

CYCLIC COMPOUNDS AND METHODS OF USING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/391,548, filed
5 July 22, 2022, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

This present application relates to tricyclic that are useful for treating proliferative disorders such as cancer, as well as autoimmune and inflammatory disorders.

BACKGROUND

10 MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) is an intracellular protein involved in lymphocyte proliferation via upstream signaling of NF- κ B to control lymphocyte activation, survival, proliferation, and differentiation. Together with a CARMA or CARD scaffold protein, (e.g., CARD11 (caspase recruitment domain family member 11, also known as CARMA1), CARD14 (caspase recruitment domain family member 14, also
15 known as CARMA2), CARD10 (caspase recruitment domain family member 10, also known as CARMA3), or CARD9 (caspase recruitment domain family member 9)) and BCL10 (B-cell CLL/Lymphoma 10), MALT1 is one of the three subunits of the CBM complex which is formed upon cell-surface antigen receptor activation. *See* Jaworski et al., *Cell Mol Life Science* 2016, 73, 459-473, and Juilland and Thome. *Frontiers in Immunology* 2018, 9, 1927. MALT1 is known to
20 mediate NF- κ B signaling by at least two mechanisms: firstly, MALT1 functions as a scaffold protein, recruiting NF- κ B signaling proteins such as TRAF6, TABs (e.g., TAB1, TAB2, TAB3), TAK1 and NEMO-IKK β ; and secondly, as a cysteine protease, it cleaves and deactivates negative regulators of NF- κ B signaling, such as RelB, A20, or CYLD. *See* Rosebeck et al., *Science*, 2011, 331, 468-472.

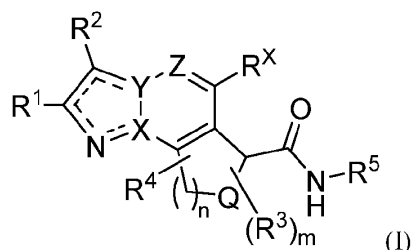
25 The protease activity of MALT1 has emerged as a potential therapeutic target, particularly where NF- κ B and related pathways are believed to play a significant role. Activated B cell-like diffuse large B cell lymphomas (ABC-DLBCLs) are aggressive lymphomas that are often characterized by NF- κ B hyperactivation, and it has been shown that MALT1 protease inhibition can dramatically inhibit growth and promote apoptosis of the highly aggressive ABC type
30 DLBCLs. *See* Ferch U, et al., *J Exp Med* 2009, 206, 2313-2320; *see also*, Hailfinger S, et al., *Proc*

Natl Acad Sci USA 2009, 106, 19946-19951. Known peptide substrates of MALT1, or fusion protein API2-MALT1, include A20, CYLD, BCL10, RelB, regnase-1, roquin-1, NIK, and LIMA la. *See* Rebeaud et al., Nat Immunol 2008, 9, 272-281; *see also*, Coornaert et al., Nat Immunol 2008, 9, 263-271; Staal et al., EMBO J 2011, 30, 1742-1752; Hailfinger et al., PNAS 2011, 108, 14596-14601; Jeltsch et al., Nat Immunol 2014, 15, 1079-1089; Uehata et al., Cell 2013, 153, 1036-1049; Nie et al., Nat Commun 2015, 6, 5908; and Baens et al., PLoS ONE 2014, 9, e103774. One general profile of MALT1 substrates is described in Kasperkiewicz, et al. Scientific Reports 8.1 (2018): 1-10.

Additionally, several chromosomal translocations that lead to the generation of constitutively active MALT1 have been identified in ABC-DLBCLs and the identification of the MALT1 fusion protein API2-MALT1/IgH-MALT1 that leads to NF- κ B activation independent of upstream stimulation further highlights the importance of this protein in cancer and various diseases. *See* Farinha et al., J Clinical Oncology 2005, 23, 6370-6378. Further, MALT1 has been shown to be involved in several different types of cancers, for example hematological malignancies such as mantle cell lymphoma, chronic lymphocytic leukemia (CLL) and solid tumors such as lung adenocarcinoma, breast cancer, pancreatic cancer, and glioblastoma. *See* Jiang et al., Cancer Research 2011, 71, 2183-2192; *see also*, Pan et al., Mol Cancer Res 2016, 14, 93-102, Penas et al., Blood 2010, 115, 2214-2219, and J Cell Mol Med. 2020 Jul;24(13):7550-7562. MALT1, as an immunomodulatory protein, is also involved in innate and adaptive immunity and may have effects on several inflammatory disorders, e.g., psoriasis, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, ulcerative colitis, and different types of allergic disorders resulting from chronic inflammation. *See* Afofina et al., FEBS Journal 2015, DOI: 10.1111/febs.13325; *see also* Lowes et al., Ann Review Immunology 2014, 32, 227-255; Jabara et al., J Allergy Clin Immunology 2013, 132, 151-158; Streubel et al., Clin Cancer Research 2004, 10, 476-480; and Liu et al., Oncotarget 2016, 1-14. Recently, findings also suggest the importance of MALT1 in the control of regulatory T cell (Treg) function and homeostasis. Studies are ongoing to confirm the potential of MALT1 inhibitors for the treatment of patients with solid tumors alone or in combination with immune-checkpoint mechanisms. However, no MALT1 inhibitors are currently approved for therapeutic use.

SUMMARY

Accordingly, provided herein is a compound of the Formula (I):



or a pharmaceutically acceptable salt thereof, wherein X, Y, Z, Q, n, R^X , R^1 , R^2 , R^3 , m, R^4 and R^5 are as defined herein.

Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Also provided are methods for treating a CBM complex pathway-associated cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a cancer in a subject in need thereof, comprising:

(a) identifying the cancer as being a CBM complex pathway-associated cancer; and

(b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a cancer in a subject in need thereof, comprising:

administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to a subject identified as having a CBM complex pathway-associated cancer.

Also provided are methods for treating a MALT1-associated cancer in a subject, comprising administering to a subject identified or diagnosed as having a MALT1-associated cancer an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating cancer in a subject in need thereof, comprising:

(a) determining that the cancer is associated with a dysregulation of a MALT1 gene, a

MALT1 protease, or expression or activity or level of any of the same; and

(b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for inhibiting metastasis in a subject having a cancer in need of such treatment, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a CBM complex pathway-associated disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a disease or disorder in a subject in need thereof, comprising:

(a) identifying the disease or disorder as being a CBM complex pathway-associated disease or disorder; and

(b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a disease or disorder in a subject in need thereof, comprising:

administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to a subject identified as having a CBM complex pathway-associated disease or disorder.

Also provided are methods for treating a MALT1-associated autoimmune disorder in a subject, comprising administering to a subject identified or diagnosed as having a MALT1-associated autoimmune disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a MALT1-associated autoimmune disorder in a subject, comprising administering to a subject identified or diagnosed as having a MALT1-

associated autoimmune disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating an autoimmune disorder in a subject in need thereof, comprising:

5 (a) determining that the autoimmune disorder is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same; and

(b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a MALT1-associated autoimmune disorder in a subject, comprising administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to
10 a subject determined to have a MALT1-associated autoimmune disorder.

Also provided are methods for treating an inflammatory disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula
15 (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

Also provided are methods for treating a MALT1-associated inflammatory disorder in a subject, comprising administering to a subject identified or diagnosed as having a MALT1-associated inflammatory disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.
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Also provided are methods for treating a MALT1-associated inflammatory disorder in a subject, comprising administering to a subject identified or diagnosed as having a MALT1-associated inflammatory disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

25 Also provided are methods for treating an inflammatory disorder in a subject in need thereof, comprising:

(a) determining that the inflammatory disorder is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same; and

(b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.
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Also provided are methods for treating a MALT1-associated inflammatory disorder in a

subject, comprising administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to a subject determined to have a MALT1-associated inflammatory disorder.

Also provided are methods for inhibiting CBM complex pathway activity in a mammalian cell, comprising contacting the mammalian cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Also provided are methods for inhibiting MALT1 protease activity in a mammalian cell, comprising contacting the mammalian cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Also provided are the use of compounds of Formula (I), or pharmaceutically acceptable salts thereof, for treating a CBM complex pathway-associated disease or disorder.

Also provided are compounds of Formula (I), or pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for the treatment of a CBM complex pathway-associated disease or disorder.

Also provided are methods of treating an individual with a MALT1-associated cancer that include administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, before, during, or after administration of other anticancer drug(s) (e.g., a first MALT1 inhibitor or another MALT1 inhibitor).

Also provided herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof obtained by a process of preparing the compound as defined herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entireties. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following

detailed description and from the claims.

DETAILED DESCRIPTION

The term “compound,” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopically enriched variants of the structures depicted. Compounds
5 herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The term “tautomer,” as used herein refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium, and it is to be understood that compounds provided herein may be depicted as different tautomers, and when compounds
10 have tautomeric forms, all tautomeric forms are intended to be within the scope of the disclosure, and the naming of the compounds does not exclude any tautomer. The following is an example of included tautomeric forms:



It will be appreciated that certain compounds provided herein may contain one or more
15 centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers such as a racemic mixture, or in an enantiomerically pure form.

The term “halo or halogen” refers to one of the halogens, group 17 of the periodic table. In particular, the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to fluorine or chlorine.

20 The term “C1-C6 alkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, *tert*-butyl, n-pentyl and n-hexyl. Similarly, a C1-C3 alkyl group is linear or branched hydrocarbon chain containing 1, 2, or 3 carbon atoms.

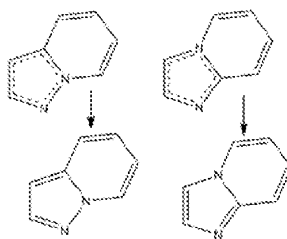
The term “C1-C6 haloalkyl” refers to a hydrocarbon chain substituted with at least one
25 halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. The halogen atom may be present at any position on the hydrocarbon chain. Similarly, a C1-C3 haloalkyl group is linear or branched hydrocarbon chain containing 1, 2, or 3 carbon atoms substituted with at least one halogen atom. For example, C1-C3 haloalkyl may refer to chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloroethyl and 2-

chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl.

The term “C1-C3 alkoxy” refers to a C1-C3 alkyl group which is attached to a molecule via oxygen. This includes moieties where the alkyl part may be linear or branched, such as methoxy, ethoxy, n-propoxy, and iso-propoxy.

The term “C1-C3 haloalkoxy” refers to a C1-C3 alkyl group which is attached to a molecule via oxygen and where at least one hydrogen atom of the alkyl group is replaced with a halogen. This includes moieties where the alkyl part may be linear or branched, such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, or trifluoropropoxy.

A  represents a single or double bond, valence permitting. For example,



As used herein, the term “cyano” refers to a –CN radical.

As used herein, the term “hydroxyl” refers to an –OH radical.

As used herein, the term “amino” refers to an –NH₂ group.

As used herein, the term “aryl” refers to a 6–10 all carbon mono- or bicyclic group wherein at least one ring in the system is aromatic. Non-limiting examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl. In bicyclic ring systems where only one ring is aromatic, the non-aromatic ring can be a cycloalkyl group, as defined herein.

As used herein, the term “heteroaryl” refers to a 5–10 membered, or 5-9 membered, mono- or bicyclic group wherein at least one ring in the system is aromatic; wherein one or more carbon atoms in at least one ring in the system is/are replaced with a heteroatom independently selected from N, O, and S. Heteroaryl groups include rings where one or more atoms are oxidized (e.g., carbon, nitrogen, and sulfur), such as a pyridone moiety. Non-limiting examples of heteroaryl groups include pyridine, pyrimidine, pyridazine, pyrimidinone, pyrrole, pyrazole, imidazole, triazole, thiazole, and indole. In bicyclic ring systems where only one ring is aromatic, the non-

aromatic ring can be a cycloalkyl or heterocyclyl group, as defined herein.

As used herein, the term “cycloalkyl” refers to a saturated or partially unsaturated 3–10 or 3-7 mono- or bicyclic hydrocarbon group, or a 3-6 membered monocyclic hydrocarbon group; wherein bicyclic systems include fused, spiro (optionally referred to as “spirocycloalkyl” groups), and bridged ring systems. Non-limiting examples of cycloalkyl groups include cyclopropyl, cyclohexyl, spiro[2.3]hexyl, and bicyclo[1.1.1]pentyl.

The term “heterocyclyl” refers to a saturated or partially unsaturated 3-12 membered, 3-8 membered, or 4-6 membered hydrocarbon monocyclic or bicyclic ring system, that is not aromatic, having at least one heteroatom within the ring selected from N, O and S. Bicyclic heterocyclyl groups include fused, spiro (optionally referred to as “spiroheterocyclyl” groups), and bridged ring systems. The heterocyclyl ring system may include oxo substitution at one or more C, N, or S ring members. The heterocyclyl group may be denoted as, for example, a “5-10 membered heterocyclyl group,” which is a ring system containing 5, 6, 7, 8, 9 or 10 atoms at least one being a heteroatom. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The heterocyclyl group may be bonded to the rest of the molecule through any carbon atom or through a heteroatom such as nitrogen. Exemplary heterocyclyl groups include, but are not limited to, piperidinyl, piperazinyl, morpholino, tetrahydropyranyl, azetidiny, oxetanyl, 2-azaspiro[3.3]heptanyl, pyrrolidin-2-one, sulfolane, isothiazoline S,S-dioxide, and decahydronaphthalenyl.

As used herein, the term “oxo” refers to an “=O” group attached to a carbon atom.

As used herein, the symbol  depicts the point of attachment of an atom or moiety to the indicated atom or group in the remainder of the molecule.

It is to be understood that the ring in compounds of Formula (I) comprising atoms X, Y and Z does not contain more than two adjacent nitrogen atoms.

The compounds of Formula (I) include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula (I) also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I) and/or for separating enantiomers of compounds of Formula (I). Non-limiting examples of pharmaceutically acceptable salts of compounds of Formula (I) include trifluoroacetic acid and hydrochloride salts.

It will further be appreciated that the compounds of Formula (I) or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope

of the present disclosure. For example, compounds of Formula (I) and salts thereof can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like.

In some embodiments, the compounds of Formula (I) include the compounds of Examples 1-196 and stereoisomers and pharmaceutically acceptable salts thereof. In some embodiments, the compounds of Formula (I) include the compounds of Examples 1-196 and pharmaceutically acceptable salts thereof. In some embodiments, the compounds of Examples 1-196 are in the free base form. In some embodiments, the compounds of Examples 1-196 are in the form of pharmaceutically acceptable salts.

The term “pharmaceutically acceptable” indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the subject being treated therewith.

Protecting groups can be a temporary substituent which protects a potentially reactive functional group from undesired chemical transformations. The choice of the particular protecting group employed is well within the skill of one of ordinary skill in the art. A number of considerations can determine the choice of protecting group including, but not limited to, the functional group being protected, other functionality present in the molecule, reaction conditions at each step of the synthetic sequence, other protecting groups present in the molecule, functional group tolerance to conditions required to remove the protecting group, and reaction conditions for the thermal decomposition of the compounds provided herein. The field of protecting group chemistry has been reviewed (Greene, T. W. and Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed. Wiley: New York, **1991**).

A nitrogen protecting group can be any temporary substituent which protects an amine moiety from undesired chemical transformations. Examples of moieties formed when such protecting groups are bonded to an amine include, but are not limited to allylamine, benzylamines (e.g., benzylamine, *p*-methoxybenzylamine, 2,4-dimethoxybenzylamine, and tritylamine), acetamide, trichloroacetamide, trifluoroacetamide, pent-4-enamide, phthalimides, carbamates (e.g., methyl carbamate, *t*-butyl carbamate, benzyl carbamate, allyl carbamates, 2,2,2-trichloroethyl carbamate, and 9-fluorenylmethyl carbamate), imines, and sulfonamides (e.g., benzene sulfonamide, *p*-toluenesulfonamide, and *p*-nitrobenzenesulfonamide).

An oxygen protecting group can be any temporary substituent which protects a hydroxyl

moiety from undesired chemical transformations. Examples of moieties formed when such protecting groups are bonded to a hydroxyl include, but are not limited to esters (e.g., acetyl, *t*-butyl carbonyl, and benzoyl), benzyl (e.g., benzyl, *p*-methoxybenzyl, and 2,4-dimethoxybenzyl, and trityl), carbonates (e.g., methyl carbonate, allyl carbonate, 2,2,2-trichloroethyl carbonate and benzyl carbonate) ketals, and acetals, and ethers.

Compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in particular when mentioned in relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of that atom, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, when hydrogen is mentioned, it is understood to refer to ^1H , ^2H , ^3H or mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C , ^{12}C , ^{13}C , ^{14}C or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N , ^{14}N , ^{15}N or mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O , ^{15}O , ^{16}O , ^{17}O , ^{18}O or mixtures thereof; and when fluoro is mentioned, it is understood to refer to ^{18}F , ^{19}F or mixtures thereof; unless expressly noted otherwise. For example, in deuterioalkyl and deuterioalkoxy groups, where one or more hydrogen atoms are specifically replaced with deuterium (^2H). As some of the aforementioned isotopes are radioactive, the compounds provided herein therefore also comprise compounds with one or more isotopes of one or more atoms, and mixtures thereof, including radioactive compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive enriched isotopes. Radiolabeled compounds are useful as therapeutic agents, e.g., cancer therapeutic agents, research reagents, e.g., assay reagents, and diagnostic agents, e.g., *in vivo* imaging agents. All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

For illustrative purposes, general methods for preparing the compounds are provided herein as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light

of this disclosure using conventional chemistry well known to those skilled in the art.

The ability of selected compounds to act as MALT1 inhibitors may be demonstrated by the biological assays described herein. IC₅₀ values are shown in Table A.

Compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are useful for
5 treating diseases and disorders which can be treated with a MALT1 inhibitor, such as MALT1-associated cancers, including hematological cancers and solid tumors, MALT1-associated autoimmune disorders, and MALT1-associated inflammatory disorders.

As used herein, terms “treat” or “treatment” refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part,
10 of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

15 As used herein, the term “subject” refers to any animal, including mammals such as humans. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented.

The term “pediatric subject” as used herein refers to a subject under the age of 21 years at
20 the time of diagnosis or treatment. The term “pediatric” can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. *Nelson Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. *Rudolph’s Pediatrics*, 21st Ed.
25 New York: McGraw-Hill, 2002; and Avery MD, First LR. *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the
30 twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than

four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

In certain embodiments, compounds of Formula (I), or a pharmaceutically acceptable salt thereof are useful for preventing diseases and disorders as defined herein (for example, autoimmune disorders, inflammatory disorders, and cancer). The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

Signaling through the NF- κ B pathway has been implicated in many cancers. *See, e.g.,* Staudt, Cold Spring Harbor Perspectives in Biology 2.6 (2010): a000109, Xia, et al. Cancer Immunol. Res. 2.9 (2014): 823-830, Xia, et al. OncoTargets and Therapy 11 (2018): 2063. NF- κ B is a family of transcription factors, including p50, p52, p65 (RelA), RelB, and c-Rel, which can bind to the κ B enhancer element as various homo- and heterodimers to induce transcription of a number of genes. Following activation of certain cell-surface receptors (e.g., CD28, BCR, HER1 (also known as EGFR (Epidermal Growth Factor Receptor) and ERBB1), or HER2 (also known as HER2/neu or ERBB2)), a CBM complex is formed via phosphorylation of a CARD or CARMA protein, likely by a protein kinase C (e.g., protein kinase C beta or protein kinase C theta) and recruitment of the BCL10-MALT1 complex. *See, e.g.,* Xia, et al. OncoTargets and Therapy 11 (2018): 2063, Shi, and Sun. Mol. Immunol. 68.2 (2015): 546-557, Xia, et al. Cancer Immunol. Res. 2.9 (2014): 823-830, and Pan, Mol. Cancer Res. 14.1 (2016): 93-102.

As noted hereinabove, the CBM complex can function as a scaffold protein in the activation of the NF- κ B pathway. When formed, the CBM complex can activate the IKK complex (e.g., IKK γ (also called NEMO), IKK α , and IKK β), likely by ubiquitination (e.g., K63-linked ubiquitination) of MALT1, which results in the recruitment, ubiquitination (e.g., K63-linked ubiquitination), and degradation of IKK γ , thereby releasing IKK α and IKK β to phosphorylate I κ B,

resulting in the ubiquitination (e.g., K48-linked ubiquitination) and degradation of I κ B, releasing the NF- κ B transcription factors (typically of the NF- κ B1 subtype: p50-RelA and p50-cRel) to the nucleus. This cascade is likely mediated by the ubiquitin ligase TRAF6 (Tumor necrosis factor receptor (TNFR)-associated factor 6). The CBM complex may also affect NF- κ B signaling through additional protein complexes, such as TAB1/2-TAK and the linear ubiquitin chain assembly complex (LUBAC). *See, e.g.,* Israël, Cold Spring Harbor Perspectives in Biology 2.3 (2010): a000158, Xia, et al. OncoTargets and Therapy 11 (2018): 2063, Juilland, Front. Immunol. 9 (2018): 1927. MALT1 can also activate the JNK pathway (also called the JNK/AP-1 pathway), though less work has been done to study this area. *See, e.g.,* Juilland, Front. Immunol. 9 (2018): 1927, and Wang, et al., Oncogenesis 6.7 (2017): e365-e365.

In addition, MALT1 has cysteine protease activity. Non-limiting examples of substrates of wild-type MALT1 include BCL10, A20, CYLD, RelB, Regnase 1, roquin-1, and HOIL1. In addition, the API2-MALT1 (also called cIAP2; amino terminus of inhibitor of apoptosis 2) fusion protein has also been shown to cleave NIK and LIMA1 α . BCL10 cleavage by MALT1 is believed to result in BCL10-independent NF- κ B activation. By cleaving A20 (TNF Alpha Induced Protein 3), MALT1 can reduce negative regulation of the NF- κ B pathway, as A20 is a deubiquitinating enzyme that has been suggested to reduce the ubiquitination of MALT1 and thus recruitment and activation of the IKK complex. CYLD (CYLD Lysine 63 Deubiquitinase) is a deubiquitinating enzyme, and by cleavage of this enzyme, it is believed that MALT1 increases signaling through the NF- κ B pathway and/or JNK pathway. Cleavage of RelB typically results in relief of negative regulation of the NF- κ B pathway, as RelB forms transcriptionally inactive complexes with RelA and c-Rel. By cleaving HOIL1 (also known as RBCK1), it is believed that negative regulation of the NF- κ B is relieved, as HOIL1 is thought to decrease linear ubiquitination. MALT1 can also autoproces, which promotes signaling through the NF- κ B pathway through a mechanism that is not fully understood. By cleaving NIK (NF- κ B inducing kinase), the API2-MALT1 protease generates a c-terminal fragment of NIK that is resistant to proteasomal degradation and thereby increases noncanonical NF- κ B signaling. By cleaving LIMA1 α (LIM domain and actin-binding protein 1), the tumor-suppressing properties of this protein are diminished, and it believed that the remaining fragment has oncogenic properties and enhances cell proliferation, colony formation, and cell adhesion. Cleavage of Regnase 1 (Regulatory RNase 1, also known as MCPIP-1 or Zc3h12a), and roquin-1 (also known as RC3H1) is believed to result in the stabilization of mRNAs,

including those of cytokines, chemokines, and costimulatory proteins such as ICOS, OX40, and TNF. This activity may be independent of MALT1 activity in the NF- κ B and JNK pathways. *See, e.g.,* Afonina, et al. FEBS J. 282.17 (2015): 3286-3297 Klein et al. Nat. Comm. 6.1 (2015): 1-17, Baens, et al. PloS one 9.8 (2014): e103774, and Juilland, Front. Immunol. 9 (2018): 1927. MALT1
 5 is also involved in oncogenic BCR signalling in ibrutinib-responsive cell lines and biopsy samples, coordinated by a multiprotein supercomplex formed by MYD88, TLR9 and the BCR (hereafter termed the My-T-BCR supercomplex). The My-T-BCR supercomplex co-localizes with mTOR on endolysosomes, where it drives pro-survival NF- κ B and mTOR signalling. *See* Phelan et al., Nature 2018 Aug;560(7718):387-391.

10 Accordingly, inhibition of MALT1 can provide beneficial effects to many types of disorders associated with aberrant signaling in the NF- κ B pathway or JNK pathway. For example, inhibition of MALT1 can decrease flux through the NF- κ B or JNK pathways resulting from one or more of:

(1) An inactivated tumor suppressor gene. Non-limiting examples of tumor suppressor
 15 genes that can be inactivated include BRCA1 and p53 (e.g., p53 H61L or I123T). *See, e.g.,* Sau, et al. Cell Stem Cell 19.1 (2016): 52-65, Xia, et al. Cancer Immunol. Res. 2.9 (2014): 823-830, Johansson, et al. Oncotarget 7.38 (2016): 62627.

(2) A dysregulated cell surface receptor. Non-limiting examples of cell surface receptors include HER1 and HER2. *See, e.g.,* Xia, et al. Cancer Immunol. Res. 2.9 (2014): 823-830 and Pan,
 20 Mol. Cancer Res. 14.1 (2016): 93-102.

(3) Dysregulation of one or more components of a CBM complex. Non-limiting examples of components of a CBM complex include MALT1, CARD11, CARD14, CARD10, CARD9, and BCL10.

(4) Dysregulation of one or more substrates of a MALT1 protease (e.g., a wild-type
 25 MALT1 protease or a dysregulated MALT1 protease). Non-limiting examples of substrates of a MALT1 protease include BCL10, A20, CYLD, RelB, Regnase 1, roquin-1, HOIL1, NIK, and LIMA1 α .

(5) Dysregulation of one or more components of the NF- κ B pathway downstream of a CBM complex. Non-limiting examples of a component of the NF- κ B pathway downstream of a
 30 CBM complex include TRAF6, IKK α , IKK β , IKK γ (also called NEMO), I κ B α , p50, p52, p65 (RelA), RelB, and c-Rel.

(6) Dysregulation of one or more components of the JNK pathway downstream of a CBM complex. Non-limiting examples of a component of the JNK pathway downstream of a CBM complex include JNK1 (Mitogen-Activated Protein Kinase 8), JNK2 (Mitogen-Activated Protein Kinase 9), JNK3 (Mitogen-Activated Protein Kinase 10), or an AP-1 transcription factor (e.g., a heterodimer of any of the c-Fos, c-Jun, ATF, or JDP families).

(7) Dysregulation of one or more fusion proteins caused by chromosome translocation of MALT1 gene. Non-limiting example includes the cIAP-MALT1 fusion protein.

(8) Dysregulation of one or more components of the My-T-BCR supercomplex. Non-limiting examples of a component of the My-T-BCR supercomplex include MYD88, TLR9, and mTOR.

The term "CBM complex pathway" as associated herein includes genes, transcripts, and proteins in a signaling pathway that includes a CBM. For example, many aspects of the NF- κ B pathway are part of a CBM complex pathway. A CBM complex pathway can include, for example, cell surface receptors (e.g., CD28, BCR, HER1, and HER2), a signal transducer between a cell surface receptor and a CBM complex (e.g., a protein kinase C beta or protein kinase C theta), a component of a CBM complex (e.g., MALT1, CARD11, CARD14, CARD10, CARD9, or BCL10), substrates of a MALT1 protease (e.g., BCL10, A20, CYLD, RelB, Regnase 1, roquin-1, HOIL1, NIK, and LIMA1 α), a component of the NF- κ B pathway downstream of a CBM complex (e.g., TAK1, TRAF6, TAB1, TAB2, TAB3, MKK7, IKK α , IKK β , IKK γ , I κ B α , p50, p65 (RelA), or c-Rel), a component of the JNK pathway downstream of a CBM complex (e.g., JNK1, JNK2, JNK3, or an AP-1 transcription factor), or a components of the My-T-BCR supercomplex (e.g., MYD88, TLR9, or mTOR).

As used herein, the term "CBM complex pathway-associated disease or disorder" refers to diseases or disorders associated with or having a dysregulation of a gene in a CBM complex pathway, a protein in a CBM complex pathway, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a gene in a CBM complex pathway, a protein in a CBM complex pathway, or the expression or activity or level of any of the same, as described herein). Non-limiting examples of a CBM complex pathway-associated diseases or disorders include, for example, CBM-related primary immunodeficiency diseases, autoimmune disorders, multiple sclerosis, colitis, psoriasis, and cancer. *See, e.g., McGuire, et al. J. Neuroinflamm. 11.1 (2014): 1-12, Lu, et al., Front. Immunol. 9 (2018): 2078, Jaworski, et al.,*

EMBO J. 33.23 (2014): 2765-2781. Non-limiting examples of a CBM complex pathway-associated disease or disorder include MALT1-associated diseases or disorders such as MALT1-associated cancers, MALT1-associated autoimmune disorders, and MALT1-associated inflammatory disorders.

5 The term “CBM complex pathway-associated autoimmune disorder” as used herein refers to autoimmune disorders associated with or having a dysregulation of a CBM complex pathway gene, a CBM complex pathway protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CBM complex pathway gene, a CBM complex pathway protein, or the expression or activity or level of any of the same described
10 herein). Non-limiting examples of a CBM complex pathway-associated autoimmune disorders are described herein.

 The term “CBM complex pathway-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a CBM complex pathway gene, a CBM complex pathway protein, or the expression or activity or level of any (e.g., one or
15 more) of the same (e.g., any of the types of dysregulation of a CBM complex pathway gene, a CBM complex pathway protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of a CBM complex pathway-associated inflammatory disorders are described herein.

 In some embodiments, a CBM complex pathway-associated disease or disorder is a CBM
20 complex pathway-associated cancer, such as a CBM complex pathway cell surface receptor-associated cancer (e.g., a CD28-associated cancer, a BCR-associated cancer, a HER1-associated cancer, or a HER2-associated cancer), a cancer associated with a signal transducer between a cell surface receptor and a CBM complex (e.g. a protein kinase C beta (PKC β)-associated cancer or a protein kinase C theta (PCK θ)-associated cancer), a component of a CBM complex-associated
25 cancer (e.g., a MALT1-associated cancer, a CARD11-associated cancer, a CARD14-associated cancer, a CARD10-associated cancer, a CARD9-associated cancer, or a BCL10-associated cancer), a MALT1 protease substrate-associated cancer (e.g., a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, a RelB-associated cancer, a Regnase 1-associated cancer, a roquin-1-associated cancer, a HOIL1-associated cancer, a NIK associated cancer, or a
30 LIMA1 α -associated cancer), a cancer associated with a component of the NF- κ B pathway downstream of a CBM complex (e.g., TAK1-associated cancer, a TRAF6-associated cancer, a

TAB1-associated cancer, a TAB2-associated cancer, a TAB3-associated cancer, a MKK7-associated cancer, an IKK α -associated cancer, an IKK β -associated cancer, an IKK γ -associated cancer, an I κ B α -associated cancer, a p50-associated cancer, a p65 (RelA)-associated cancer, or a c-Rel-associated cancer), a cancer associated with a component of the JNK pathway downstream of a CBM complex (e.g., a JNK1-associated cancer, a JNK2-associated cancer, a JNK3-associated cancer, or an AP-1 transcription factor-associated cancer), a MYD88-associated cancer, or a combination thereof.

The term "CBM complex pathway-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a gene in a CBM complex pathway, a protein in a CBM complex pathway, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a gene in a CBM complex pathway, a protein in a CBM complex pathway, or the expression or activity or level of any of the same, as described herein) (e.g., upon diagnosis or after developing resistance to previous therapies. Non-limiting examples of a CBM complex pathway-associated cancer are described herein. In some embodiments, a CBM pathway-associated cancer can be a CBM complex pathway cell surface receptor-associated cancer (e.g., a CD28-associated cancer, a BCR-associated cancer, a HER1-associated cancer, or a HER2-associated cancer), a cancer associated with a signal transducer between a cell surface receptor and a CBM complex (e.g., a protein kinase C beta (PKC β)-associated cancer or a protein kinase C theta (PCK θ)-associated cancer, a component of a CBM complex-associated cancer (e.g., a MALT1-associated cancer, a CARD11-associated cancer, a CARD14-associated cancer, a CARD10-associated cancer, a CARD9-associated cancer, or a BCL10-associated cancer), a MALT1 protease substrate-associated cancer (e.g., a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, a RelB-associated cancer, a Regnase 1-associated cancer, a roiquin-1-associated cancer, a HOIL1-associated cancer, a NIK associated cancer, or a LIMA1 α -associated cancer), a cancer associated with a component of the NF- κ B pathway downstream of a CBM complex (e.g., TAK1-associated cancer, a TRAF6-associated cancer, a TAB1-associated cancer, a TAB2-associated cancer, a TAB3-associated cancer, a MKK7-associated cancer, an IKK α -associated cancer, an IKK β -associated cancer, an IKK γ -associated cancer, an I κ B α -associated cancer, a p50-associated cancer, a p65 (RelA)-associated cancer, or a c-Rel-associated cancer), a cancer associated with a component of the JNK pathway downstream of a CBM complex (e.g., a JNK1-associated cancer, a JNK2-associated

cancer, a JNK3-associated cancer, or an AP-1 transcription factor-associated cancer), or a combination thereof.

In some embodiments, a dysregulation can be a dysregulation that results in aberrant activation of a gene, protein, or expression or activity or level of any of the same. Activation can be through any appropriate mechanism, including, but not limited to, gene amplification, activating mutation, activating translocation, transcriptional activation, epigenetic alteration, and/or overexpression of the protein product of the oncogene. In some embodiments, a dysregulation can be a dysregulation that results in aberrant inactivation of a gene, protein, or expression or activity or level of any of the same. Inactivation can be through any appropriate mechanism, including, but not limited to, gene deletion, inactivating mutation, inactivating translocation, transcriptional silencing, epigenetic alteration, and degradation of mRNA and/or protein products of the gene. Typically, as used herein, a dysregulation, whether it be activation or inactivation, is a dysregulation that results in increased signaling through the NF- κ B or JNK signaling pathways.

The term “wild-type” describes a nucleic acid (e.g., a MALT1 gene or a MALT1 mRNA) or protein (e.g., a MALT1 protein) that is found in a subject that does not have a disease or disorder associated with the nucleic acid or the protein (e.g., the MALT1 gene, MALT1 mRNA, or MALT1 protein) (and optionally also does not have an increased risk of developing a disease or disorder associated with the nucleic acid or the protein and/or is not suspected of having a disease or disorder associated with the gene or the protein), or is found in a cell or tissue from a subject that does not have a disease or disorder associated with the gene or the protein (e.g., a MALT1-associated cancer, autoimmune disorder, or inflammatory disorder) (and optionally also does not have an increased risk of developing a disease or disorder associated with the nucleic acid or the protein and/or is not suspected of having a disease or disorder associated with the nucleic acid or the protein).

In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a cancer resistant to one or more previous therapies. In some embodiments, the subject has a tumor that is positive for a dysregulation of a CBM complex pathway-associated

gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject with a tumor(s) that is positive for a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a
5 CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or a level of the same (e.g., where the
10 tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject has a tumor resistant to one or more previous therapies. In some embodiments, the subject is suspected of having a CBM complex pathway-associated-associated cancer. In some embodiments, the subject has a tumor that is suspected of being resistant to one or more previous therapies. In some embodiments, the subject has a clinical record indicating that
15 the subject has a tumor that has a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject. In some embodiments, the subject has a clinical
20 record indicating that the subject has a tumor resistant to one or more previous therapies. In some embodiments, the subject has been identified or diagnosed as having a cancer that, based on histological examination, is determined to be associated with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated cancer).
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In some embodiments, the subject has been identified or diagnosed as having an autoimmune disorder with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated autoimmune disorder) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a
30

dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject is suspected of having a CBM complex pathway-associated-associated autoimmune disorder. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

10 In some embodiments, the subject is a pediatric subject. In some embodiments, the subject has been identified or diagnosed as having an autoimmune disorder that, based on histological examination, is determined to be associated with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated autoimmune disorder).

15 In some embodiments, the subject has been identified or diagnosed as having an inflammatory disorder with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated inflammatory disorder) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit).

20 In some embodiments, the subject is suspected of having a CBM complex pathway-associated-associated inflammatory disorder. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

30 In some embodiments, the subject is a pediatric subject. In some embodiments, the subject has

been identified or diagnosed as having an inflammatory disorder that, based on histological examination, is determined to be associated with a dysregulation of a CBM complex pathway-associated gene (e.g., a MALT1 gene), a CBM complex pathway-associated protein (e.g., a MALT1 protein), or expression or activity, or level of any of the same (a CBM complex pathway-associated-associated inflammatory disorder).

The term “CBM complex pathway cell surface receptor-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a gene, a protein, or the expression or activity or level of any (e.g., one or more) of the same associated with a CBM complex pathway cell surface receptor. In some embodiments, a CBM complex pathway cell surface receptor-associated cancer is selected from the group consisting of a CD28-associated cancer, a BCR-associated cancer, a HER1-associated cancer, a HER2-associated cancer, and combinations thereof.

The term “*-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a * gene, a * protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a * gene, a * protein, or the expression or activity or level of any of the same described herein), where “*” refers to a particular CBM complex pathway gene or protein, described herein. In some embodiments, the *-associated cancer is selected from the group consisting of: CD28-associated cancer, BCR-associated cancer, HER1-associated cancer, HER2-associated cancer, PKC β -associated cancer, PKC θ -associated cancer, MALT1-associated cancer, CARD11-associated cancer, CARD14-associated cancer, A20-associated cancer, CYLD-associated cancer, RelB-associated cancer, HOIL1-associated cancer, NIK-associated cancer, Regnase 1-associated cancer, LIMA1 α -associated cancer, roquin-1-associated cancer, TRAF6-associated cancer, TAK1-associated cancer, TAB1-associated cancer, TAB2-associated cancer, TAB3-associated cancer, MKK7-associated cancer, IKK α -associated cancer, IKK β -associated cancer, IKK γ -associated cancer, I κ B α -associated cancer, p50-associated cancer, p65-associated cancer, c-Rel-associated cancer, JNK1-associated cancer, JNK2-associated cancer, JNK3-associated cancer, MYD88 transcription factor-associated cancer, and an AP-1 transcription factor-associated cancer. In some embodiments, the *-associated cancer is a CD28-associated cancer. In some embodiments, the *-associated cancer is a BCR-associated cancer. In some embodiments, the *-associated cancer is a HER1-associated cancer. In some embodiments, the *-associated cancer is a HER2-associated cancer. In some embodiments, the *-associated

cancer is a PKC β -associated cancer. In some embodiments, the *-associated cancer is a PKC θ -associated cancer. In some embodiments, the *-associated cancer is a MALT1-associated cancer. In some embodiments, the *-associated cancer is a CARD11-associated cancer. In some embodiments, the *-associated cancer is a CARD14-associated cancer. In some embodiments, the

5 *-associated cancer is an A20-associated cancer. In some embodiments, the *-associated cancer is a CYLD-associated cancer. In some embodiments, the *-associated cancer is a RelB-associated cancer. In some embodiments, the *-associated cancer is a HOIL1-associated cancer. In some embodiments, the *-associated cancer is a NIK-associated cancer. In some embodiments, the *-associated cancer is a Regnase 1-associated cancer. In some embodiments, the *-associated cancer

10 is a LIMA1 α -associated cancer. In some embodiments, the *-associated cancer is a roquin-1-associated cancer. In some embodiments, the *-associated cancer is a TRAF6-associated cancer. In some embodiments, the *-associated cancer is a TAK1-associated cancer. In some embodiments, the *-associated cancer is a TAB1-associated cancer. In some embodiments, the *-associated cancer is a TAB2-associated cancer. In some embodiments, the *-associated cancer is

15 a TAB3-associated cancer. In some embodiments, the *-associated cancer is a MKK7-associated cancer, and an IKK α -associated cancer. In some embodiments, the *-associated cancer is an IKK β -associated cancer. In some embodiments, the *-associated cancer is an IKK γ -associated cancer. In some embodiments, the *-associated cancer is an Ikb α -associated cancer. In some embodiments, the *-associated cancer is a p50-associated cancer. In some embodiments, the *-associated cancer

20 is a p65-associated cancer. In some embodiments, the *-associated cancer is a c-Rel-associated cancer. In some embodiments, the *-associated cancer is a JNK1-associated cancer. In some embodiments, the *-associated cancer is a JNK2-associated cancer. In some embodiments, the *-associated cancer is a JNK3-associated cancer. In some embodiments, the *-associated cancer is a AP-1 transcription factor-associated cancer. In some embodiments, the *-associated cancer is a

25 MYD88 transcription factor-associated cancer.

The phrase “dysregulation of a * gene, a * protein, or the expression or activity or level of any of the same” (where * is a particular CBM complex pathway gene or protein, described herein) refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a * domain and a fusion partner, a mutation in a * gene that results in the

30 expression of a * protein that includes a deletion of at least one amino acid as compared to a wild-type * protein, a mutation in a * gene that results in the expression of a * protein with one or more

point mutations as compared to a wild-type * protein, a mutation in a * gene that results in the expression of a * protein with at least one inserted amino acid as compared to a wild-type * protein, a gene duplication that results in an increased level of * protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of * protein in a cell), an alternative spliced version of a * mRNA that results in a * protein having a deletion of at least one amino acid in the * protein as compared to the wild-type * protein, or increased expression (e.g., increased levels) of a wild-type * protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As a further example, an increased copy number of the * gene can result in overexpression of the * protein. For example, a dysregulation of a * gene, a * protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of *, and a second portion of a partner protein (i.e., that is not *). In some examples, dysregulation of a * gene, a * protein, or expression or activity or level of any of the same can be a result of a gene translocation of one * gene with another non-* gene. In some embodiments, the * gene, a * protein, or the expression or activity or level of any of the same is selected from the group consisting of: CD28, BCR, HER1, HER2, PKC β , PKC θ , MALT1, CARD11, CARD14, A20, CYLD, RelB, HOIL1, NIK, Regnase 1, LIMA1 α , roquin-1, TRAF6, TAK1, TAB1, TAB2, TAB3, MKK7, IKK α , IKK β , IKK γ , I κ B α , p50, p65, c-Rel, JNK1, JNK2, JNK3, MYD88, and an AP-1 transcription factor. In some embodiments, the * gene or * protein is CD28. In some embodiments, the * gene or * protein is BCR. In some embodiments, the * gene or * protein is HER1. In some embodiments, the * gene or * protein is HER2. In some embodiments, the * gene or * protein is PKC β . In some embodiments, the * gene or * protein is PKC θ . In some embodiments, the * gene or * protein is MALT1. In some embodiments, the * gene or * protein is CARD11. In some embodiments, the * gene or * protein is CARD14. In some embodiments, the * gene or * protein is A20. In some embodiments, the * gene or * protein is CYLD. In some embodiments, the * gene or * protein is RelB. In some embodiments, the * gene or * protein is HOIL1. In some embodiments, the * gene or * protein is NIK. In some embodiments, the * gene or * protein is Regnase 1. In some embodiments, the * gene or * protein is LIMA1 α . In some embodiments, the * gene or * protein is roquin-1. In some embodiments, the * gene or * protein is TRAF6. In some embodiments, the * gene or * protein is TAK1. In some embodiments, the * gene or * protein is TAB1. In some

embodiments, the * gene or * protein is TAB2. In some embodiments, the * gene or * protein is TAB3. In some embodiments, the * gene or * protein is MKK7. In some embodiments, the * gene or * protein is IKK α . In some embodiments, the * gene or * protein is IKK β . In some embodiments, the * gene or * protein is IKK γ . In some embodiments, the * gene or * protein is I κ B α . In some
5 embodiments, the * gene or * protein is p50. In some embodiments, the * gene or * protein is p65. In some embodiments, the * gene or * protein is c-Rel. In some embodiments, the * gene or * protein is JNK1. In some embodiments, the * gene or * protein is JNK2. In some embodiments, the * gene or * protein is JNK3. In some embodiments, the * gene or * protein is MYD88 transcription factor. In some embodiments, the * gene or * protein is AP-1 transcription factor.

