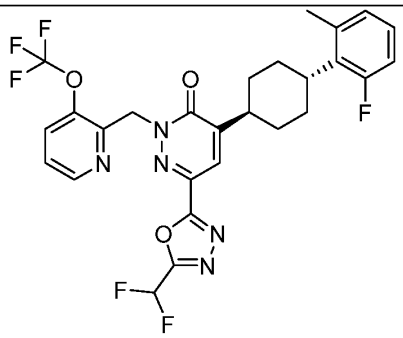
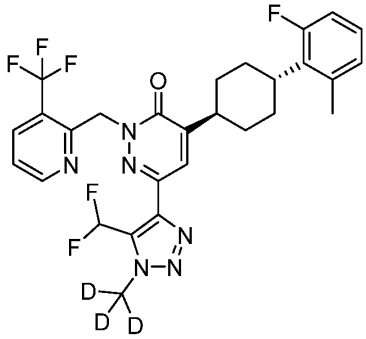
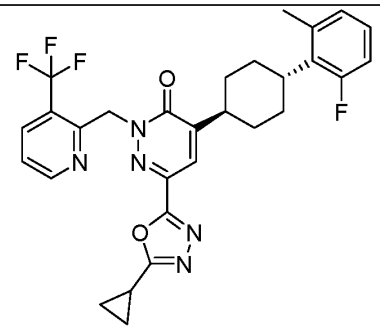
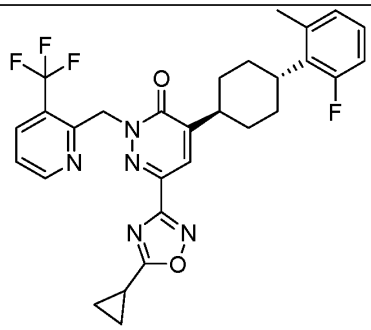
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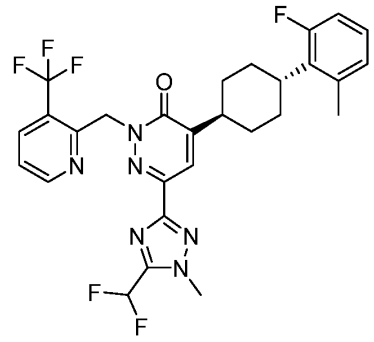
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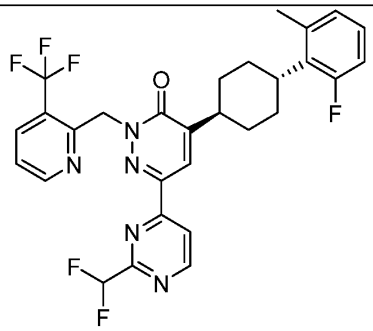
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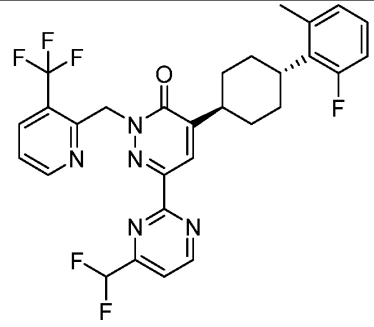
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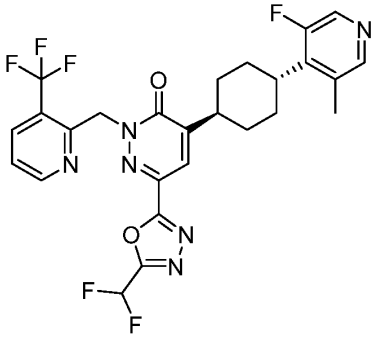
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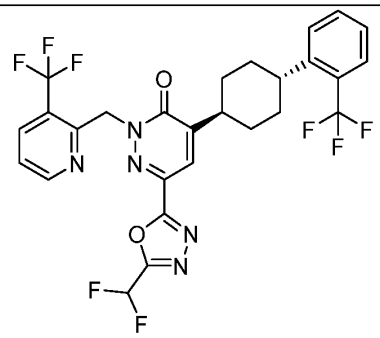
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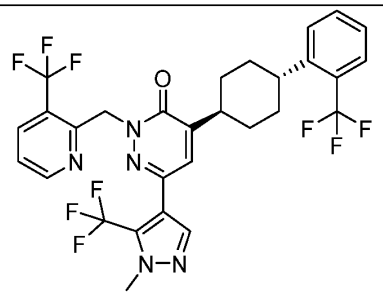
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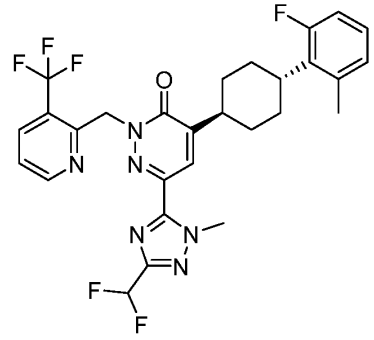