10 In some embodiments, dysregulation of a * gene, a * protein, or expression or activity, or level of any of the same, can be a mutation in a * gene that encodes a * protein that is constitutively active or has increased activity as compared to a protein encoded by a * gene that does not include the mutation. In some embodiments, an increased copy number of the * gene can result in overexpression of * protein. In some embodiments, the * gene, * protein, or expression or activity,
15 or level of any of the same, is CD28. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is BCR. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is HER1. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is HER2. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is PKC β . In some
20 embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is PKC θ . In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is CARD14. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is CARD9. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is CARD10. In some embodiments, the * gene, * protein, or expression
25 or activity, or level of any of the same, is CARD11. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is MALT1.

As another example, a dysregulation of an * gene, an * protein, or expression or activity, or level of any of the same, can be a mutation in an * gene that encodes an * protein that is constitutively inactive or has decreased activity as compared to a protein encoded by an * gene
30 that does not include the mutation. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is A20. In some embodiments, the * gene, * protein, or

expression or activity, or level of any of the same, is CYLD. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is RelB. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is HOIL1. In some embodiments, the * gene, * protein, or expression or activity, or level of any of the same, is NIK.

5 Diseases or disorders “associated” with a particular gene or protein described herein refer to diseases or disorder associated with or having a dysregulation of the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of such diseases or
10 disorders are described herein. Likewise, cancers “associated” with a particular gene or protein described herein refer to cancers associated with or having a dysregulation of the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of such
15 cancers are described herein.

Exemplary sequences of the proteins described herein are shown below.

An exemplary sequence of human CD28 is shown below:

SEQ ID NO: 1 (UniParc Accession No. UPI0000043F4D)

MLRLLALNLFPSTQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSREFRASLHKGLD
20 SAVEVCVVYGNYSQQQLQVYSKTGFNCDGKLGNESVTFYLLQNLVYNQTDIYFCKIEVMYPP
PYLDNEKSNGTIIHVKGKHLCPSPFLFPGPSKPFWVLVVGGVLACYSLLVTVAFIIFWVR
SKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS

Non-limiting examples of dysregulation of a CD28 gene or a CD28 protein can be found
in, for example, Rohr, et al., *Leukemia* 30.5 (2016): 1062-1070, Yoo, et al., *Haematologica* 101.6
25 (2016): 757-763, and Lee, et al., *Haematologica* 100.12 (2015): e505.

An exemplary sequence of human BCR is shown below:

SEQ ID NO: 2 (UniParc Accession No. UPI000016A088)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLQEVDNQERFRMIYLQ
TLLAKEKKSYDRQWGFRRAAQAPDGASEPRASASRPQPAPADGADPPPAEEPEARPDGE
30 GSPGKARPGTARRPGAAASGERDDRGPPASVAALRSNFERIRKGGHQPADAEPFYVNV
EFHHERGLVKVNDKEVSDRISSLGSAQMQRKKSQHGAGSSVGDASRPPYGRSSSESSC
GVDGDYEDAEELNPRFLKDNLIDANGGSRPPWPPLYQPYQSIYVGGMMEGEGKGPLLRSQ

STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPPTY
 RMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVSEATIVGVRKTGQIWPNDGEG
 AFHGDADGSFGTPPGYGCAADRAEEQRRHQDGLPYIDDSPSSSPHLSSKGRGSRDALVSG
 ALESTKASELDLEKGLEMRKWVLSGILASEETYLSHLEALLPMKPLKAAATTSQPVLT
 5 QQIETIFFKVPELYEIHKEFYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFVDNYGV
 AMEMAEEKCCQANAQFAEISENLRARSNKDAKDPTTKNSLETLLYKPVDRVTRSTLVLHDL
 LKHTPASHPDHPLLQDALRISQNFLLSSINEEITPRRQSM TVKKGEHRQLLKDSFMVELVE
 GARKLRHVLFITDLLLLCTKLKQSGGKTQQYDCKWYIPLTDLFSQMVDELEAVNIPILVP
 DEELDALKIKISQIKNDIQREKRANKGSKATERLKKKLSEQESLLLLMSPSMAFRVHSRN
 10 GKS YTFLISSDYERA EWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN
 KEDDESPGLYGFNLNIVHSATGFKQSSNLYCTLEVDSFGYFVNKAKTRVYRDTAEPN WNE
 EFEIELEGSQTLRILCYEKCYNKTIPKEDGESTDRLMGKGQVQLDPQALQDRDWQRTVI
 AMNGIEVKLSVKFNSREFSLKRMP SRKQTGVFGVKIAVVTKRERSKVPYIVRQCVEEIER
 RGMEEVGIIYRVSGVATDIQALKA AFDVNNDVSVMMSEMDVNAIAGTLKLYFRELPELPE
 15 TDEFYPNFAEGIALSDPVAKESCMLNLLLSLPEANLLTFLFLDHLKRVAEKEAVNKMSL
 HNLATVFGPTLLRPSEKESKLPANPSQPITMTDSWSLEVMSQVQVLLYFLQLEAIPAPDS
 KRQSILFSTEV

Non-limiting examples of dysregulation of a BCR gene or a BCR protein (e.g., a BCR-
 ABL fusion) can be found in, for example, Yang and Fu, Crit. Rev. Oncol./Hematol. 93.3 (2015):
 277-292, Weisberg, et al. Nat. Rev. Cancer 7.5 (2007): 345-356, and Jabbour, et al. Cancer 117.9
 20 (2011): 1800-1811.

An exemplary sequence of human HER1 is shown below:

SEQ ID NO: 3 (UniParc Accession No. UPI000003E750)

MRPSGTAGAALLALLAALCPASRALEEKKVCQGTSNKLTQLGTFEDHFLSLQRMFN NCEV
 25 VLG NLEITYVQRNYDLSFLKTIQEVAGYVLIALNTVERIPILENLQIIRGNMY YENS YALA
 VLSNYDANKTGLKELPMRNLQEILHGAVRFSNNPALCNVESIQWRDIVSSDFLSNMSMDF
 QNHLGSCQKCDPSCPNGSCWGAGEENCQKLTKIICAQQCSGRCRGKSPSDCCHNQCAAGC
 TGPRES DCLVCRKFRDEATCKDTCPPMLYNPTTYQMDVNPEGKYSFGATCVKKCP RNYV
 VTDHGSCVRACGADSYEMEE DGVRKCKKCEGPCRKVCNGIGIGEFKDSLSINATNIKHFK
 30 NCTISISGDLHILPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAF
 ENLEIIRGR TKQH GQFSLAVVSLNITSLGLRSLKEISDGDV IISGNKNLCYANTINWKKL
 FGTSGQKTKIISNRGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRNVSRGRECVDKCN
 LLEGEPREFVENSECIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVM
 GENNTLVWKYADAGHVCHLCHPNCTYGTGPGLEGCP TNGPKIPSIATGMVGALLLLLVV

ALGIGLFMRRRHIVRKRTLRLRLQERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGS
 GAFGTVYKGLWIPEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLGI
 CLTSTVQLITQLMPFGCLLDYVREHKDNIGSQYLLNWCQIAKGMNYLEDRLVHRDLAA
 RNVLVKTPQHVKITDFGLAKLLGAEKEYHAEGGKVPKWMALLESILHRIYTHQSDVWSY
 5 GVTWELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRLK
 FRELIIEFSKMARDPQRYLVIQGDERMHLPSPDTSNFYRALMDEEDMDDVVDADAYLIPQ
 QGFFSSPSTSRTPLLSSLSATSNNSTVACIDRNLQSCPIKEDSFLQRYSSDPTGALTED
 SIDDFTFLPVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLN
 TVQPTCVNSTFDSPAHWAKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRV
 10 APQSSEFIGA

Non-limiting examples of dysregulation of a HER1 gene or a HER1 protein can be found
 in, for example, Zhang, et al., *Oncotarget* 7.48 (2016): 78985, Ellison, et al., *Journal of Clinical
 Pathology* 66.2 (2013): 79-89, Midha, et al., *American Journal of Cancer Research* 5.9 (2015):
 2892, and Yamamoto, et al., *Lung Cancer* 63.3 (2009): 315-321.

15 An exemplary sequence of human HER2 is shown below:
 SEQ ID NO: 4 (UniParc Accession No. UPI000003F55F)
 MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNL
 ELTYLPTNASLSFLQDIQEVQGYVLIHNAHQVRQVPLQRLRIVRGTLQFEDNYALAVLDNG
 DPLNNTTPVTGASPGGLRELQRLSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLA
 20 LTLIDTNRSRACHPCSPMCKGSRGWGESSEDCQSLTRTVCAAGGCARCKGPLPTDCCHEQC
 AAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRTYTFGASCVTACP
 YNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRVTSAN
 IQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSL
 DLSVFQNLQVIRGRILHNGAYSITLQGLGISWLGLRSLRELGSGLALIHNNHLCFVHTV
 25 PWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRGQEC
 VEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVCACAHYKDPPFCVARC
 PSGVKPDLSPYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVG
 ILLVVVLGVVFGILIKRRQQKIRKYTMRLLQETELVEPLTPSGAMPNQAQMRILKETEL
 RKVKVLGSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGS
 30 YVSRLLGICLTSTVQLVTQLMPYGCCLLDHVRENRRGLGSQDLLNWCQIAKGMSYLEDVR
 LVHRDLAARNVLKSPNHVKITDFGLARLLDIDETEHADGGKVPKWMALLESILRRRFT
 HQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWM
 IDSECRPRFRELVSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDA
 EEYLVPQQGFFCPDPAPGAGGMVHHRHRSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEG

AGSDVFDGDLGMGAAKGLQSLPTHDP SPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYV
 NQPDVRFQPPSPREGPLPAARFAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEYLTPQ
 GGAAPQPHPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV

Non-limiting examples of dysregulation of a HER2 gene or a HER2 protein can be found,
 5 for example, Petrelli, Fausto, et al., Breast Cancer Research and Treatment 166.2 (2017): 339-349,
 Yan, et al., Cancer and Metastasis Reviews 34.1 (2015): 157-164, Koshkin, et al., Bladder Cancer
 5.1 (2019): 1-12, and Connell, et al., ESMO Open 2.5 (2017).

The term “cancer associated with a signal transducer between a cell surface receptor and a
 CBM complex” as used herein refers to cancers associated with or having a dysregulation of a
 10 gene, a protein, or the expression or activity or level of any (e.g., one or more) of the same
 associated with a signal transducer between a cell surface receptor and a CBM complex. In some
 embodiments, a cancer associated with a signal transducer between a cell surface receptor and a
 CBM complex is selected from the group consisting of a PKC β -associated cancer, PKC θ -
 associated cancer, and a combination thereof. The cancers “associated” with a particular gene or
 15 protein described in this paragraph refer to cancers associated with or having a dysregulation of
 the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or
 more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular
 protein, or the expression or activity or level of any of the same described herein). Non-limiting
 examples of such cancers are described herein.

20 An exemplary sequence of human PKC β is shown below:

SEQ ID NO: 5 (UniParc Accession No. UPI000012DF67)

MADPAAGPPPSEGEESTVRFARKGALRQKNVHEVKNHKFTARFFKQPTFC SHCTDFIWGF
 GKQGFQCQVCCFVVHKRCHEFVTFSCPGADKGPASDDPRSKHKFKIHTYSSPTFCDHCGS
 LLYGLIHQGMKCDTCMMNVHKRCVMNVP SLCGTDHTERRGRIYIQAHIDRDVLIVLRDA
 25 KNLVPMDPNGLSDPYVKLKLIPDPKSESKQKTKTIKCSLNPEWNETFRFQLKESDKDRRL
 SVEIWDWDLTSRNDFMGSLSFGISSELQKASVDGWFKLLSQEEGEYFNVPVPPEGSEANEE
 LRQKFERAKISQGTKVPEEKTINTVSKFDNNGNRDRMKLTDFNFLMVLGKGSFGKVMLSE
 RKGTDELYAVKILKKDVVIQDDVECTMVEKRVLALPGKPPFLTQLHSCFQTMDRLYFVM
 EYVNGGDLMYHIQQVGRFKEPHAVFYAAEIAIGLFFLQSKGIIYRDLKLDNVMLDSEGHI
 30 KIADFGMCKENIWDGVTTKTFCTGTPDYIAPEIIAYQPYGKSVDWWAFGVLLYEMLAGQAP
 FEGEDEDELFSIMEHNVAYPKSMSKEAVAICKGLMTKHPGKRLGCGPEGERDIKEHAFF
 RYIDWEKLERKEIQPPYKPKARDKRDTSNFDKEFTRQPVELTPTDKLFINMLDQNEFAGF
 SYTNPEFVINV

An exemplary sequence of human PKC θ is shown below:

SEQ ID NO: 6 (UniParc Accession No. UPI000012DF74)

MSPFLRIGLSNFDGSCQSCQGEAVNPYCAVLVKEYVESENGQMYIQKKPTMYPPWDSTF
 DAHINKGRVMQIIIVKGKNVDLISETTVELYSLAERCCKNNNGKTEIWLELKPQGRMLMNAR
 5 YFLEMSDTKDMNEFETEGFFALHQRRGAIKQAKVHHVKCHEFTATFFPQPTFCVCHFEV
 WGLNKQGYQCRQCNAAIHKKCIDKVIKCTGSAINSRETMFHKERFKIDMPHRFKVYNYK
 SPTFCEHCGTLLWGLARQGLKCDACGMNVHRCQTKVANLCGINQKLMAEALAMIESTQQ
 ARCLRDTEQIFREGPVEIGLPCSIKNEARPPCLPTPGKREPQGISWESPLDEVDKMCHLP
 EPELNKERPSLQIKLKIEDFILHKMLGKGSFGKVFLAEFKKTNQFFAIKALKKDVVLMD
 10 DVECTMVEKRVLSLAWEHFPLTFMFCFQTKENLFFVMEYLNGGDLMYHIQSCHKFDLSR
 ATFYAAEIIILGLQFLHSGIVYRDLKLDNILLDKDGHKIADFGMCKENMLGDAKTNTFC
 GTPDYIAPEILLGQKYNHSVDWWSFGVLLYEMLIGQSPFHGQDEEELFHSIRMDNPFYPR
 WLEKEAKDLLVKLFVREPEKRLGVRGDIRQHPLFREINWHEELERKEIDPPFRPKVKSPFD
 CSNFDKEFLNEKPRLSFADRALINSMDQNMFRNFSFMNPGMERLIS

15 The term “component of a CBM complex-associated cancer” as used herein refers to
 cancers associated with or having a dysregulation of a gene, a protein, or the expression or activity
 or level of any (e.g., one or more) of the same associated with a component of a CBM complex.
 In some embodiments, a component of a CBM complex-associated cancer is selected from the
 group consisting of a MALT1-associated cancer, a CARD11-associated cancer, a CARD14-
 20 associated cancer, a CARD10-associated cancer, a CARD9-associated cancer, a BCL10-
 associated cancer, and combinations thereof. In some embodiments, a CBM complex-associated
 cancer is selected from the group consisting of a MALT1-associated cancer, a CARD11-associated
 cancer, a BCL10-associated cancer, and combinations thereof. The cancers “associated” with a
 particular gene or protein described in this paragraph refer to cancers associated with or having a
 25 dysregulation of the particular gene, the particular protein, or the expression or activity or level of
 any (e.g., one or more) of the same (e.g., any of the types of dysregulation of the particular gene,
 the particular protein, or the expression or activity or level of any of the same described herein).
 Non-limiting examples of such cancers are described herein.

30 The term “MALT1-associated autoimmune disorder” as used herein refers to autoimmune
 disorders associated with or having a dysregulation of a MALT1 gene, a MALT1 protein (also
 called herein MALT1 protease protein or MALT1 protease), or the expression or activity or level
 of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a MALT1 gene, a

MALT1 protease, a MALT1 protease domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a MALT1-associated autoimmune disorders are described herein.

5 The term “MALT1-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a MALT1 gene, a MALT1 protein (also called herein MALT1 protease protein or MALT1 protease), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a MALT1 gene, a MALT1 protease, a MALT1 protease domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a MALT1-associated
10 inflammatory disorders are described herein.

The term “MALT1-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a MALT1 gene, a MALT1 protein (also called herein MALT1 protease protein or MALT1 protease), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a MALT1 gene, a MALT1 protein, a MALT1
15 protease domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a MALT1-associated cancer are described herein.

The phrase “dysregulation of a MALT1 gene, a MALT1 protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a MALT1 protease domain and a fusion
20 partner, a mutation in a MALT1 gene that results in the expression of a MALT1 protein that includes a deletion of at least one amino acid as compared to a wild-type MALT1 protein, a mutation in a MALT1 gene that results in the expression of a MALT1 protein with one or more point mutations as compared to a wild-type MALT1 protein, a mutation in a MALT1 gene that results in the expression of a MALT1 protein with at least one inserted amino acid as compared to
25 a wild-type MALT1 protein, a gene duplication that results in an increased level of MALT1 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of MALT1 protein in a cell), an alternative spliced version of a MALT1 mRNA that results in a MALT1 protein having a deletion of at least one amino acid in the MALT1 protein as compared to the wild-type MALT1 protein, or increased expression (e.g., increased levels) of a
30 wild-type MALT1 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another

example, a dysregulation of a MALT1 gene, a MALT1 protein, or expression or activity, or level of any of the same, can be a mutation in a MALT1 gene that encodes a MALT1 protein that is constitutively active or has increased activity as compared to a protein encoded by a MALT1 gene that does not include the mutation. As a further example, an increased copy number of the MALT1 gene can result in overexpression of MALT1 protease. For example, a dysregulation of a MALT1 gene, a MALT1 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of MALT1 that includes a functional protease domain, and a second portion of a partner protein (i.e., that is not MALT1). In some examples, dysregulation of a MALT1 gene, a MALT1 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one MALT1 gene with another non-MALT1 gene.

An exemplary sequence of human MALT1 is shown below:

SEQ ID NO: 7 (UniParc Accession No. UPI000004D05E)

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MSLLGDPLQALPPSAAPTGPLLAPPAGATLNRLREPLLRRLSELLDQAPEGRGWRRRLAEL
AGSRGRLRLSCLDLEQCSLKVLEPEGSPSLCLLKLMEKGCTVTELSDFLQAMEHTEVLQ
LLSPPGIKITVNPESKAVLAGQFVKLCCRATGHPFVQYQWFKMNKEIPNGNTSELIFNAV
HVKDAGFYVCRVNNNFTFEFSQWSQLDVCDIPESFQRSVDGVSESKLQICVEPTSQKLMF
GSTLVLQCVAVGSPIPHYQWFKNELPLTHETKKLYMVPYVDLEHQGTYWCHVYNDRDSQD
SKKVEIIIGRTDEAVECTEDELNNLGHPDNKEQTTDQPLAKDKVALLIGNMNYREHPKIK
APLVDVYELTNLLRQLDFKVVSLLDLTEYEMRNAVDEFLLLLDKGVYGLLYYAGHGYENF
GNSFMVPVDAPNPYRSENCLCVQNILKLMQEKETGLNVFLDMCRKRNDYDDTIPILDAL
KVTANIVFGYATCQGAEAFEIQHSGLANGIFMKFLKDRILLEDKKITVLLDEVAEDMGKCH
LTKGKQALEIRSSLSEKRALTDPIQGTEYSAESLVRNLQWAKAHELPESMCLKFDCGVQI
QLGFAAEFSNVMIIYTSIVYKPPEIIMCDAYVTDPLDLIDPKDANKGTPEETGSYLVS
KDLPKHCLYTRLSSLQKLKEHLVFTVCLSYQYSGLEDTVEDKQEVNVGKPLIAKLDMHRG
LGRKTCFQTCLMSNGPYQSSAATSGGAGHYHSLQDPFHGVYHSHPGNPSNVTPADSCHCS
RTPDAFISSFAHHASCHFSRSNVFVETTDEIPFSFSDRLRISEK

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Non-limiting examples of dysregulation of a MALT1 gene or a MALT1 protein are shown in Table B1 below.

Table B1.

MALT1 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary MALT1-associated Cancers
717	M717I ⁴	
MALT Fusion Partners		
Fusion Partner	Non-limiting Exemplary MALT1-Associated Cancer(s)	
BIRC3 (Also called IAP2; CIAP2; and API2) ¹	Diffuse Large B-cell Lymphoma (DLBCL) ¹ ; Extra nodal low-grade MALT lymphoma ²	
IGH	ABC DLBCL ²	
SEC11C	Breast Cancer ³	

¹United States Patent US 10,711,036

²United States Patent Application Publication US20190160045A1

³United States Patent Application Publication US20130096021A1

⁴United States Patent Application Publication US20150320754A1

The term “CARD11-associated autoimmune disorder” as used herein refers to autoimmune disorders associated with or having a dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any of the same described herein).

The term “CARD11-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any of the same described herein).

The term “CARD11-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of a CARD11-associated cancer are described herein.

The phrase “dysregulation of a CARD11 gene, a CARD11 protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a CARD11 domain and a fusion partner,

a mutation in a CARD11 gene that results in the expression of a CARD11 protein that includes a deletion of at least one amino acid as compared to a wild-type CARD11 protein, a mutation in a CARD11 gene that results in the expression of a CARD11 protein with one or more point mutations as compared to a wild-type CARD11 protein, a mutation in a CARD11 gene that results in the expression of a CARD11 protein with at least one inserted amino acid as compared to a wild-type CARD11 protein, a gene duplication that results in an increased level of CARD11 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of CARD11 protein in a cell), an alternative spliced version of a CARD11 mRNA that results in a CARD11 protein having a deletion of at least one amino acid in the CARD11 protein as compared to the wild-type CARD11 protein, or increased expression (e.g., increased levels) of a wild-type CARD11 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a CARD11 gene, a CARD11 protein, or expression or activity, or level of any of the same, can be a mutation in a CARD11 gene that encodes a CARD11 protein that is constitutively active or has increased activity as compared to a protein encoded by a CARD11 gene that does not include the mutation. As a further example, an increased copy number of the CARD11 gene can result in overexpression of CARD11 protein. For example, a dysregulation of a CARD11 gene, a CARD11 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of CARD11, and a second portion of a partner protein (i.e., that is not CARD11). In some examples, dysregulation of a CARD11 gene, a CARD11 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one CARD11 gene with another non-CARD11 gene.

An exemplary sequence of human CARD11 is shown below:

SEQ ID NO: 8 (UniParc Accession No. UPI00003FED38)

MPGGGPEMDDYMETLKDEEDALWENVECNRHMLSRYPINPAKLTPYLRQCKVIDEQDEDEV
 LNAPMLPSKINRAGRLDILHTKGQRGYVVFLESLEFYYPELYKLVTGKEPTRRFSTIVV
 EEGHEGLTHFLMNEVIKLQQQMKAKDLQRCCELLARLRQLEDEKKQMTLTRVELLTFQERY
 YKMKEERDSYNDELVKVKDDNYNLAMRYAQLSEEKNMAVMRSRDLQLEIDQLKHRLNKME
 EECKLERNQSLKLNNDIENRPKKEQVLELERENEMLKTKNQELQSIIQAGKRSPLPDSKA
 ILDILEHDRKEALEDRLQELVNRIYNLQEEARQAEELRDKYLEEKEDLELKCSTLGKDCEM
 YKHRMNTVMLQLEEVERERDQAFHSRDEAQTQYSQCLIEKDKYRKQIRELEEKNDEMRIE

MVRREACIVNLESKLRRLSKDSNNLDQSLPRNLPVTIISQDFGDASPRNGQEADDSSTS
EESPEDSKYFLPYHPPQRRMNLKGIQLQRAKSPISLKRTSDFQAKGHEEEGTDASPSSCG
SLPITNSFTKMQPPRSRSSIMSITAEPFGNDSIVRRYKEDAPHRSTVEEDNDSGGFDALD
LDDDSHERYSFGPSSIHSSSSSHQSEGLDAYDLEQVNL MFRKFSLERPFRPSVTSVGHVR
5 GPGPSVQHTTLNGDSLTSQLTLLGGNARGSFVHSV KPGSLAEKAGLREGHQLLLLEGCIR
GERQSVPLDTCTKEEAHWTIQRCSGPVTLHYKVNHEGYRKLVKDMEDGLITSGDSFYIRL
NLNISSQLDACTMSLKCD DVVHVRDTMYQDRHEWLCARVDPFTDHDLDMG TIPSYSRAQQ
LLLVLQRLMHRGSREEVDGTHHTLRALRNTLQPEEALSTSDPRVSPRLSRASFLFGQLL
QFVSRSENKYKRMNSNERVRIISGSP LGSLARSSLDATKLLTEKQEELDPESELGKNLSL
10 IPYSLVRAFYCERRRPVLF TPTVLAKTLVQRL LNSSGGAMEFTICKSDIVTRDEF LRRQKT
ETIYSREKNPNAFECIAPANIEAVAANKHCLLEAGIGCTRD LIKSNIYPIVLFIRVCE
KNIKRFRKLLRPETEEEF LRVCLKEKELEALPCLYATVEPDMWGSVEELLRVVKDKIG
EEQRKTIWVDEDQL

Non-limiting examples of dysregulation of a CARD11 gene or a CARD11 protein are
15 shown in Table B2 below.

Table B2.

CARD11 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary CARD11-associated Cancers
47	R47C ²	Cutaneous squamous cell carcinoma ²
123	G123S ¹	Lymphoma ¹
126	G126D ¹	Lymphoma ¹
130	F130V ²	Cutaneous squamous cell carcinoma ²
167	T167M ²	Cutaneous squamous cell carcinoma ²
215	K215M, K215N ¹	Lymphoma ¹
230	D230N ¹	Lymphoma ¹
357	D357E ¹	Lymphoma ¹
360	M360V ¹	Lymphoma ¹
361	Y361C ¹	Lymphoma ¹
368	V368I ²	Cutaneous squamous cell carcinoma ²
737	H737L ²	Cutaneous squamous cell carcinoma ²
750	H750R ²	Cutaneous squamous cell carcinoma ²
833	P833L ²	Cutaneous squamous cell carcinoma ²

CARD11 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary CARD11-associated Cancers
900	L900I ²	Cutaneous squamous cell carcinoma ²
1015	L1015F ²	Cutaneous squamous cell carcinoma ²
1016	R1016L ²	Cutaneous squamous cell carcinoma ²
1085	R1085S ²	Cutaneous squamous cell carcinoma ²
1086	F1086S ²	Cutaneous squamous cell carcinoma ²

¹ Wu, et al., Oncotarget 7.25 (2016): 38180.

² Watt, et al. The American Journal of Pathology 185.9 (2015): 2354-2363.

The term “CARD14-associated autoimmune disorder” as used herein refers to autoimmune disorders associated with or having a dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any of the same described herein).

The term “CARD14-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any of the same described herein).

The term “CARD14-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD14 gene, a CARD14 protein, or the expression or activity or level of any of the same described herein).

An exemplary sequence of human CARD14 is shown below:

SEQ ID NO: 9 (UniParc Accession No. UPI000013D81B)

MGELCRRDSALTALDEETLWEMMESHRHRIVRCICPSRLTPYLRQAKVLCQLDEEEVLHS
PRLTNSAMRAGHLLDLLKTRGKNGAIAFLESCLKFHNPVYTLVTGLQPDVDFSNFSGLME
TSKLTECLAGAIGSLQEELNQEKQKEVLLRRCQQLQEHLGLAETRAEGLHQLEADHSRM
KREVSAAHFHEVLRRLKDEMLSLSLHYSNALQEKELAASRCRSLQEELYLLKQELQRANMVS
SCELELQEQSLRTASDQESGDEELNRLKEENEKLSLTFSLAEKDILEQSLDEARGSRQE

LVERIHSLRERAVAAERQREQYWEEKEQTLQFQKSKMACQLYREKVNALQAQVCELQKE
 RDQAYSARDSAQREISQSLVEKDSLRRQVFELTDQVCELRTQLRQLQAEPPGVLKQEART
 REPCPREKQRLVRMHAICPRDDSDCSLVSTESQLLSDLSATSSRELVDSEFRSSSPAPPS
 QQSLYKRVAEDFGEEPWSFSSCLEIPEGDPGALPGAKAGDPHLDYELLDLTADLPQLESSL
 5 QPVSPGRLDVSESGVLMRRRPARRILSQVTMLAFQGDALLEQISVIGGNLTGIFIHRVTP
 GSAADQMALRPGTQIVMVDYEASEPLFKAVLEDTTLEEAVGLLRRVDGFCCLSVKVNTDG
 YKRLQLDLEAKVATSGDSFYIRVNLAMEGRAKELQVHCNEVLHVTDTMFQGCWCWHAHR
 VNSYTMKDTAAHGTIPNYSRAQQQLIALIQDMTQQCTVTRKPSSGGFPQKLVRIVSMDKAK
 ASPLRLSFDRGQLDPSRMEGSSTCFWAESCLTLVPYTLVRPHRPARPRPVLLVPRAVGKI
 10 LSEKLCLLQGFKKCLAEYLSQEEYEAWSQRGDIIQEGEVSGGRCWVTRHAVESLMEKNTH
 ALLDVQLDSVCTLHRMDIFPIVIVHSVNEKMAKKLKKGLQRLGTSEEQLLEAARQEEGDL
 DRAPCLYSSLAPDGWSDLDGLLSCVRQAIADQKKVWTEQSPR

The term “CARD10-associated autoimmune disorder” as used herein refers to autoimmune disorders associated with or having a dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any of the same described herein).

The term “CARD10-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any of the same described herein).

The term “CARD10-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any of the same described herein).

The phrase “dysregulation of a CARD10 gene, a CARD10 protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a CARD10 domain and a fusion partner, a mutation in a CARD10 gene that results in the expression of a CARD10 protein that includes a deletion of at least one amino acid as compared to a wild-type CARD10 protein, a mutation in a CARD10 gene that results in the expression of a CARD10 protein with one or more point

mutations as compared to a wild-type CARD10 protein, a mutation in a CARD10 gene that results in the expression of a CARD10 protein with at least one inserted amino acid as compared to a wild-type CARD10 protein, a gene duplication that results in an increased level of CARD10 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of CARD10 protein in a cell), an alternative spliced version of a CARD10 mRNA that results in a CARD10 protein having a deletion of at least one amino acid in the CARD10 protein as compared to the wild-type CARD10 protein, or increased expression (e.g., increased levels) of a wild-type CARD10 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a CARD10 gene, a CARD10 protein, or expression or activity, or level of any of the same, can be a mutation in a CARD10 gene that encodes a CARD10 protein that is constitutively active or has increased activity as compared to a protein encoded by a CARD10 gene that does not include the mutation. As a further example, an increased copy number of the CARD10 gene can result in overexpression of CARD10 protein. For example, a dysregulation of a CARD10 gene, a CARD10 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of CARD10, and a second portion of a partner protein (i.e., that is not CARD10). In some examples, dysregulation of a CARD10 gene, a CARD10 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one CARD10 gene with another non-CARD10 gene.

An exemplary sequence of human CARD10 is shown below:

SEQ ID NO: 10 (UniParc Accession No. UPI0000044645)

MPGRAEAGEAEEEEAGAGSGSEAEEDALWERIEGVRHRLARALNPAKLTPYLRCRVIDEQ
 DEEEVLSTYRFPCRNVNRTGRIMDILRCRGKRGYEAFLAELFYYPEHFTLLTGQEPAQRC
 25 SMILDEEGPEGLTQFLMTEVRRRLREARKSQLQREQQQLQARGRVLEERAGLEQRLRDQQQ
 AQERCQRLREDWEAGSLELLRLKDENYMIAMRLAQLSEEKNSAVLRSRDLQLAVDQLKLG
 VSRLEEECALLRRARGPPPGAEKEKEKEKEKEPDNVDIVSELRAENQRLTASLRELQEG
 LQQEASRPGAPGSERILLDILEHDWREAQDSRQELCQKLHAVQGELQWAEELRDQYLQEM
 EDLRLKHRTLQKDCDLYKHRMATVLAQLEEIEKERDQAIQSRDRIQLQYSQSLIEKDQYR
 30 KQVRGLEAERDELLTTLSLEGTKALLEVQLQRAQGGTCLKACASSHSLCSNLSSTWSLS
 EFPSP LGGPEATGEAAVMGGPEPHNSEATDSEKEINRLSILPFPPSAGSILRRQREEDP
 APPKRSFSSMSDITGSVTLKPWSPGLSSSSSSSDSVWPLGKPEGLLARGCGLDFLNRSLAI

RVSGRSPPGGPEPQDKGPDGLSFYGDWVGAVVRRVLSGPGSARMEPREQRVEAAGLEGA
 CLEAEAQQRTLLWNQGSTLPSLMDSKACQSFHEALEAWAKGPGAEPFYIRANLTLPERAD
 PHALCVKAQEILRLVDSAYKRRQEWFCRVDPLTLRDLDRTVPNYQRAQQLLLEVQEKCL
 PSSRHRGPRSNLKKRALDQLRLVRPKPVGAPAGDSPDQLLEPCAEPEPSLRPYSLVRPL
 5 LVSAIRFPVLLPECLAPRLIRNLLDLFSSRLDFQVCPAESLSGEELCPSSAPGAPKAQPA
 TPGLGSRIRAIQESVGKKHCLELGARGVRELQNEIYPIVIHVEVTEKNVREVRGLLGR
 PGWRDSELLRQCRGSEQVLWGLPCSWSVQVPAHEWGHAEELAKVVRGRILQEQRARLVWVEC
 GSSRGCPSSSEA

The term “CARD9-associated autoimmune disorder” as used herein refers to autoimmune
 10 disorders associated with or having a dysregulation of a CARD9 gene, a CARD9 protein, or the
 expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of
 dysregulation of a CARD9 gene, a CARD9 protein, or the expression or activity or level of any of
 the same described herein).

The term “CARD9-associated inflammatory disorder” as used herein refers to
 15 inflammatory disorders associated with or having a dysregulation of a CARD9 gene, a CARD9
 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of
 the types of dysregulation of a CARD9 gene, a CARD9 protein, or the expression or activity or
 level of any of the same described herein).

The term “CARD9-associated cancer” as used herein refers to cancers associated with or
 20 having a dysregulation of a CARD9 gene, a CARD9 protein, or the expression or activity or level
 of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a CARD9 gene, a
 CARD9 protein, or the expression or activity or level of any of the same described herein).

The phrase “dysregulation of a CARD9 gene, a CARD9 protein, or the expression or
 activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation
 25 that results in the expression of a fusion protein including a CARD9 domain and a fusion partner,
 a mutation in a CARD9 gene that results in the expression of a CARD9 protein that includes a
 deletion of at least one amino acid as compared to a wild-type CARD9 protein, a mutation in a
 CARD9 gene that results in the expression of a CARD9 protein with one or more point mutations
 as compared to a wild-type CARD9 protein, a mutation in a CARD9 gene that results in the
 30 expression of a CARD9 protein with at least one inserted amino acid as compared to a wild-type
 CARD9 protein, a gene duplication that results in an increased level of CARD9 protein in a cell,
 or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an

increased level of CARD9 protein in a cell), an alternative spliced version of a CARD9 mRNA that results in a CARD9 protein having a deletion of at least one amino acid in the CARD9 protein as compared to the wild-type CARD9 protein, or increased expression (e.g., increased levels) of a wild-type CARD9 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a CARD9 gene, a CARD9 protein, or expression or activity, or level of any of the same, can be a mutation in a CARD9 gene that encodes a CARD9 protein that is constitutively active or has increased activity as compared to a protein encoded by a CARD9 gene that does not include the mutation. As a further example, an increased copy number of the CARD9 gene can result in overexpression of CARD9 protein. For example, a dysregulation of a CARD9 gene, a CARD9 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of CARD9, and a second portion of a partner protein (i.e., that is not CARD9). In some examples, dysregulation of a CARD9 gene, a CARD9 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one CARD9 gene with another non-CARD9 gene.

An exemplary sequence of human CARD9 is shown below:

SEQ ID NO: 11 (UniParc Accession No. UPI000013E4EB)

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MSDYENDDECWSVLEGFRVTLTSVIDPSRITPYLRQCKVLNPDDEEQVLSDPNLVIRKRRK
20 VGVLLDILQRTGHKGYVAFLESLELYYPQLYKKVTGKEPARVFSMIIDASGESGLTQLLM
TEVMKLQKKVQDLTALLSSKDDFIKELRVKDSLLRKHQERVQRLKEECEAGSRELKRCKE
ENYDLAMRLAHQSEEKGAALMRNLDLQLEIDQLKHSMLKAEDDCKVERKHTLKL RHAMEQ
RPSQELLWELQQEKALLQARVQELEASVQEGKLD RSSPYIQVLEEDWRQALRDHQEQANT
IFSLRKDLRQGEARRLRCEEMEFELQCLALRKDSKMYKDRIEAILLQMEEVAIERDQA
25 IATREELHAQHARGLQEKDALRKQVRELGEKADELQLQVFQCEAQLLAVEGRLRRQQLT
LVLSSDLEDGSPRRSQELSLPQDLEDQLSDKGCLAGGGSPKQPF AALHQEQVLRNPHDA
GLSSGEPPEKERRRLKESFENYRRKRALRKMQKGWRQGEEDRENTTGSDNTDTEGS

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The term “BCL10-associated autoimmune disorder” as used herein refers to autoimmune disorders associated with or having a dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any of the same described herein).

The term “BCL10-associated inflammatory disorder” as used herein refers to inflammatory disorders associated with or having a dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any of the same described herein).

The term “BCL10-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any of the same described herein).

The phrase “dysregulation of a BCL10 gene, a BCL10 protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a BCL10 domain and a fusion partner, a mutation in a BCL10 gene that results in the expression of a BCL10 protein that includes a deletion of at least one amino acid as compared to a wild-type BCL10 protein, a mutation in a BCL10 gene that results in the expression of a BCL10 protein with one or more point mutations as compared to a wild-type BCL10 protein, a mutation in a BCL10 gene that results in the expression of a BCL10 protein with at least one inserted amino acid as compared to a wild-type BCL10 protein, a gene duplication that results in an increased level of BCL10 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of BCL10 protein in a cell), an alternative spliced version of a BCL10 mRNA that results in a BCL10 protein having a deletion of at least one amino acid in the BCL10 protein as compared to the wild-type BCL10 protein, or increased expression (e.g., increased levels) of a wild-type BCL10 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). For example, a dysregulation of a BCL10 gene, a BCL10 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of BCL10, and a second portion of a partner protein (i.e., that is not BCL10). In some examples, dysregulation of a BCL10 gene, a BCL10 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one BCL10 gene with another non-BCL10 gene.

An exemplary sequence of human BCL10 is shown below:

SEQ ID NO: 12 (UniParc Accession No. UPI000012682F)

MEPTAPSLTEEDLTEVKKDALENLRVYLCEKIIAERHFDHLRAKKILSREDTEEISCRTS
SRKRAGKLLDYLQENPKGLDTLVESIRREKTQNFLIQKITDEVKLKRNKLEHLKGLKCS
SCEFFPDGATNNLSRSNSDESINFSEKLRASVTMYHPEGESSTTPFFSTNSSLNLPVLEVG
RTENTIFSSTTLPRPGDPGAPPLPPDLQLEEEGTCANSSEMFLPLRSRTVSRQ

Non-limiting examples of dysregulation of a BCL10 gene or a BCL10 protein are shown in Table B3 below.

Table B3.

BCL10 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary BCL10-associated Cancers
5	A5S ²	Lymphoma ²
16	V16E ²	Lymphoma ²
20	A20T ¹	Germ cell tumor ¹
31	K31E	Lymphoma ²
32	I32V ¹	Lymphoma ¹
43	A43* ²	Lymphoma ²
46	I46* ¹	T-ALL ¹ , colonic carcinoma ¹
49	R49G ¹	Lymphoma ¹
52	T52I ¹	Mesothelioma ¹
55	I55* ¹	Lymphoma ¹
57	C57R ²	Lymphoma ²
58	R58G ¹ , R58* ¹	Germ cell tumor ¹
64	R64K ²	Lymphoma ²
77	K77* ¹	Lymphoma ¹
80	D80N	Lymphoma ¹
91	T91* ¹	Germ cell tumor ¹
100	T100S ¹	Lymphoma ¹
101	D101E ²	Lymphoma ²
115	K115* ¹	Lymphoma ¹
116-126	Splice mutation ¹	Lymphoma ¹
116-121	Splice mutation ²	Lymphoma ²
116-120	Splice mutation ¹	Mesothelioma ¹
133	L133* ¹	Lymphoma ¹
134	S134P ²	Lymphoma ²
137	N137* ¹	Lymphoma ¹
143	F143* ¹	Lymphoma ¹
152	V152* ²	Lymphoma ²
165	F165* ²	Lymphoma ²
167	S167* ¹	Lymphoma ¹
168	T168A ²	Lymphoma ²

BCL10 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary BCL10-associated Cancers
170-180	del S170-G180 ¹	Lymphoma ¹
175-181	del P175-G180 ¹	Lymphoma ¹
210	del 210 ¹	Lymphoma ¹
213	G213E	Lymphoma ²
218	S218F ¹	Germ cell tumor ¹
230	V230I ²	Lymphoma ²
Stop	Stop->R	Lymphoma ²

¹ Willis, et al. Cell 96.1 (1999): 35-45.

² Zhang, et al. Nature Genetics 22.1 (1999): 63-68.

The term “MALT1 protease substrate-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a gene, a protein, or the expression or activity or level of any (e.g., one or more) of the same associated with a MALT1 protease substrate. In some embodiments, a MALT1 protease substrate-associated cancer is selected from the group consisting of a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, a RelB-associated cancer, a Regnase 1-associated cancer, a roquin-1-associated cancer, a HOIL1-associated cancer, a NIK associated cancer, a LIMA1 α -associated cancer, and combinations thereof. In some embodiments, a MALT1 protease substrate-associated cancer is selected from the group consisting of a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, and combinations thereof. The cancers “associated” with a particular gene or protein described in this paragraph refer to cancers associated with or having a dysregulation of the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of such cancers are described herein.

An exemplary sequence of human A20 is shown below:

SEQ ID NO: 13 (UniParc Accession No. UPI000000D92D)

MAEQVLPQALYLSNMRKAVKIRERTPEDIFKPTNGIIHHFKTMHRYTLEMFRTCQFCPQF
REIIHKALIDRNIQATLESQKKLNWCREVRLVAKTNGDGNCLMHATSQYMWGVQDIDL
VLRKALFSTLKETDTRNFKFRWQLESLSQEFVETGLCYDTRNWNDEWDNLIKMASTDTP
MARSGLQYNSLEEIHIFVLCNIIIRRP IIVISDKMLRSLESQSNFAPLKVGGIYLP LHWPA
QECYRYP IVLGYDSHHFVPLVTLKDSGPEIRAVPLVNRDRGRFEDLKVHFLTDPENEMKE
KLLKEYLMVIEIPVQGWHDGTHLINA AKLDEANLPKEINLVDDYFELVQHEYKKWQENS

5 EQQRREGHAQNPMEPSVPQLSLMDVKCETPNCPFFMSVNTQPLCHECSERRQKNQNKLPK
LNSKPGPEGLPGMALGASRGEAYEPLAWNPEESTGGPHSAPPTAPSPFLFSETTAMKCRS
PGCPFTLNVQHNGFCERCHNARQLHASHAPDHRHLDPGKCQACLQDVTRTFNGICSTCF
KRTTAEASSSLSTSLPPSCHQRSKSDPSRLVRSPSPHSCHRAGNDAPAGCLSQAARTPGD
RTGTSKCRKAGCVYFGTPENKGFCTLCFIEYRENKHFAAASGKVSP TASRFQNTIPCLGR
ECGTLGSTMFEGYCQKCFIEAQNRQFHEAKRTEEQLRSSQRRDVPRTTQSTSRPKCARAS
CKNILACRSEELCMECQHPNQRMGPGAHRGEPAPEDPPKQRCRAPACDHF GNAKCNNGYCN
ECFQFKQMYG

10 Non-limiting examples of dysregulation of an A20 gene or an A20 protein are shown in Table B4 below.

Table B4.

A20 Protein Amino Acid Substitutions/Insertions/Deletions		
Amino Acid Position(s)	Non-limiting Exemplary Mutations	Non-Limiting Exemplary A20-associated Cancers
100	D100* ²	Extranodal marginal zone lymphoma ²
162	R162* ²	Nodal marginal zone lymphoma ²
183	R183X ¹	Lymphoma ¹
271	R271X ¹	Lymphoma ¹
278	R278* ²	Nodal marginal zone lymphoma ²
288	V288* ²	Splenic marginal zone lymphoma ²
491	H491* ²	Nodal marginal zone lymphoma ²
633	E633* ²	Extranodal marginal zone lymphoma ²

¹ Johansson et al. Oncotarget 7.38 (2016): 62627.

² Novak, et al. Blood 113.20 (2009): 4918-4921.

15 An exemplary sequence of human CYLD is shown below:

SEQ ID NO: 14 (UniParc Accession No. UPI0000073A15)

20 MSSGLWSQEKVTSPLYWEERIFYLLLQECSVTDKQTQKLLKVPKGSIGQYIQDRSVGHSRI
PSAKGKKNQIGLKILEQPHAVLFVDEKDVVEINEKFTELLLAITNCEERFSLFKNRNRLS
KGLQIDVGCPVKVQLRSGEKFFPGVVRFRGPLLAERTVSGIFFGVELLEGRGQGF TDGV
YQKGQLFQCDEDCGVFVALDKLELIEDDDTALES DYAGPGDTMQVELPPLEINSRVSLKV
GETTIESGTVIFCDVLPKGESLG YFVGVDMDNPIGNWDGRFDGVQLCSFACVESTILLHIN
DIIPALSESVTQERRPPKLA FMSRGVGDKGSSSHNKP KATGSTSDPGNRNRSELFYT LING

SSVDSQPQSKSKNTWYIDEVAEDPAKSLTEISTDFDRSSPPLQPPPVNSLT TENRFHSLP
 FSLTKMPNTNGSIGHSPLSLSAQSVMEELNTAPVQESPPPLAMPPGNSHGLEVGSLAEVKE
 NPPFYGVIRWIGQPPGLNEVLAGLELEDECAGCTDGTFRGTRYFTCALKKALFVKLKSCR
 PDSRFASLQPVSNQIERCNSLAFGGYLSEVVEENTPPKMEKEGLEIMIGKKKGIQGHYNS
 5 CYLDSTLFLCLFAFSSVLDTVLLRPKEKNDVEYYSETQELLRTEIVNPLRIYGYVCATKIM
 KLRKILEKVEAASGFTSEEKDP EEFLNLFHHILRVEPLLKIRSAGQKVQDCYFYQIFME
 KNEKVGVP TIQQ LLEWSFINSNLKFAEAPSCLIIQMPRFGKDFKLFKKIFPSLELNITDL
 LEDTPRQCRICGGLAMYECRECYDDPDISAGKIKQFCKTCNTQVHLHPKRLNHKYNPVS
 PKDLDPDWDWRHGCIPCQNMELFAVLCIETSHYVAFVKY GKDDSAWLFFDSMADRDRGGQNG
 10 FNIPQVTPCPEVGEY LKMSLEDLHSLDSRRIQGCARRLLCDAYMCMYQSPTMSLYK

Non-limiting examples of dysregulation of a CYLD gene or a CYLD protein can be found, for example, in Massoumi, *Future Oncology* 7.2 (2011): 285-297, Alameda, J. P., et al., *Oncogene* 29.50 (2010): 6522-6532, Williams, et al., *Modern Pathology* (2020): 1-13, and Courtois and Gilmore. *Oncogene* 25.51 (2006): 6831-6843.

15 An exemplary sequence of human RelB is shown below:

SEQ ID NO: 15 (UniParc Accession No. UPI00000012B7)

MLRSGPASGPSVPTGRAMPSRRVARPPAAPEL GALGSPDLSSLSLAVSRSTDELEI IDEY
 IKENGFGLDGGQPGPGEGLPRLVSRGAASLSTVT LGPVAPPATPPPWGCPLGRLVSPAPG
 PGPQPHLVITEQPKQRMRFYECGRSAGSILGESSTEASKTLPAIELRDCGGLREVEV
 20 TACL VWKDWPHRVHPHSLVGKDCTD GICRVRLRPHVSPRHSFNNLGIQCVRKKEIEAAIE
 RKIQLGIDPYNAGSLKNHQEVD MNVVRICFQASYRDQQGQMRMDPVLSEPVYDKKSTNT
 SELRICRINKESGPCTGGEELYLLCDKVQKEDISVVF SRASWEGRADFSQADVHRQIAIV
 FKTPPYEDLEIVEPVTVNVFLQRLTDGVCSEPLPFTYLP RDHDSYGVDKRRKRGMPDVLG
 ELNSSDPHGIESKRRKKKPAILDHFLPNHSGSPFLPPSALLPD PDDFFSGTVSLPGLEPPG
 25 GPDLLDDGFAYDPTAPT LFTMLDLLPPAPPHASAVVCSGGAGAVVGETPGPEPLTLD SYQ
 APGPGDGGTASLVGSNMFPNHYREAAFGGGLLSPGPEAT

An exemplary sequence of human Regnase 1 is shown below:

SEQ ID NO: 16 (UniParc Accession No. UPI000004D30E)

MSGPCGEKPVLEASPTMSLWFEFEDSHSRQGT PRPGQELAAEEASALELQMKVDFFRKLGY
 30 SSTEIHSV LQKLGVQADTNTVLGELVKHGTATERERQTS PDPCPQLPLVPRGGGTPKAPN
 LEPLPEEEKEGSDLRPVVIDGSNVAMSHGNKEVF SCRGILLAVNWFLERGHTDITVFVP
 SWRKEQRPDPVITDQHILRELEKKKILVFTPSRRVGGKRVVCYDDR FIVKLAYESDGIV
 VSDNTYRDLQGERQEWKRFIEERLLMYSFVNDKFMPPDDPLGRHGPSLDNFLRKKPLTLE
 HRKQPCPYGRKCTYGIKCRFFHPERPSCPQRSVADEL RANALLSPPRAPSKDKNGRRPSP

SSQSSSLLTESEQCSLDGKKLGAQASPGSRQEGLTQTYAPSGRSLAPSGGSGSSFGPTDW
 LPQTLDSLPIVVSQDCLDSGIGSLESQMSSELWGVRGGGPGEPPPRAPYTGYSYGSELPA
 TAAFSAFGRAMGAGHFSVPADYPPAPPAPPPREYWSEPYPLPPPTSVLQEPPVQSPGAGR
 SPWGRAGSLAKEQASVYTKLCGVFPPHLVEAVMGRFPQLLDPQQLAAEILSYKSQHPSE

5 An exemplary sequence of human roquin-1 is shown below:

SEQ ID NO: 17 (UniParc Accession No. UPI00001D7DA8)

MPVQAPQWTDFLSCPICTQTFDETIRKPIISLGC GHTVCKMCLNKLHRKACPFDTTINTD
 IELLPVNSALLQLVGAQVPEQQPITLCSGVEDTKHYEEAKKCEELALYLKPLSSARGVG
 LNSTTQSVLSRPMQRKLVTLVHCQLVEEEGRIRAMRAARSLGERTVTELILQHQNPPQQLS
 10 SNLWAAVRARGCQFLGPAMQEEALKLVLLALEDGSSALSRKVLVLFVVQRLEPRFPQASKT
 SIGHVVQLLYRASC FKVTKRDEDSSLMQLKEEFRTYEALRREHDSQIVQIAMEAGLRIAP
 DQWSSLLYGDSHKSHMQSIIDKLQTPASFAQSVQELTIALQRTGDPANLNRLRPHLELL
 ANIDFSPDAPPPTWEQLENGLVAVRTVVHGLVDYIQNHSSKKGADQQPPQHSKYKTYMCR
 DMKQRGGCPRGASCTFAHSQEELEKFRKMKNRVLVPRRPLSASLGQLNEVGLPSAAILPDE
 15 GAVDLPSRKPPALPNGIVSTGNTVTQLIPRGTDPSYDSSLKPGKIDHLSSSAPGSPDDL
 ESVPKSIISALPVNPHSIPPRGPADLPMPVTKPLQMVPGRGSLYPAQQTDVYYQDPRGAA
 PPFEPAPYQQGMYTTPPPQCVSRFVRPPPSAPEPAPPYLDHYPPYLQERVVNSQYGTQPQ
 QYPPFIYPSHYDGRRVYPAPSYTREEIFRESPIPIEIPPAAVPSYVPESRERYQQIESYYP
 VAPHPTQIRPSYLRPEPPYSRLPPPPQPHPSLDELHRRRKEIMAQLEERKVISPPPFAPSP
 20 TLPPTFHPEEFLDEDLVAGKYKGNDYSQYSPWSCDTIGSYIGTKDAKPKDVVAAGSVEM
 MNVESKGMRDQRLDLQRRAAETSDDDLIPFGDRPTVSRFGAISRTSKTIYQGAGPMQAMA
 PQGAPTKSINISDYSPIYTHGGWGASPYSPHQNIPSQGHFSEERERISMSEVASHGKPLPS
 AEREQLRLELQQLNHQISQQTQLRGLEAVSNRVLVQREANTLAGQSQPPPPPPKWP GMI
 SSEQLSLELHQVEREIGKRTRELSMENQCSLDMKSKLNTSKQAENGQPEPQNKVPAEDLT
 25 LTFSDVPNGSALTQENISLLSNKTSSNLSEDPEGGDNDNSQSRSGVTPSSAP

An exemplary sequence of human HOIL1 is shown below:

SEQ ID NO: 18 (UniParc Accession No. UPI000006F045)

MDEKTKKAEEMALSLTRAVAGGDEQVAMKCAIWLAEQRVPLSVQLKPEVSPTQDIRLWVS
 VEDAQMHTVTIWLTVRPDMTVASLKDMVFLDYGFPPVLQQWVIGQRLARDQETLHSHGVR
 30 QNGDSAYLYLLSARNTSLNPQELQRERQLRMLEDLGFKDLTLQPRGPLEPGPPKPGVPQE
 PGRGQPDVPEPPPVGWQCPGCTFINKPTRPGCEMCCRARPEAYQVPASYQPDEEERARL
 AGEFEEALRQYQQRKQQQEGNYLQHVQLDQRSVLNTEPAECPVCYSVLAPGEAVVLR
 LHTFCRECLQGTIRNSQEAEVSCPFIDNTYSCSGKLLEREIKALLTPEDYQRFDLGISI
 AENRFAFSYHCKTPDCKGWCFEDDVNEFTCPVCFHVNCLLCKAIEQMNCKEYQEDLAL

RAQNDVAARQTTEMLKVMLQQGEAMRCPQCQIVVQKKDGCWIRCTVCHTEICWVTKGPR
WGPGGPGDTSGGCRCRVNGIPCHPSCQNCN

An exemplary sequence of human NIK is shown below:

SEQ ID NO: 19 (UniParc Accession No. UPI0000074220)

5 MAVMEMACPGAPGSAVGQQKELPKAKEKTPPLGKKQSSVYKLEAVEKSPVFCGKWEILND
VITKGTAKGSEAGPAAISIIAQAECEMSQEFSPTFSERIFIAGSKQYSQSESLDQIPNN
VAHATEGKMARVCWKGKRRSKARKKRRKKSSKSLAHAGVALAKPLPRTPEQESCTIPVQE
DESPLGAPYVRNTPQFTKPLKEFGLGQLCFKQLGEGLRPALPRSELHKLISPLQCLNHVW
KLHHPQDGGPLPLPTHFPYSRLPHFPFPHPLQPWKHPHPLESFLGKLACVDSQKPLDPH
10 LSKLACVDSPKPLPGPHLEPSCLSRGAHEKFSVEEYLVHALQGSVSSGQAHSLTSLAKTW
AARGSRSPKTEDNEGVLLTEKLKPVDEYREEVHWATHQLRLGRGSFGEVHRMEDK
QTGFQCAVKKVRLEVFRAEELMACAGLTSPRIVPLYGAVREGPWVNIFMELLEGGSLGQL
VKEQGCLPEDRALYYLGQALEGLEYLHSRRILHGDVKADNVLLSSDGSAAALCDFGHAVC
LQPDGLGKSLTGDYIPGTETHMAPEVVLGRSCDAKVDVWSSCCMMLHMLNGCHPWTQFF
15 RGPLCLKIASEPPPVREIPPSCAPLTAQAIQEGLRKEPIHRVSAAELGGKVNRAQQVGG
LKSPWRGEYKEPRHPPNQANYHQTLHAQPRELSPRAPGPRPAEETTGRAPKLQPPLPPE
PPEPNKSPPLTSLKEESGMWEPLPLSSLEPAPARNPSSPERKATVPEQELQQLEIELFLN
SLSQFFSLEEQQILSCLSIDSLSLSDDEKKNPSKASQSSRDTLSSGVHSSWSSQAEARSS
SWNMVLARGRPDTPTSYFNGVKVQIQSLNGEHLHIREFHRVKVGDIAITGISSQIPAAAFS
20 LVTKDGPVRYDMEVPDSDGIDLQCTLAPDGSFAWSWRVKGHGLENR

An exemplary sequence of human LIMA1 α is shown below:

SEQ ID NO: 20 (UniParc Accession No. UPI000002A906)

MENCLGESRHEVEKSEISENTDASGKIEKYNVPLNRLKMMFEKGEPQTQKILRAQSRAS
GRKISENSYSLLDLEIGPGQLSSSTFDSEKNESRRNLELPRLSETSIKDRMAKYQAAVSK
25 QSSSTNYTNELKASGGEIKIHKMEQKENVPPGPEVCITHQEGEKISANENSLAVRSTPAE
DDSRDSQVKSEVQQPVHPKPLSPDSRASSLSESSPPKAMKKFQAPARETCVECQKTVYPM
ERLLANQQVFHISCFRCSYCNKLSLGTYSASLHGRIYCKPHFNQLFKSKGNVDEGFHGRP
HKDLWASKNENEEILERPAQLANARETPHSPGVEDAPIAKVGVLAASMEAKASSQQEKED
KPAETKKLRIAWPPPTLGSSESALEEGIKMSKPKWPPPEDEISKPEVPEDVDLDLKKLRR
30 SSSLKERSRPFTVAASFQSTSVKSPKTVSPPIRKGWSMSEQSEESVGG RVAERKQVENAK
ASKKNGNVGKTTWQNKESKGETGKRSKEGHSLEMENENLVENGADSDDDNSFLKQQSPQ
EPKSLNWSSFVDNTFAEEFTTQNKQSQDVELWEGEVVKELSVEEQIKRNRYYDEDEDEE

The term “cancer associated with a component of the NF- κ B pathway downstream of a CBM complex” as used herein refers to cancers associated with or having a dysregulation of a

gene, a protein, or the expression or activity or level of any (e.g., one or more) of the same associated with a component of the NF- κ B pathway downstream of a CBM complex. In some embodiments, a cancer associated with a component of the NF- κ B pathway downstream of a CBM complex is selected from the group consisting of a TAK1-associated cancer, a TRAF6-associated cancer, a TAB1-associated cancer, a TAB2-associated cancer, a TAB3-associated cancer, a MKK7-associated cancer, an IKK α -associated cancer, an IKK β -associated cancer, an IKK γ -associated cancer, an I κ B α -associated cancer, a p50-associated cancer, a p65 (RelA)-associated cancer, a c-Rel-associated cancer, and combinations thereof. In some embodiments, a cancer associated with a component of the NF- κ B pathway downstream of a CBM complex is an IKK γ -associated cancer. The cancers “associated” with a particular gene or protein described in this paragraph refer to cancers associated with or having a dysregulation of the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of such cancers are described herein.

An exemplary sequence of human TAK1 is shown below:

SEQ ID NO: 21 (UniParc Accession No. UPI000012EAD6)

MSTASAASSSSSSSAGEMIEAPSQVLNFEEIDYKEIEVEEVVGRGAFGVVCKAKWRAKDV
 AIKQIESESERKAFIVELRQLSRVNHNPNIKLYGACLNPCVLMVEYAEAGGSLYNLHGAE
 PLPYYTAAHAMSWCLQCSQGVAYLHSMQPKALIHRLKPPNLLVAGGTVLKICDFGTAC
 DIQTHMTNNKGSAAWMAPEVFEGSNYSEKCDVFSWGIIILWEVITRRKPFDEIGGPAFRIM
 WAVHNGTRPPLIKNLKPKIESLMTRCWSKDPSQRPSMEEIVKIMTHLMRYFFGADEPLQY
 PCQYSDEGQSNSATSTGSFMDIASTNTSNKSDTNMEQVPATNDTIKRLESKLLKNQAKQQ
 SESGRLSLGASRGSSVESLPPTSEGKRMSADMSEIEARIAATTAYSKPKRGHRKTASFGN
 ILDVPEIVISGNGQPRRRSIQDLTVTGTEPGQVSSRSSPSVRMITTSIPTSEKPTRSHP
 WTPDDSTDINGSDNSIPMAYLTLDHQLQPLAPCPNSKESMAVFEQHCKMAQEYMKVQTEI
 ALLLQRKQELVAELDQDEKDQNTSRLVQEHKKLLDENKSLSTYYQQCKKQLEVIRSQQQ
 KRQGTS

An exemplary sequence of human TRAF6 is shown below:

SEQ ID NO: 22 (UniParc Accession No. UPI000000D924)

MSLLNCENSCGSSQSESDCCVAMASSCSAVTKDDSVGGTASTGNLSSSFMEEIQGYDVEF
 DPPLSKYECPICLMALREAVQTPCGHRFCKACIIKSIRDAGHKCPVDNEILLENQLFPD

NFAKREILSLMVKCPNEGCLHKMELRHLEDHQAHCEFALMDCPQCQRPFQKFHINIHLK
DCPRRQVSCDNCAASMAFEDKEIHDQNCPLANVICEYCNILIREQMPNHYDLDCPTAPI
PCTFSTFGCHEKMQRNHLARHLQENTQSHMRMLAQAVHSLSVIPDSGYISEVRNFQETIH
QLEGRILVRQDHQIRELTAKMETQSMYVSELKRTIRTLEDKVAEIEAQQCNGIYIWKIGNF
5 GMHLKCQEEKPVVIHSPGFYTGKPGYKLCMRLHLQLPTAQRCAANYISLHVHTMQGEYDS
HLPWPFQGTIRLTILDQSEAPVRQNHEEIMDAKPELLAFQRPTIPRNPKGFGYVTFMHLE
ALRQRTFIKDDTLVRCEVSTRFDMGSLRREGFQPRSTDAGV

An exemplary sequence of human TAB1 is shown below:

SEQ ID NO: 23 (UniParc Accession No. UPI0000136861)

10 MAAQRRLQLQSEQQPSWTDDLPLCHLSGVGSASNRSYSADGKGTESHPEDSWLKFRSEN
NCFLYGVFNQYDGNRVTNFVAQRLSAELLGQLNAEHAEDVRRVLLQAFDVVERSFLS
IDDALAEKASLQSQLPEGVPQHQLPPQYQKILERLKTLEIREISGGAMAVVAVLLNNKLYV
ANVGTNRALLCKSTVDGLQVTQINVDHTTENEDELFRLSQLGLDAGKIKQVGIICGQEST
RRIGDYKVKYGYTDIDLLSAAKSKPIIAEPEIHGAQPLDGVTFGLVLMSEGLYKALEAAH
15 GPGQANQEIAAMIDTEFAKQTSIDAVAQAVVDRVKRIHSDTFASGGERARFCPRHEDMTL
LVRNFGYPLGEMSQPTSPAPAAAGGRVYPVSVPYSSAQSTSKTSVTLSLVMPSQGQMUNG
AHSASTLDEATPTLTNQSPTLTLQSTNTHTQSSSSSDGGLFRSRPAHSLPPGEDGRVEP
YVDFAEFYRLWSVDHGEQSVVTAP

An exemplary sequence of human TAB2 is shown below:

SEQ ID NO: 24 (UniParc Accession No. UPI0000073C75)

20 MAQGSHQIDFQVLHDLRQKFPEVPEVVVSRCLQNNNNLDACCAVLSQESTRYLYGEGDL
NFSDDSGISGLRNHMTSLNLDLQSQNIYHHGREGSRMNGSRTLTHSISDGQLQGGQSNSE
LFQQEPQTAPAQVPQGFNVFGMSSSSGASNSAPHLGFHLGSKGTSSLSQQTPRFNPIMVT
LAPNIQTGRNTPTSLHIHGVPVPLNSPQGNISYIRPYITTPGGTTROTQOHSGWVSQFN
25 PMNPQQVYQPSQPGPWTTCPASNPLSHTSSQQPNQQGHQTSHVYMPISSPTTSQPPTIHS
SGSSQSSAHSQYNIQNIISTGPRKNQIEIKLEPPQRNNSSKLRSSGPRTSSTSSSVNSQTL
NRNQPTVYIAASPPNTDELMRSRQPKVYISANAATGDEQVMRNQPTLFI STNSGASAASR
NMSGQVSMGPAFIIHHPPKSRAIGNNSATSPRVVVTQPNKYTFKITVSPNKPPAVSPGV
VSPTFELTNLLNHPDHYVETENIQHLTDPTLAHVDRISETRKLMSGSDDAAYTQALLVHQ
30 KARMERLQRELEIQKKKLDKLVSEVNEMENNLTRRLKRSNSISQIPSLEEMQQLRSCNR
QLQIDIDCLTKEIDLFQARGPHFNPSAIHNFYDNIGFVGPVPPKPKDQRSIIKTPKTQDT
EDDEGAQWNCTACTFLNHPALIRCEQCEMPRHF

An exemplary sequence of human TAB3 is shown below:

SEQ ID NO: 25 (UniParc Accession No. UPI0000071648)

MAQSSPQLDIQVLHDLRQRFPEIPEGVVSQCMLQNNNNLEACCRALSQESSKYLMEYHS
 PDDNRMNRNRLHINLGIHSPSSYHPGDGAQLNGGRTLHVSSSDGHIDPQHAAGKQLICL
 5 VQEPHSAPAVVAATPNYNPFMNEQNRSAATPPSQPPQQPSSMQTGMNPSAMQGPSPPPP
 PPSYMHIPRYSTNPITVTVSQNLPSGQTVPRALQILQIPSNLYGSPGSIYIRQTSQSSS
 GRQTPQSTPWQSSPQGPVPHYSQRPLPVYPHQQNYQPSQYSPKQQQIPQSAYHSPPPSQ
 PSPFSSPQHQQVPSQLGHIFMPPSPSTTPPHPYQQGPPSYQKQGSHSVAYLPYTASSLSK
 GSMKKIEITVEPSQRPGTAINRSPSPISNQPSRNQHSLYTATTPSSSPSRGISSQPKP
 10 PFSVNPVYITYTQPTGSPCTSPSPRVIPNPTTVFKITVGRATTENLLNLVDQEERSAAP
 EPIQPISVIPGSGGEGKSHKYQRSSSSGDDYAYTQALLLHQRARMERLAKQLKLEKEEL
 ERLKSEVNGMEHDLMQRRLLRVSCCTTAIPTPEEMTRLRSMNRQLQINVDCTLKEVDLLQS
 RGNFDPKAMNNFYDNIEGPPVPPKPSKKDSSDPCTIERKARRISVTSKVQADIHDTQAA
 AADEHRTGSTQSPRTQPRDEDEYEGAPWNCDSCTFLNHPALNRCEQCEMPRYT

15 An exemplary sequence of human MKK7 is shown below:

SEQ ID NO: 26 (UniParc Accession No. UPI000012F494)

MAASSLEQKLSRLEAKLKQENREARRRIDLNLDISPQRPRPTLQLPLANDGGSRSPSES
 SPQHPTPPARPRHMLGLPSTLFTPRSMESIEIDQKLQEIMKQTGYLTIGGQRYQAEINDL
 ENLGEMGSGTCGQVWKMFRKTGHVIAVKQMRRSGNKEENKRILMDLDVVLKSHDCPYIV
 20 QCFGTFTINTDVFIAELMGTCAEKLKKRMQGPIPERILGKMTVAIVKALYYLKEKHGVI
 HRDVKPSNILLDERGQIKLCDFGISGRLVDSKAKTRSAGCAAYMAPERIDPPDPTKPDYD
 IRADVWSLGISLVELATGQFPYKNCKTDFEVLTKVLQEEPPLLPGHMGFSGDFQSFVKDC
 LTKDHRKRPKYNKLLHSFIKRYETLEVDVASWFKDVMAKTESPRTSGVLSQPHLPFFR

An exemplary sequence of human IKK α is shown below:

25 SEQ ID NO: 27 (UniParc Accession No. UPI000013D6C7)

MERPPGLRPGAGGPWEMRERLGTGGFGNVCLYQHRELDLKIATKSCRLELSTKNRERWCH
 EIQIMKKLNHANVVKACDVPEELNILIHDVPLAMEYCSGGDLRKLLNKPENCCGLKESQ
 ILSLLSDIGSGIRYLHENKIIHRDLKPENIVLQDVGGKIIHKIIDLGYAKDVDQGSLLCTS
 FVGTLYLAPELFENKPYTATVDYWSFGTMVFECIAGYRPFLLHLLQPFTWHEKIKKKDPK
 30 CIFACEEMSGEVRFSSHLPQPNLSCLSVVEPMENWLQLMLNWDPPQRRGGPVDLTLLKQPRC
 FVLMDHILNLKIVHILNMTSAKIIISFLPPDESLHSLQSRIERETGINTGSQELLSETGI
 SLDPRKPASQCVLDGVRGCDSYMVYLFDKSKTVYEGPFASRSLSDCVNYIVQDSKIQLPI
 IQIRKVVAAEAVHYVSGLKEDYSRLFQGGQRAAMLSLLRYNANLTKMKNTLISASQQLKAKL
 EFFHKSIIQLDLERYSEQMTYGISSEKMLKAWKEMEKAIIHYAEVGVIGYLEDQIMSLHAE

IMELQKSPYGRRQGDLMESLEQRAIDLKQLKHRPSDHSYSDSTEMVKIIVHTVQSQDRV
 LKELFGHLSKLLGCKQKIIDLKPKVEVALSNIKEADNTVMFMQGRQKEIWHLLKIACTQ
 SSARSLVGSSLEGAVTPQTSAWLPPTSAEHDHSLSCVVTPQDGETSAQMIEENLNCLGHL
 STIIEANEEQGNMNMNDWSWLTE

5 An exemplary sequence of human IKK β is shown below:

SEQ ID NO: 28 (UniParc Accession No. UPI0000033729)

MSWSPSLTTQTCGAWEMKERLGTGGFGNVIRWHNQETGEQIAIKQCRQELSPNRERWCL
 EIQIMRRLTHPNVVAARDVPEGMQNLAPNDLPLLAMEYCQGGDLRKYLNQFENCCLREG
 AILTLLSDIASALRYLHENRIIHRDLKPENIVLQQGEQRLIHKIIDLGYAKELDQGSCLT
 10 SFVGTLLQYLAPELLEQQKYTVTVDYWSFGTLAFECITGFRPFLPNWQPVQWHSKVRQKSE
 VDIVVSEDLNGTVKFSSSLPYPNLNSVLAERLEKWLQMLMWHPRQRGTDPYGPNGCF
 KALDDILNLKLVHILNMVTGTIHTYPTVEDSLQSLKARIQQDTGIPEEDQELLQEAGLA
 LIPDKPATQCISDGKLNEGHTLDMDLVFLFDNSKITETQISPRPQPEVSCILQEPKRN
 LAFFQLRKVWGQVWHSIQTLKEDCNRLQQGQRAAMNLLRNNSCLSKMKNMSMSQQLK
 15 AKLDFFKTSIQIDLEKYSEQTEFGITSDKLLLAWREMEQAVELCGRENEVKLLVERMMAL
 QTDIVDLQSPMGRKQGGTLDLEEQAARELYRRLREKPRDQRTQEGDSQEMVRLLLQAIQS
 FEKKVRVIYTLQSKTVVCKQKALELLPKVEEVVSLMNEDEKTVVRLQEKQKELWNLLKI
 ACSKVRGPVSGSPDSMNASRLSQPGQLMSQPSTASNSLPEPAKKSEELVAEHNLCITLLE
 NAIQDTVREQDQSFTALDWSWLQTEEEHSCLEQAS

20 An exemplary sequence of human IKK γ is shown below:

SEQ ID NO: 29 (UniParc Accession No. UPI0000000CC4)

MNRHLWKSQLCMVQPSGGPAADQDVLGEESPLGKPAMLHLPSEQGAPETLQRCLEENQE
 LRDAIRQSNQILRERCEELLHFQASQREEKEFLMCKFQEARLVERLGLEKLDLKRQKEQ
 ALREVEHLKRCQQQMAEDKASVKAQVTSLLGELQESQSRLEAATKECQALEGRARAASEQ
 25 ARQLESEREALQQQHSVQVDQLRMQGSVEAALRMERQAASEEKRLAQLQVAYHQLFQE
 YDNHIKSSVVGSEKRGMLQLEDLKQQLQQAEEALVAKQEVIDKLKEEAEQHKIVMETVPV
 LKAQADIYKADFQAEKQAREKLAKEKELLQEQLEQLQREYSKLKASCQESARIEDMRKRH
 VEVSQAPLPPAPAYLSSPLALPSQRRSPPEEPPDFCCPKCQYQAPDMDTLQIHVMETCIE

Non-limiting examples of dysregulation of an IKK γ gene or an IKK γ protein are described
 30 in, for example, Courtois and Gilmore, Oncogene 25.51 (2006): 6831-6843.

An exemplary sequence of human Ikb α is shown below:

SEQ ID NO: 30 (UniParc Accession No. UPI000004F0A9)

MFQAAERPQEWAMEGPRDGLKKERLLDDRHDGLDSMKDEEYEQMVKELQEIIRLEPQEV
 RGSEPWKQQLTEDGDSFLHLAIIEEKALTMVIRQVKGDALFNLNQNNLQQTPLHLAVI

TNQPEIAEALLGAGCDPELRDFRGNTPLHLACEQGCLASVGVLTQSCTTPHLHSILKATN
 YNGHTCLHLASIHGYLGIVELLVSLGADVNAQEPCNGRTALHLAVDLQNPDLVSLLLKCG
 ADVNRVTYQGYSPLYQLTWGRPSTRIQQQLGQLTLENLQMLPESEDEESYDTESEFTEFTE
 DELPYDDCVFGGQRLTL

5 An exemplary sequence of human p105, which is processed into p50, is shown below:

SEQ ID NO: 31 (UniParc Accession No. UPI000000D917)

MAEDDPYLGRPEQMFHLDPSLTHITIFNPEVFQPMALPTDGPYLQILEQPKQGRGFRFRYV
 CEGPSHGGPLPGASSEKNKKSYPQVKICNYVGPAKVIVQLVTNGKNIHLHAHSLVGKHCE
 GICTVTAGPKDMVVGAFANLILHVTKKKVFETLEARMTEACIRGYNPGLLVHPDLAYLQA
 10 EGGGDRQLGDREKELIRQAALQQTKEMDLSVVRMLMFTAFLPDSTGSFTRLEPVVSDAIY
 DSKAPNASNLKIVRMDRTAGCVTGGEIYLLCDKVQKDDIQIRFYEEEEENGWEGFGDF
 SPIDVHRQFAIVFKTPKYKDINITKPASVVFVQLRRKSDLETSEPKPFLYYPEIKDKEEVQ
 RKRQKLPNFSDFSFGGSGAGAGGGGGMFGSGGGGGGTGSTGPGYSFPHYGFPTYGGITFH
 PGTTKSNAGMKHGTMDTESKKDPEGCDKSDDKNTVNLFGKVIETTEQDQEPSEATVGNGE
 15 VTLTYATGTKEESAGVQDNLFLEKAMQLAKRANALFDYAVTGDVKMLLAVQRHLTAVQD
 ENGDSVLHLAIHLSQLVRDLLEVTSGLISDDIINMRNDLYQTPHLAVITKQEDVVED
 LLRAGADLSLLDRLGNSVLHLAAKEGHDKVLISILLKHKAALLLDHPNGDGLNAIHLAMM
 SNSLPCLLLLVAAGADVNAQEQQSGRTALHLAVEHDNISLAGCLLLEGDAHVDSTTYDGT
 TPLHIAAGRGSTRLAALLKAAGADPLVENFEPLYDLDDSWENAGEDEGVVPGTTPLDMAT
 20 SWQVFDILNGKPYEPEFTSDDLQAQGMKQLAEDVKLQLYKLEIPDPDKNWATLAQKLG
 LGILNNAFRLSPAPSKTLMNYEVSGGTVRELVEALRQMGYTEAIEVIQAASSPVKTTTSQ
 AHSPLSPASTRQQIDELRDSDSVCDSGVETSFRKLSFTESLTSGASLLTLNKMHPHYGQ
 EGPLEGKI

An exemplary sequence of human p65 is shown below:

25 SEQ ID NO: 32 (UniParc Accession No. UPI000013ED68)

MDELFPILFPAEPAQASGPYVEIIEQPKQGRGMRFRYKCEGRSAGSIPGERSTDTTKTHPT
 IKINGYTGPVTRISLVTKDPPHRPHPHLVGKDCRDGFYEALCPDRCIHSFQNLGIQC
 VKKRDLEQAISQRIQTNNNPFQVPIEEQRGDYDLNAVRLCFQVTVRDPSSGRPLRLPPVLS
 HPIDNRPNTAELKICRVNRNSGSCLGDEIFLLCDKVQKEDIEVYFTGPGWEARGSF
 30 QADVHRQVAIVFRTPPYADPSLQAPVRVSMQLRRPSDRELSEPMFQYLPDTRDRHRIE
 KKRKYETFKSIMKKSFPSTGPTDRPPPRRIAVPSRSSASVPKPAPQPYPTSSLSTINY
 DEFPTMVFPSTGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQAPAPVPVLAPGPPQA
 VAPPAPKPTQAGEGTLSEALLQLQFDDDELGALLGNSTDPVFTDLASVDNSEFQQLLNQ
 GIPVAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGAAPGLPGLLSGDEDFSSIADM

DFSALLSQISS

An exemplary sequence of human c-Rel is shown below:

SEQ ID NO: 33 (UniParc Accession No. UPI000013367B)

MASGAYNPYIEIIEQPRQGMRFYKCEGRSAGSIPGEHSTDNNRTYPSIQIMNYYGKGK
 5 VRITLVTKNDPYKPHPHDLVGKDCRDGYEAEFGQERRPLFFQNLGIRCVKKKEVKEAII
 TRIKAGINPFNVPEKQLNDIEDCDLNVVRLCFQVFLPDEHGNLTALPPVVSNIYDNRA
 PNTAELRICRVNKNCGSVRGGDEIFLLCDKVQKDDIEVRFVLNDWEAKGIFSQADVHRQV
 AIVFKTPPYCKAITEPVTVKMLRRPSDQEVSESMDFRYLPDEKDTYGNKAKKQKTTLLF
 QKLCQDHVETGFRHVDQDGLELLTSGDPPTLASQSAGITVNFPERPRPGLLGSIGEGRYF
 10 KKEPNLFSHDAVVREMTGVSSQAESYYPSPGPISSGLSHHSMAPLPSSSWSSVAHPTP
 RSGNTNPLSSFSTRITLPSNSQGIPFLRIPVGNDLNASNACIYNNADDIVGMEASSMP
 DLYGISDPNMLSNCSVNMMTTSSDSMGETDNPRLLSMNLENPSCNSVLDPRDLRQLHQMS
 SSSMSAGANSNTTVFVSQSDAFEGSDFSCADNSMINESGPSNSTNPNSHGFVQDSQYSGI
 GSMQNEQLSDSFPEFFQV

15 The term “cancer associated with a component of the JNK pathway downstream of a CBM complex” as used herein refers to cancers associated with or having a dysregulation of a gene, a protein, or the expression or activity or level of any (e.g., one or more) of the same associated with a component of the JNK pathway downstream of a CBM complex. In some embodiments, a cancer associated with a component of the JNK pathway downstream of a CBM complex is selected from
 20 the group consisting of a JNK1-associated cancer, a JNK2-associated cancer, a JNK3-associated cancer, a MYD88 transcription factor-associated cancer, an AP-1 transcription factor-associated cancer, and combinations thereof. The cancers “associated” with a particular gene or protein described in this paragraph refer to cancers associated with or having a dysregulation of the particular gene, the particular protein, or the expression or activity or level of any (e.g., one or
 25 more) of the same (e.g., any of the types of dysregulation of the particular gene, the particular protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of such cancers are described herein.