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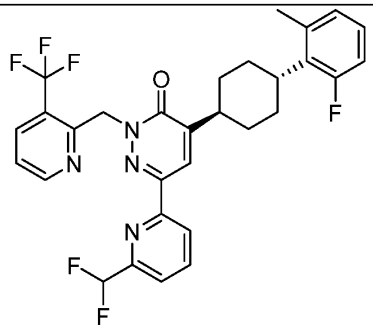
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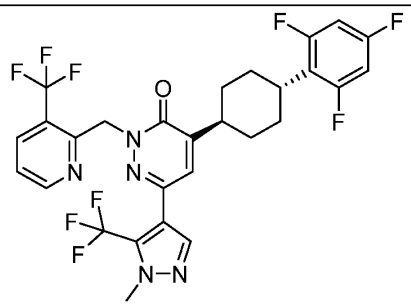
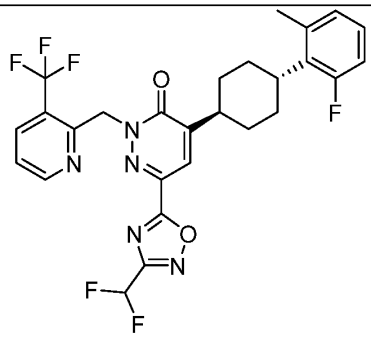
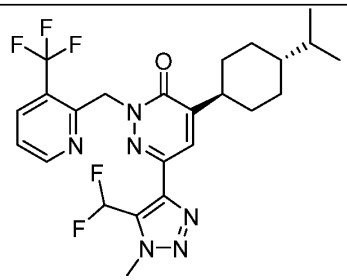
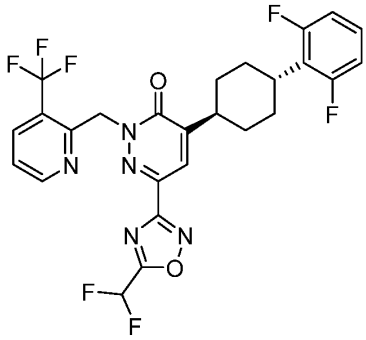
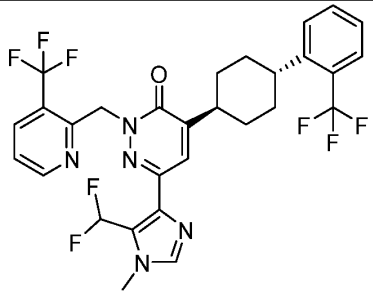
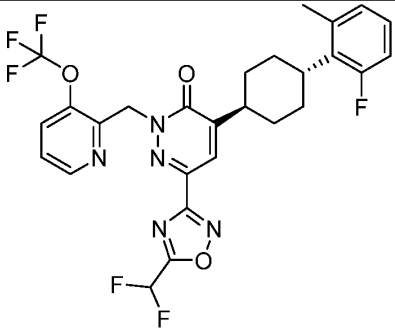
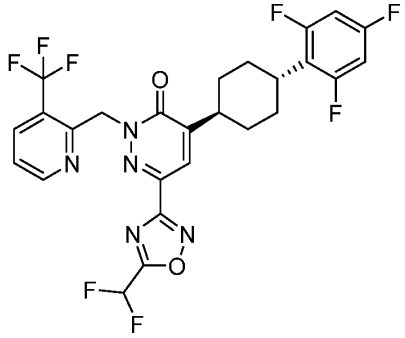
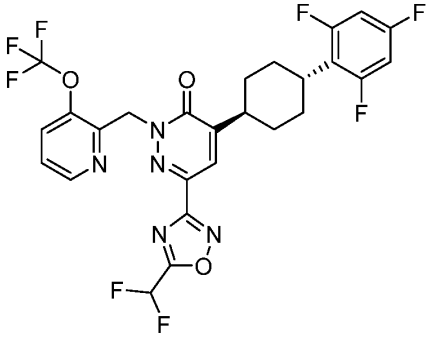
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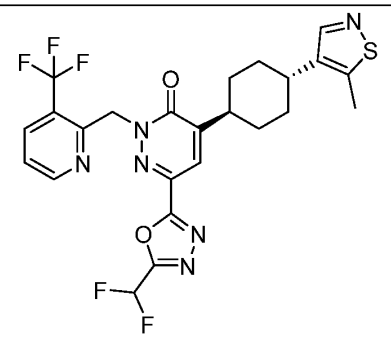
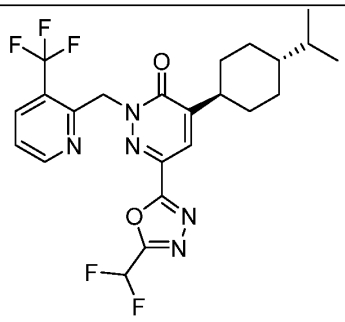
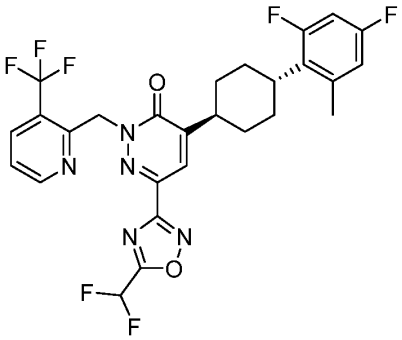
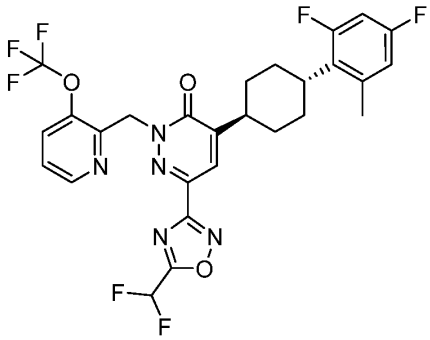
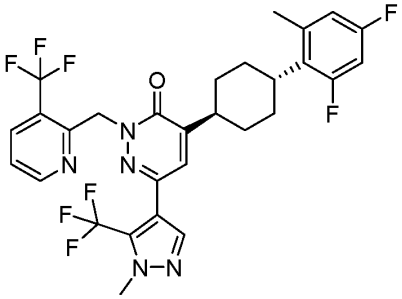
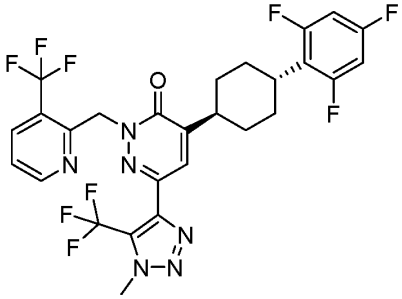
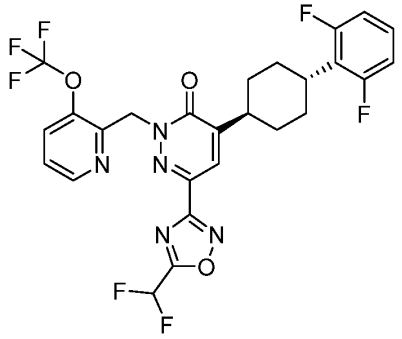
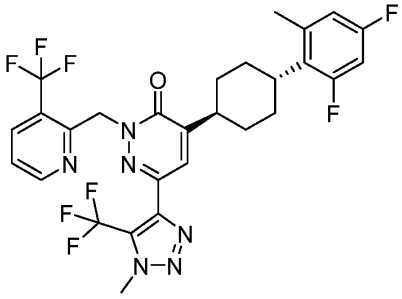