An exemplary sequence of human JNK1 is shown below:

SEQ ID NO: 34 (UniParc Accession No. UPI000012F17A)

30 MSRSKRDNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILERNVAIKKLSRP
 FQNQTHAKRAYRELVLKCVNHKNIIGLNVFTPQKSLEEFQDVYIVMELMDANLCQVIQ
 MELDHERMSYLLYQMLCGIKHLHSAGIIHRDLKPSNIVVKS DCTLKILDFGLARTAGTSF
 MMTPLYVVTRYRAPEVILGMGYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVIEQ

LGTPCPEFMKKLQPTVRTYVENRPKYAGYSFEKLPDVLFPADSEHNKLKASQARDLLSK
MLVIDASKRISVDEALQHPYINVWYDPSEAEAPPPKIPDKQLDEREHTIEEWKELIYKEV
MDLEERTKNGVIRGQPSPLGAAVINGSQHPSSSSSVNDVSSMSTDPTLASD TDSSLEAAA
GPLGCCR

5 An exemplary sequence of human JNK2 is shown below:

SEQ ID NO: 35 (UniParc Accession No. UPI000006E3AD)

MSDSKCD SQFYSVQVADSTFTVLKRYQQLKPIGSGAQGIVCAAFDTV LGIN VAVKKLSRP
FQNQTHAKRAYRELVLKCVNHKNII SLLNVFTPQKTLEEFQDVYLVME LMDANLCQVIH
MELDHERMSYLLYQMLCGIKHLHSAGI IHRDLKPSNIVVKSDCTLKILDFGLARTACTNF
10 MMTFYVVTRYRAPEVILGMGYKENVDIWSVGCIMGELVKGCVIFQGT DHIDQWNKVIEQ
LGTPSAEFMKKLQPTVRNYVENRPKYPGIKFEELFPDWIFPSESERDKIKTSQARDLLSK
MLVIDPDKRISVDEALRHPYITVWYDPAEAEAPPPQIYDAQLEEREHAIEEWKELIYKEV
MDWEERSKNGVVKDQPSDAAVSSNATPSQSSSINDISSMSTEQT LASD TDSSLDASTGPL
EGCR

15 An exemplary sequence of human JNK3 is shown below:

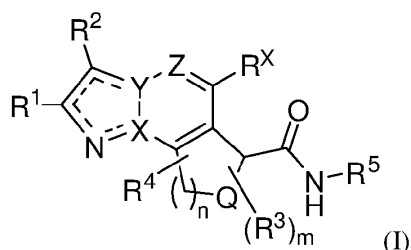
SEQ ID NO: 36 (UniParc Accession No. UPI0000049042)

MSLHFLYYCSEPTLDVKIAFCQGFQDVSYIAKHYNMSKSKVDNQFYSVEVG DSTFTV
LKRYQNLKPIGSGAQGIVCAAYDAVLDRNVAIKKLSRPFQNQTHAKRAYRELVL MKCVNH
KNII SLLNVFTPQKTLEEFQDVYLVME LMDANLCQVIQ MELDHERMSYLLYQMLCGIKHL
20 HSAGI IHRDLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYRAPEVILGMGY
KENVDIWSVGCIMGEMVRHKILFPGRDYIDQWNKVIEQLGTPCPEFMKKLQPTVRNYVEN
RPKYAGLTFPKLPDSLFPADSEHNKLKASQARDLLSKMLVIDPAKRISVDDALQHPYIN
VWYDPAEVEAPPPQIYDKQLDEREHTIEEWKELIYKEVMNSEEKTKNGVVKGQPSPSGAA
VNSSES LPPSSSVNDISSMSTDQTLASD TDSSLEASAGPLGCCR

25

Compounds of Formula (I)

Provided herein are compounds of Formula (I), or a pharmaceutically acceptable salt thereof;



5 wherein:

each  is a single or double bond;

Q is $-\text{CH}_2-$, O, or NH;

X is N or C;

Y is N or C;

10 Z is N or CR^6 ;

wherein when one of X and Y is N, the other of X and Y is C;

n is 1, 2, or 3;

R^x is hydrogen or halogen;

R¹ is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, -NR^AR^B, or C1-C3 alkyl optionally substituted with 1-3 substituents selected from hydroxyl and C1-C3 alkoxy;

R² is hydrogen, halogen, amino, or C1-C3 alkyl;

each R³ is independently deuterium, halogen, C3-C6 cycloalkyl, C1-C3 alkyl, C1-C3 alkoxy, C1-C3 haloalkoxy, or C1-C3 haloalkyl;

20 m is 0, 1, 2, or 3;

R⁴ is 5-10 membered heteroaryl optionally substituted with one to three substituents each independently selected from R⁷;

R⁵ is phenyl or 5-9 membered heteroaryl, wherein each R⁵ group is optionally substituted with 1-3 substituents independently selected from R⁸;

25 R⁶ is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, -NR^cR^d, and C1-C3 alkyl;

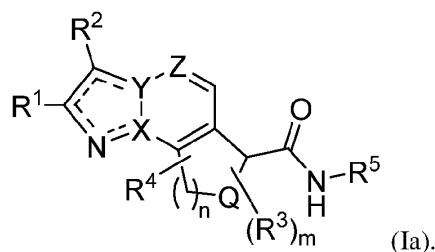
each R^7 is independently selected from the group consisting of halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, oxetanyl, $-NR^C R^D$, C1-C3 alkyl optionally substituted with one cyclopropyl; and C3-C7 cycloalkyl optionally substituted with one C1-C3 alkyl;

5 each R^8 is independently selected from halogen; cyano; amino; $-N=(S=O)(C1-C3 \text{ alkyl})_2$; $-S(=O)_p(C1-C3 \text{ alkyl})$; 1-imino-1-lambda⁶-thietanyl 1-oxide, $-(C=O)NR^E R^F$; C1-C3 alkoxy; C1-C3 haloalkyl optionally substituted with hydroxyl; C1-C3 haloalkoxy; 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, amino, C1-C3 haloalkyl, 4-6 membered heterocyclyl, or C1-C3 alkyl
10 optionally substituted with hydroxyl or $-NR^E R^F$; C1-C4 alkyl optionally substituted with hydroxyl, $-NR^E R^F$, or C1-C3 alkoxy; 3-8 membered heterocyclyl; and C3-C6 cycloalkoxy;

p is 1 or 2; and

R^A , R^B , R^C , R^D , R^E , and R^F , are independently hydrogen, C1-C3 alkyl, C3-C6 cycloalkyl, or R^A and R^B , or R^C and R^D , or R^E and R^F , together with the nitrogen atom to which they are attached
15 come together to form a 4-6 membered heterocyclyl optionally substituted with 1-2 halogens.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



In some embodiments, Q is $-CH_2-$. In some embodiments, Q is O. In some embodiments,
20 Q is NH.

In some embodiments, the five-membered nitrogen-containing ring, formed in part by X and Y, is a heteroaromatic ring.

In some embodiments, X is C and Y is C.

In some embodiments, X is N and Y is C.

25 In some embodiments, X is C and Y is N.

In some embodiments, Z is N. In some embodiments, Z is CR⁶. In some embodiments, Z is CR⁶ wherein R⁶ is hydrogen.

In some embodiments, X is C; Y is C; and Z is CR⁶. In some embodiments, X is N; Y is C; and Z is CR⁶. In some embodiments, X is C; Y is N; and Z is CR⁶. In some embodiments, X is C; Y is N; and Z is CR⁶ wherein R⁶ is hydrogen. In some embodiments, X is C; Y is C; and Z is N. In some embodiments, X is N; Y is C; and Z is N. In some embodiments, X is C; Y is N; and Z is N.

In some embodiments, R⁶ is hydrogen.

In some embodiments, R⁶ is halogen. For example, R⁶ is fluoro. For example, R⁶ is chloro. In some embodiments, R⁶ is cyano. In some embodiments, R⁶ is hydroxyl.

In some embodiments, R⁶ is C1-C3 alkoxy. In some embodiments, R⁶ is methoxy or ethoxy.

In some embodiments, R⁶ is C1-C3 haloalkoxy. In some embodiments, R⁶ is trifluoromethoxy, difluoromethoxy, or fluoromethoxy.

In some embodiments, R⁶ is C1-C3 haloalkyl. In some embodiments, R⁶ is trifluoromethyl or 2,2,2-trifluoroethyl.

In some embodiments, R¹ is halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkyl, -NR^AR^B, or C1-C3 alkyl optionally substituted with 1-3 substituents selected from hydroxyl and C1-C3 alkoxy.

In some embodiments, R¹ is halogen or cyano. In some embodiments, R¹ is chloro or cyano. In some embodiments, R¹ is hydrogen. In some embodiments, R¹ is halogen. In some embodiments, R¹ is fluoro or chloro. In some embodiments, R¹ is fluoro. In some embodiments, R¹ is chloro. In some embodiments, R¹ is cyano. In some embodiments, R¹ is hydroxyl.

In some embodiments, R¹ is C1-C3 alkoxy. In some embodiments, R¹ is methoxy or ethoxy.

In some embodiments, R¹ is C1-C3 haloalkoxy. In some embodiments, R¹ is trifluoromethoxy, difluoromethoxy, or fluoromethoxy.

In some embodiments, R¹ is C1-C3 haloalkyl. In some embodiments, R¹ is difluoromethyl, trifluoromethyl or 2,2,2-trifluoroethyl.

In some embodiments, R¹ is C1-C3 alkyl optionally substituted with 1-3 substituents selected from hydroxyl and C1-C3 alkoxy.

In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is halogen. In some embodiments, R^2 is fluoro. In some embodiments, R^2 is chloro. In some embodiments, R^2 is amino. In some embodiments, R^2 is C1-C3 alkyl, such as methyl.

In some embodiments, n is 1, 2, or 3. In some embodiments, n is 1 or 2. In some
5 embodiments, n is 2 or 3. In some embodiments, n is 1 or 3. In some embodiments, n is 1. In
some embodiments, n is 2. In some embodiments, n is 3.

In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some
embodiments, m is 1, 2, or 3. In some embodiments, m is 0, 2, or 3. In some embodiments, m is
0, 1, or 3. In some embodiments, m is 0 or 1. In some embodiments, m is 0 or 2. In some
10 embodiments, m is 0 or 3. In some embodiments, m is 1 or 2. In some embodiments, m is 1 or 3.
In some embodiments, m is 2 or 3. In some embodiments, m is 0. In some embodiments, m is 1.
In some embodiments, m is 2. In some embodiments, m is 3.

In some embodiments, each R^3 is independently deuterium, halogen, C3-C6 cycloalkyl,
C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

15 In some embodiments, each R^3 is independently halogen. In some embodiments, R^3 is
fluoro. In some embodiments, R^3 is chloro. In some embodiments, each R^3 is independently
hydroxyl.

In some embodiments, each R^3 is independently C3-C6 cycloalkyl, C1-C3 alkyl,
C1-C3 alkoxy, C1-C3 haloalkoxy, or C1-C3 haloalkyl.

20 In some embodiments, each R^3 is independently C1-C3 alkyl. For example, R^3 is methyl
or ethyl. In some embodiments, each R^3 is independently C1-C3 alkoxy. For example, R^3 is
methoxy or ethoxy. In some embodiments, each R^3 is independently C1-C3 haloalkoxy. For
example, R^3 is trifluoromethoxy, difluoromethoxy, or fluoromethoxy. In some embodiments, each
 R^3 is independently C1-C3 haloalkyl. For example, each R^3 is trifluoromethyl or
25 2,2,2-trifluoroethyl.

In some embodiments, m is 1 and R^3 is methyl or trifluoromethyl.

In some embodiments, R^4 is a 5 or 6 membered heteroaryl optionally substituted with one
to three substituents each independently selected from R^7 .

In some embodiments, R^4 is a 6 membered heteroaryl optionally substituted with one to
30 three substituents each independently selected from R^7 .

In some embodiments, R^4 is a 5 membered heteroaryl optionally substituted with one to three substituents each independently selected from R^7 .

In some embodiments, R^4 is 4H-pyrazolyl, 3H-pyrazolyl, or thiazolyl optionally substituted with one to three substituents each independently selected from R^7 .

- 5 In some embodiments R^4 is unsubstituted. For example, R^4 is unsubstituted 4H-pyrazolyl, 3H-pyrazolyl, or thiazolyl.

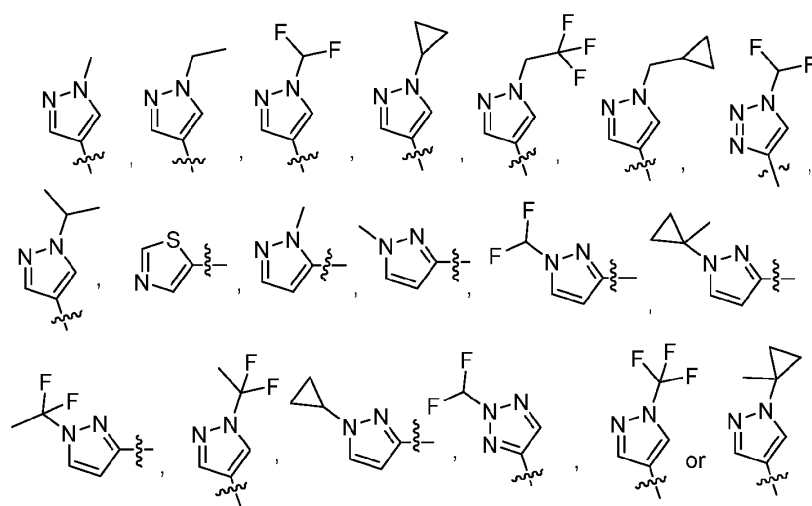
In some embodiments R^4 is a 5 or 6 membered heteroaryl substituted with one or three substituents each independently selected from R^7 . In other embodiments, R^4 is a 5 or 6 membered heteroaryl substituted with one substituent selected from R^7 .

- 10 In some embodiments, each R^7 is independently selected from the group consisting of C1-C3 haloalkyl, C1-C3 alkyl, and cycloalkyl. In some embodiments R^7 is methyl, ethyl, cyclopropyl, or difluoromethyl.

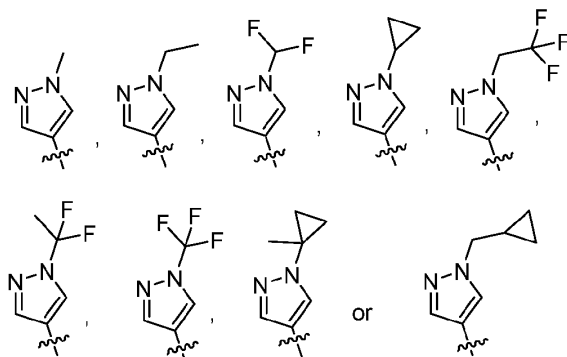
In some embodiments, each R^7 is independently selected from the group consisting of C1-C3 alkyl optionally substituted with one cyclopropyl.

- 15 In some embodiments, each R^7 is independently selected from the group consisting of C3-C7 cycloalkyl optionally substituted with one C1-C3 alkyl. In some embodiments the C3-C7 alkyl is cyclopropyl.

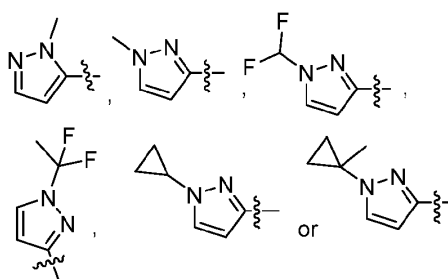
In some embodiments, R^4 is:



In some embodiments, R^4 is:

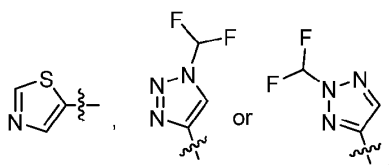


In some embodiments, R^4 is:

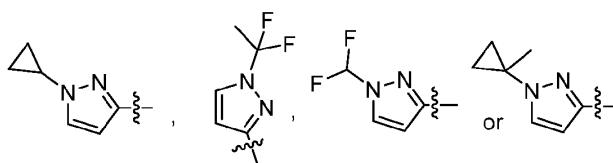


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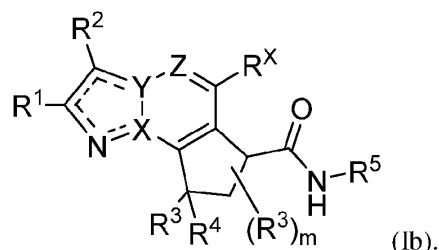
In some embodiments, R^4 is:



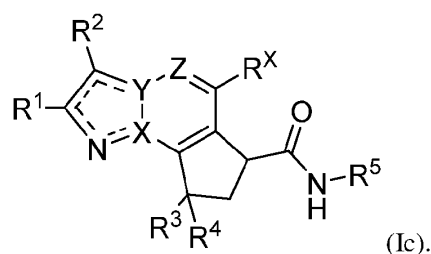
In some embodiments, R^4 is:



In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^5 group is optionally substituted with 1-2 independently selected R^8 . In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^5 group is optionally substituted with 2-3 independently selected R^8 . In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^5 group is optionally substituted with 1 to 3 independently selected R^8 . In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^5 group is optionally substituted with 1 R^8 . In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^8 group is optionally substituted with 2 independently selected R^8 . In some embodiments, R^5 is phenyl or 5-6 membered heteroaryl; wherein each R^5 group is optionally substituted with 3 independently selected R^8 .

In some embodiments, R^5 is phenyl or 5 membered heteroaryl; wherein each R^5 group is optionally substituted with 1-3 substituents independently selected from R^8 . In some embodiments, R^5 is phenyl or 6 membered heteroaryl; wherein each R^5 group is optionally substituted with 1-3 substituents independently selected from R^8 .

In some embodiments, R⁵ is phenyl optionally substituted with 1-3 independently selected R⁸. In certain embodiments, R⁵ is phenyl optionally substituted with 1 R⁸. In certain embodiments, R⁵ is phenyl optionally substituted with 2 independently selected R⁸. In certain embodiments, R⁵ is phenyl optionally substituted with 3 independently selected R⁸.

5 In some embodiments, R⁵ is unsubstituted phenyl.

In some embodiments, R⁵ is 5-6 membered heteroaryl optionally substituted with 1-3 (e.g., 2) substituents independently selected from R⁸. In some embodiments, R⁵ is 6 membered heteroaryl optionally substituted with 1-3 (e.g., 2) substituents independently selected from R⁸.

In some embodiments, R⁵ is unsubstituted 5-6 membered heteroaryl.

10 In some embodiments, R⁵ is 5-6 membered heteroaryl substituted with 1-3 substituents independently selected from R⁸.

In some embodiments, R⁵ is unsubstituted 5-6 membered heteroaryl. In some embodiments, at least one of R⁸ is halogen. In some embodiments, at least one of R⁸ is fluoro. In some embodiments, at least one of R⁸ is chloro. In some embodiments, one of R⁸ is halogen. In some embodiments, one of R⁸ is fluoro. In some embodiments, one of R⁸ is chloro. In some embodiments, two of R⁸ is halogen. In some embodiments, two of R⁸ is fluoro. In some embodiments, two of R⁸ is chloro. In some embodiments, three of R⁸ is halogen. In some embodiments, three of R⁸ is fluoro. In some embodiments, three of R⁸ is chloro. In some embodiments, at least one of R⁸ is cyano. In some embodiments, at least one of R⁸ is amino.

20 In some embodiments, at least one of R⁸ is C1-C3 alkoxy. In some embodiments, at least one of R⁸ is methoxy or ethoxy.

In some embodiments, at least one of R⁸ is C1-C3 haloalkyl optionally substituted with hydroxyl. In some embodiments, at least one of R⁸ is unsubstituted C1-C3 haloalkyl. In some embodiments, at least one of R⁸ is C1-C3 haloalkyl substituted with hydroxyl. In some embodiments, at least one of R⁸ is trifluoromethyl, 2,2-difluoroethyl, or 2,2,2-trifluoroethyl. In some embodiments, at least one of R⁸ is 1-hydroxy-2,2-difluoroethyl.

In some embodiments, at least one of R⁸ is C1-C3 haloalkoxy. In some embodiments, at least one of R⁸ is trifluoromethoxy.

30 In some embodiments, at least one of R⁸ is 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, amino, C1-C3 haloalkyl, 4-6 membered heterocyclyl, or C1-C3 alkyl optionally substituted with hydroxyl or -NR^ER^F. In

some embodiments, at least one of R^8 is 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$, amino, or C1-C3 haloalkyl. In some embodiments, R^8 is 5-6 membered heteroaryl optionally substituted with C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$.

- 5 In some embodiments, at least one of R^8 is 5-6 membered heteroaryl optionally substituted with halogen, C1-C3 haloalkyl, or C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$. In some embodiments, R^8 is 5-6 membered heteroaryl substituted with C1-C3 alkyl substituted with hydroxyl or $-NR^E R^F$. In some embodiments, R^8 is 5-6 membered heteroaryl substituted with hydroxymethyl, aminomethyl, hydroxyethyl, aminoethyl, propan-2-ol, or propan-2-amine. In
- 10 some embodiments, at least one of R^8 is 5-6 membered heteroaryl optionally substituted with a 4-6 membered heterocyclyl.

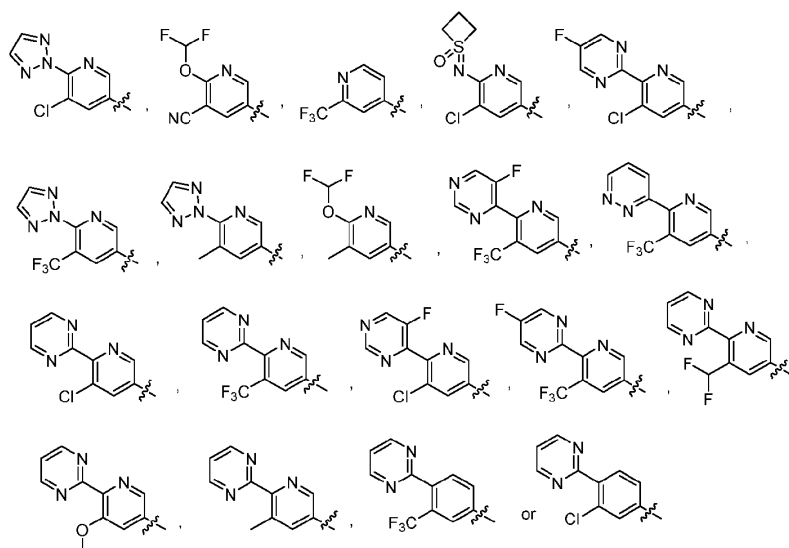
- In some embodiments, R^5 is pyridyl, pyrimidinyl, pyrazinyl, pyrrolyl, or imidazolyl; each of which is substituted with two R^8 : one R^8 is triazolyl, imidazolyl, oxazolyl, pyrazolyl, or pyrrolidinyl; and the other R^8 is methyl, methoxy, trifluoromethyl, trifluoromethoxy, chloro, or
- 15 cyano. In some embodiments, R^5 is pyridyl, pyrimidinyl, or pyrazinyl; each of which is substituted with two R^8 : one R^8 is triazolyl, imidazolyl, oxazolyl, pyrazolyl, or pyrrolidinyl; and the other R^8 is methyl, methoxy, trifluoromethyl, trifluoromethoxy, chloro, or cyano. In some embodiments, R^5 is pyridyl substituted with two R^8 , one R^8 is triazolyl, imidazolyl, or oxazolyl; and the other R^8 is methyl, methoxy, trifluoromethyl, trifluoromethoxy, chloro, or cyano.

- 20 In some embodiments, R^5 is 3-pyridyl or 4-pyridyl substituted with 1-3 independently selected R^8 .

- In some embodiments, R^5 is substituted with two R^8 wherein one R^8 is selected from the group consisting of: cyano, fluoro, chloro, methyl, ethyl, methoxy, trifluoromethyl, and the other R^8 is selected from the group consisting of: 1,2,3-triazol-2-yl, 4-methyl-1,2,3-triazol-2-yl, 4-methyl-1,2,3-triazol-1-yl, 4-amino-1,2,3-triazol-2-yl, 5-cyano-1,2,3-triazol-1-yl, 1,2,3-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 5-amino-1,2,4-triazol-1-yl, 1-methyl-5-amino-1,2,4-triazol-3-yl, 1,2,4-triazol-4-on-2-yl, tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 1-methyl-tetrazol-5-yl, imidazol-1-yl, 1-methyl-imidazol-3-yl, 1-methyl-5-amino-imidazol-3-yl, 3-methylimidazol-2-on-1-yl, 1-methyl-pyrazol-3-yl, 1-methyl-pyrazol-4-yl, 1-methyl-pyrazol-5-yl, pyrrol-1-yl, thiazol-2-yl, isothiazolidin-2-yl-1,1-dioxide, pyrrolidin-2-on-1-yl, oxazol-2-yl, oxadiazol-2-yl, 2-amino-pyrimidin-4-yl, $-(C=O)4$ -methylpiperazin-1-yl, 2-oxoazetidin-1-yl,
- 30

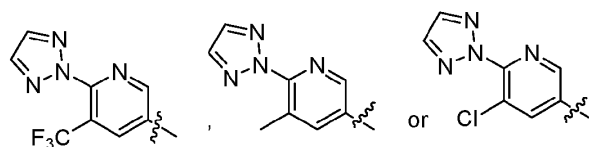
azetidin-1-yl, $-(C=O)N(CH_3)_2$, $-(C=O)NHCH_3$, $-(C=O)NHCH_2CH_3$, $-(C=O)NHCyclopropyl$, $-(C=O)(3,3\text{-difluoroazetidin-1-yl})$, 2-hydroxypropan-2-yl, 1-hydroxyethyl, dimethyl(oxo)- λ^6 -sulfaneylidene, methoxy, ethoxy, difluoromethoxy, methyl, cyano.

In some embodiments, R^5 is:

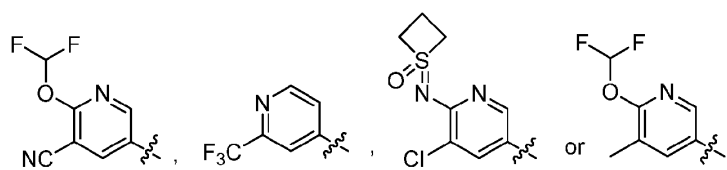


5

In some embodiments, R^5 is:



In some embodiments, R^5 is:

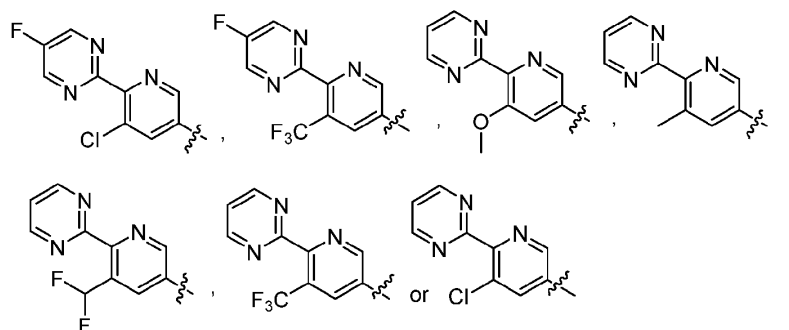


10

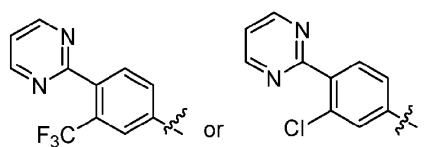
In some embodiments, R^5 is:



In some embodiments, R⁵ is:



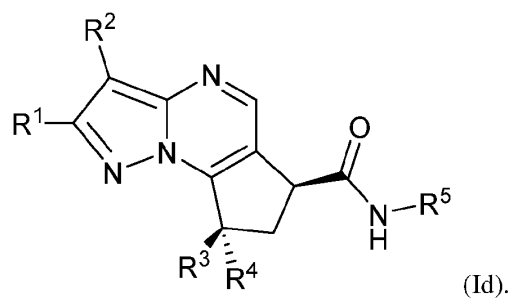
In some embodiments, R⁵ is:



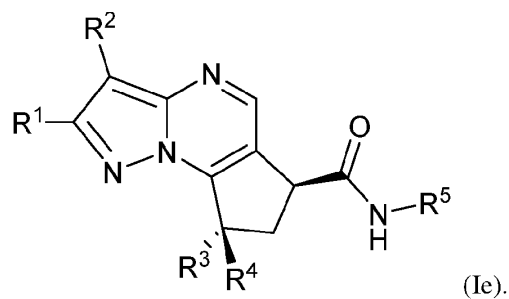
5 In some embodiments, R^X is hydrogen. In some embodiments, R^X is halogen. In some embodiments, R^X is fluoro. In some embodiments, R^X is chloro.

In some embodiments, R^A, R^B, R^C, R^D, R^E, and R^F, are independently hydrogen or C1-C3 alkyl.

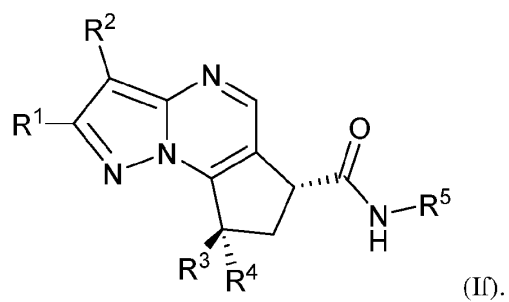
10 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



5 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:



In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has the structure:

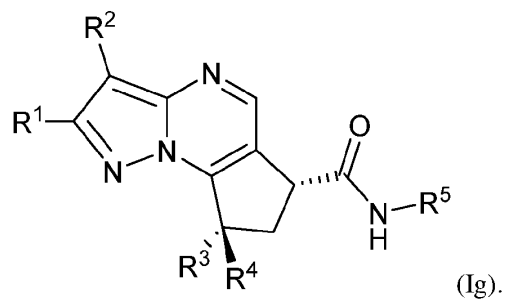
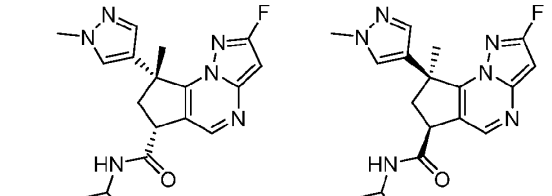
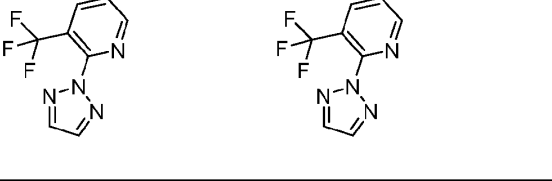
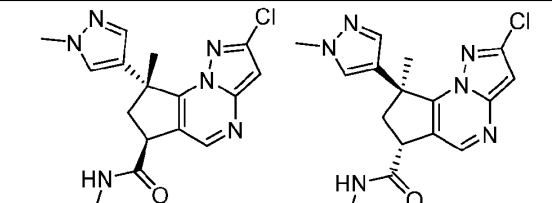
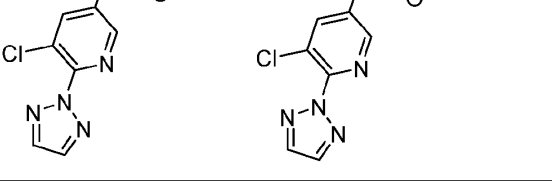
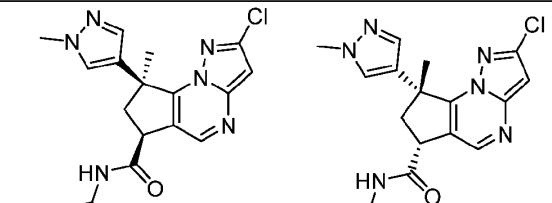
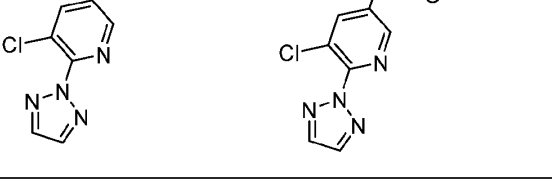
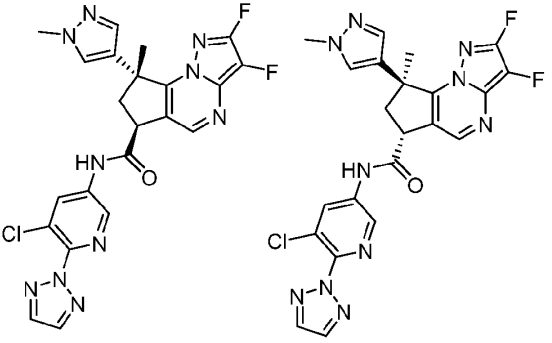
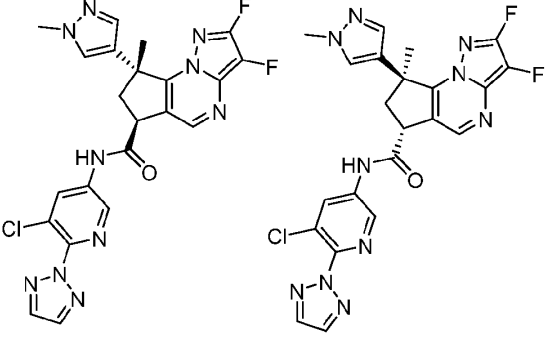
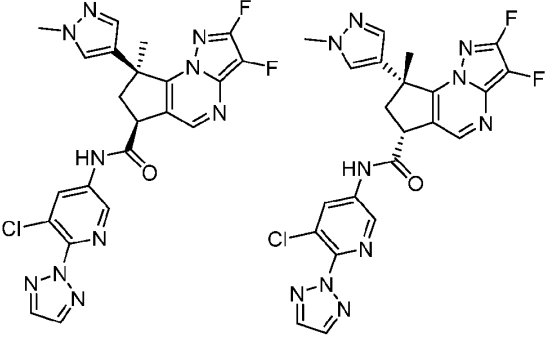
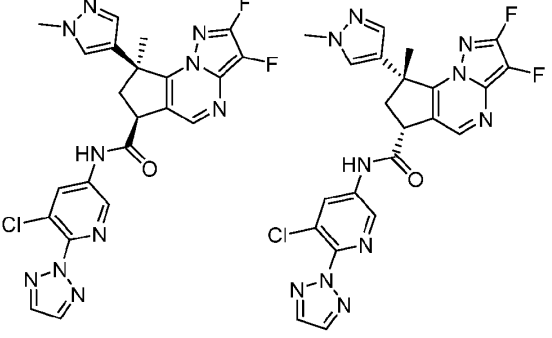
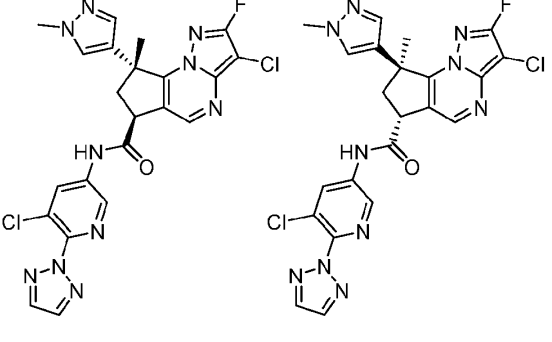
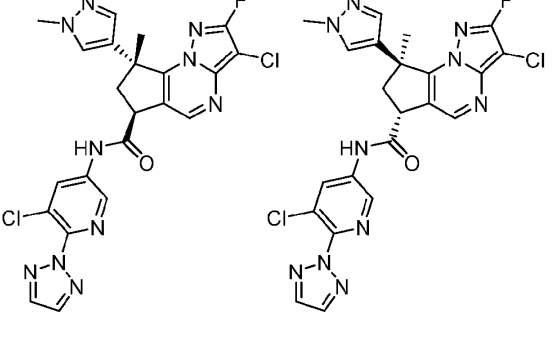
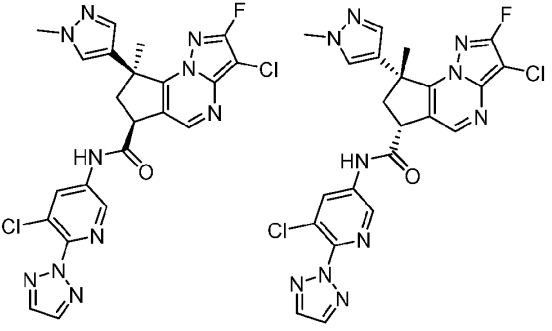
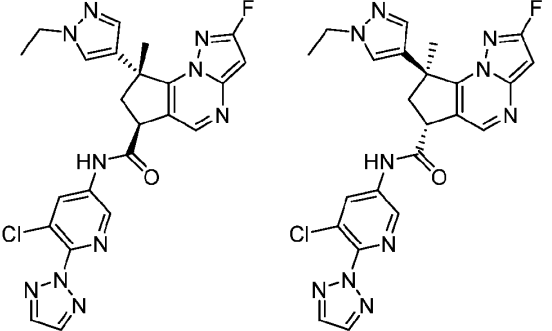
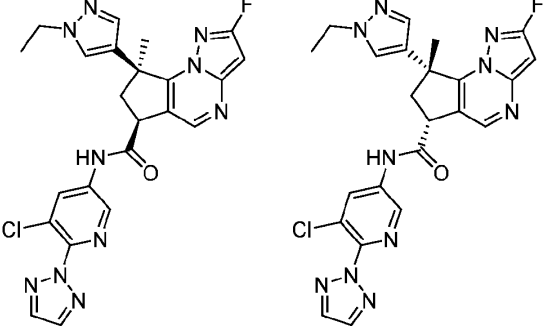
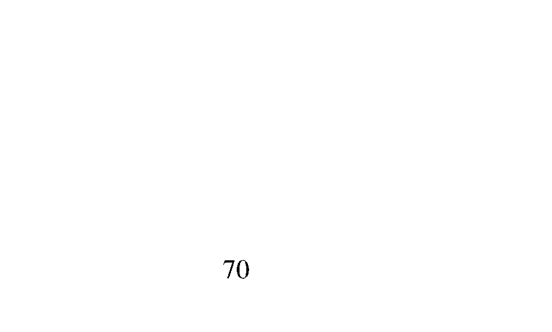


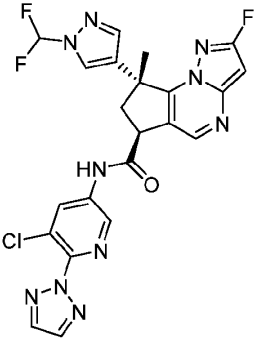
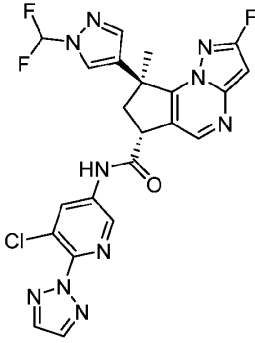
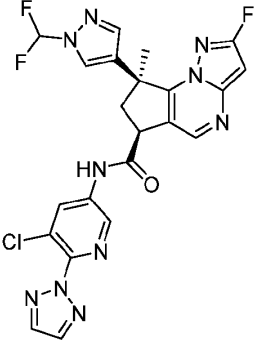
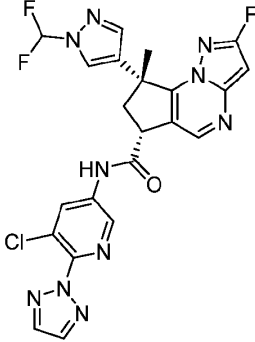
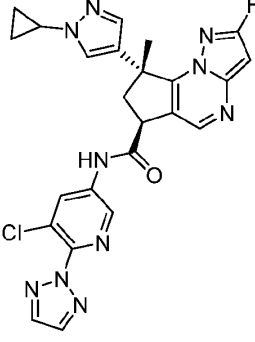
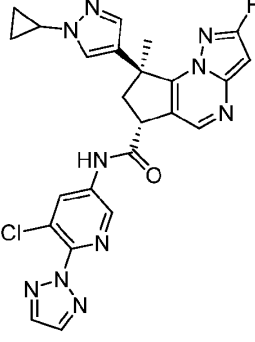
Table 1. Representative examples include the following:

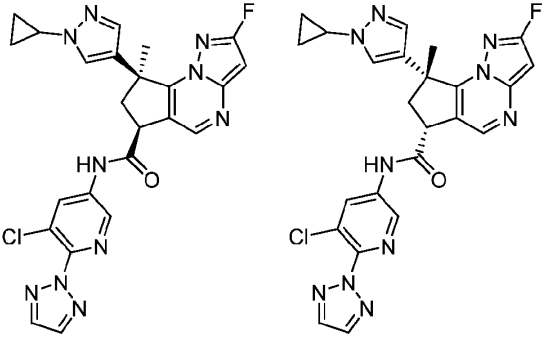
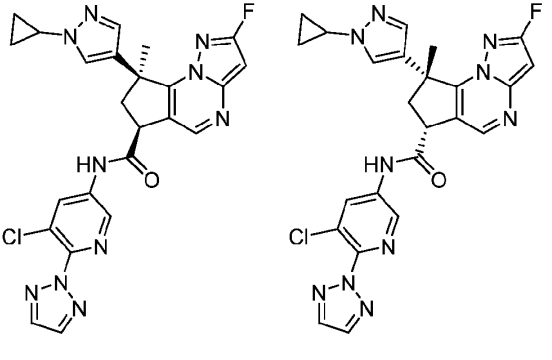
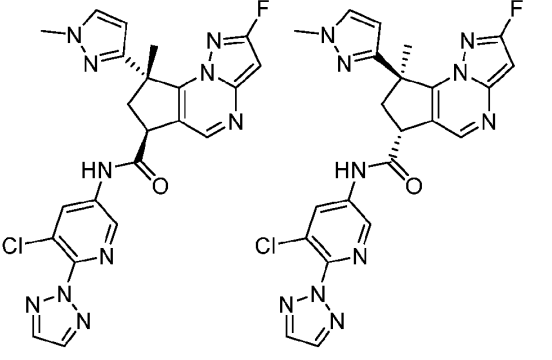
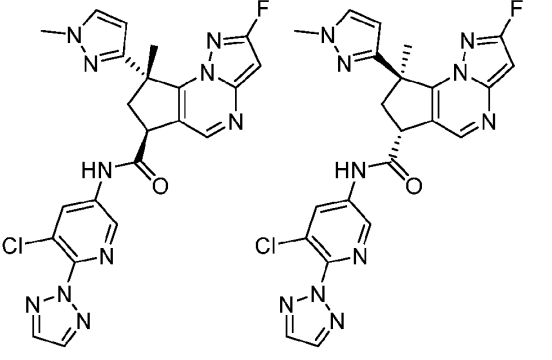
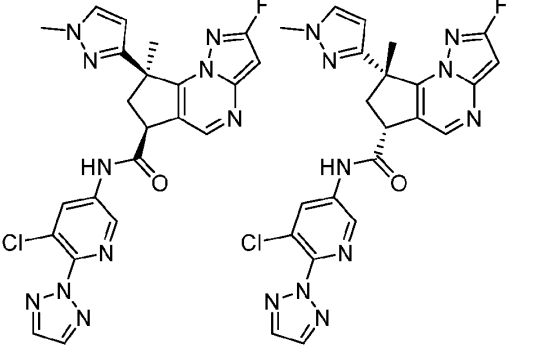
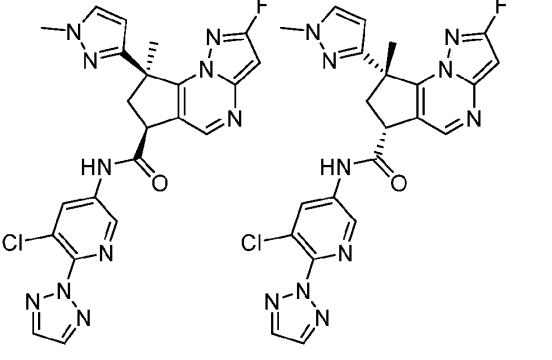
Example Number	Structure
1 (first eluting isomer)* 2 (second eluting isomer)*	
3	
4 (first eluting isomer)* 5 (second eluting isomer)*	

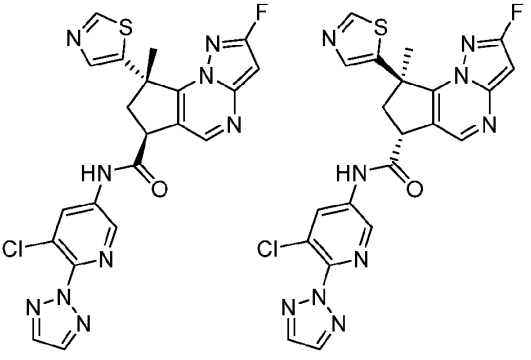
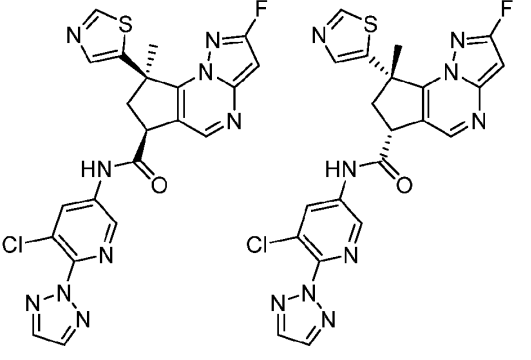
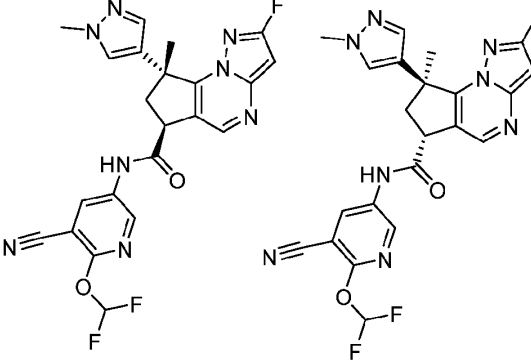
Example Number	Structure
6 (first eluting isomer)*	
7 (second eluting isomer)*	
8 (second eluting isomer)*	
9 (first eluting isomer)*	
10 (first eluting isomer)*	
11 (second eluting isomer)*	