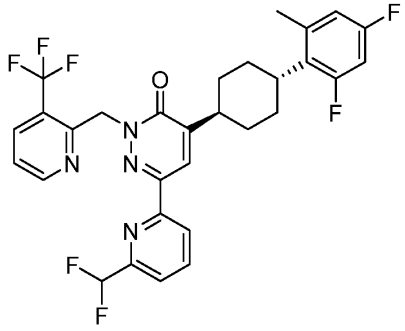
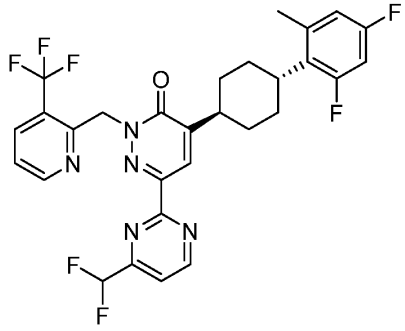
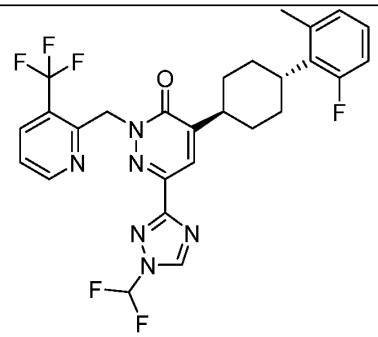
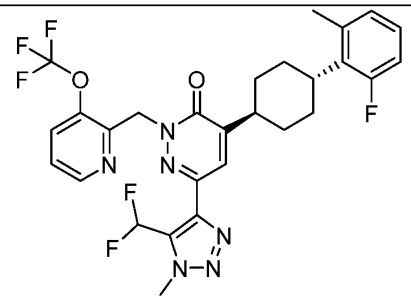
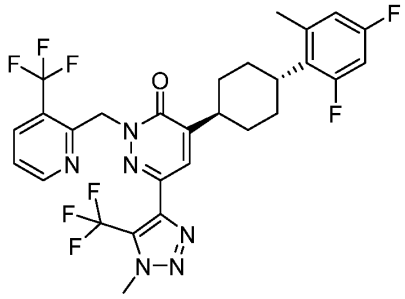
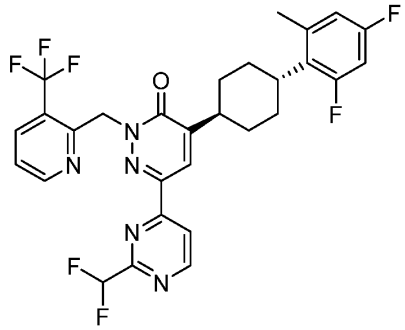
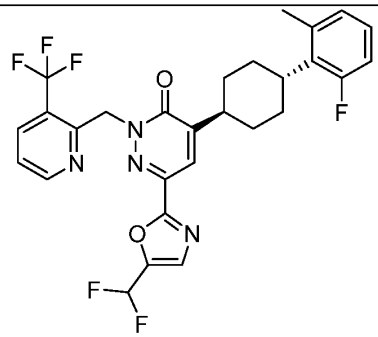
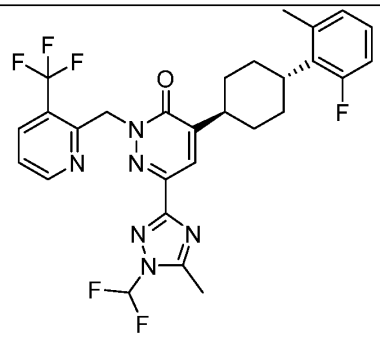
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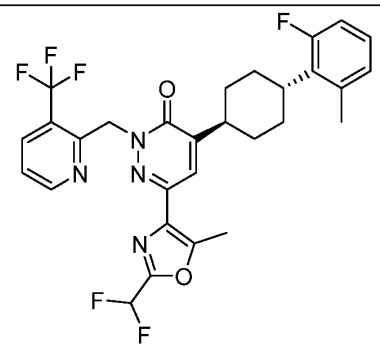
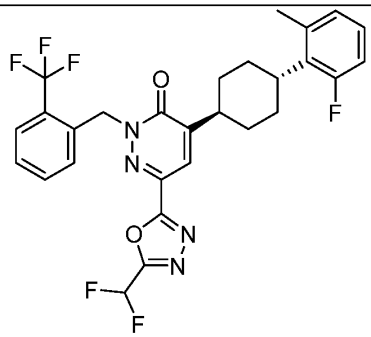
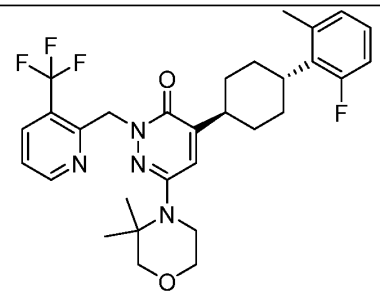
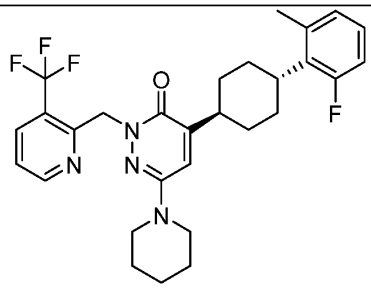
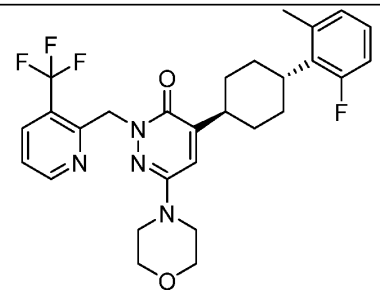
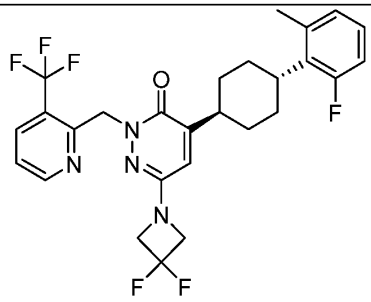
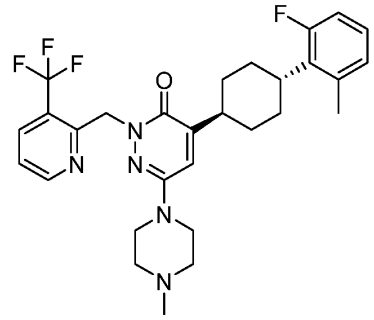
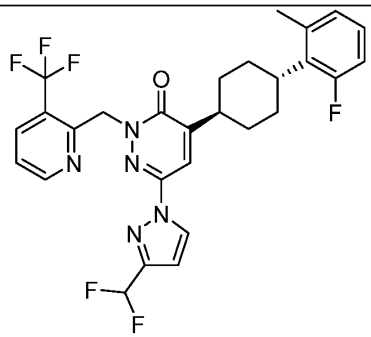