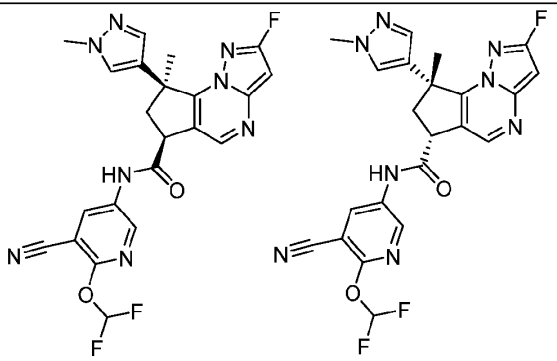
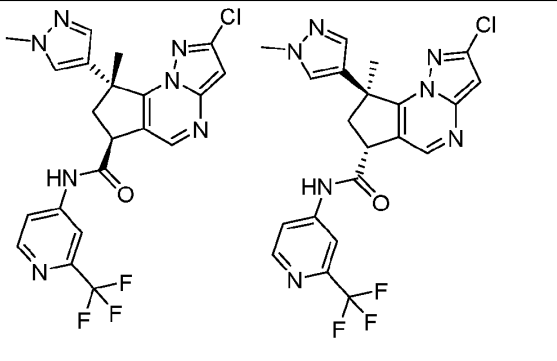
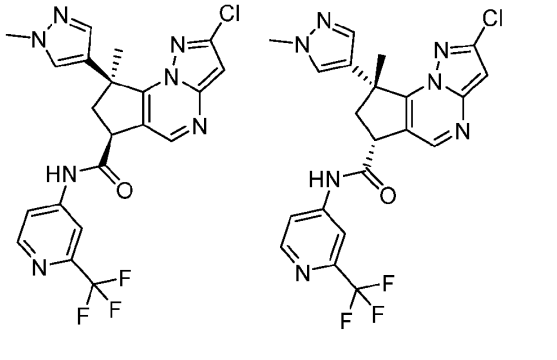
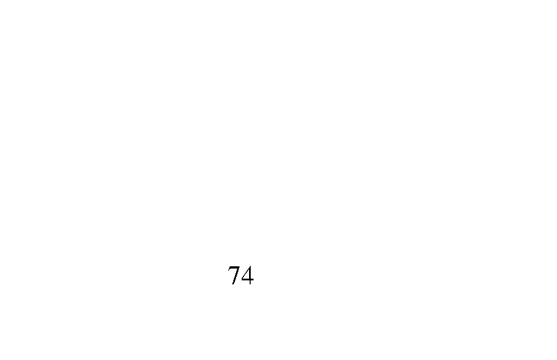
Example Number	Structure
12 (second eluting isomer)*	
13 (first eluting isomer)*	
14 (second eluting isomer)*	
15 (first eluting isomer)*	
16 (second eluting isomer)*	
17 (first eluting isomer)*	

Example Number	Structure
18 (first eluting isomer)*	
19 (second eluting isomer)*	
20 (second eluting isomer)*	
21 (first eluting isomer)*	
22 (second eluting isomer)*	
23 (first eluting isomer)*	

Example Number	Structure
24 (second eluting isomer)*	
25 (first eluting isomer)*	
26 (second eluting isomer)*	
27 (first eluting isomer)*	
28 (second eluting isomer)*	
29 (first eluting isomer)*	

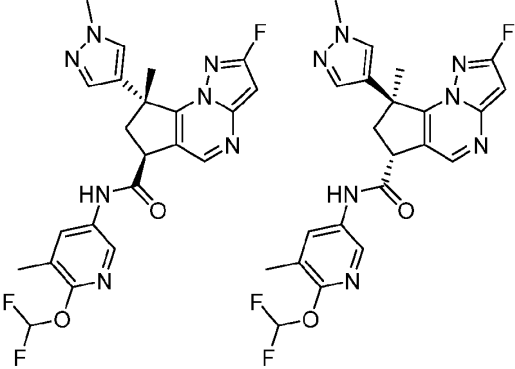
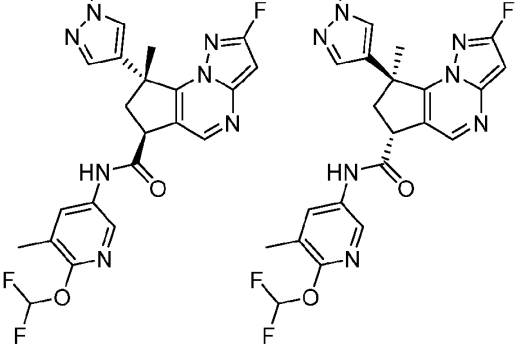
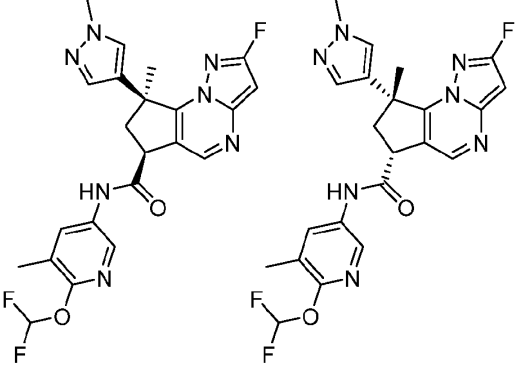
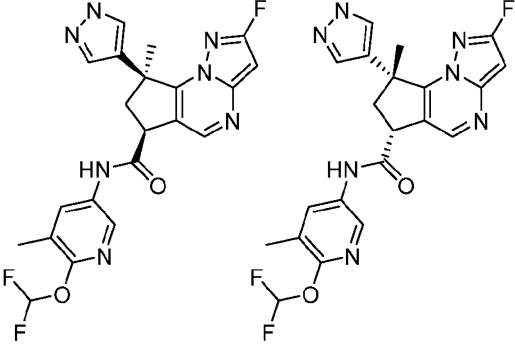
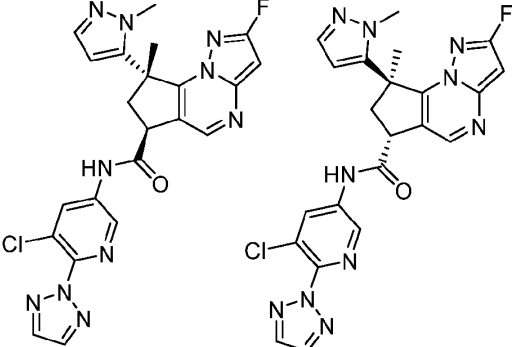
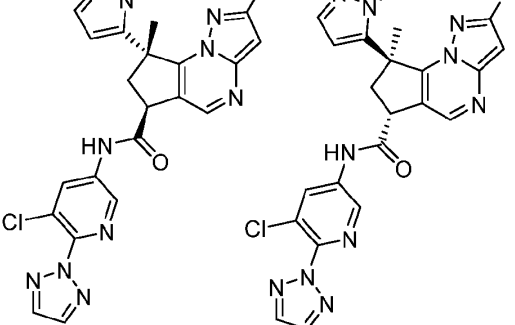
Example Number	Structure
30 (second eluting isomer)*	
31 (first eluting isomer)*	
32 (second eluting isomer)*	
33 (first eluting isomer)*	
34 (first eluting isomer)*	
35 (second eluting isomer)*	

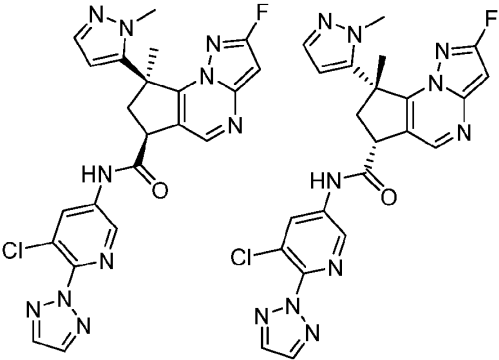
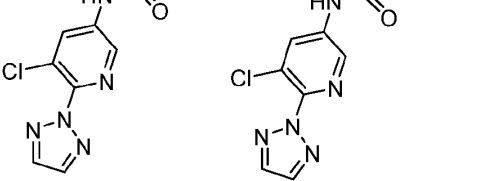
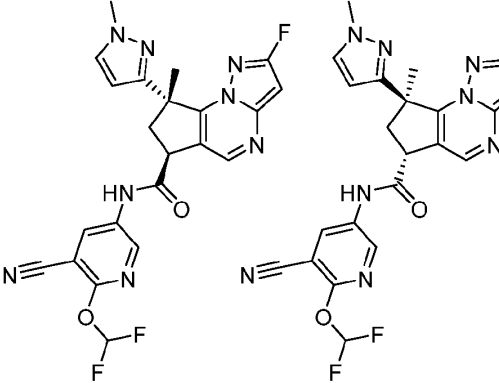
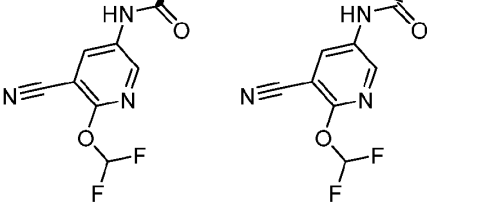
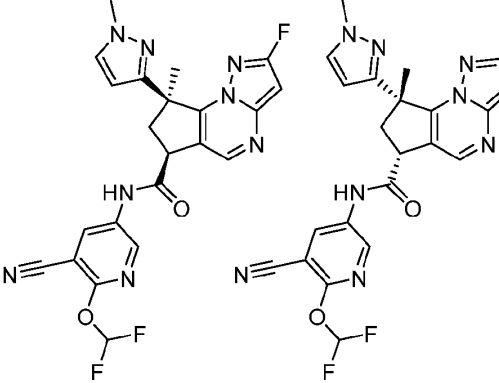
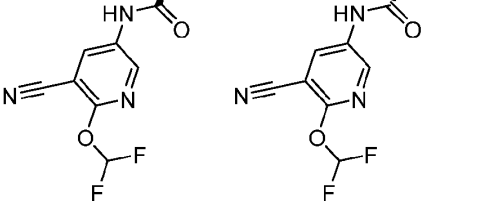
Example Number	Structure
36 (second eluting isomer)* 37 (first eluting isomer)*	
38 (first eluting isomer)* 39 (second eluting isomer)*	
40 (second eluting isomer)* 41 (first eluting isomer)*	

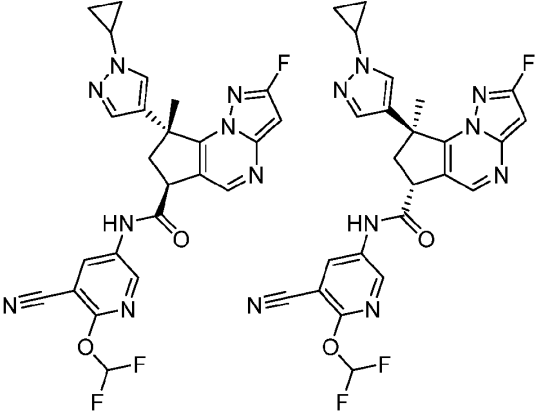
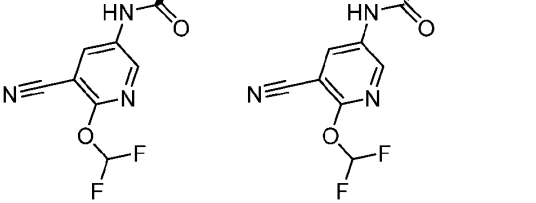
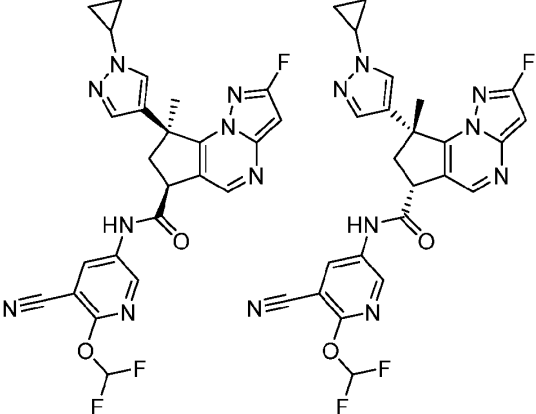
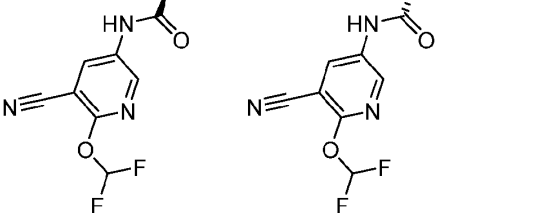
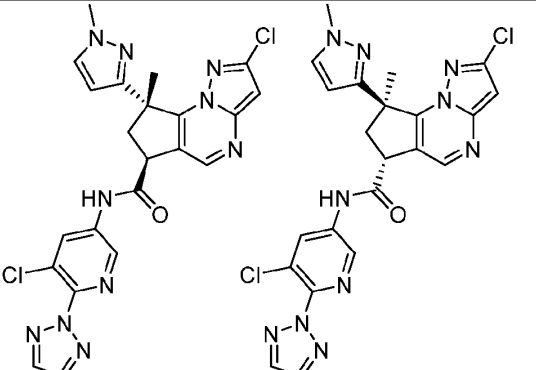
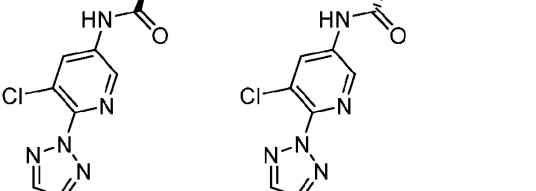
Example Number	Structure
42 (second eluting isomer)*	
43 (first eluting isomer)*	
44 (second eluting isomer)*	
45 (first eluting isomer)*	
46 (first eluting isomer)*	
47 (second eluting isomer)*	

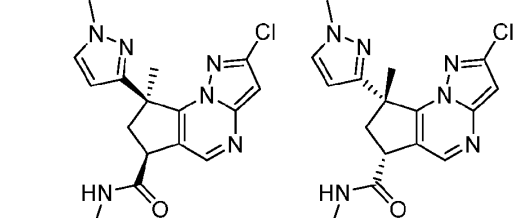
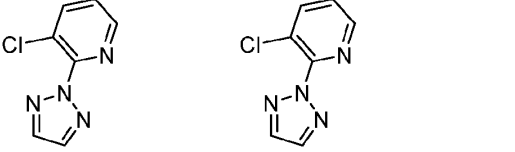
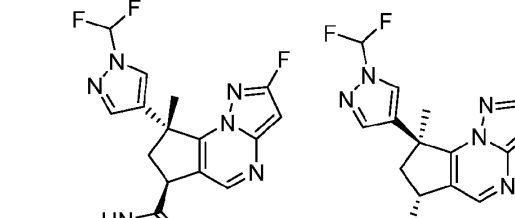
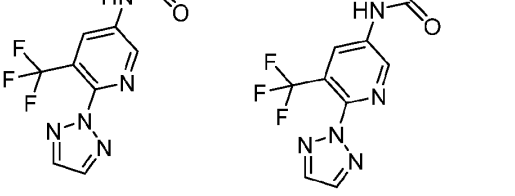
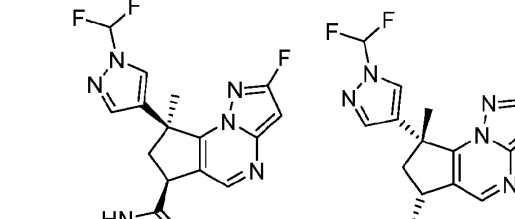
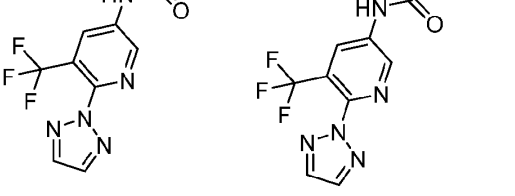
Example Number	Structure
48 (second eluting isomer)* 49 (first eluting isomer)*	
50 (second eluting isomer)* 51 (first eluting isomer)*	
52 (second eluting isomer)* 53 (first eluting isomer)*	

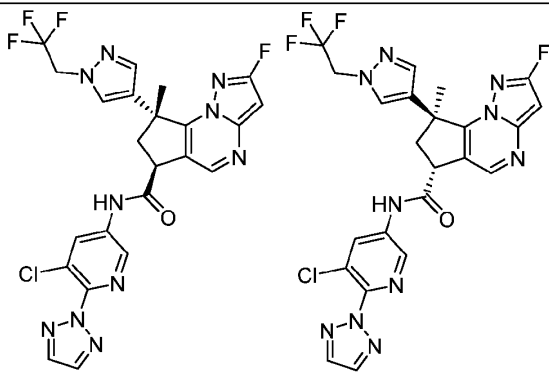
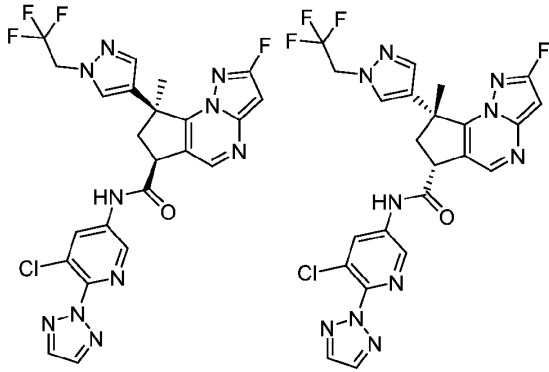
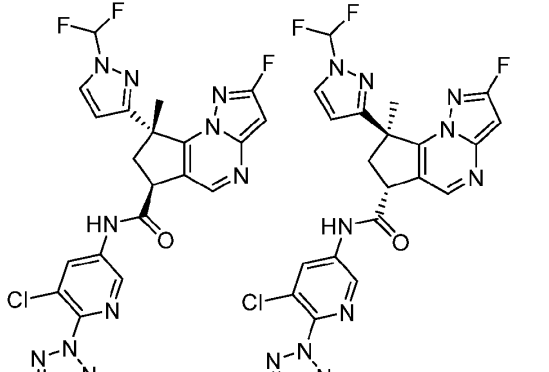
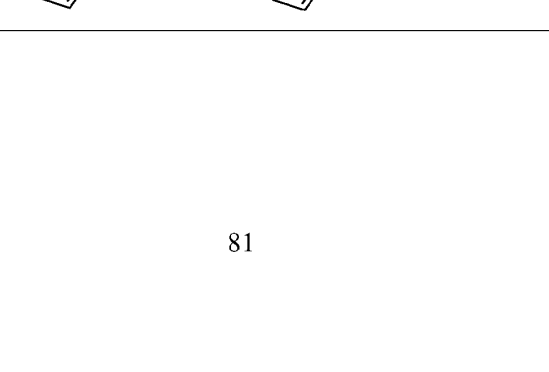
Example Number	Structure
54 (second eluting isomer)* 55 (first eluting isomer)*	
56 (second eluting isomer)* 57 (first eluting isomer)*	
58 (second eluting isomer)* 59 (first eluting isomer)*	

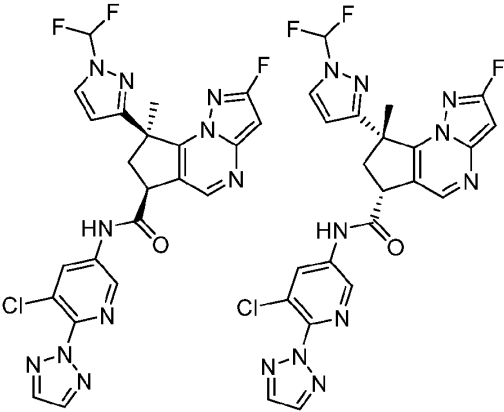
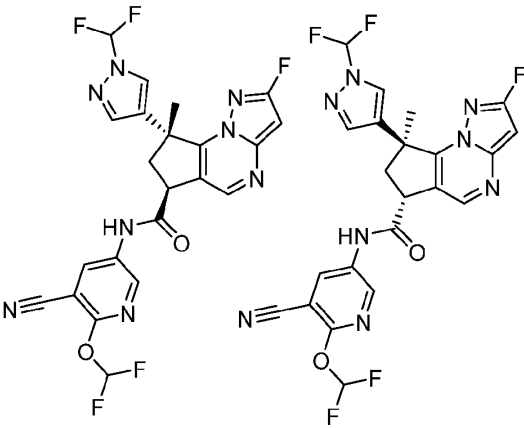
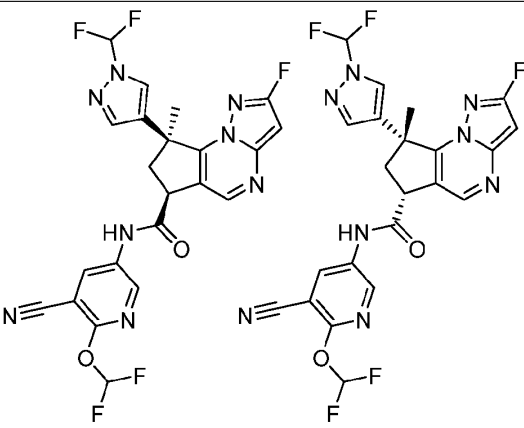
Example Number	Structure
60 (second eluting isomer)*	
61 (first eluting isomer)*	
62 (first eluting isomer)*	
63 (second eluting isomer)*	
64 (second eluting isomer)*	
65 (first eluting isomer)*	

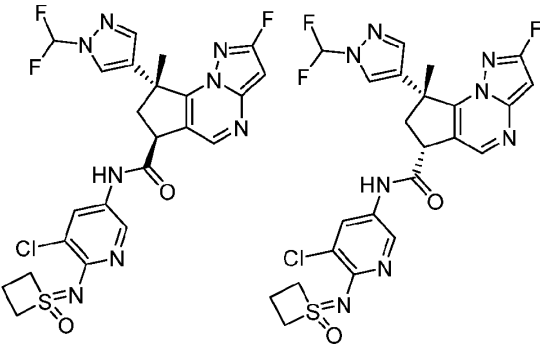
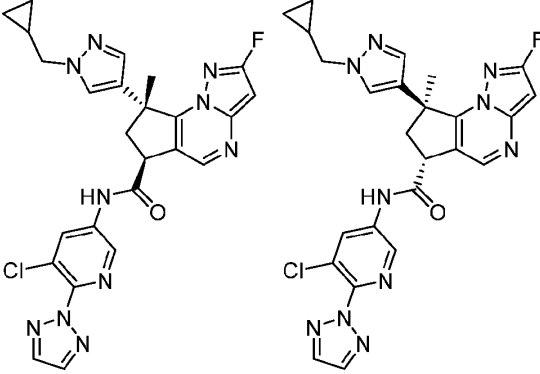
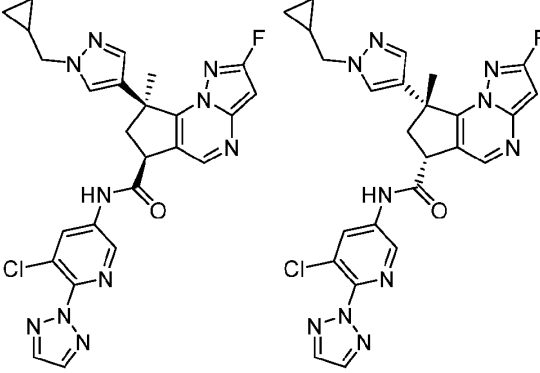
Example Number	Structure
66 (second eluting isomer)*	
67 (first eluting isomer)*	
68 (second eluting isomer)*	
69 (first eluting isomer)*	
70 (second eluting isomer)*	
71 (first eluting isomer)*	

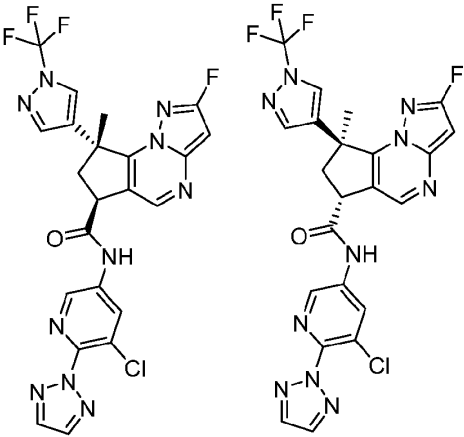
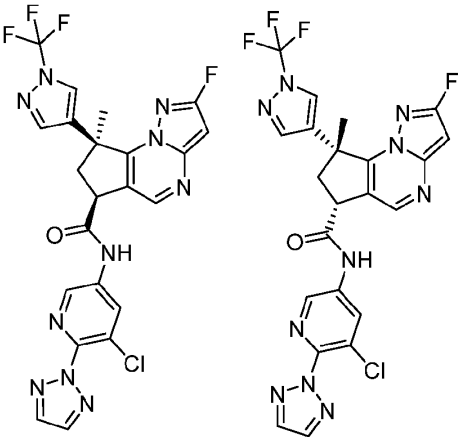
Example Number	Structure
72 (second eluting isomer)*	
73 (first eluting isomer)*	
74 (first eluting isomer)*	
75 (second eluting isomer)*	
76 (second eluting isomer)*	
77 (first eluting isomer)*	

Example Number	Structure
78 (first eluting isomer)*	
79 (second eluting isomer)*	
80 (second eluting isomer)*	
81 (first eluting isomer)*	
82 (second eluting isomer)*	
83 (first eluting isomer)*	

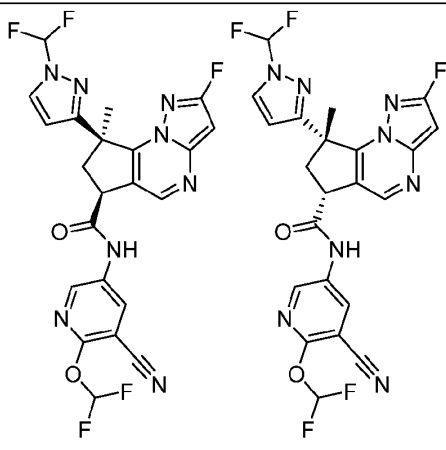
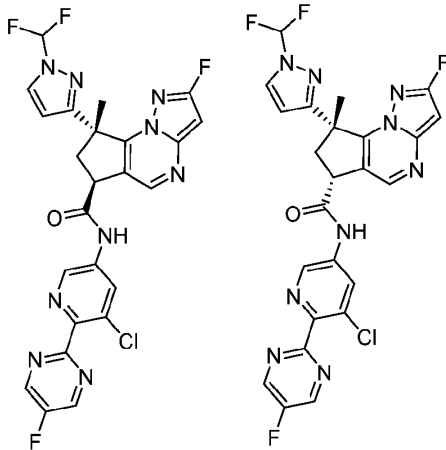
Example Number	Structure
84 (second eluting isomer)*	
85 (first eluting isomer)*	
86 (second eluting isomer)*	
87 (first eluting isomer)*	
88 (second eluting isomer)*	
89 (first eluting isomer)*	

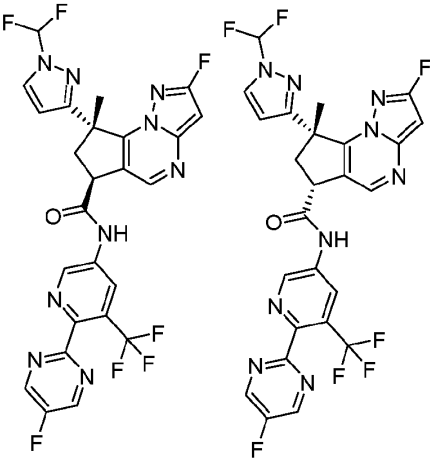
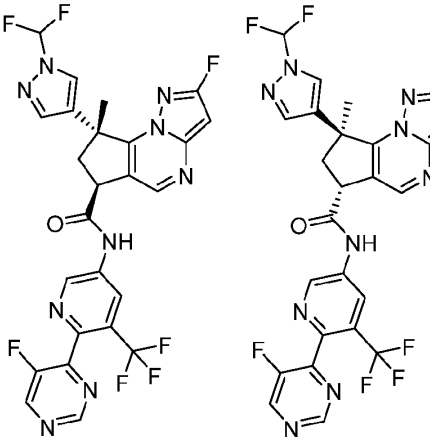
Example Number	Structure
90 (second eluting isomer)* 91 (first eluting isomer)*	
92 (second eluting isomer)* 93 (first eluting isomer)*	
94 (second eluting isomer)* 95 (first eluting isomer)*	

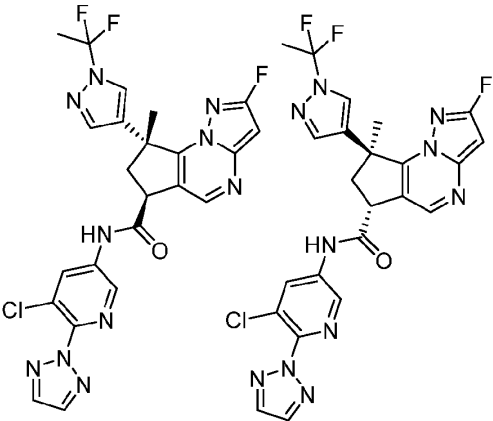
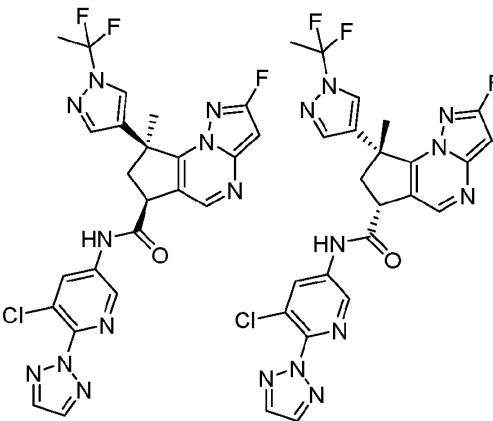
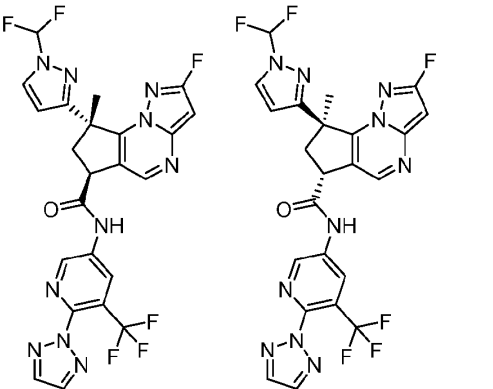
Example Number	Structure
96 and 97	
98 (second eluting isomer)* 99 (first eluting isomer)*	
100 (second eluting isomer)* 101 (first eluting isomer)*	

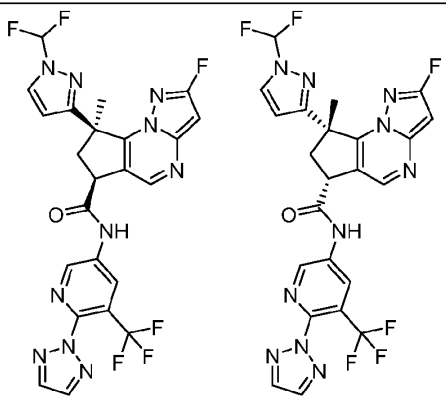
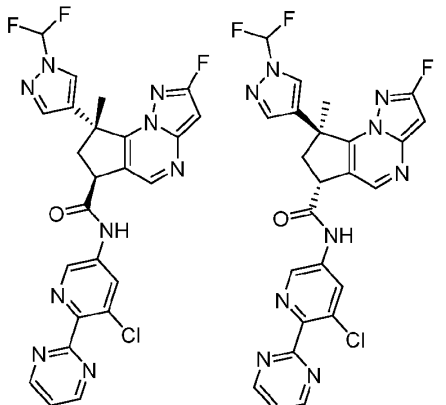
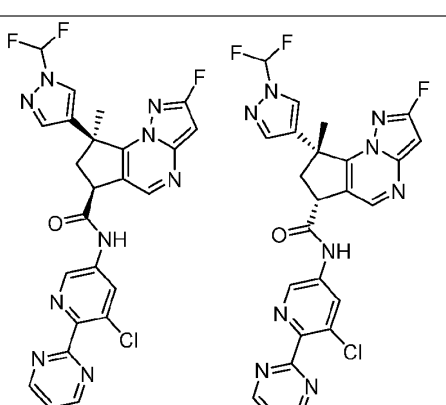
Example Number	Structure
102 (second eluting isomer)* 103 (first eluting isomer)*	
104 (second eluting isomer)* 105 (first eluting isomer)*	

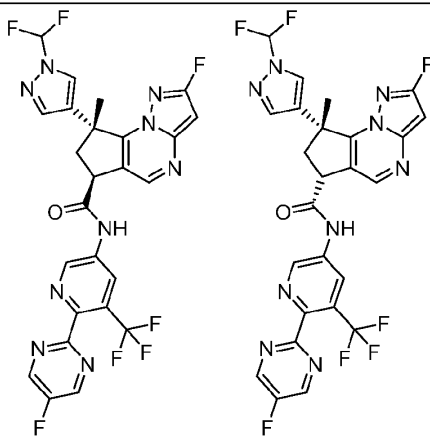
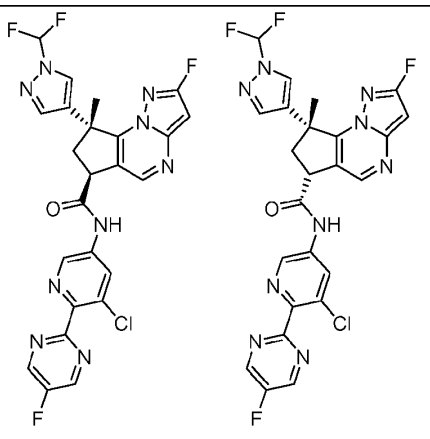
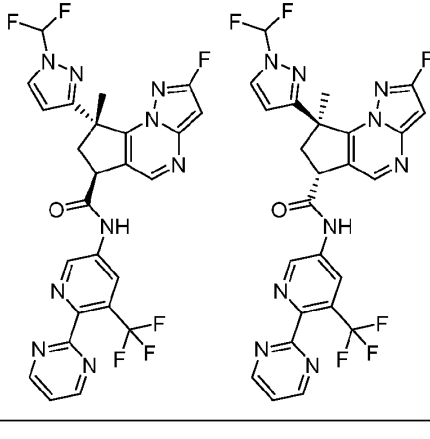
Example Number	Structure
106, 107, 108 and 109 (multiple separation methods)*	
110 (second eluting isomer)* 111 (first eluting isomer)*	

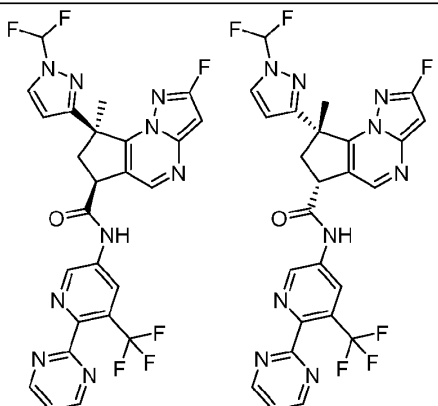
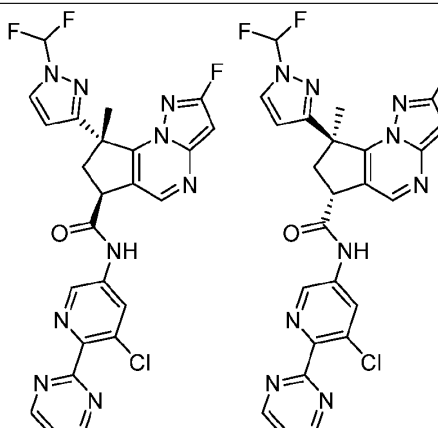
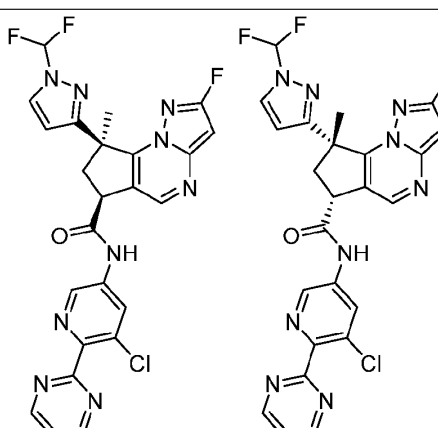
Example Number	Structure
112 (second eluting isomer)* 113 (first eluting isomer)*	
114 and 115	

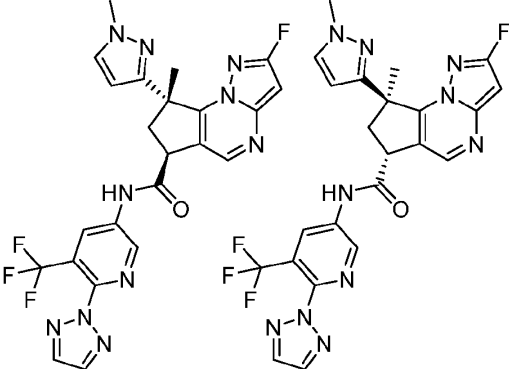
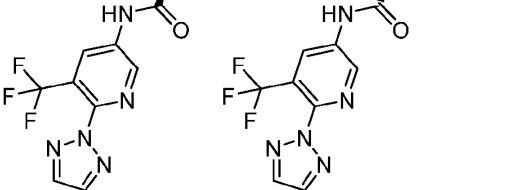
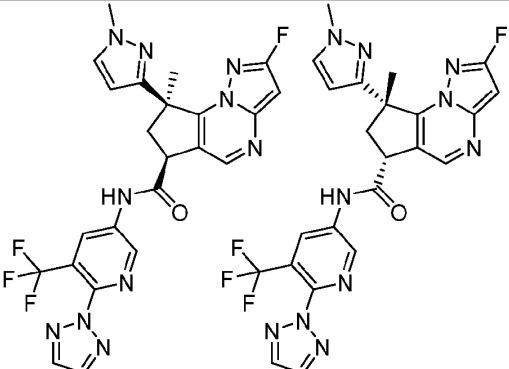
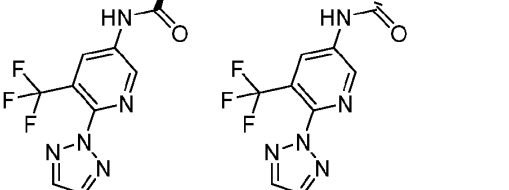
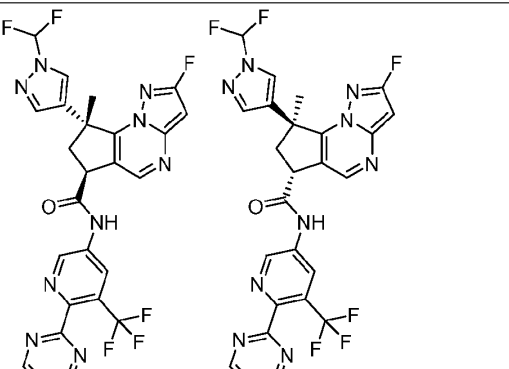
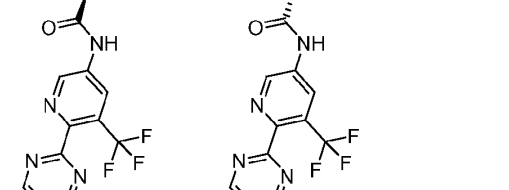
Example Number	Structure
116 and 117	
118 (first eluting isomer)* 119 (second eluting isomer)*	

Example Number	Structure
120 (first eluting isomer)* 121 (second eluting isomer)*	
122 (first eluting isomer)* 123 (second eluting isomer)*	
124 (first eluting isomer)* 125 (second eluting isomer)*	

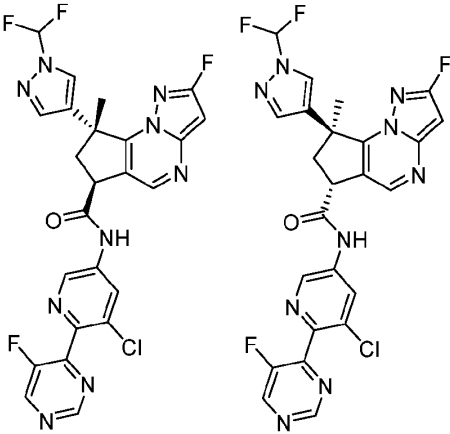
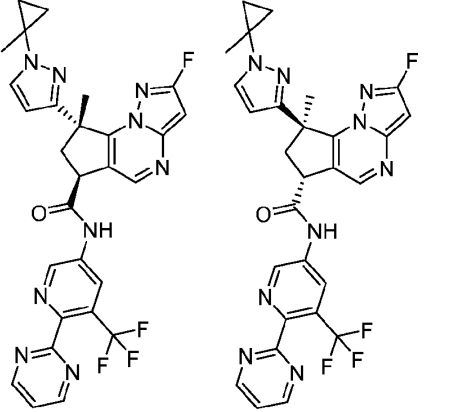
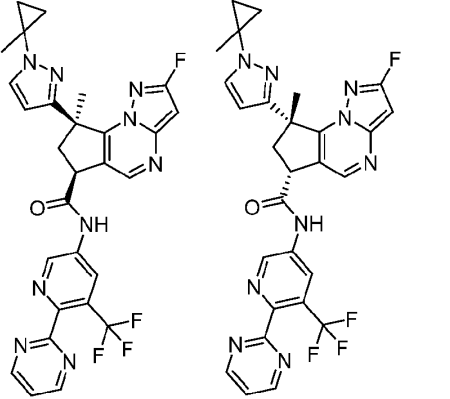
Example Number	Structure
126 (second eluting isomer)* 127 (first eluting isomer)*	
128 (second eluting isomer)* 129 (first eluting isomer)*	
130 (first eluting isomer)* 131 (second eluting isomer)*	