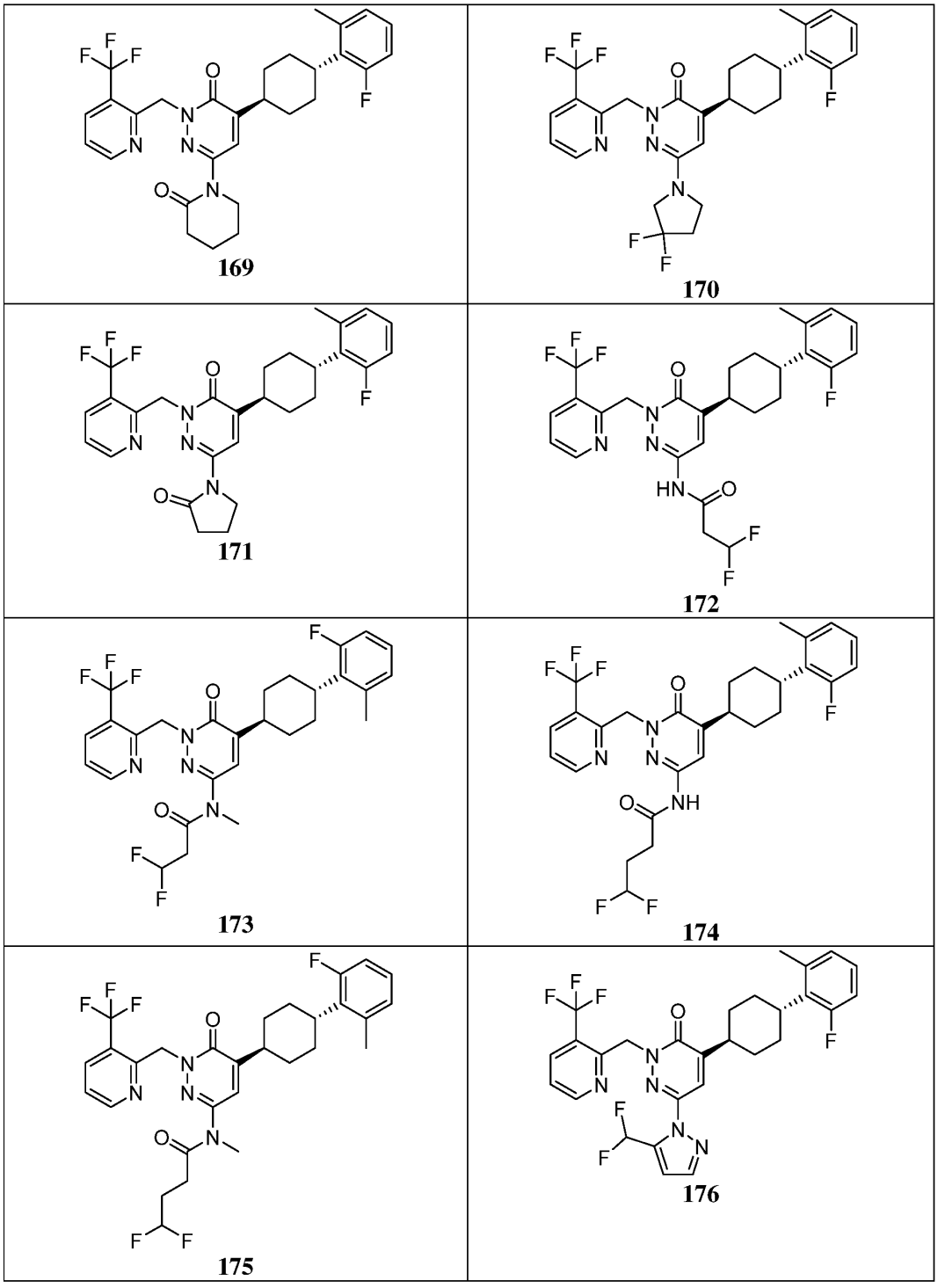
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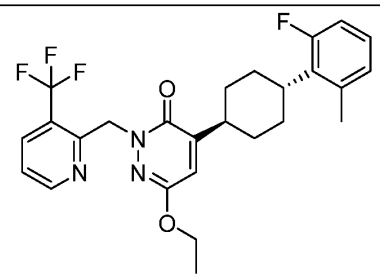
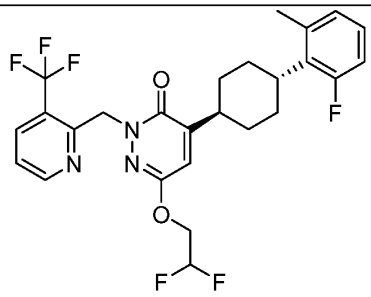
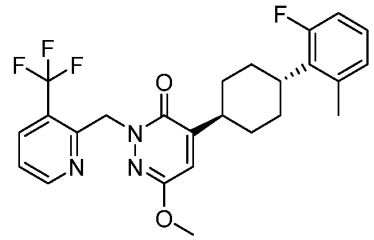
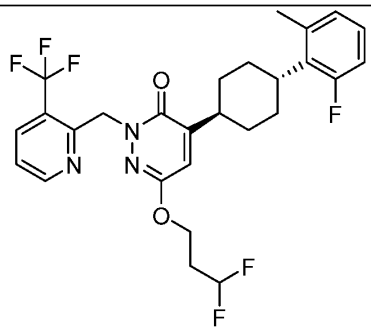
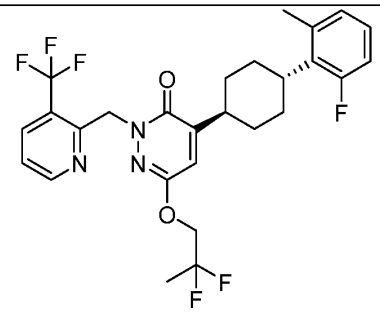
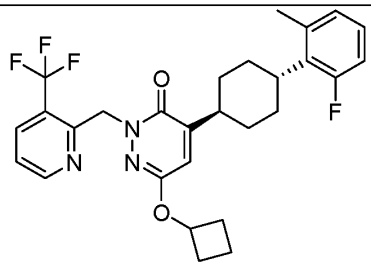
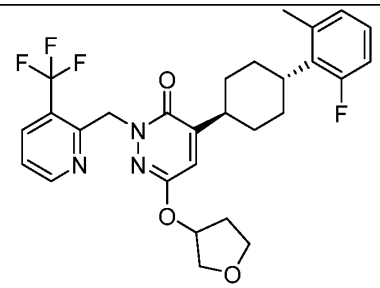
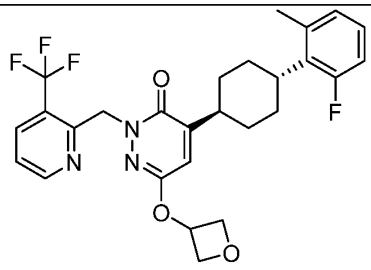
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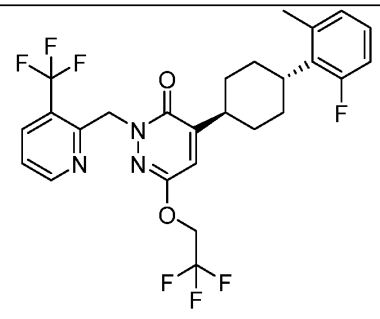
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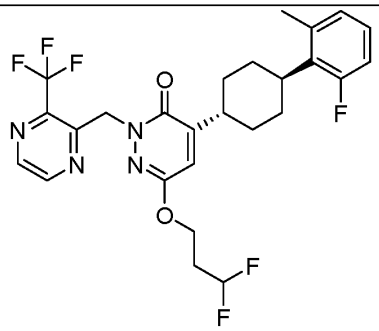
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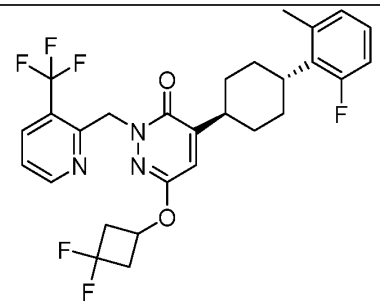
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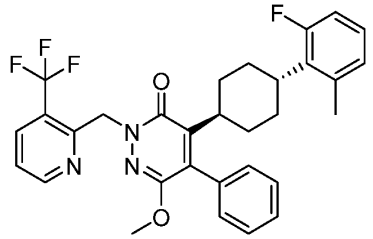
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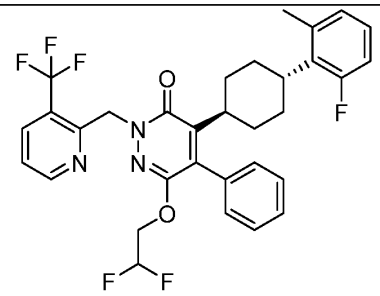
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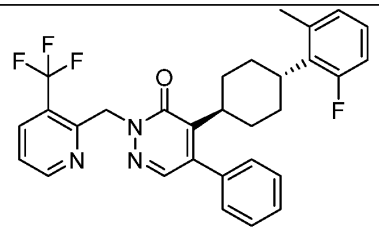
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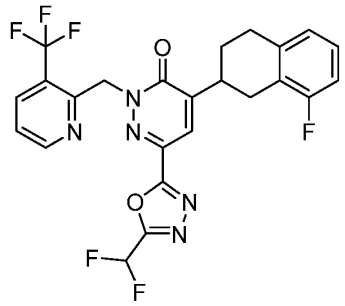
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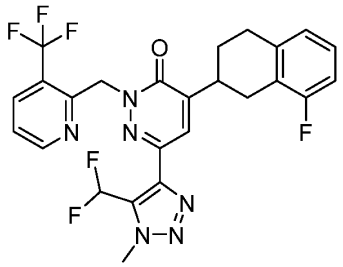
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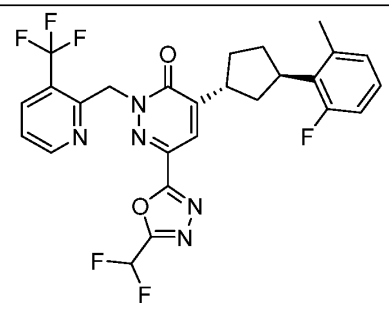
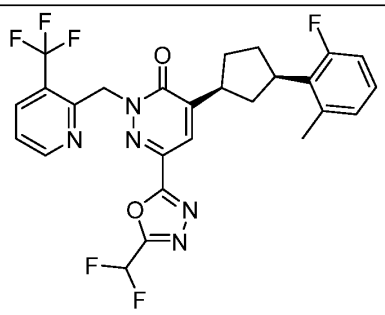
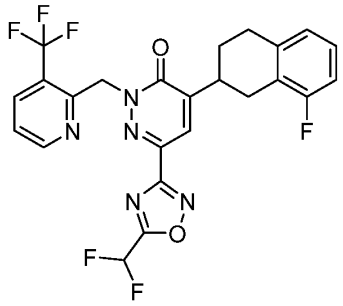
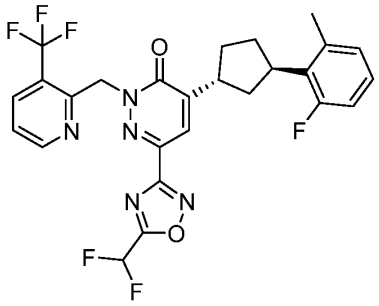
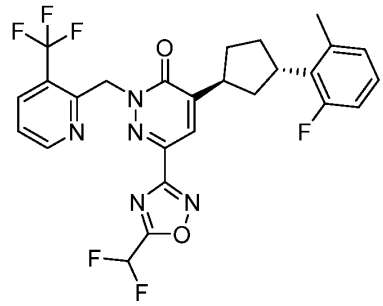
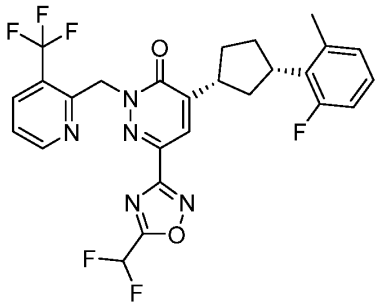
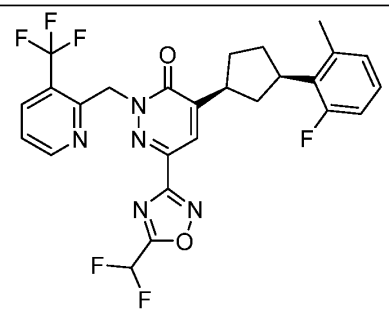
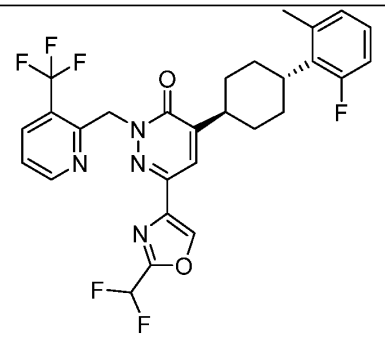
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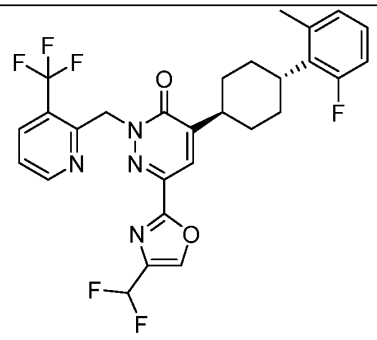