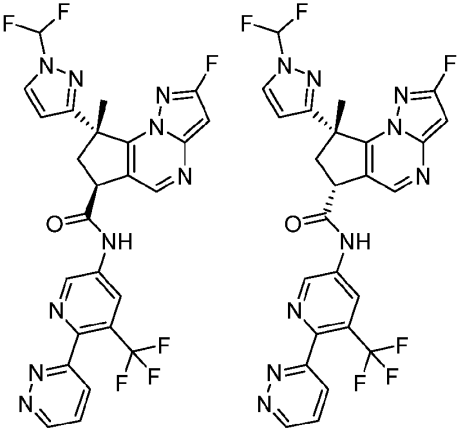
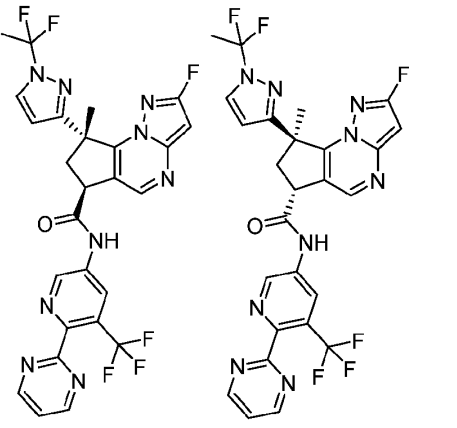
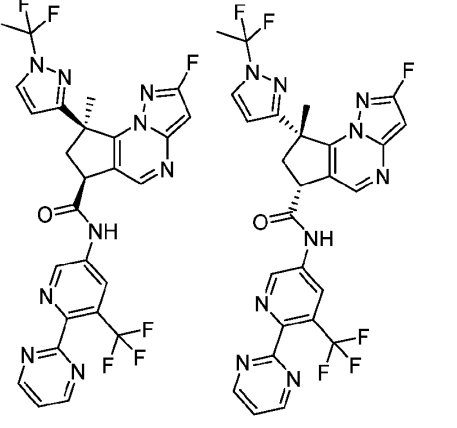
Example Number	Structure
132 and 133	
134 and 135	
136 (second eluting isomer)* 137 (first eluting isomer)*	

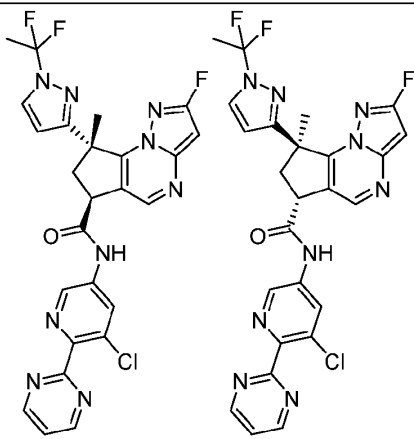
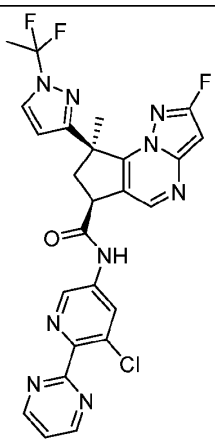
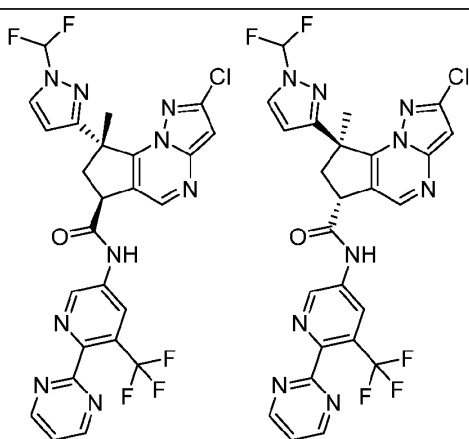
Example Number	Structure
138 (first eluting isomer)* 139 (second eluting isomer)*	
140 (second eluting isomer)* 141 (first eluting isomer)*	
142 (second eluting isomer)* 143 (first eluting isomer)*	

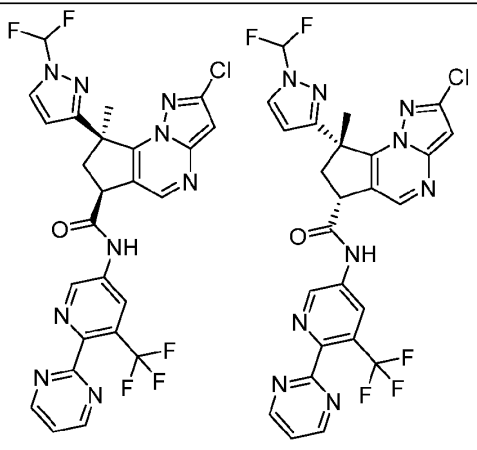
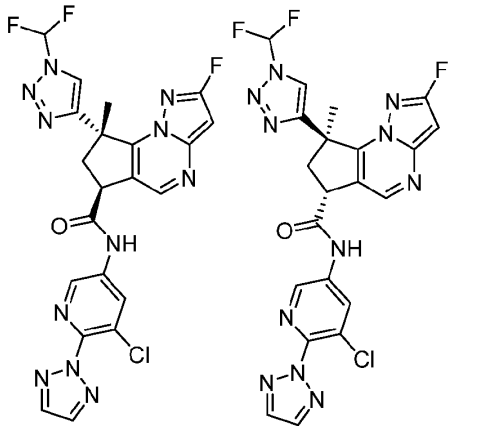
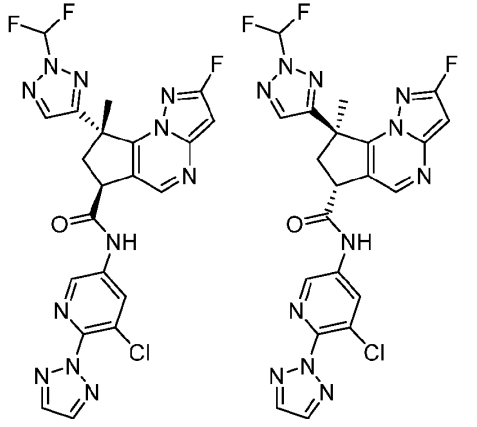
Example Number	Structure
144 (second eluting isomer)*	
145 (first eluting isomer)*	
146 (first eluting isomer)*	
147 (second eluting isomer)*	
148 (second eluting isomer)*	
149 (first eluting isomer)*	

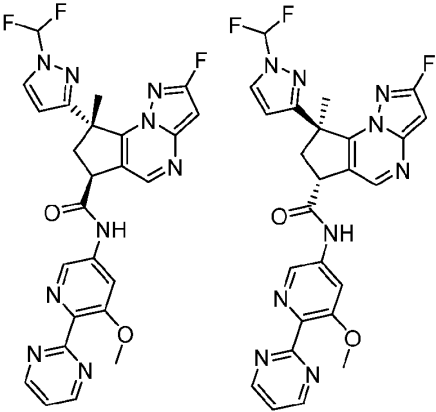
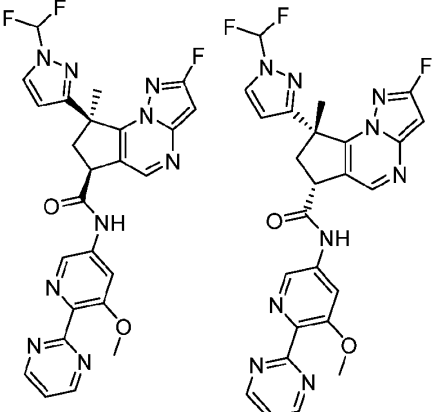
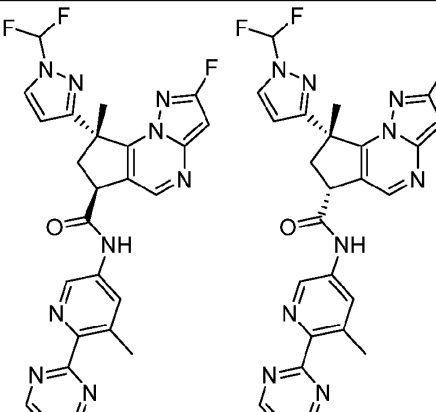
Example Number	Structure
150 (first eluting isomer)* 151 (second eluting isomer)*	
152 (second eluting isomer)* 153 (first eluting isomer)*	
154 (first eluting isomer)* 155 (second eluting isomer)*	

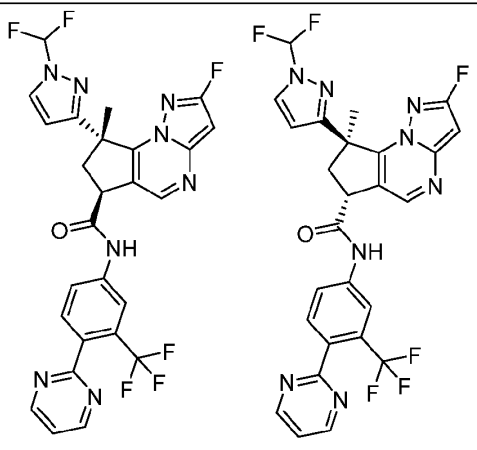
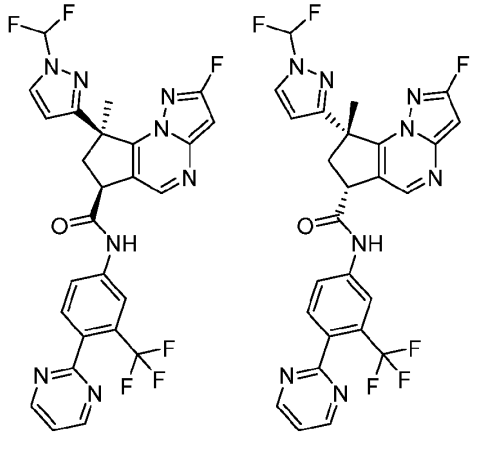
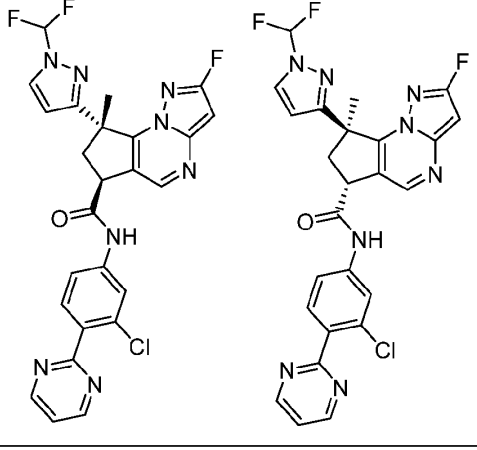
Example Number	Structure
156 (second eluting isomer)* 157 (first eluting isomer)*	
158 (second eluting isomer)* 159 (first eluting isomer)*	
160 (first eluting isomer)* 161 (second eluting isomer)*	

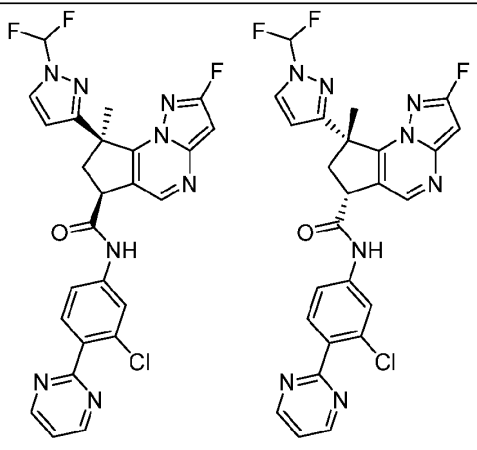
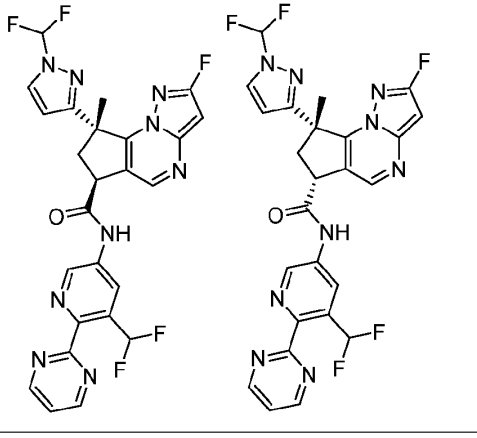
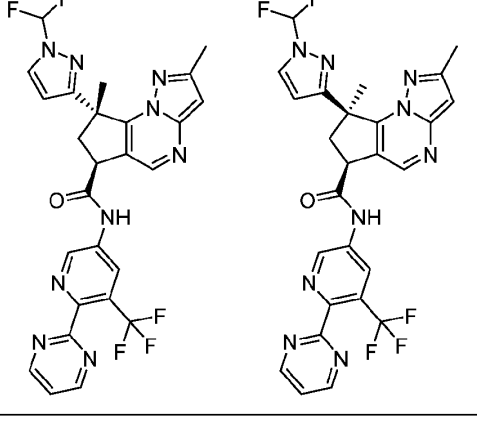
Example Number	Structure
162 and 163	
164 (second eluting isomer)* 165 (first eluting isomer)*	
166 (second eluting isomer)* 167 (first eluting isomer)*	

Example Number	Structure
168 (second eluting isomer)* 169 (first eluting isomer)*	
170	
171 (second eluting isomer)* 172 (first eluting isomer)*	

Example Number	Structure
173 (second eluting isomer)* 174 (first eluting isomer)*	
175 (second eluting isomer)* 176 (first eluting isomer)*	
177 (second eluting isomer)* 178 (first eluting isomer)*	

Example Number	Structure
179 (first eluting isomer)* 180 (second eluting isomer)*	
181 (first eluting isomer)* 182 (second eluting isomer)*	
183 and 184	

Example Number	Structure
185 (second eluting isomer)* 186 (first eluting isomer)*	
187 (second eluting isomer)* 188 (first eluting isomer)*	
189 (second eluting isomer)* 190 (first eluting isomer)*	

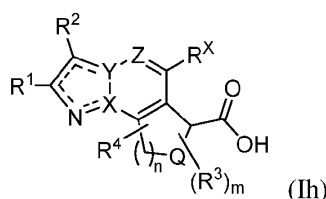
Example Number	Structure
191 (first eluting isomer)* 192 (second eluting isomer)*	
193 and 194	
195 and 196	

*See experimental procedures on details for separation of isomers. The absolute stereochemistry for each separated isomer was not determined.

Processes of Preparation

Provided herein is a process of preparing a compound of Formula (I) (e.g., any compound described herein), comprising:

reacting a compound of Formula (Ih)



with R^5-NH_2 ;

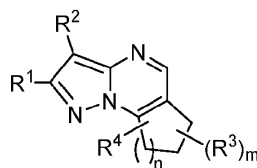
to form the compound of Formula (I).

10 In some embodiments, reacting the compound of Formula (Ih) with R^5-NH_2 (e.g., 5-chloro-6-(triazolyl)pyridin-3-amine) is performed in the presence of $POCl_3$ and pyridine.

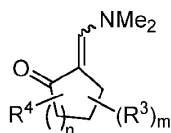
In some embodiments, reacting the compound of Formula (Ih) with R^5-NH_2 is performed in the presence of N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH).

15 In some embodiments, reacting the compound of Formula (Ih) with R^5-NH_2 is performed in the presence of N-methylimidazole (NMI).

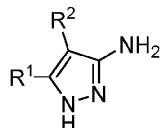
In some embodiments, the compound of Formula (Ih) is prepared from a compound of Formula (Ih-N):



20 In some embodiments (when the compound of Formula (Ih) is prepared from a compound of Formula (Ih-N)), the process comprises reacting a compound of Formula (Ih-N-i)



with a compound of Formula (Ih-N-ii)



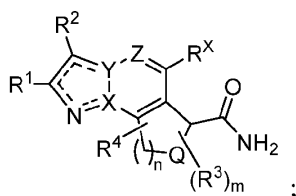
to form the compound of Formula (Ih-N).

In certain embodiments, reacting the compound of Formula (Ih-N-i) with the compound of
 5 Formula (Ih-N-ii) is performed in the presence of acid.

In certain of these embodiments, the acid is selected from the group consisting of hydrochloric acid and acetic acid.

Provided herein is a process of preparing a compound of Formula (I) (e.g., any compound described herein), comprising:

10 reacting a compound of Formula (Ij)



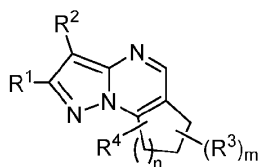
with R⁵-Hal, where Hal is selected from the group consisting of Cl, Br, I, and OSO₂CF₃; to form the compound of Formula (I).

In some embodiments, reacting the compound of Formula (Ij) with R⁵-Hal is performed in
 15 the presence of a catalyst and a ligand.

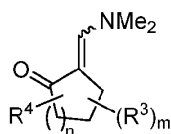
In some embodiments (when reacting the compound of Formula (Ij) with R⁵-Hal is performed in the presence of a catalyst and a ligand), the catalyst is tris(dibenzylideneacetone)dipalladium(0).

In some embodiments (when reacting the compound of Formula (Ij) with R⁵-Hal is
 20 performed in the presence of a catalyst and a ligand), the ligand is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

In some embodiments, the compound of Formula (Ij) is prepared from a compound of Formula (Ih-N):

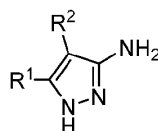


In some embodiments, the process comprises reacting a compound of Formula (Ih-N-i)



5

with a compound of Formula (Ih-N-ii)



to form the compound of Formula (Ih-N).

In some embodiments, reacting the compound of Formula (Ih-N-i) with the compound of Formula (Ih-N-ii) is performed in the presence of acid.

In some embodiments (when reacting the compound of Formula (Ih-N-i) with the compound of Formula (Ih-N-ii) is performed in the presence of acid), the acid is selected from the group consisting of hydrochloric acid and acetic acid.

Methods of Treatment

Some embodiments provide a method of treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder) in a subject in need of such treatment, the method comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, or systemic lupus erythematosus (SLE).

Some embodiments provide a method of treating an inflammatory disorder (e.g., a MALT1-associated inflammatory disorder) in a subject in need of such treatment, the method comprising administering to the subject an effective amount of a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the inflammatory disorder is chronic graft versus host disease (cGVHD).

Some embodiments provide a method of treating cancer (e.g., a MALT1-associated cancer) in a subject in need of such treatment, the method comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating a MALT1-associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of a MALT1 gene, a MALT1 protease, or the expression or activity or level of any of the same in a sample from the subject; and b) administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease, or the expression or activity or level of any of the same includes one or more fusion proteins.

In some embodiments of any of the methods or uses described herein, the cancer (e.g., MALT1-associated cancer) is a hematological cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., MALT1-associated cancer) is a solid tumor. In some embodiments of any of the methods or uses described herein, the cancer (e.g., MALT1-associated cancer) is a lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (e.g., papillary thyroid cancer, medullary thyroid cancer (e.g., sporadic medullary thyroid cancer or hereditary medullary thyroid cancer), differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid adenoma, endocrine gland neoplasms, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, or cervical cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., MALT1-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer,

childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, neoplasms by site, neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, cutaneous angiosarcoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, 5
ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, thoracic neoplasms, head and 10
neck neoplasms, CNS tumor, primary CNS tumor, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, 15
melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, neoplasms by site, neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, 20
neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, lung neoplasm, pulmonary cancer, pulmonary neoplasms, respiratory tract neoplasms, bronchogenic carcinoma, bronchial neoplasms, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, 25
plasma cell neoplasm, pleuropulmonary blastoma, pregnancy-associated breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, colon cancer, colonic neoplasms, renal cell cancer, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cancer, Spitz tumors, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell 30
lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis, unknown primary carcinoma, urethral cancer, uterine

cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

In some embodiments, the cancer is a hematological cancer, such as a leukemia or a lymphoma. In some embodiments, a hematological cancer (e.g., hematological cancers that are MALT1-associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In some embodiments, the hematological cancer (e.g., the hematological cancer that is a MALT1-associated cancer) is AML or CMML.

In some embodiments, the cancer is glioblastoma, chronic myelogenous leukemia, myeloid leukemia, or non-Hodgkin's lymphoma.

In some embodiments, cancer is non-Hodgkin's lymphoma. In other embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL). In other embodiments the cancer is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL). In other embodiments the cancer is mantle cell lymphoma (MCL). In other embodiments, the cancer is marginal zone lymphoma (MZL). In other embodiments the cancer is chronic lymphatic leukemia (CLL). In other embodiments the cancer is mature B-cell neoplasms.

In some embodiments the cancer is T-cell acute lymphoblastic leukemia.

In some embodiments, the cancer (e.g., the MALT1-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are MALT1-associated cancers) include, for example, lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, breast cancer, colon cancer, colorectal cancer, prostate cancer, renal cell carcinoma, neuroblastoma, and melanoma. *See, e.g.,* Jiang et al., Cancer Research 2011, 71, 2183-2192; *see also*, Pan et al., Mol Cancer Res 2016, 14, 93-102 and Penas et al., Blood 2010,

115, 2214-2219.

In some embodiments, the subject is a human.

Compounds of Formula (I) and pharmaceutically acceptable salts thereof are also useful for treating a MALT1-associated cancer. Compounds of Formula (I) and pharmaceutically acceptable salts thereof are also useful for treating a MALT1-associated autoimmune disorder. Compounds of Formula (I) and pharmaceutically acceptable salts thereof are also useful for treating a MALT1-associated inflammatory disease.

Accordingly, also provided herein is a method for treating a subject diagnosed with or identified as having a MALT1-associated cancer, e.g., any of the exemplary MALT1-associated cancers disclosed herein, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

In some embodiments of any of the methods provided herein, a compound of Formula (I) is selected from Examples 1-196.

Dysregulation of a MALT1 protease, a MALT1 gene, or the expression or activity or level of any (e.g., one or more) of the same can contribute to tumorigenesis. For example, a fusion protein can have increased protease activity as compared to a wild-type MALT1 protein, increased expression (e.g., increased levels) of a wild-type MALT1 protease in a mammalian cell can occur due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell), MALT1 mRNA splice variants may also result in dysregulation of MALT1.

In some aspects, provided herein is a method for treating cancer in a subject in need thereof, including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided herein is a method for treating a CBM complex pathway-associated cancer (such as any of those disclosed herein) in a subject in need thereof, including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided is a method for treating a cancer in a subject in need thereof, including (a) identifying the cancer as being a CBM complex pathway-associated cancer; and (b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Identifying the cancer identifying the cancer in the subject as a CBM complex pathway-

associated cancer can be performed by any appropriate method. In some embodiments, the step of identifying the cancer in the subject as a CBM complex pathway-associated cancer includes performing an assay to detect dysregulation in a CBM complex pathway-associated gene, a CBM complex pathway-associated protease protein, or expression or activity or level of any of the same in a sample from the subject. In some embodiments, the method further includes obtaining a sample from the subject (e.g., a biopsy sample). An assay can be any appropriate assay. In some embodiments, the assay is selected from the group consisting of sequencing (e.g., pyrosequencing or next generation sequencing), immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

Also provided herein is a method for treating a cancer in a subject in need thereof, including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a subject identified as having a CBM complex pathway-associated cancer.

Also provided herein is a method of treating a MALT1-associated cancer in a subject, including administering to a subject identified or diagnosed as having a MALT1-associated cancer an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Provided herein is also a method for treating cancer in a subject in need thereof, including: (a) determining that the cancer is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same; and (b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Determining that the cancer is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same can be performed using any appropriate method. In some embodiments, the step of determining that the cancer in the subject is a MALT1-associated cancer includes performing an assay to detect dysregulation in a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same in a sample from the subject. In some embodiments, the method further includes obtaining a sample from the subject (e.g., a biopsy sample). An assay can be any appropriate assay. In some embodiments, the assay is selected from the group consisting of sequencing (e.g., pyrosequencing or next generation sequencing), immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

As described herein, a CBM complex pathway-associated cancer can be any appropriate CBM complex pathway-associated cancer (such as any of those described herein). In some embodiments, a CBM complex pathway-associated cancer is selected from the group consisting of a CBM complex pathway cell surface receptor-associated cancer, a cancer associated with a signal transducer between a cell surface receptor and a CBM complex, a component of a CBM complex-associated cancer, a MALT1 protease substrate-associated cancer, a cancer associated with a component of the NF- κ B pathway downstream of a CBM complex, a cancer associated with a component of the JNK pathway downstream of a CBM complex, and a combination thereof. In some embodiments, the CBM complex pathway cell surface receptor-associated cancer is selected from the group consisting of a CD28-associated cancer, a BCR-associated cancer, a HER1-associated cancer, a HER2-associated cancer, and combinations thereof. In some embodiments, the cancer associated with a signal transducer between a cell surface receptor and a CBM complex is a protein kinase C beta (PKC β)-associated cancer, a protein kinase C theta (PCK θ)-associated cancer, or a combination thereof. In some embodiments, the component of a CBM complex-associated cancer is selected from the group consisting of a MALT1-associated cancer, a CARD11-associated cancer, a CARD14-associated cancer, a CARD10-associated cancer, a CARD9-associated cancer, a BCL10-associated cancer, and combinations thereof. In some embodiments, the component of a CBM complex-associated cancer is selected from the group consisting of a MALT1-associated cancer, a CARD11-associated cancer, a BCL10-associated cancer, and combinations thereof. See, e.g., Tables B1, B2, and B3 for exemplary dysregulations in MALT1, CARD11, and BCL10. In some embodiments, the MALT1 protease substrate-associated cancer is selected from the group consisting of a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, a RelB-associated cancer, a Regnase 1-associated cancer, a roquin-1-associated cancer, a HOIL1-associated cancer, a NIK associated cancer, a LIMA1 α -associated cancer, and a combination thereof. In some embodiments, the MALT1 protease substrate-associated cancer is selected from the group consisting of a BCL10-associated cancer, an A20-associated cancer, a CYLD-associated cancer, and combinations thereof. See, e.g., Tables B3 and B4 for exemplary dysregulations in BCL10 and A20. In some embodiments, the cancer associated with a component of the NF- κ B pathway downstream of a CBM complex is selected from the group consisting of a TAK1-associated cancer, a TRAF6-associated cancer, a TAB1-associated cancer, a TAB2-associated cancer, a TAB3-associated cancer, a MKK7-

associated cancer, an IKK α -associated cancer, an IKK β -associated cancer, an IKK γ -associated cancer, an I κ B α -associated cancer, a p50-associated cancer, a p65 (RelA)-associated cancer, a c-Rel-associated cancer, and combinations thereof. In some embodiments, the cancer associated with a component of the NF- κ B pathway downstream of a CBM complex is an IKK γ -associated cancer.

5 In some embodiments, the cancer associated with a component of the JNK pathway downstream of a CBM complex is selected from the group consisting of a JNK1-associated cancer, a JNK2-associated cancer, a JNK3-associated cancer, a MYD88 transcription factor-associated cancer, an AP-1 transcription factor-associated cancer, and combinations thereof.

In some embodiments, the CBM complex pathway-associated cancer is a MALT1-associated cancer. A MALT1-associated cancer can have any appropriate dysregulation, such as
10 any of those described herein. In some embodiments, the MALT1-associated cancer comprises an IAP2-MALT1 fusion. In some embodiments, the MALT1-associated cancer comprises an IGH-MALT1 fusion.

Also provided herein are methods of treating CBM complex pathway-associated diseases
15 or disorders, autoimmune disorders, and inflammatory disorders. Accordingly, provided herein is a method for treating an autoimmune disorder in a subject in need thereof, including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided herein is a method of treating a MALT1-associated autoimmune disorder in a subject, including administering to a subject identified or diagnosed as having a
20 MALT1-associated autoimmune disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some cases, provided herein is a method for treating an autoimmune disorder in a subject in need thereof, including: (a) determining that the autoimmune disorder is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same; and (b) administering to the subject an effective
25 amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Provided also herein is a method of treating a MALT1-associated autoimmune disorder in a subject, including administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a subject determined to have a MALT1-associated autoimmune disorder. In addition, provided herein is a method for treating an inflammatory disorder in a subject in need thereof,
30 including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some cases, provided herein is a method of treating a

MALT1-associated inflammatory disorder in a subject, including administering to a subject identified or diagnosed as having a MALT1-associated inflammatory disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided herein is a method for treating an inflammatory disorder in a subject in need thereof, including: (a) 5 determining that the inflammatory disorder is associated with a dysregulation of a MALT1 gene, a MALT1 protease, or expression or activity or level of any of the same; and (b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Provided also herein is a method of treating a MALT1-associated inflammatory disorder in a subject, including administering an effective amount of a compound of Formula (I), 10 or a pharmaceutically acceptable salt thereof to a subject determined to have a MALT1-associated inflammatory disorder

Additionally provided herein is a method for treating a CBM complex pathway-associated disease or disorder in a subject in need thereof, including administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided 15 is a method for treating a disease or disorder in a subject in need thereof, including: (a) identifying the cancer as being a CBM complex pathway-associated disease or disorder; and (b) administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In addition, provided herein is a method for treating a disease or disorder in a subject in need thereof, including: administering to the subject an effective amount of a compound of 20 Formula (I), or a pharmaceutically acceptable salt thereof to a subject identified as having a CBM complex pathway-associated disease or disorder.

A CBM complex pathway-associated disease or disorder can be any appropriate CBM complex pathway-associated disease or disorder, such as any of those described herein. In some embodiments, the CBM complex pathway-associated disease or disorder is an autoimmune 25 disease. In some embodiments, the CBM complex pathway-associated disease or disorder is an inflammatory disease. In some embodiments, the CBM complex pathway-associated cancer is selected from the group consisting of a CBM complex pathway cell surface receptor-associated cancer, a disease or disorder associated with a signal transducer between a cell surface receptor and a CBM complex, a component of a CBM complex-associated cancer, a MALT1 protease 30 substrate-associated cancer, a disease or disorder associated with a component of the NF- κ B pathway downstream of a CBM complex, a disease or disorder associated with a component of the

JNK pathway downstream of a CBM complex, and a combination thereof. In some embodiments, the CBM complex pathway-associated disease or disorder is a MALT1-associated disease or disorder.

In some cases, compounds of Formula (I), or a pharmaceutically acceptable salt thereof
5 can be useful for inhibiting the processes of cells, such as inhibiting the proliferation of cells. Accordingly, provided herein is a method for inhibiting mammalian cell proliferation, including contacting the mammalian cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Also provided herein is a method for inhibiting CBM complex pathway activity in a mammalian cell, including contacting the mammalian cell with a compound of Formula (I), or a
10 pharmaceutically acceptable salt thereof. Provided also herein is a method for inhibiting MALT1 protease activity in a mammalian cell, including contacting the mammalian cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting occurs *in vivo*. In some embodiments, the contacting occurs *in vitro*. A mammalian cell can be any appropriate cell. In some embodiments, the mammalian cell is a mammalian immune cell. In some
15 embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is a mammalian CBM complex pathway-associated cancer cell. In some embodiments, the mammalian cancer cell is a mammalian MALT1-associated cancer cell. In some embodiments, the mammalian cell has dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same. In some embodiments, the
20 dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same is an IAP2-MALT1 fusion, an IGH-MALT1 fusion, or a combination thereof.

Compounds of Formula (I), or a pharmaceutically acceptable salt thereof can also be useful in the manufacture of medicaments. Accordingly, provided herein is a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for
25 the treatment of a CBM complex pathway-associated disease or disorder. A CBM complex pathway-associated disease or disorder can be any appropriate CBM complex pathway-associated disease or disorder, such as those described herein. In some embodiments, the CBM complex pathway-associated disease or disorder is selected from the group consisting of a CBM complex pathway cell surface receptor-associated cancer, a disease or disorder associated with a signal
30 transducer between a cell surface receptor and a CBM complex, a component of a CBM complex-associated cancer, a MALT1 protease substrate-associated cancer, a disease or disorder associated

with a component of the NF- κ B pathway downstream of a CBM complex, a disease or disorder associated with a component of the JNK pathway downstream of a CBM complex, and a combination thereof. In some embodiments, the CBM complex pathway-associated disease or disorder is a CBM complex pathway-associated autoimmune disorder. In some embodiments, the
5 CBM complex pathway-associated disease or disorder is a CBM complex pathway-associated inflammatory disorder. In some embodiments, the CBM complex pathway-associated disease or disorder is a CBM complex pathway-associated cancer. In some embodiments, the CBM complex pathway-associated disease or disorder is a MALT1-associated disease or disorder. In some
10 embodiments, the MALT1-associated disease or disorder comprises a dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same is an IAP2-MALT1 fusion, an IGH-MALT1 fusion, or a combination thereof.

In some embodiments, the compounds provided herein exhibit brain and/or central nervous
15 system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a MALT1 protease in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in an effective amount. For example, treatment of a subject with cancer (e.g., a MALT1-associated cancer such as a
20 MALT1-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the subject. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas such as glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and
25 craniopharyngiomas (see, for example, the tumors listed in Louis, D.N. et al. *Acta Neuropathol* 131(6), 803-820 (June 2016)). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the subject has previously been treated with another anticancer agent, e.g., another protease inhibitor (e.g., a compound that is not a compound of Formula (I)). In some
30 embodiments, the brain tumor is a metastatic brain tumor. In some embodiments, the subject has previously been treated with another anticancer agent, e.g., another protease inhibitor (e.g., a compound that is not a compound of Formula (I)).

In some embodiments of any of the methods or uses described herein, an assay used to determine whether the subject has a dysregulation of a gene (e.g., a MALT1 gene), or a protein (e.g., a MALT1 protein), or expression or activity or level of any of the same, using a sample from a subject can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or expression or activity or levels of any of the same. In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the subject. In some embodiments, the subject is a subject suspected of having a MALT1-associated cancer, a subject having one or more symptoms of a MALT1-associated cancer, and/or a subject that has an increased risk of developing a MALT1-associated cancer).

In some embodiments, dysregulation of a gene (e.g., a MALT1 gene), a MALT1 protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a gene (e.g., a MALT1 protein), a MALT1 protein (e.g., a MALT 1 protein), or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments,

cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same.

In some embodiments, ctDNA derived from a single gene can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more, or any number of genes in between these numbers) can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes can be detected using any of a variety of commercially-available testing panels (e.g., commercially available testing panels designed to detect dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same). Liquid biopsies can be used to detect dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same including, without limitation, point mutations or single nucleotide variants (SNVs), copy number variants (CNVs), genetic fusions (e.g., translocations or rearrangements), insertions, deletions, or any combination thereof. In some embodiments, a liquid biopsy can be used to detect a germline mutation. In some embodiments, a liquid biopsy can be used to detect a somatic mutation. In some embodiments, a liquid biopsy can be used to detect a primary genetic mutation (e.g., a primary mutation or a primary fusion that is associated with initial development of a disease, e.g., cancer). In some embodiments, a dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same identified using a liquid biopsy is also present in a cancer cell that is present in the subject (e.g., in a tumor). In some embodiments, any of the types of dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same described herein can be detected using a liquid biopsy. In some embodiments, a genetic mutation identified via a liquid biopsy can be used to identify the subject as a candidate for a particular treatment. For example, detection of dysregulation of a gene (e.g., a MALT1 gene), a protein (e.g., a MALT1 protein), or the expression or activity or level of any of the same in the subject can indicate that the subject will be responsive to a treatment that includes administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Liquid biopsies can be performed at multiple times during a course of diagnosis, a course of monitoring, and/or a course of treatment to determine one or more clinically relevant parameters including, without limitation, progression of the disease and/or efficacy of a treatment. For example, a first liquid biopsy can be performed at a first time point and a second liquid biopsy can be performed at a second time point during a course of diagnosis, a course of monitoring, and/or a course of treatment. In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), and the second time point can be a time point after subject has developed the disease (e.g., the second time point can be used to diagnose the subject with the disease). In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), after which the subject is monitored, and the second time point can be a time point after monitoring the subject. In some embodiments, the first time point can be a time point after diagnosing a subject with a disease, after which a treatment is administered to the subject, and the second time point can be a time point after the treatment is administered; in such cases, the second time point can be used to assess the efficacy of the treatment (e.g., if the genetic mutation(s) detected at the first time point are reduced in abundance or are undetectable). In some embodiments, a treatment to be administered to a subject can include a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the efficacy of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be determined by assessing the allele frequency of a dysregulation of a gene (e.g., a *MALT1* gene) in cfDNA obtained from a subject at different time points, e.g., cfDNA obtained from the subject at a first time point and cfDNA obtained from the subject at a second time point, where at least one dose of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject between the first and second time points. Some embodiments of these methods can further include administering to the subject at least one dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, between the first and second time points. For example, a reduction (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a

45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction, a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10%
5 to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99% reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99%
10 reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to
15 about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction) in the allele frequency (AF) of the dysregulation of a gene (e.g., MALT1 gene) in the cfDNA obtained from the subject at the second time point as compared to the allele frequency (AF) of the dysregulation of a gene (e.g., MALT1 gene) in the cfDNA obtained from the subject at the first time point indicates that the compound of Formula (I), or a pharmaceutically acceptable
20 salt thereof, was effective in the subject. In some embodiments, the AF is reduced such that the level is below the detection limit of the instrument. Alternatively, an increase in the allele frequency (AF) of the dysregulation of a gene (e.g., MALT1 gene) in the cfDNA obtained from the subject at the second time point as compared to the allele frequency (AF) of the dysregulation of a gene (e.g., MALT1 gene) in the cfDNA obtained from the subject at the first time point
25 indicates that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, was not effective in the subject. Some embodiments of these methods can further include, administering additional doses of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject in which a compound of Formula (I), or a pharmaceutically acceptable salt thereof, was determined to be effective. Some embodiments of these methods can further include,
30 administering a different treatment (e.g., a treatment that does not include the administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as a monotherapy) to a

subject in which a compound of Formula (I), or a pharmaceutically acceptable salt thereof, was determined not to be effective.

In some examples of these methods, the time difference between the first and second time points can be about 1 day to about 1 year, about 1 day to about 11 months, about 1 day to about 10 months, about 1 day to about 9 months, about 1 day to about 8 months, about 1 day to about 7 months, about 1 day to about 6 months, about 1 day to about 5 months, about 1 day to about 4 months, about 1 day to about 3 months, about 1 day to about 10 weeks, about 1 day to about 2 months, about 1 day to about 6 weeks, about 1 day to about 1 month, about 1 day to about 25 days, about 1 day to about 20 days, about 1 day to about 15 days, about 1 day to about 10 days, about 1 day to about 5 days, about 2 days to about 1 year, about 5 days to about 1 year, about 10 days to about 1 year, about 15 days to about 1 year, about 20 days to about 1 year, about 25 days to about 1 year, about 1 month to about 1 year, about 6 weeks to about 1 year, about 2 months to about 1 year, about 3 months to about 1 year, about 4 months to about 1 year, about 5 months to about 1 year, about 6 months to about 1 year, about 7 months to about 1 year, about 8 months to about 1 year, about 9 months to about 1 year, about 10 months to about 1 year, about 11 months to about 1 year, about 1 day to about 7 days, about 1 day to about 14 days, about 5 days to about 10 days, about 5 day to about 20 days, about 10 days to about 20 days, about 15 days to about 1 month, about 15 days to about 2 months, about 1 week to about 1 month, about 2 weeks to about 1 month, about 1 month to about 3 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 8 months, or about 7 months to about 9 months. In some embodiments of these methods, the subject can be previously identified as having a cancer having a dysregulated gene (e.g., any of the examples of a dysregulated gene described herein) (e.g., a MALT1 gene). In some embodiments of these methods, a subject can have been previously diagnosed as having any of the types of cancer described herein. In some embodiments of these methods, the subject can have one or more metastases (e.g., one or more brain metastases).

In some of the above embodiments, the cfDNA comprises ctDNA such as MALT1-associated ctDNA. For example, the cfDNA is ctDNA such as MALT1-associated ctDNA. In some embodiments, at least some portion of cfDNA is determined to be MALT1-associated ctDNA, for example, a sequenced and/or quantified amount of the total cfDNA is determined to have a MALT1 fusion and/or overexpression of MALT1.

Although the genetic basis of tumorigenesis may vary between different cancer types, the

cellular and molecular mechanisms required for metastasis appear to be similar for all solid tumor types. During a metastatic cascade, the cancer cells lose growth inhibitory responses, undergo alterations in adhesiveness and produce enzymes that can degrade extracellular matrix components. This leads to detachment of tumor cells from the original tumor, infiltration into the
5 circulation through newly formed vasculature, migration and extravasation of the tumor cells at favorable distant sites where they may form colonies.

Accordingly, also provided herein are methods for inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula
10 (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. Such methods can be used in the treatment of one or more of the cancers described herein. *See, e.g.*, US Publication No. 2013/0029925; International Publication No. WO 2014/083567; and US Patent No. 8,568,998. *See also, e.g.*, Hezam K et al., *Rev Neurosci* 2018 Jan 26;29:93-98; Gao L, et al., *Pancreas* 2015 Jan;44:134-143; Ding K et al., *J Biol Chem* 2014 Jun 6; 289:16057-71; and Amit
15 M et al., *Oncogene* 2017 Jun 8; 36:3232-3239. In some embodiments, the cancer is a MALT1-associated cancer. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is used in combination with an additional therapy or another therapeutic agent, as described herein. For example, a first or second MALT1 protease inhibitor.

The term “metastasis” is an art known term and means the formation of an additional tumor
20 (e.g., a solid tumor) at a site distant from a primary tumor in a subject, where the additional tumor includes the same or similar cancer cells as the primary tumor.

Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer that include: selecting, identifying, or diagnosing a subject as having a MALT1-associated cancer, and administering an
25 effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to the subject selected, identified, or diagnosed as having a MALT1-associated cancer. Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer that includes administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a subject having a
30 MALT1-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer can be compared to the risk of

developing a metastasis or an additional metastasis in the subject prior to treatment, or as compared to a subject or a population of subjects having a similar or the same MALT1-associated cancer that has received no treatment or a different treatment.

5 The phrase “risk of developing a metastasis” means the risk that a subject having a primary tumor will develop an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject over a set period of time, where the additional tumor includes the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing a metastasis in a subject having a cancer are described herein.

10 The phrase “risk of developing additional metastases” means the risk that a subject having a primary tumor and one or more additional tumors at sites distant from the primary tumor (where the one or more additional tumors include the same or similar cancer cells as the primary tumor) will develop one or more further tumors distant from the primary tumor, where the further tumors include the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing additional metastasis are described herein.

15 Some embodiments described herein provide methods of treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder), such as rheumatoid arthritis, multiple sclerosis, and SLE, the method comprising administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

20 Some embodiments described herein provide methods of treating an inflammatory disorder (e.g., a MALT1-associated autoimmune disorder), such as chronic graft versus host disease, the method comprising administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

Also provided is a method for inhibiting MALT1 protease activity in a mammalian cell, comprising contacting the mammalian cell with a compound of Formula (I). In some
25 embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some embodiments, the contacting is *in vivo*, wherein the method comprises administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a subject having a mammalian cell having MALT1 protease activity. In some embodiments, the mammalian cell is a mammalian immune cell. In some embodiments, the mammalian cell is a mammalian
30 cancer cell. In some embodiments, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a MALT1-associated mammalian cancer cell.

Also provided is a method for inhibiting MALT1 protease activity in a mammalian mammalian cell, comprising contacting the mammalian cell with a compound of Formula (I). In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some embodiments, the contacting is *in vivo*, wherein the method comprises administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a mammal having a mammalian cell having MALT1 protease activity. In some embodiments, the mammalian cell is a mammalian immune cell. In some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a MALT1-associated mammalian cancer cell. In some embodiments, the mammalian cell is a gastrointestinal mammalian cell.

As used herein, the term “contacting” refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, “contacting” a MALT1 protease with a compound provided herein includes the administration of a compound provided herein to a subject, such as a human, having a MALT1 protease, as well as, for example, introducing a compound provided herein into a sample containing a mammalian cellular or purified preparation containing the MALT1 protease.

Also provided herein is a method of inhibiting mammalian cell proliferation, *in vitro* or *in vivo*, the method comprising contacting a mammalian cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

A “MALT1 protease inhibitor” as defined herein includes any compound exhibiting MALT1 inhibition activity. In some embodiments, a MALT1 protease inhibitor is selective for a MALT1 protease. Exemplary MALT1 protease inhibitors can exhibit inhibition activity (IC₅₀) against a MALT1 protease of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a MALT1 protease inhibitor can exhibit inhibition activity (IC₅₀) against a MALT1 protease of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

As used herein, a “first MALT1 protease inhibitor” or “first MALT1 inhibitor” is a MALT1

protease inhibitor as defined herein, but which does not include a compound of Formula (I), or a pharmaceutically acceptable salt thereof as defined herein. As used herein, a “second MALT1 protease inhibitor” or a “second MALT1 inhibitor” is a MALT1 protease inhibitor as defined herein, but which does not include a compound of Formula (I), or a pharmaceutically acceptable salt thereof as defined herein. When both a first and a second MALT1 inhibitor are present in a method provided herein, the first and second MALT1 protease inhibitor are different.

Exemplary first and second MALT1 protease inhibitors are described herein. In some embodiments, a first or second MALT1 protease inhibitor can be, for example, JNJ-67856633 or CTX-177 (ONO-7018)

The phrase “effective amount” means an amount of compound that, when administered to a subject in need of such treatment, is sufficient to (i) treat a MALT1-associated disease or disorder (such as a MALT1-associated cancer), (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

Another embodiment features a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use as a medicament.

Another embodiment features a compound of formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting MALT1 in a subject.

Another embodiment features a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating cancer, an autoimmune disorder, or an inflammatory disorder.

Other embodiments provide a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder) in a subject. In some embodiments, the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, or systemic lupus erythematosus (SLE).

Some embodiments provide a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating an inflammatory disorder (e.g., a MALT1-associated inflammatory disorder) in a subject. In some embodiments, the inflammatory disorder is chronic graft versus host disease (cGVHD).

5 Some embodiments provide a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating cancer (e.g., a MALT1-associated cancer) in a subject. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease, or the expression or activity or level of any of the same includes one or more fusion proteins.

10 Accordingly, also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method for treating a subject diagnosed with or identified as having a MALT1-associated cancer, e.g., any of the exemplary MALT1-associated cancers disclosed herein.

15 Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt of pharmaceutical composition thereof, for use in a method for treating diffuse large B-cell lymphoma (DLBCL), activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), mantel cell lymphoma (MCL), marginal zone lymphoma (MZL), chronic lymphatic leukemia (CLL) or mature B-cell neoplasms.

20 Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt of pharmaceutical composition thereof, for use in a method for treating T-cell acute lymphoblastic leukemia.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method for treating a CBM complex pathway-associated cancer (such as any of those disclosed herein) in a subject.

25 Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a cancer in a subject identified as having a CBM complex pathway-associated cancer.

30 Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a MALT1-associated cancer in a subject.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in methods of treating CBM complex pathway-associated diseases or disorders, autoimmune disorders, and inflammatory disorders in a subject.

Accordingly, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method for treating an autoimmune disorder in a subject. Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a MALT1-associated autoimmune disorder in a subject. Provided also herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a MALT1-associated autoimmune disorder in a subject.

In addition, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating an inflammatory disorder in a subject. In some cases, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a MALT1-associated inflammatory disorder in a subject identified or diagnosed as having a MALT1-associated inflammatory disorder. Provided also herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a MALT1-associated inflammatory disorder in a subject determined to have a MALT1-associated inflammatory disorder.

Additionally provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a CBM complex pathway-associated disease or disorder in a subject. In addition, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating a disease or disorder in a subject identified as having a CBM complex pathway-associated disease or disorder.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting mammalian cell proliferation. Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting CBM complex pathway activity in a mammalian cell. Provided also herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of

inhibiting MALT1 protease activity in a mammalian cell. A mammalian cell can be any appropriate cell. In some embodiments, the mammalian cell is a mammalian immune cell. In some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is a mammalian CBM complex pathway-associated cancer cell. In some
5 embodiments, the mammalian cancer cell is a mammalian MALT1-associated cancer cell. In some embodiments, the mammalian cell has dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same is an IAP2-MALT1 fusion, an IGH-MALT1 fusion, or a combination thereof.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in methods of inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a subject. Such methods can be used in the treatment of one or more of the cancers described herein. *See, e.g.*, US Publication No. 2013/0029925; International Publication No. WO 2014/083567; and US Patent No. 8,568,998.
15 *See also, e.g.*, Hezam K et al., *Rev Neurosci* 2018 Jan 26;29:93-98; Gao L, et al., *Pancreas* 2015 Jan;44:134-143; Ding K et al., *J Biol Chem* 2014 Jun 6; 289:16057-71; and Amit M et al., *Oncogene* 2017 Jun 8; 36:3232-3239. In some embodiments, the cancer is a MALT1-associated cancer. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is used in combination with an additional therapy or another therapeutic agent, as
20 described herein. For example, a first or second MALT1 protease inhibitor.

Also provided are a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in methods of decreasing the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a subject having a
25 MALT1-associated cancer can be compared to the risk of developing a metastasis or an additional metastasis in the subject prior to treatment, or as compared to a subject or a population of subjects having a similar or the same MALT1-associated cancer that has received no treatment or a different treatment.

Some embodiments described herein provide a compound of Formula (I), or a
30 pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in methods of

treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder), such as rheumatoid arthritis, multiple sclerosis, and SLE in a subject.

Some embodiments described herein provide a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in methods of
5 treating an inflammatory disorder (e.g., a MALT1-associated autoimmune disorder), such as chronic graft versus host disease in a subject.

Also provided is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting MALT1 protease activity in a mammalian cell. In some embodiments, the mammalian cell is a mammalian immune cell. In
10 some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a MALT1-associated mammalian cancer cell.

Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting mammalian cell
15 proliferation.

In another aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or
20 subsequent to treatment with an effective amount of the compound, pharmaceutically acceptable salt or pharmaceutical composition.

In another aspect, the invention provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for the manufacture of a medicament.

In another aspect, the invention provides the use of a compound of Formula (I), a
25 pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in inhibiting MALT1 in a subject.

In yet another aspect, the invention provides the use of a compound of Formula (I), a
30 pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating cancer, an autoimmune disorder, or an inflammatory disorder in a subject.

Some embodiments provide the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder) in a subject. In some embodiments, the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, or
5 systemic lupus erythematosus (SLE).

Some embodiments provide the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an inflammatory disorder (e.g., a MALT1-associated inflammatory disorder) in a subject. In some embodiments, the inflammatory disorder is chronic graft versus host disease
10 (cGVHD).

Some embodiments provide the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating cancer (e.g., a MALT1-associated cancer) in a subject. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease, or the expression or activity or level of any
15 of the same includes one or more fusion proteins.

Accordingly, also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a subject diagnosed with or identified as having a MALT1-associated cancer, e.g., any of the exemplary MALT1-associated cancers disclosed herein.
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Accordingly, also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a subject with diffuse large B-cell lymphoma (DLBCL), activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), chronic lymphatic leukemia (CLL) or mature B-cell neoplasms.
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Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt of pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a subject with T-cell acute lymphoblastic
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Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a CBM complex pathway-associated cancer (such as any of those disclosed herein) in a subject.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a cancer in a subject identified as having a CBM complex pathway-associated cancer.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a MALT1-associated cancer in a subject.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating CBM complex pathway-associated diseases or disorders, autoimmune disorders, and inflammatory disorders in a subject. Accordingly, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an autoimmune disorder in a subject. Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a MALT1-associated autoimmune disorder in a subject. Provided also herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a MALT1-associated autoimmune disorder in a subject. In addition, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an inflammatory disorder in a subject. In some cases, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a MALT1-associated inflammatory disorder in a subject identified or diagnosed as having a MALT1-associated inflammatory disorder. Provided also herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a MALT1-associated inflammatory disorder in a subject determined to have a MALT1-associated inflammatory disorder.

Additionally provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a CBM complex pathway-associated disease or disorder in a subject. In addition, provided herein is the use of a compound of Formula (I), or a pharmaceutically

acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating a disease or disorder in a subject identified as having a CBM complex pathway-associated disease or disorder.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting mammalian cell proliferation. Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting CBM complex pathway activity in a mammalian cell. Provided also herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting MALT1 protease activity in a mammalian cell. A mammalian cell can be any appropriate cell. In some embodiments, the mammalian cell is a mammalian immune cell. In some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is a mammalian CBM complex pathway-associated cancer cell. In some embodiments, the mammalian cancer cell is a mammalian MALT1-associated cancer cell. In some embodiments, the mammalian cell has dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same. In some embodiments, the dysregulation of a MALT1 gene, a MALT1 protease protein, or expression or activity or level of any of the same is an IAP2-MALT1 fusion, an IGH-MALT1 fusion, or a combination thereof.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a subject. In some embodiments, the cancer is a MALT1-associated cancer. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is used in combination with an additional therapy or another therapeutic agent, as described herein. For example, a first or second MALT1 protease inhibitor.

Also provided is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in decreasing the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a subject having a MALT1-associated cancer can be compared to the risk of

developing a metastasis or an additional metastasis in the subject prior to treatment, or as compared to a subject or a population of subjects having a similar or the same MALT1-associated cancer that has received no treatment or a different treatment.

Some embodiments described herein provide the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an autoimmune disorder (e.g., a MALT1-associated autoimmune disorder), such as rheumatoid arthritis, multiple sclerosis, and SLE in a subject.

Some embodiments described herein provide the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in treating an inflammatory disorder (e.g., a MALT1-associated autoimmune disorder), such as chronic graft versus host disease in a subject.

Also provided is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting MALT1 protease activity in a mammalian cell. In some embodiments, the mammalian cell is a mammalian immune cell. In some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a MALT1-associated mammalian cancer cell.

Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutical composition thereof, in the manufacture of a medicament for use in inhibiting mammalian cell proliferation.

In yet another aspect, the invention provides the use of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

In the field of medical oncology, it is normal practice to use a combination of different forms of treatment to treat each subject with cancer. In medical oncology the other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as other protease inhibitors, kinase inhibitors, signal transduction inhibitors, and/or monoclonal antibodies.

For example, a surgery may be open surgery or minimally invasive surgery. Compounds

of Formula (I), or a pharmaceutically acceptable salt thereof therefore may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example, a chemotherapeutic agent that works by the same or by a different mechanism of action. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used prior to administration of an additional therapeutic agent or additional therapy. For example, a subject in need thereof can be administered one or more doses of a compound of Formula (I), or a pharmaceutically acceptable salt thereof for a period of time and then undergo at least partial resection of the tumor. In some embodiments, the treatment with one or more doses of a compound of Formula (I), or a pharmaceutically acceptable salt thereof reduces the size of the tumor (e.g., the tumor burden) prior to the at least partial resection of the tumor. In some embodiments, a subject in need thereof can be administered one or more doses of a compound of Formula (I), or a pharmaceutically acceptable salt thereof for a period of time and under one or more rounds of radiation therapy. In some embodiments, the treatment with one or more doses of a compound of Formula (I), or a pharmaceutically acceptable salt thereof reduces the size of the tumor (e.g., the tumor burden) prior to the one or more rounds of radiation therapy.

In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to standard therapy (e.g., administration of a chemotherapeutic agent), such as a first MALT1 inhibitor, a kinase inhibitor, immunotherapy, cell or gene therapy, or radiation (e.g., radioactive iodine). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to prior therapy (e.g., administration of a chemotherapeutic agent, such as a first MALT1 inhibitor or another protease inhibitor, immunotherapy, cell or gene therapy, or radiation (e.g., radioactive iodine). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that has no standard therapy. In some embodiments, a subject is MALT1-protease inhibitor naïve. For example, the subject is naïve to treatment with a selective MALT1-protease inhibitor. In some embodiments, a subject is not MALT1-protease inhibitor naïve.

In some embodiments of any of the methods described herein, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with an effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic or immunomodulatory) agents. An additional therapy or

therapeutic agent can be any appropriate additional therapy or therapeutic agent, such as any of those described herein.

Non-limiting examples of additional therapeutic agents include: other MALT1-targeted therapeutic agents (i.e. a first or second MALT1 protease inhibitor, e.g., JNJ-67856633 or CTX-177 (ONO-7018)), other protease inhibitors, kinase inhibitors (e.g., receptor tyrosine kinase-targeted therapeutic agents such as BTK or EGFR inhibitors), signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g., venetoclax or obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents (including antibody and cell-based immunotherapies, and antibody-drug conjugates) and radiotherapy.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order.

In some embodiments, the other MALT1-targeted therapeutic is another protease inhibitor exhibiting MALT1 inhibition activity. In some embodiments, the other MALT1-targeted therapeutic inhibitor is selective for a MALT1 protease. Exemplary MALT1 protease inhibitors can exhibit inhibition activity (IC_{50}) against a MALT1 protease of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a MALT1 protease inhibitors can exhibit inhibition activity (IC_{50}) against a MALT1 protease of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

Non-limiting examples of protease-targeted therapeutic agents (e.g., a first MALT1 inhibitor or a second MALT1 inhibitor) include JNJ-67856633 and CTX-177 (ONO-7018).

Non-limiting examples of multi-kinase inhibitors include alectinib (9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile); amuvatinib (MP470, HPK56) (N-(1,3-benzodioxol-5-ylmethyl)-4-([1]benzofuro[3,2-d]pyrimidin-4-yl)piperazine-1-carbothioamide); apatinib (YN968D1) (N-[4-(1-cyanocyclopentyl) phenyl-2-(4-picolyl)amino-3-Nicotinamide methanesulphonate); cabozantinib (Cometriq XL-184) (N-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-

fluorophenyl)cyclopropane-1,1-dicarboxamide); dovitinib (TKI258; GFKI-258; CHIR-258) ((3Z)-4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1,3-dihydrobenzimidazol-2-ylidene]quinolin-2-one); famitinib (5-[2-(diethylamino)ethyl]-2-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-3-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4-one); fedratinib (SAR302503, TG101348) (N-(2-Methyl-2-propanyl)-3-{[5-methyl-2-({4-[2-(1-pyrrolidinyl)ethoxy]phenyl}amino)-4-pyrimidinyl]amino}benzenesulfonamide); foretinib (XL880, EXEL-2880, GSK1363089, GSK089) (N1'-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-N1-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); fostamantinib (R788) (2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one, 6-[[5-fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl]amino]-2,2-dimethyl-4-[(phosphonooxy)methyl]-, sodium salt (1:2)); ilarasertib (ABT-348) (1-(4-(4-amino-7-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-3-yl)phenyl)-3-(3-fluorophenyl)urea); lenvatinib (E7080, Lenvima) (4-[3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy]-7-methoxy-6-quinolinecarboxamide); motesanib (AMG 706) (N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)amino]pyridine-3-carboxamide); nintedanib (3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone); ponatinib (AP24534) (3-(2-Imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]benzamide); PP242 (torkinib) (2-[4-Amino-1-(1-methylethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-1H-indol-5-ol); quizartinib (1-(5-(tert-Butyl)isoxazol-3-yl)-3-(4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)urea); regorafenib (BAY 73-4506, stivarga) (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbonyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); RXDX-105 (CEP-32496, agerafenib) (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea); semaxanib (SU5416) ((3Z)-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1,3-dihydro-2H-indol-2-one); sitravatinib (MGCD516, MG516) (N-(3-Fluoro-4-{[2-(5-[(2-methoxyethyl)amino]methyl)-2-pyridinyl]thieno[3,2-b]pyridin-7-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide); sorafenib (BAY 43-9006) (4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide); vandetanib (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine); vatalanib (PTK787, PTK/ZK, ZK222584)

(N-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine); AD-57 (N-[4-[4-amino-1-(1-methylethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]-N'-[3-(trifluoromethyl)phenyl]-urea); AD-80 (1-[4-(4-amino-1-propan-2-ylpyrazolo[3,4-d]pyrimidin-3-yl)phenyl]-3-[2-fluoro-5-(trifluoromethyl)phenyl]urea); AD-81 (1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea); ALW-II-41-27 (N-(5-((4-(4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbonyl)-2-methylphenyl)-5-(thiophen-2-yl)nicotinamide); BPR1K871 (1-(3-chlorophenyl)-3-(5-(2-((7-(3-(dimethylamino)propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-yl)urea); CLM3 (1-phenethyl-N-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); EBI-907 (N-(2-chloro-3-(1-cyclopropyl-8-methoxy-3H-pyrazolo[3,4-c]isoquinolin-7-yl)-4-fluorophenyl)-3-fluoropropane-1-sulfonamide); NVP-AST-487 (N-[4-[(4-ethyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-N'-[4-[[6-(methylamino)-4-pyrimidinyl]oxy]phenyl]-urea); NVP-BBT594 (BBT594) (5-((6-acetamidopyrimidin-4-yl)oxy)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)indoline-1-carboxamide); PD173955 (6-(2,6-dichlorophenyl)-8-methyl-2-(3-methylsulfanylanilino)pyrido[2,3-d]pyrimidin-7-one); PP2 (4-amino-5-(4-chlorophenyl)-7-(dimethylethyl)pyrazolo[3,4-d]pyrimidine); PZ-1 (N-(5-(*tert*-butyl)isoxazol-3-yl)-2-(4-(5-(1-methyl-1H-pyrazol-4-yl)-1Hbenzo[d]imidazol-1-yl)phenyl)acetamide); RPI-1 (1,3-dihydro-5,6-dimethoxy-3-[(4-hydroxyphenyl)methylene]-H-indol-2-one); (3E)-3-[(4-hydroxyphenyl)methylidene]-5,6-dimethoxy-1H-indol-2-one); SGI-7079 (3-[2-[[3-fluoro-4-(4-methyl-1-piperazinyl)phenyl]amino]-5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-benzeneacetonitrile); SPP86 (1-Isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); SU4984 (4-[4-[(E)-(2-oxo-1H-indol-3-ylidene)methyl]phenyl]piperazine-1-carbaldehyde); sunitinib (SU11248) (N-(2-Diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide); TG101209 (N-*tert*-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide); Withaferin A ((4 β ,5 β ,6 β ,22R)-4,27-Dihydroxy-5,6:22,26-diepoxyergosta-2,24-diene-1,26-dione); XL-999 ((Z)-5-((1-ethylpiperidin-4-yl)amino)-3-((3-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methylene)indolin-2-one); BPR1J373 (a 5-phenylthiazol-2-ylamine-pyrimidine derivative); CG-806 (CG'806); DCC-2157; GTX-186; HG-6-63-01 ((E)-3-(2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)vinyl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide); SW-01 (Cyclobenzaprine hydrochloride);

XMD15-44 (N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(pyridin-3-ylethynyl)benzamide (generated from structure)); ITRI-305 (D0N5TB, DIB003599); BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide);

5 BLU6864; DS-5010; GSK3179106; GSK3352589; NMS-E668; TAS0286/HM05; TPX0046; and N-(3-(2-(dimethylamino)ethoxy)-5-(trifluoromethyl)phenyl)-2-(4-(4-ethoxy-6-oxo-1,6-dihydropyridin-3-yl)-2-fluorophenyl)acetamide.

Non-limiting examples of receptor tyrosine kinase (e.g., Trk) targeted therapeutic agents, include afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib,

10 imatinib, lapatinib, lestaurtinib, nilotinib, pazopanib, panitumumab, pertuzumab, sunitinib, trastuzumab, 1-((3S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea, AG 879, AR-772, AR-786, AR-256, AR-618, AZ-23, AZ623, DS-6051, Gö 6976, GNF-5837, GTx-186, GW 441756, LOXO-101, MGCD516, PLX7486, RXDX101, VM-902A, TPX-0005, TSR-011, GNF-4256, N-[3-[[2,3-

15 dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-urea, AZ623, AZ64, (S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine, AZD7451, CEP-751, CT327, sunitinib, GNF-8625, and (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-[2,4'-bipyridin]-2'-yl)piperidin-4-ol.

20 In some embodiments, the additional therapeutic agent is a BRAF inhibitor. Non-limiting examples of a BRAF inhibitor include dabrafenib, vemurafenib (also called RG7204 or PLX4032), sorafenib tosylate, PLX-4720, GDC-0879, BMS-908662 (Bristol-Meyers Squibb), LGX818 (Novartis), PLX3603 (Hofmann-LaRoche), RAF265 (Novartis), RO5185426 (Hofmann-LaRoche), and GSK2118436 (GlaxoSmithKline). Additional examples of a BRAF inhibitor are

25 known in the art.

In some embodiments, the additional therapeutic agent is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR). For example, EGFR inhibitors can include osimertinib (merelectinib, Tagrisso), erlotinib (Tarceva), gefitinib (Iressa), cetuximab (Erbix), necitumumab (Portrazza), neratinib (Nerlynx), lapatinib (Tykerb), panitumumab (Vectibix), and vandetanib

30 (Caprelsa).

In some embodiments, the additional therapeutic agent is a Ras-Raf-MEK-ERK pathway

inhibitors (e.g., binimetinib, selumetinib, encorafenib, sorafenib, trametinib, and vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g., everolimus, rapamycin, perifosine, temsirolimus), and other kinase inhibitors, such as baricitinib, brigatinib, capmatinib, danusertib, ibrutinib, milciclib, quercetin, regorafenib, ruxolitinib, semaxanib, AP32788, BLU285, BLU554, INCB39110, INCB40093, INCB50465, INCB52793, INCB54828, MGCD265, NMS-088, NMS-1286937, PF 477736 ((R)-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1H-pyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-cyclohexaneacetamide), PLX3397, PLX7486, PLX8394, PLX9486, PRN1008, PRN1371, RXDX103, RXDX106, RXDX108, and TG101209 (N-*tert*-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide).

In some embodiments, the additional therapeutic agent is a BTK inhibitor. Non-limiting examples of BTK inhibitors include ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib, and NX-2127.

In some embodiments, the additional therapeutic agent is a Bcl-2 inhibitor. Non-limiting examples of Bcl-2 inhibitors include venetoclax, navitoclax, oblimersen, obatoclax, and AT-101.

In some embodiments, the additional therapeutic agent is a PI3K inhibitor. Non-limiting examples of PI3K inhibitors include idelalisib, copanlisib, duvelisib, alpelisib, taselisib, buparlisib, umbralisib, and copanlisib.

In some embodiments, the additional therapeutic agent is a mTOR inhibitor. Non-limiting examples of mTOR inhibitors include everolimus, temsirolimus, and ridaforolimus.

In some embodiments, the additional therapeutic agent is a HDAC inhibitor. Non-limiting examples of HDAC inhibitors include vorinostat, romidepsin, belinostat, chidamide, panobinostat, CXD101, and abexinostat.

In some embodiments, the additional therapeutic agent is a checkpoint inhibitor. Non-limiting examples of checkpoint inhibitors include ipilimumab, tremelimumab, nivolumab, pidilizumab, MPDL3208A, MEDI4736, MSB0010718C, BMS-936559, BMS-956559, BMS-935559 (MDX-1105), AMP-224, and pembrolizumab.

In some embodiments, the additional therapeutic agent is a cytotoxic chemotherapeutic. Non-limiting example of cytotoxic chemotherapeutics include arsenic trioxide, bleomycin, bendamustine, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine,

irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

In some embodiments, the additional therapeutic agent is an angiogenesis-targeted therapeutic. Non-limiting examples of angiogenesis-targeted therapies include lenalidomide, 5 enzastaurine, aflibercept, and bevacizumab.

In some embodiments, an additional therapy or therapeutic agent can include a histidyl-tRNA synthetase (HRS) polypeptide or an expressible nucleotide that encodes the HRS polypeptide.

The term “immunotherapy” refers to an agent that modulates the immune system. In some 10 embodiments, an immunotherapy can increase the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can decrease the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can recruit and/or enhance the activity of an immune cell.

In some embodiments, the immunotherapy is a cellular immunotherapy (e.g., adoptive 15 T-cell therapy, dendritic cell therapy, natural killer cell therapy). In some embodiments, the cellular immunotherapy is sipuleucel-T (APC8015; Provenge™; Plosker (2011) Drugs 71(1): 101-108). In some embodiments, the cellular immunotherapy includes cells that express a chimeric antigen receptor (CAR). In some embodiments, the cellular immunotherapy is a CAR-T cell therapy. In some embodiments, the CAR-T cell therapy is tisagenlecleucel (Kymria). In some 20 embodiments, the CAR-T cell therapy is axicabtagene ciloleucel (Yescarta). In some embodiments, the CAR-T cell therapy is brexucabtagene autoleucel (Tecartus). In some embodiments, the CAR-T cell therapy is relmacabtagene autoleucel. In some embodiments, the CAR-T cell therapy is ALLO-501.

In some embodiments, the immunotherapy is an antibody therapy (e.g., a monoclonal 25 antibody, a conjugated antibody, or a bispecific antibody). In some embodiments, the antibody therapy is bevacizumab (Mvasti™, Avastin®), trastuzumab (Herceptin®), avelumab (Bavencio®), rituximab (MabThera™, Rituxan®), rituximab with human hyaluronidase (Rituxan Hycela™), edrecolomab (Panorex), daratumumab (Darzalex®), olaratumab (Lartruvo™), ofatumumab (Arzerra®), alemtuzumab (Campath®), cetuximab (Erbix®), oregovomab, 30 pembrolizumab (Keytruda®), dinutuximab (Unituxin®), obinutuzumab (Gazyva®), tremelimumab (CP-675,206), ramucirumab (Cyramza®), ublituximab (TG-1101), panitumumab

(Vectibix®), elotuzumab (Empliciti™), avelumab (Bavencio®), necitumumab (Portrazza™), cirtumuzumab (UC-961), ibritumomab (Zevalin®), isatuximab (SAR650984), nimotuzumab, fresolimumab (GC1008), lirilumab (INN), mogamulizumab (Poteligeo®), ficlatuzumab (AV-299), denosumab (Xgeva®), lenzilumab, avelumab, spartalizumab, pembrolizumab, utomilumab, ublituximab, blinatumomab ganitumab, urelumab, pidilizumab, amatuximab, mosunetuzumab (BTCT4465A), CD20-TCB, RO7082859, XmAb13676, glofitamab, CD20-TDB, odronextamab (REGN1979), IGM-2323, BTCT4465A, AMG-562, or TTI-621.

In some embodiments, the immunotherapy is an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate is gemtuzumab ozogamicin (Mylotarg™), inotuzumab ozogamicin (Besponsa®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (TDM-1; Kadcyla®), mirvetuximab soravtansine (IMGN853), anetumab ravtansine, polatuzumab vedotine, loncastuximab tesirine (ADCT-402), camidanlumab tesirine (ADCT-301), or naratuximab emtansine (Decbio 1562).

In some embodiments, the immunotherapy includes blinatumomab (AMG103; Blincyto®) or midostaurin (Rydapt).

In some embodiments, the immunotherapy includes a toxin. In some embodiments, the immunotherapy is denileukin diftitox (Ontak®).

In some embodiments, the immunotherapy is a cytokine therapy. In some embodiments, the cytokine therapy is an interleukin 2 (IL-2) therapy, an interferon alpha (IFN α) therapy, a granulocyte colony stimulating factor (G-CSF) therapy, an interleukin 12 (IL-12) therapy, an interleukin 15 (IL-15) therapy, an interleukin 7 (IL-7) therapy or an erythropoietin-alpha (EPO) therapy. In some embodiments, the IL-2 therapy is aldesleukin (Proleukin®). In some embodiments, the IFN α therapy is IntronA® (Roferon-A®). In some embodiments, the G-CSF therapy is filgrastim (Neupogen®).

In some embodiments, the immunotherapy is an immune checkpoint inhibitor. In some embodiments, the immunotherapy includes one or more immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the CTLA-4 inhibitor is ipilimumab (Yervoy®) or tremelimumab (CP-675,206). In some embodiments, the PD-1 inhibitor is pembrolizumab (Keytruda®) or nivolumab (Opdivo®). In some embodiments, the PD-L1 inhibitor is atezolizumab (Tecentriq®), avelumab (Bavencio®) or durvalumab (Imfinzi™).

In some embodiments, the immunotherapy is mRNA-based immunotherapy. In some embodiments, the mRNA-based immunotherapy is CV9104 (see, e.g., Rausch et al. (2014) Human Vaccin Immunother 10(11): 3146-52; and Kubler et al. (2015) J. Immunother Cancer 3:26).

In some embodiments, the immunotherapy is bacillus Calmette-Guerin (BCG) therapy.

5 In some embodiments, the immunotherapy is an oncolytic virus therapy. In some embodiments, the oncolytic virus therapy is talimogene alherparepvec (T-VEC; Imlygic®).

In some embodiments, the immunotherapy is a cancer vaccine. In some embodiments, the cancer vaccine is a human papillomavirus (HPV) vaccine. In some embodiments, the HPV vaccine is Gardasil®, Gardasil9® or Cervarix®. In some embodiments, the cancer vaccine is a hepatitis B virus (HBV) vaccine. In some embodiments, the HBV vaccine is Engerix-B®, Recombivax HB® or GI-13020 (Tarmogen®). In some embodiments, the cancer vaccine is Twinrix® or Pediarix®. In some embodiments, the cancer vaccine is BiovaxID®, Oncophage®, GVAX, ADXS11-001, ALVAC-CEA, PROSTVAC®, Rindopepimut®, CimaVax-EGF, lapulcuccl-T (APC8024; Neuvenge™), GRNVAC1, GRNVAC2, GRN-1201, hepcortespenlisimut-L (Hepko-V5),
 10 DCVAX®, SCIB1, BMT CTN 1401, PrCa VBIR, PANVAC, ProstAtak®, DPX-Survivac, or viagenpumatucl-L (HS-110).

In some embodiments, the immunotherapy is a peptide vaccine. In some embodiments, the peptide vaccine is nelipepimut-S (E75) (NeuVax™), IMA901, or SurVaxM (SVN53-67). In some embodiments, the cancer vaccine is an immunogenic personal neoantigen vaccine (see, e.g., Ott et al. (2017) Nature 547: 217-221; Sahin et al. (2017) Nature 547: 222-226). In some embodiments, the cancer vaccine is RGS4K, or NEO-PV-01. In some embodiments, the cancer vaccine is a DNA-based vaccine. In some embodiments, the DNA-based vaccine is a mammaglobin-A DNA vaccine (see, e.g., Kim et al. (2016) OncoImmunology 5(2): e1069940).
 20

In some embodiments, immune-targeted agents are selected from aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, and sipuleucel-T.
 25

In some embodiments, the additional therapy is radiotherapy. Non-limiting examples of radiotherapy include radioiodide therapy, external-beam radiation, and radium 223 therapy.

In some embodiments, the additional therapeutic agent is GSK-3368715, PF-06821497, ceralasertib; AZD6738, BI-894999, MAK-683, AZD-6738, taminadenant, TAK-981, MIK-665, or danvatirsen.
 30

Additional kinase inhibitors include those described in, for example, U.S. Patent No.

7,514,446; 7,863,289; 8,026,247; 8,501,756; 8,552,002; 8,815,901; 8,912,204; 9,260,437; 9,273,051; U.S. Publication No. US 2015/0018336; International Publication No. WO 2007/002325; WO 2007/002433; WO 2008/080001; WO 2008/079906; WO 2008/079903; WO 2008/079909; WO 2008/080015; WO 2009/007748; WO 2009/012283; WO 2009/143018; 5 WO 2009/143024; WO 2009/014637; 2009/152083; WO 2010/111527; WO 2012/109075; WO 2014/194127; WO 2015/112806; WO 2007/110344; WO 2009/071480; WO 2009/118411; WO 2010/031816; WO 2010/145998; WO 2011/092120; WO 2012/101032; WO 2012/139930; WO 2012/143248; WO 2012/152763; WO 2013/014039; WO 2013/102059; WO 2013/050448; WO 2013/050446; WO 2014/019908; WO 2014/072220; WO 2014/184069; WO 2016/075224; 10 WO 2016/081450; WO 2016/022569; WO 2016/011141; WO 2016/011144; WO 2016/011147; WO 2015/191667; WO 2012/101029; WO 2012/113774; WO 2015/191666; WO 2015/161277; WO 2015/161274; WO 2015/108992; WO 2015/061572; WO 2015/058129; WO 2015/057873; WO 2015/017528; WO/2015/017533; WO 2014/160521; and WO 2014/011900, each of which is hereby incorporated by reference in its entirety.

15 In some embodiments, the subject was previously administered one or more standard of care therapies for a lymphoma. In some embodiments, the previously administered standard of care therapy is polatuzumab vedotine, selinexor, axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), bendamustine in combination with rituximab and polatuzumab vedotin, tafasitamab in combination with lenalidomide, or rituximab with human hyaluronidase 20 (Rituxan Hycela).

In some embodiments, the subject is concomitantly receiving standard of care therapy for a lymphoma. In some embodiments, the standard of care therapy is polatuzumab vedotine, selinexor, axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), bendamustine in combination with rituximab and polatuzumab vedotin, tafasitamab in combination with 25 lenalidomide, or rituximab with human hyaluronidase (Rituxan Hycela).

Pharmaceutical Compositions

When employed as pharmaceuticals, compounds of Formula (I), including pharmaceutically acceptable salts thereof, can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical 30 art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including

transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral
5 administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or can be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids
10 and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula (I) or pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients. For example, a pharmaceutical
15 composition prepared using a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-
20 solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some
25 embodiments, the composition is formulated for oral administration. In some embodiments, the composition is a solid oral formulation. In some embodiments, the composition is formulated as a tablet or capsule.

Further provided herein are pharmaceutical compositions containing a compound of Formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable
30 carrier. Pharmaceutical compositions containing a compound of Formula (I) or a pharmaceutically acceptable salt thereof as the active ingredient can be prepared by intimately mixing the compound

of Formula (I), or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending upon the desired route of administration (*e.g.*, oral, parenteral). In some embodiments, the composition is a solid oral composition.

5 Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers can be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

10 Methods of formulating pharmaceutical compositions have been described in numerous publications such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded*, Volumes 1-3, edited by Lieberman et al; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2, edited by Avis et al; and *Pharmaceutical Dosage Forms: Disperse Systems*, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

15 In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without
20 limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Solid oral preparations can also be coated with substances such as sugars or be enteric-coated so as to
25 modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients can be added to increase solubility or preservation. Injectable suspensions or solutions can also be prepared utilizing aqueous carriers along with appropriate additives. The pharmaceutical compositions herein will contain, per dosage unit, *e.g.*, tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary
30 to deliver an effective dose as described herein.

The compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term “unit dosage form” refers to physically discrete units suitable as unitary dosages for human subjects and other subjects, each unit containing a predetermined quantity of active material (*i.e.*, a compound of Formula (I) or a pharmaceutically acceptable salt thereof) calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient. In some embodiments, the compositions provided herein contain about 10 mg, about 20 mg, about 80 mg, or about 160 mg of the active ingredient.

In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

The daily dosage of the compound of Formula (I) or a pharmaceutically acceptable salt thereof can be varied over a wide range from 1.0 to 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 160, 200,

250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein. Preferably, the range is from about 0.5 to about 500 mg/kg of body weight per day, or any range
5 therein. More preferably, from about 1.0 to about 250 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 100 mg/kg of body weight per day, or any range therein. In an example, the range can be from about 0.1 to about 50.0 mg/kg of body weight per day, or any amount or range therein. In another example, the range can be from about 0.1 to about 15.0 mg/kg of body weight per day, or any range therein. In yet another example, the range can be
10 from about 0.5 to about 7.5 mg/kg of body weight per day, or any amount to range therein. Pharmaceutical compositions containing a compound of Formula (I) or a pharmaceutically acceptable salt thereof can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

The active compound may be effective over a wide dosage range and is generally
15 administered in a pharmaceutically effective amount. Optimal dosages to be administered can be readily determined by those skilled in the art. It will be understood, therefore, that the amount of the compound actually administered will usually be determined by a physician, and will vary according to the relevant circumstances, including the mode of administration, the actual compound administered, the strength of the preparation, the condition to be treated, and the
20 advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject response, age, weight, diet, time of administration and severity of the subject's symptoms, will result in the need to adjust dosages.

In some embodiments, the compounds provided herein can be administered in an amount ranging from about 1 mg/kg to about 100 mg/kg. In some embodiments, the compound provided
25 herein can be administered in an amount of about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 40 mg/kg, about 15 mg/kg to about 45 mg/kg, about 20 mg/kg to about 60 mg/kg, or about 40 mg/kg to about 70 mg/kg. For example, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about
30 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg.

One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

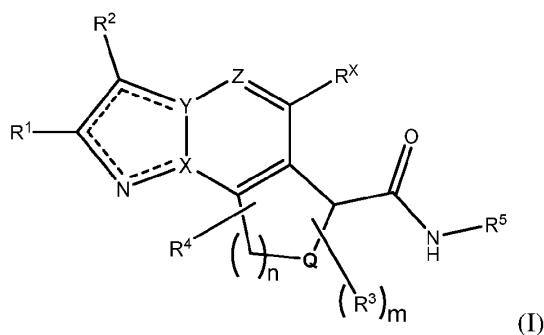
One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts.

Provided herein are pharmaceutical kits useful, for example, in the treatment of MALT1-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising an effective amount of a compound provided herein.

Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

Additional Embodiments

Embodiment 1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

- each $\text{---}\text{---}\text{---}$ is a single or double bond;
- Q is $-\text{CH}_2-$, O, or NH;
- X is N or C;
- Y is N or C;
- Z is N or CR⁵;

wherein when one of X and Y is N, the other of X and Y is C;

n is 1, 2, or 3;

R^x is hydrogen or halogen;

R¹ is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, -NR^AR^B, or C1-C3 alkyl optionally substituted with 1-3 substituents selected from hydroxyl and C1-C3 alkoxy;

R² is hydrogen, halogen, amino, or C1-C3 alkyl;

each R³ is independently deuterium, halogen, hydroxyl, C3-C6 cycloalkyl, C1-C3 alkyl, C1-C3 alkoxy, C1-C3 haloalkoxy, or C1-C3 haloalkyl;

m is 0, 1, 2, or 3;

R⁴ is 5-10 membered heteroaryl optionally substituted with one to three substituents each independently selected from R⁷;

R⁵ is phenyl or 5-9 membered heteroaryl, wherein each R⁵ group is optionally substituted with 1-3 substituents independently selected from R⁸;

R⁶ is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, -NR^CR^D, and C1-C3 alkyl;

each R⁷ is independently selected from the group consisting of halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, oxetanyl, -NR^CR^D, C1-C3 alkyl, and C3-C7 cycloalkyl;

each R⁸ is independently selected from halogen; cyano; amino; -N=(S=O)(C1-C3 alkyl)₂; -S(=O)_p(C1-C3 alkyl); -(C=O)NR^ER^F; C1-C3 alkoxy; C1-C3 haloalkyl optionally substituted with hydroxyl; C1-C3 haloalkoxy; 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, amino, C1-C3 haloalkyl, 4-6 membered heterocyclyl, or C1-C3 alkyl optionally substituted with hydroxyl or -NR^ER^F; C1-C4 alkyl optionally substituted with hydroxyl, -NR^ER^F, or C1-C3 alkoxy; 3-8 membered heterocyclyl; and C3-C6 cycloalkoxy;

p is 1 or 2; and

R^A, R^B, R^C, R^D, R^E, and R^F, are independently hydrogen, C1-C3 alkyl, C3-C6 cycloalkyl, or R^A and R^B, or R^C and R^D, or R^E and R^F, together with the nitrogen atom to which they are attached come together to form a 4-6 membered heterocyclyl optionally substituted with 1-2 halogens.

Embodiment 2. The compound of embodiment 1, wherein X is N and Y is C.

Embodiment 3. The compound of embodiment 1 or 2, wherein Z is N.

Embodiment 4. The compound of any one of embodiments 1-3, wherein R^x is hydrogen.

Embodiment 5. The compound of any one of embodiments 1-4, wherein Q is $-CH_2-$.

Embodiment 6. The compound of any one of embodiments 1-5, wherein R^1 is hydrogen.

5 Embodiment 7. The compound of any one of embodiments 1-5, wherein R^1 is halogen.

Embodiment 8. The compound of any one of embodiments 1-7, wherein R^2 is hydrogen.

Embodiment 9. The compound of any one of embodiments 1-7, wherein R^2 is halogen.

Embodiment 10. The compound of any one of embodiments 1-9, wherein n is 1.

Embodiment 11. The compound of any one of embodiments 1-10, wherein m is 1.