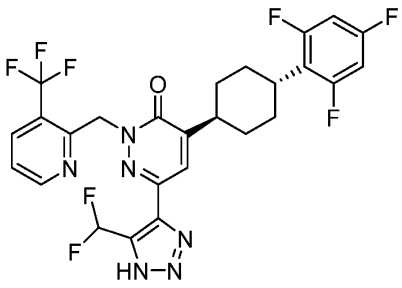
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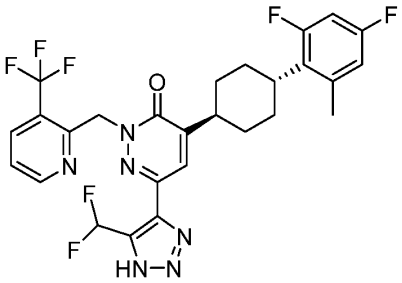


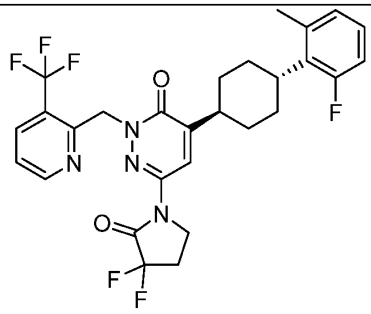
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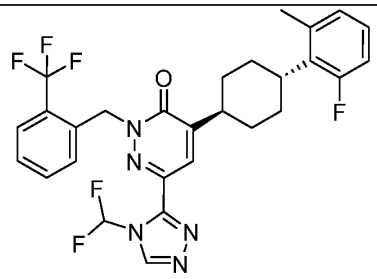
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 **194**	 **195A**
 **195B**	 **195C**
 **195D**	 **196**

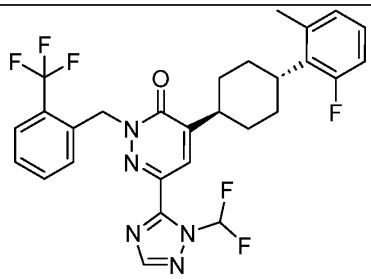

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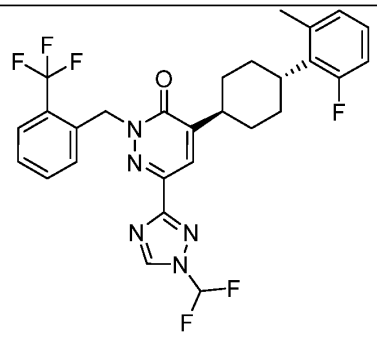

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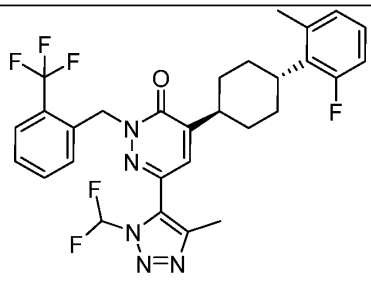

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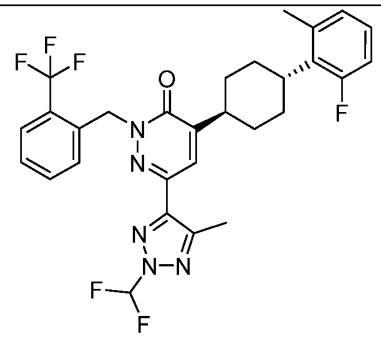
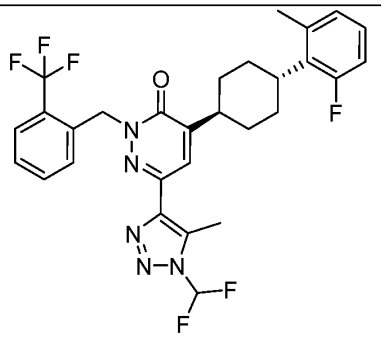
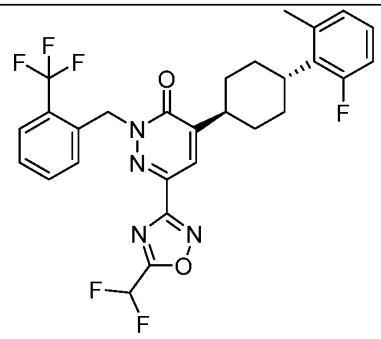
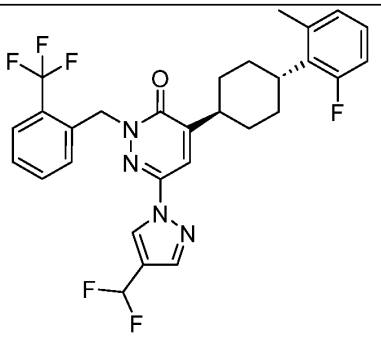
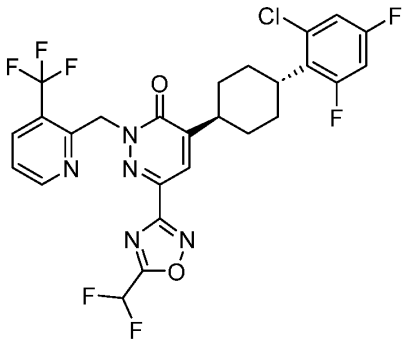
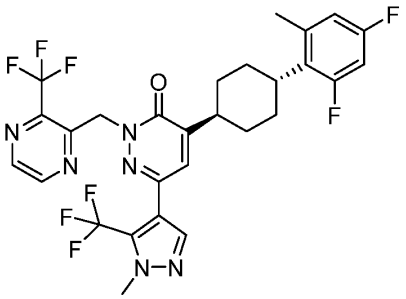
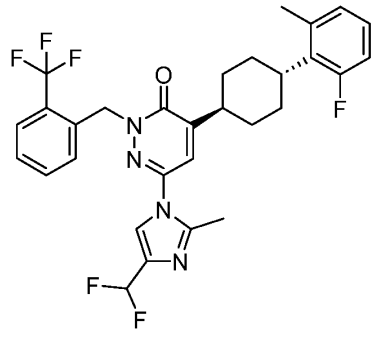
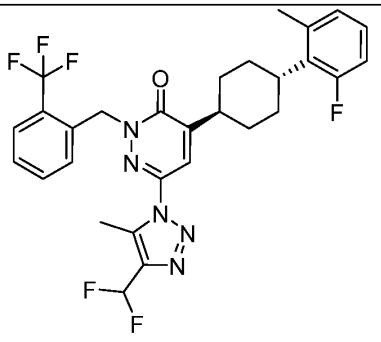

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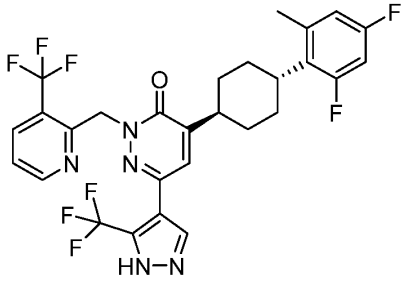
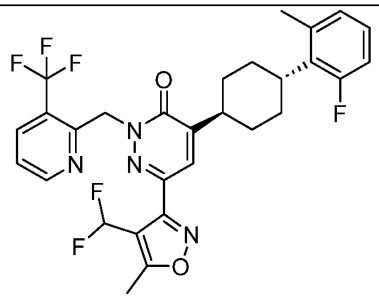
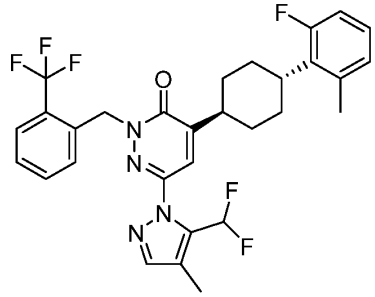
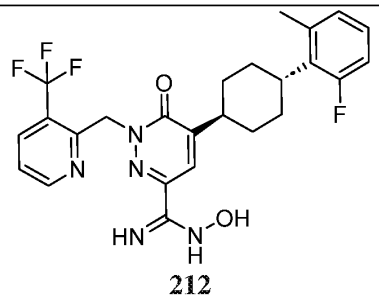
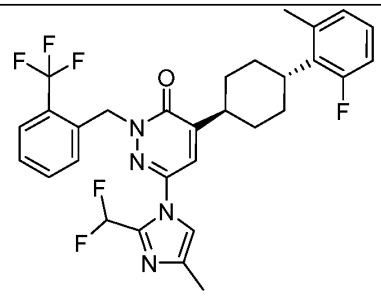
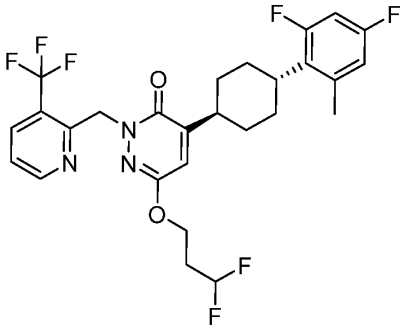
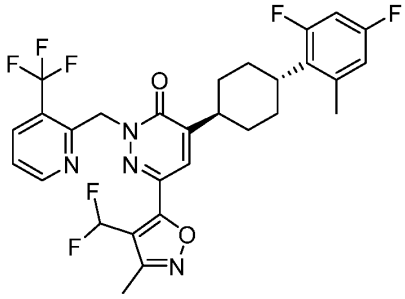

201A


201B


201C


202A

 202B	 202C
 203	 204
 205	 206
 207	 208

 209	 210
 211	 212
 213	 214
 215	

or a pharmaceutically acceptable salt thereof.

55. A pharmaceutical composition comprising a compound of any of claims 1-54, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

56. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a compound of any of claims 1-54, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 55.

57. The method of claim 56, wherein the disease or disorder is associated with C5aR1.

58. The method of claim 56 or 57, wherein the disease or disorder is cancer, an infectious disease, an autoimmune disease or disorder, an inflammatory disease or disorder, a cardiovascular disease or disorder, a cerebrovascular disease or disorder, a vasculitis disease or disorder, or a neurodegenerative disease or disorder.

59. The method of any one of claims 56-58, wherein the disease or disorder is a neurological disease or disorder.

60. A method of antagonizing C5aR1, the method comprising contacting C5aR1 with a compound of any of claims 1-54, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 55.

61. The method of claim 60, wherein the contacting is *in vitro*.

62. The method of claim 60, wherein the contacting is *in vivo*.

63. A kit comprising a compound of any of claims 1-54, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 55, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.