10 Embodiment 12. The compound of any one of embodiments 1-11, wherein each R^3 is independently deuterium, halogen, hydroxyl, C3-C6 cycloalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

Embodiment 13. The compound of any one of embodiments 1-12, wherein m is 1 and R^3 is methyl or trifluoromethyl.

15 Embodiment 14. The compound of any one of embodiments 1-13, wherein R^4 is a 5 or 6 membered heteroaryl optionally substituted with one to three substituents each independently selected from R^7 .

Embodiment 15. The compound of any one of embodiments 1-13, wherein R^4 is a 6 membered heteroaryl optionally substituted with one to three substituents each independently selected from R^7 .
20

Embodiment 16. The compound of any one of embodiments 1-13, wherein R^4 is a 5 membered heteroaryl optionally substituted with one to three substituents each independently selected from R^7 .

Embodiment 17. The compound of any one of embodiments 1-13, wherein R^4 is 4H-pyrazolyl, 3H-pyrazolyl, or thiazoyl optionally substituted with one to three substituents each independently selected from R^7 .

Embodiment 18. The compound of any one of embodiments 1-13, wherein R^4 is unsubstituted.

- 5 Embodiment 19. The compound of any one of embodiments 1-13, wherein each R^7 is independently selected from the group consisting of C1-C3 haloalkyl, C1-C3 alkyl, and cycloalkyl.

Embodiment 20. The compound of any one of embodiments 1-19, wherein R^5 is 5-9 membered heteroaryl optionally substituted with 1-3 independently selected R^8 .

- 10 Embodiment 21. The compound of any one of embodiments 1-19, wherein R^5 is 5-6 membered heteroaryl substituted with 1-3 independently selected R^8 .

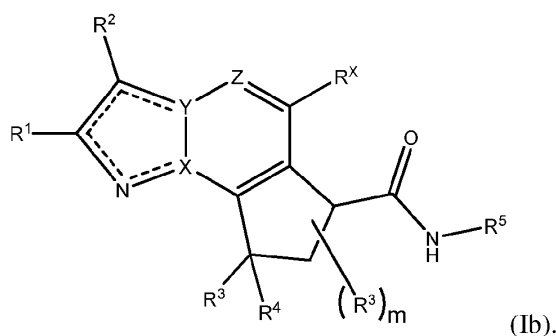
Embodiment 22. The compound of any one of embodiments 1-21, wherein R^5 is 3-pyridyl or 4-pyridyl optionally substituted with 1-3 independently selected R^8 .

Embodiment 23. The compound of any one of embodiments 1-21, wherein at least one of R^8 is halogen.

- 15 Embodiment 24. The compound of any one of embodiments 1-21, wherein at least one of R^8 is 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$, amino, or C1-C3 haloalkyl.

- 20 Embodiment 25. The compound of any one of embodiments 1-21, wherein at least one of R^8 is 5 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$, amino, or C1-C3 haloalkyl.

Embodiment 26. A compound according to anyone of embodiments 1-25, which is a compound according to formula (Ib), or a pharmaceutically acceptable salt thereof



Embodiment 27. A pharmaceutical composition comprising a compound according to any one of
 5 embodiments 1-26, or a pharmaceutically acceptable salt thereof, in combination with one or
 more pharmaceutically acceptable excipients.

Embodiment 28. A method for treating cancer in a subject in need thereof, comprising
 administering to the subject an effective amount of a compound of any one of embodiments 1-26,
 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 27.

10 Embodiment 29. The method of embodiment 28 where the cancer is a MALT1-associated cancer.

Embodiment 30. The method of embodiment 28 or 29 wherein the cancer is lymphoma.

Embodiment 31. The method of embodiment 30 wherein the lymphoma is non-Hodgkin
 lymphoma, DLBCL, refractory DLBCL, (ABC) subtype of DLBCL, mantle cell lymphoma
 (MCL), or marginal zone lymphoma (MZL).

15 Embodiment 32. The method of embodiment 28 or 29 wherein the cancer is leukemia.

Embodiment 33. The method of embodiment 32 where in the leukemia is chronic lymphocytic
 leukemia (CLL).

Embodiment 34. The method of embodiment 28 or 29 wherein the cancer is a solid tumor.

20 Embodiment 35. A method of treating an autoimmune disorder in a subject in need thereof,
 comprising administering to the subject an effective amount of a compound of any one of

embodiments 1-26, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 27.

Embodiment 36. The method according to embodiment 35 wherein the autoimmune disorder is chronic graft versus host disease.

- 5 Embodiment 37. The method of any one of embodiments 30-36, further comprising administering an additional therapy or therapeutic agent to the subject.

EXAMPLES

Materials and Methods

10 The compounds provided herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing the compounds provided herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, 15 or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of the compounds provided herein can involve the protection and deprotection 20 of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in *Protecting Group Chemistry*, 1st Ed., Oxford University Press, 2000; *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th Ed., Wiley-Interscience Publication, 2001; and Petursson, S. *et al.*, "Protecting 25 Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 74(11), 1297 (1997).

Reactions sensitive to moisture or air were performed under nitrogen or argon using anhydrous solvents and reagents. The progress of reactions was determined by either analytical thin layer chromatography (TLC) usually performed with Sanpont precoated TLC plates, silica gel GF-254, layer thickness 0.25 mm or liquid chromatography-mass spectrometry (LC-MS).

Typically, the analytical LC-MS system used consisted of Shimadzu LCMS-2020 with electrospray ionization in positive ion detection mode with 20ADXR pump, SIL-20ACXR autosampler, CTO-20AC column oven, M20A PDA Detector and LCMS 2020 MS detector. The column was usually HALO a C18 30*5.0 mm, 2.7 μ m. The mobile phase A is water containing 0.05% TFA and mobile phase B is acetonitrile containing 0.05% TFA. The gradient is from 5% mobile phase B to 100% in 2.0 min, hold 0.7 min, then reverting to 5% mobile phase B over 0.05 min and maintained for 0.25 min. The Column Oven (CTO-20AC) was operated at a temperature of 40.0 °C. The flow rate was 1.5 mL/min, and the injection volume was 1 μ l. PDA (SPD-M20A) detection was in the range 190-400 nm. The MS detector, which was configured with electrospray ionization as ionizable source; Acquisition mode: Scan; Nebulizing Gas Flow: 1.5 L/min; Drying Gas Flow: 15 L/min; Detector Voltage: Tuning Voltage $\pm$ 0.2 kv; DL Temperature: 250 °C; Heat Block Temperature: 250 °C; Scan Range: 90.00 - 900.00 m/z. ELSD (Alltech 3300) detector Parameters: Drift Tube Temperature: 60 ± 5 °C; N₂ Flow-Rate: 1.8 ± 0.2 L/min. Mobile phase gradients were optimized for the individual compounds.

The GC-MS system was usually performed with Shimadzu GCMS-QP2010 Ultra with FID and MS Detector. The MS detector of acquisition mode: Start Time: 2.00 min; End Time: 9.00 min; ACQ Mode: Scan; Event Time: 0.30 sec; Scan Speed: 2000; Start m/z: 50.00; End m/z: 550.00; Ion Source temperature: 200.00 °C; Interface temperature: 250.00 °C; Solvent Cut Time: 2.00 min.

Preparative HPLC purifications were usually performed with Waters Auto purification system (2545-2767) with a 2489 UV detector. The column was Waters C18, 19 x150 mm, 5 μ m. The mobile phases consisted of mixtures of acetonitrile (5-95%) in water containing 0.1%FA. Flow rates were maintained at 25 mL/min, the injection volume was 1200 μ L, and the UV detector used two channels 254 nm and 220 nm. Mobile phase gradients were optimized for the individual compounds.

Chiral analytical chromatography was performed on one of Chiralpak AS, AD, Chiralcel OD, OJ Chiralpak IA, IB, IC, ID, IE, IF, IG, IH columns (Daicel Chemical Industries, Ltd.); (R,R)-Whelk-O1, (S,S)-Whelk-O1 columns (Regis technologies, Inc.); CHIRAL Cellulose-SB, SC, SA columns (YMC Co., Ltd.) at different column sizes (50x4.6mm, 100x4.6mm, 150x4.6mm, 250x4.6mm, 50x3.0mm, 100x3.0mm) with noted percentage of either ethanol in hexane (%Et/Hex) or isopropanol in hexane (%IPA/Hex) as isocratic solvent systems.

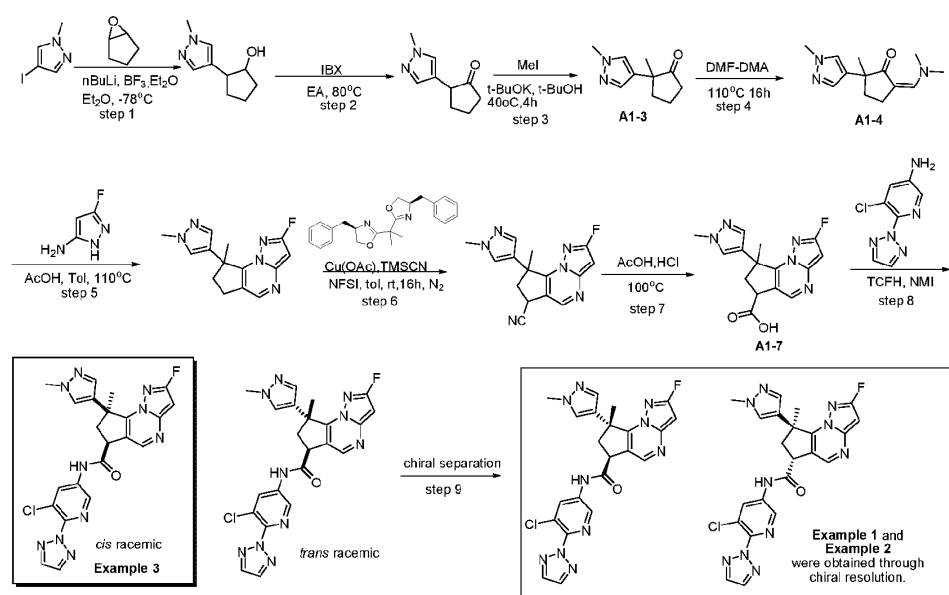
Reactions performed using microwave irradiation were normally carried out using an Initiator manufactured by Biotage. Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash column chromatography was usually performed using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (40-60 μM , 60 Å pore size) in pre-packed cartridges of the size noted. ^1H NMR spectra were acquired at 400 MHz spectrometers in DMSO-d_6 solutions unless otherwise noted. Chemical shifts were reported in parts per million (ppm). Tetramethylsilane (TMS) was used as internal reference in DMSO-d_6 solutions, and residual CH_3OH peak or TMS was used as internal reference in CD_3OD solutions. Coupling constants (J) were reported in hertz (Hz). Chiral analytical chromatography was performed on one of Chiralpak AS, Chiralpak AD, Chiralcel OD, Chiralcel IA, or Chiralcel OJ columns (250x4.6 mm) (Daicel Chemical Industries, Ltd.) with noted percentage of either ethanol in hexane (%Et/Hex) or isopropanol in heptane (%IPA/Hep) as isocratic solvent systems. Chiral preparative chromatography was conducted on one of Chiralpak AS, AD, Chiralcel OD, OJ, Chiralpak IA, IB, IC, ID, IE, IF, IG, IH columns (Daicel Chemical Industries, Ltd.); (*R,R*)-Whelk-O1, (*S,S*)-Whelk-O1 columns (Regis technologies, Inc.); CHIRAL Cellulose-SB, SC, SA columns (YMC Co., Ltd.) at different column size (250x20mm, 250x30mm, 250x50mm) with desired isocratic solvent systems identified on chiral analytical chromatography.

Abbreviations used herein include: $-\text{C}(\text{O})\text{CH}_3$ (Ac); acetic acid (AcOH); $-\text{OC}(\text{O})\text{CH}_3$ (OAc); aqueous (aq); Cbz (benzyloxycarbonyl); *N,N*-diisopropylethylamine (DIEA); *N,N*-dimethylformamide (DMF); 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI); EtOAc (EtOAc); diethyl ether (ether or Et_2O); PE (PE); gram(s) (g); hour(s) (h or hr); 2-propanol (IPA); mass spectrum (ms or MS); microliter(s) (μL); milligram(s) (mg); milliliter(s) (mL); millimole (mmol); minute(s) (min); methyl *t*-butylether (MTBE); (benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate (PyBOP); retention time (R_t); rt (rt or RT); saturated aq sodium chloride solution (brine); trifluoroacetic acid (TFA); tetrahydrofuran (THF); flash chromatography (FC); liquid chromatography (LC); liquid chromatography-mass spectrometry (LCMS or LC-MS); supercritical fluid chromatography (SFC); *t*-butyloxycarbonyl (Boc or BOC); Diethylaminosulfur trifluoride (DAST); DCM (DCM); dimethylacetamide (DMA; DMAC); dimethylsulfoxide (DMSO); 1,3-Bis(diphenylphosphino)propane (DPPP); acetic acid (HOAc); 3-chloroperoxybenzoic acid (m-CPBA); methyl (Me); methanol (MeOH); *N,N,N',N'*-

tetramethylchloroformamidinium hexafluorophosphate (TCFH); N-methylimidazole (NMI); N-bromosuccinamide (NBS); thin layer chromatography (TLC).

The following are representative procedures for the preparation of the compounds used in the following Examples, or which can be substituted for the compounds used in the following Examples which may not be commercially available.

Method A1



Examples 1, 2: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Example 3: (*cis*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 15 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(1-methyl-1*H*-pyrazol-4-yl)cyclopentan-1-ol

To a solution of 4-iodo-1-methyl-pyrazole (48 g, 231.8 mmol) in Et₂O (2 L) was added *n*-Butyllithium (14.8 g, 231.8 mmol, 2.5 M in hexane) at -78 °C. The reaction mixture was stirred at

-78 °C for 30 min under nitrogen. To the above mixture was added 6-oxabicyclo[3.1.0]hexane (15 g, 178.3 mmol) and Boron trifluoride diethyl etherate (32.9 g, 231.8 mmol). The reaction mixture was stirred at -78 °C for 30 min under nitrogen. The reaction mixture was quenched with saturated aqueous ammonium chloride (500 mL). The resulting mixture was extracted with ethyl acetate (3x 500 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with DCM/MeOH (10:1) to give the title compound (8 g, 21 % yield) as a yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.37 (s, 1H), 7.24 (s, 1H), 3.99-4.07 (m, 1H), 3.87 (s, 3H), 2.79-2.88 (m, 1H), 2.00-2.21 (m, 2H), 1.56-1.92 (m, 4H). LC-MS: m/z 167 [M+H]⁺.

10 Step 2: 2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one

To a stirred solution of 2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-ol (5 g, 30 mmol) in ethyl acetate (250 mL) was added IBX (27.4 g, 45.1 mmol, 46 % purity). The resulting mixture was stirred at 80 °C for 16 h. The mixture was allowed to cool to 25 °C. The reaction was quenched with saturated aqueous NaHSO₃ (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound (1.6 g, 32 % yield) as a yellow oil. LC-MS: m/z 165 [M+H]⁺.

Step 3: 2-methyl-2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one (**A1-3**)

20 To a stirred solution of 2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one (3.9 g, 23.7 mmol) in *t*-BuOH (60 mL) was added potassium 2-methylpropan-2-olate (2.9 g, 26.1 mmol) in portions at 25 °C. The resulting mixture was stirred at 40 °C for 0.5 h. Iodomethane (3.4 g, 23.7 mmol) was added dropwise at 40 °C and the resulting mixture was stirred at 40 °C for 2 h. The reaction was quenched with water (200 mL), and the mixture was extracted with ethyl acetate (3x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with THF/PE (1:1) to give the title compound (**A1-3**, 3.9 g, 82 % yield) as a yellow oil. LC-MS: m/z 179 [M+H]⁺.

Step 4: 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one (**A1-4**)

30 A solution of 2-methyl-2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one (5.5 g, 30.8 mmol) in 1,1-dimethoxy-N,N-dimethylmethanamine (70 mL) was stirred at 100 °C for 24 h. The

mixture was allowed to cool to 25 °C and then concentrated under reduced pressure to give the crude title compound (**A1-4**, 5.5 g) as a red oil. LC-MS: m/z 234 [M+H]⁺.

Step 5: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

5 To a stirred solution of 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-4-yl)cyclopentan-1-one (2 g, 8.5 mmol) in toluene (20 mL) were added 3-fluoro-1H-pyrazol-5-amine (1 g, 10.3 mmol) and AcOH (2 mL). The resulting mixture was stirred at 110 °C for 16 h. The mixture was allowed to cool to 25 °C. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL). The resulting solution was extracted with
10 ethyl acetate (3x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:1) to give the title compound (2 g, 60 % yield) as a light-yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.60 (s, 1H), 7.63 (s, 1H), 7.39 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 3.75 (s, 3H), 2.97-3.21 (m, 2H), 2.39-2.57 (m, 1H), 2.28-2.32 (m, 1H), 1.88 (s, 3H). LC-MS: m/z
15 272 [M+H]⁺.

Step 6: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

To a stirred solution of 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (2 g, 7.4 mmol) in toluene (80 mL) were added (4*R*)-4-benzyl-2-[1-[(4*R*)-4-benzyl-4,5-dihydrooxazol-2-yl]-1-methyl-ethyl]-4,5-dihydrooxazole (641
20 mg, 1.8 mmol), acetylcopper (181 mg, 1.5 mmol), N-Fluorobenzenesulfonimide (3.4 g, 11.1 mmol) and TMSCN (3.7 g, 36.9 mmol). The reaction was stirred at 25 °C for 16 h under nitrogen. The solvent was removed under reduced pressure and the residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to get the crude product. The crude product was further
25 purified by prep-HPLC to give the title compound (100 mg, 4% yield) as a yellow oil. LC-MS (ES, m/z): 297[M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A1-7**)

A solution of 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (130 mg, 0.44 mmol) in AcOH (2 mL) and
30 HCl (12M, 2 mL) was stirred at 100 °C for 2 h. The mixture was allowed to cool to 25 °C. The

mixture was concentrated under reduced pressure and the residue was diluted with water (50 ml). The resulting mixture was extracted with ethyl acetate (3x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (**A1-7**, 130 mg, 90 % yield) as a yellow oil. LC-MS: m/z 316 $[M+H]^+$.

5 Step 8: **Examples 3** and *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

To a stirred solution of 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (165 mg, 523 μ mol) and 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (123 mg, 628 μ mol) in ACN (10 mL) were added TCFH (587 mg, 2.1 mmol) and NMI (215 mg, 2.6 mmol). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL). The resulting mixture was extracted with ethyl acetate (3x100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with DCM/MeOH (10:1) to give the crude product. The crude product was further purified by prep-HPLC to afford **Example 3** (*cis*-racemic mixture, 80 mg, 29% yield,) as a white solid and a racemic mixture of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (120 mg, 44% yield) as a white solid.

Example 3: ^1H NMR (300 MHz, DMSO- d_6) δ 11.10 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.71 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.62 (s, 1H), 7.35 (s, 1H), 6.55 (d, J = 5.1 Hz, 1H), 4.51-4.56 (m, 1H), 3.76 (s, 3H), 2.68-2.84 (m, 2H), 1.88 (s, 3H). LC-MS: m/z 493 $[M+H]^+$.

Step 9: Separation of enantiomers to obtain **Example 1** and **Example 2**

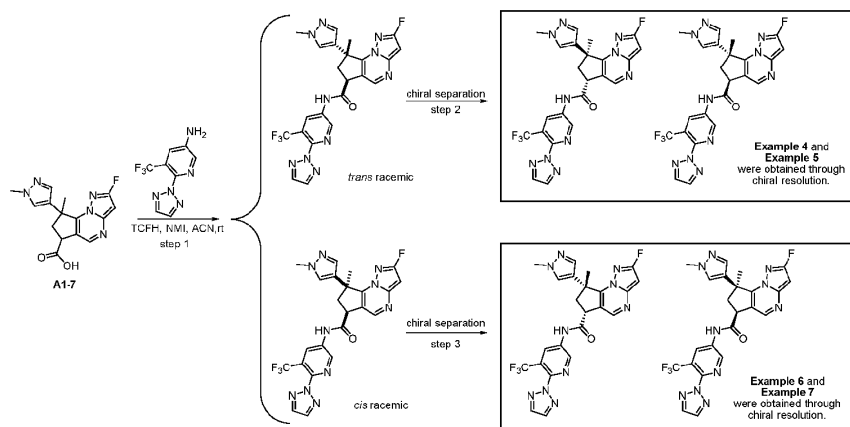
25 120 mg of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; isocratic: 50% B in 25 min; Wave Length: 220/254 nm; RT1(min): 10.008; RT2(min): 19.257; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 3). The first eluting isomer was concentrated and lyophilized to afford **Example 1** (40.7 mg, 33 % yield) as a

white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 2** (33.9 mg, 28 % yield) as a white solid.

Example 1: ^1H NMR (300 MHz, DMSO- d_6) δ 11.07 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.67 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.65 (s, 1H), 7.43 (s, 1H), 6.58 (d, J = 5.1 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 3.76 (s, 3H), 2.85-2.98 (m, 1H), 2.50-2.56 (m, 1H), 1.97 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

Example 2: ^1H NMR (300 MHz, DMSO- d_6) δ 11.07 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.67 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.65 (s, 1H), 7.43 (s, 1H), 6.58 (d, J = 5.1 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 3.76 (s, 3H), 2.85-2.98 (m, 1H), 2.50-2.56 (m, 1H), 1.97 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

Method A2



Examples 4, 5: (6*R*,8*S*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*S*,8*R*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 6, 7: (6*R*,8*R*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*S*,8*S*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: *trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A1-7**, 128 mg, 405.9 μ mol) and 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine (93 mg, 405.9 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (65 mg, 30 % yield) as a white solid, LC-MS: m/z 527 $[M+H]^+$; *cis*-isomer (60 mg, 28 % yield) as a white solid, LC-MS: m/z 527 $[M+H]^+$.

Step 2: Separation of enantiomers to obtain **Example 4** and **Example 5**

65 mg of *trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; isocratic: 50% B in 20 min; Wave Length: 220/254 nm; RT1(min): 7.514; RT2(min): 19.166; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 4** (17 mg, 26 % yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 5** (24.6 mg, 37 % yield) as a white solid.

Example 4: ^1H NMR (300 MHz, DMSO- d_6) δ : 11.21 (s, 1H), 9.02 (d, J = 2.4 Hz, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.69 (s, 1H), 8.20 (s, 2H), 7.65 (s, 1H), 7.42 (s, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.53-4.58 (m, 1H), 3.76 (s, 3H), 2.88-2.99 (m, 1H), 2.51-2.58 (m, 1H), 1.97 (s, 3H). LC-MS: m/z 527 $[M+H]^+$.

Example 5: ^1H NMR (300 MHz, DMSO- d_6) δ : 11.21 (s, 1H), 9.02 (d, J = 2.1 Hz, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.69 (s, 1H), 8.20 (s, 2H), 7.65 (s, 1H), 7.43 (s, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.53-4.58 (m, 1H), 3.76 (s, 3H), 2.88-2.95 (m, 1H), 2.50-2.58 (m, 1H), 1.97 (s, 3H). LC-MS: m/z 527 $[M+H]^+$.

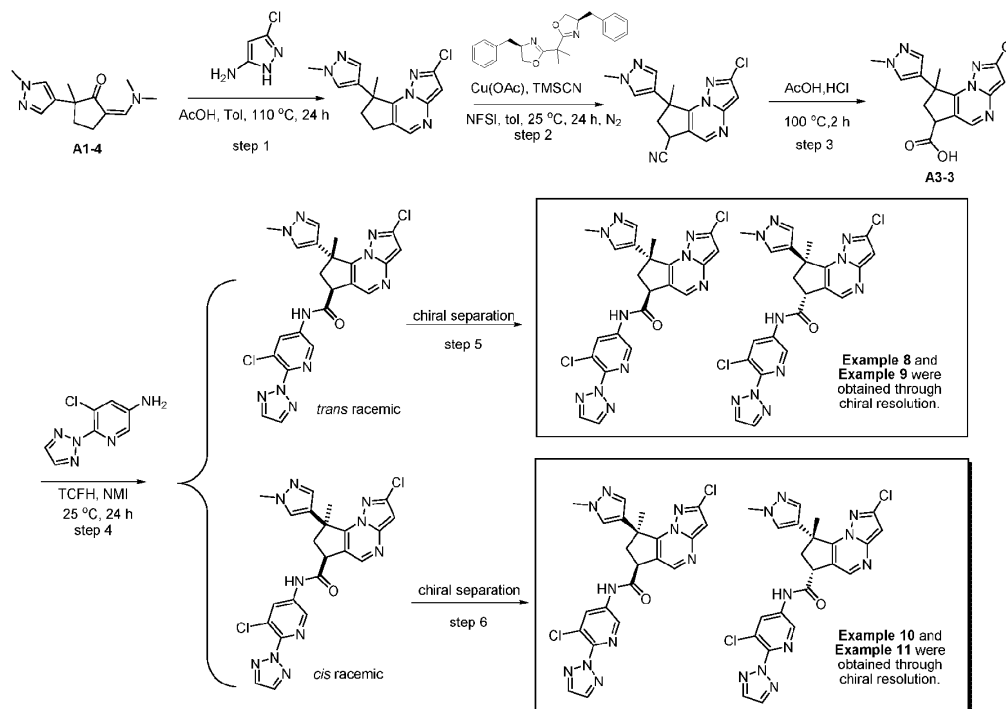
Step 3: Separation of enantiomers to obtain **Example 6** and **Example 7**

60 mg of *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; isocratic: 25% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.968; RT2(min): 11.575; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 8). The first eluting isomer was concentrated and lyophilized to afford **Example 6** (23 mg, 38 % yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 7** (24.6 mg, 41 % yield) as a white solid.

Example 6: ^1H NMR (300 MHz, DMSO- d_6) δ : 11.20 (s, 1H), 9.03 (d, J = 2.1 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H), 8.72 (s, 1H), 8.19 (s, 2H), 7.62 (s, 1H), 7.35 (s, 1H), 6.55 (d, J = 4.8 Hz, 1H), 4.54-4.57 (m, 1H), 3.74 (s, 3H), 2.69-2.88 (m, 2H), 1.87 (s, 3H). LC-MS: m/z 527 [M+H] $^+$.

Example 7: ^1H NMR (300 MHz, DMSO- d_6) δ : 11.21 (s, 1H), 9.03 (d, J = 2.4 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H), 8.72 (s, 1H), 8.19 (s, 2H), 7.62 (s, 1H), 7.34 (s, 1H), 6.55 (d, J = 5.1 Hz, 1H), 4.54-4.57 (m, 1H), 3.75 (s, 3H), 2.69-2.88 (m, 2H), 1.87 (s, 3H). LC-MS: m/z 527 [M+H] $^+$.

Method A3



Examples 8, 9: (6*S*,8*R*)-2-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 10, 11: (6*S*,8*S*)-2-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-chloro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine

To a stirred solution of 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1*H*-pyrazol-4-yl)cyclopentan-1-one (A1-4, 2.2 g, 9.43 mmol) in Toluene (15 mL) were added 3-chloro-1*H*-

pyrazol-5-amine (1.3 g, 11.3 mmol) and AcOH (1.5 mL). The resulting mixture was stirred at 110 °C for 24 h. The mixture was allowed to cool to 25 °C. The reaction mixture was concentrated under reduced pressure, and the residue was applied onto a silica gel column and eluted with EtOAc/PE (10:1) to give 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1.5 g, 44 % yield) as a light yellow solid. LC-MS: m/z 288 [M+H]⁺.

Step 2: 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

To a stirred solution of 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1.1 g, 3.82 mmol) in toluene (40 mL) were added (4*R*)-4-benzyl-2-[1-[(4*R*)-4-benzyl-4,5-dihydrooxazol-2-yl]-1-methyl-ethyl]-4,5-dihydrooxazole (1.4 g, 3.8 mmol), acetoxycopper (94 mg, 764 μmol), N-Fluorobenzenesulfonimide (1.8 g, 5.7 mmol) and TMSCN (1.9 g, 19.1 mmol). The reaction was stirred at 25 °C for 24 h under nitrogen. The solvent was removed under reduced pressure. The residue was diluted with water (100 mL). The resulting mixture was extracted with ethyl acetate (3x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to give crude product, which was further purified by HPLC to give the title compound (240 mg, 17% yield) as a yellow oil. LC-MS (ES, m/z): 313[M+H]⁺.

Step 3: 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A3-3**)

In analogy to **Method A1 step 7** but using 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (240 mg, 0.77 mmol), the title compound was obtained as a yellow oil (**A3-3**, 235 mg, 94% yield). LC-MS: m/z 332 [M+H]⁺.

Step 4: *trans*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (120 mg, 362 μ mol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (141 mg, 723 μ mol) and stirring at 25°C for 24 h, racemic mixtures of the title compounds were obtained: *trans* isomer (25mg, 13 % yield) as a white solid, LC-MS: m/z 509 [M+H]⁺; *cis*-isomer (15 mg, 8 % yield) as a white solid, LC-MS: m/z 509 [M+H]⁺.

Step 5: Separation of enantiomers to obtain **Example 8** and **Example 9**

25 mg of *trans*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 13.764; RT2(min): 19.041; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 8** (8.9 mg, 43 % yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 9** (8.4 mg, 40% yield) as a white solid.

Example 8: ¹H NMR (300 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.72 (d, J = 2.1 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.18 (s, 2H), 7.63 (s, 1H), 7.41 (s, 1H), 6.96 (s, 1H), 4.51-4.57 (m, 1H), 3.76 (s, 3H), 2.86-2.93 (m, 1H), 2.50-2.51 (m, 1H), 1.99 (s, 3H). LC-MS: m/z 509 [M+H]⁺.

Example 9: ¹H NMR (300 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.72 (d, J = 2.1 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.18 (s, 2H), 7.63 (s, 1H), 7.41 (s, 1H), 6.96 (s, 1H), 4.50-4.54 (m, 1H), 3.76 (s, 3H), 2.86-2.93 (m, 1H), 2.50-2.51 (m, 1H), 1.99 (s, 3H). LC-MS: m/z 509 [M+H]⁺.

Step 6: Separation of enantiomers to obtain **Example 10** and **Example 11**

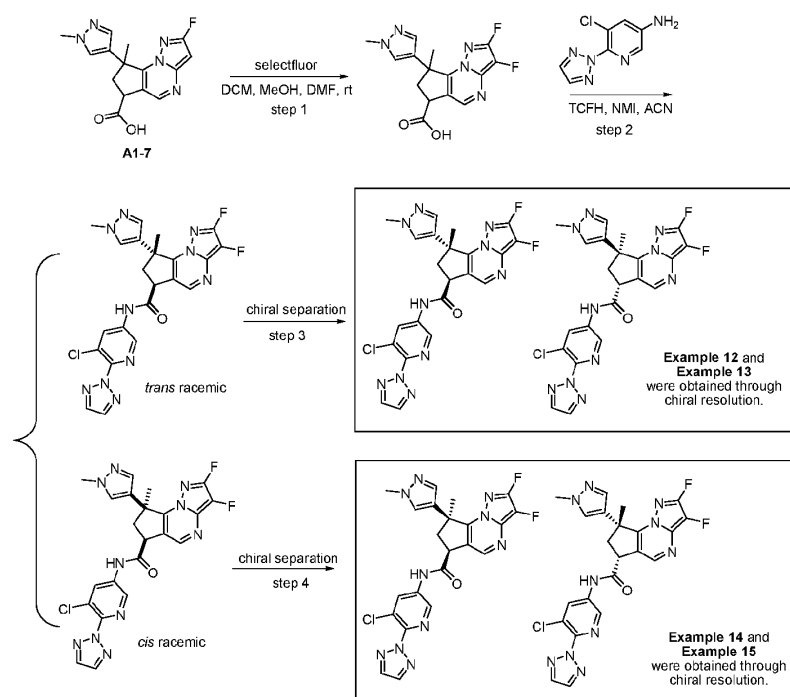
15 mg of *cis*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 14.519; RT2(min): 26.523; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2).

The first eluting isomer was concentrated and lyophilized to afford **Example 10** (2.4 mg, 15 % yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 11** (1.7 mg, 11 % yield) as a white solid.

Example 10: ^1H NMR (300 MHz, DMSO- d_6) δ 11.09 (s, 1H), 8.70-8.72 (m, 2H), 8.57 (d, $J = 2.4$ Hz, 1H), 8.17 (s, 2H), 7.61 (s, 1H), 7.34 (s, 1H), 6.94 (s, 1H), 4.51-4.56 (m, 1H), 3.75 (s, 3H), 2.66-2.88 (m, 2H), 1.89 (s, 3H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

Example 11: ^1H NMR (300 MHz, DMSO- d_6) δ 11.09 (s, 1H), 8.70-8.72 (m, 2H), 8.57 (d, $J = 2.4$ Hz, 1H), 8.17 (s, 2H), 7.61 (s, 1H), 7.34 (s, 1H), 6.94 (s, 1H), 4.51-4.56 (m, 1H), 3.75 (s, 3H), 2.67-2.88 (m, 2H), 1.89 (s, 3H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

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Method A4

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Examples 12, 13: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 14, 15: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid

To a solution of 2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A1-7**, 592 mg, 1.88 mmol) in DCM (18 mL) and MeOH (18 mL) was added Selectfluor fluorinating reagent (2.0 g, 5.63 mmol) in DMF (6 mL). The reaction was stirred at 25 °C for 16 h under nitrogen. The solvent was concentrated under reduced pressure and the residue was diluted with water (50 mL). The resulting solution was extracted with ethyl acetate (3x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by prep-HPLC to give the title compound (130 mg, 12 % yield) as a yellow oil. LC-MS: *m/z* 334 [*M*+*H*]⁺.

Step 2: *trans*-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and *cis*-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (124 mg, 372 μmol) and 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine (109 mg, 557 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (50 mg, 25 % yield) as a white solid, LC-MS: *m/z* 511 [*M*+*H*]⁺; *cis*-isomer (25 mg, 13 % yield) as a white solid, LC-MS: *m/z* 511 [*M*+*H*]⁺.

Step 3: Separation of enantiomers to obtain **Example 12** and **Example 13**

50 mg of *trans*-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-

carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.925; RT2(min): 16.35; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of
5 Runs: 6). The second eluting isomer was concentrated and lyophilized to afford **Example 12** (22.5 mg, 43% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 13** (11.6 mg, 23% yield) as a white solid.

Example 12: ^1H NMR (400 MHz, DMSO- d_6) δ 11.08 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.71 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.64 (s, 1H), 7.42 (s, 1H), 4.53 (t, J = 8.4 Hz,
10 1H), 3.74 (s, 3H), 2.87-2.93 (m, 1H), 2.50-2.56 (m, 1H), 1.93 (s, 3H). LC-MS: m/z 511 [M+H] $^+$.

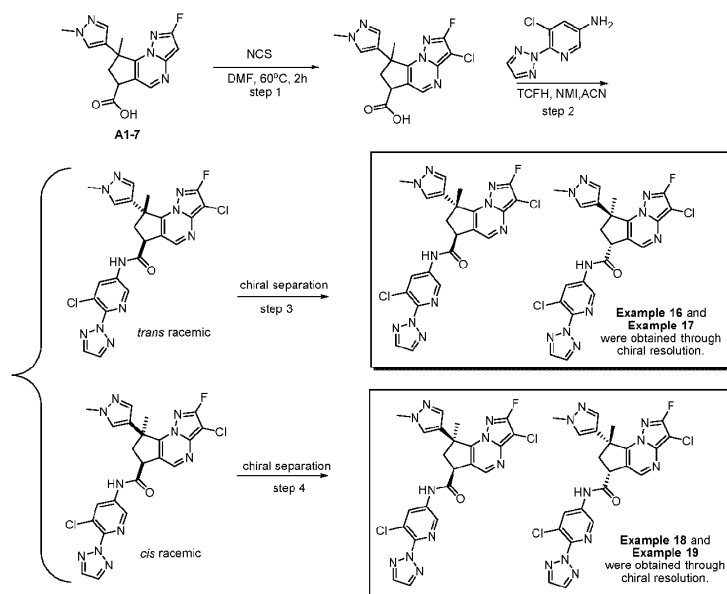
Example 13: ^1H NMR (400 MHz, DMSO- d_6) δ 11.08 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.71 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.64 (s, 1H), 7.42 (s, 1H), 4.53 (t, J = 8.4 Hz, 1H), 3.74 (s, 3H), 2.87-2.93 (m, 1H), 2.50-2.56 (m, 1H), 1.93 (s, 3H). LC-MS: m/z 511 [M+H] $^+$.

Step 4: Separation of enantiomers to obtain **Example 14** and **Example 15**

15 25 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2,3-difluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min):
20 9.465; RT2(min): 13.025; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 14** (9.8 mg, 38% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 15** (6.4 mg, 25% yield) as a white solid.

Example 14: ^1H NMR (400 MHz, DMSO- d_6) δ 11.09 (s, 1H), 8.74 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.62 (s, 1H), 7.34 (s, 1H), 4.52-4.56 (m, 1H), 3.74 (s, 3H), 2.81-2.87 (m, 1H), 2.66-2.71 (m, 1H), 1.86 (s, 3H). LC-MS: m/z 511 [M+H] $^+$.

Example 15: ^1H NMR (400 MHz, DMSO- d_6) δ 11.08 (s, 1H), 8.74 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.62 (s, 1H), 7.34 (s, 1H), 4.52-4.56 (m, 1H), 3.74 (s, 3H), 2.81-2.87 (m, 1H), 2.66-2.71 (m, 1H), 1.86 (s, 3H). LC-MS: m/z 511 [M+H] $^+$.

Method A5

Examples 16, 17: (6*S*,8*R*)-3-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-3-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 18, 19: (6*S*,8*S*)-3-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-3-chloro-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-chloro-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid

To a solution of 2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A1-7**, 100 mg, 317 μmol) in DMF (10 mL) was added NCS (85 mg, 634 μmol). The reaction was stirred at 60 $^\circ\text{C}$ for 2 h under nitrogen. The reaction was allowed to cool to 25 $^\circ\text{C}$. The reaction was diluted with water (50 mL), and the

resulting mixture was extracted with ethyl acetate (3x 50 mL). The combined organic layers were washed with brine (3x 50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by HPLC to give the title compound (100 mg, 81 % yield) as a yellow oil. LC-MS: m/z 350 [M+H]⁺.

5 Step 2: *trans*-3-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-3-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

10 In analogy to **Method A1 step 8** but using 3-chloro-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (130 mg, 372 μmol) and 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (110 mg, 556 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (35 mg, 17% yield) as a white solid, LC-MS: m/z 527 [M+H]⁺; *cis*-isomer (25 mg, 12% yield) as a white solid, LC-MS: m/z 527
15 [M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 16** and **Example 17**

35 mg of *trans*-3-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm,
20 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 12.633; RT2(min): 17.731; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 6). The second eluting isomer was concentrated and lyophilized to afford **Example 16** (7.1 mg, 19% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford
25 **Example 17** (11.5 mg, 31% yield) as a white solid.

Example 16: ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.77 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.64 (s, 1H), 7.44 (s, 1H), 4.56 (t, J = 8.4 Hz, 1H), 3.75 (s, 3H), 2.90-2.95 (m, 1H), 2.50-2.56 (m, 1H), 1.95 (s, 3H). LC-MS: m/z 527 [M+H]⁺.

Example 17: ¹H NMR (400 MHz, DMSO-d₆) δ 11.22 (s, 1H), 8.77 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.64 (s, 1H), 7.44 (s, 1H), 4.55 (t, J = 8.4 Hz, 1H), 3.75 (s, 3H), 2.90-2.95 (m, 1H), 2.50-2.56 (m, 1H), 1.95 (s, 3H). LC-MS: m/z 527 [M+H]⁺.

30

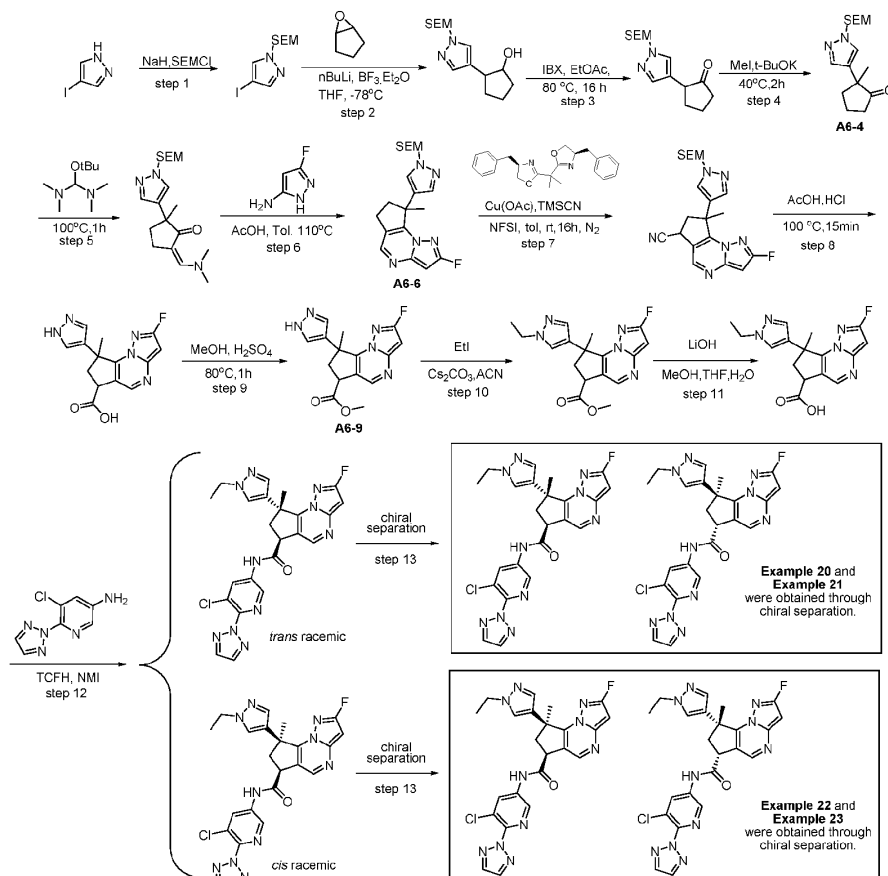
Step 4: Separation of enantiomers to obtain **Example 18** and **Example 19**

25 mg of *cis*-3-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 8.045; RT2(min): 9.61; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 6). The first eluting isomer was concentrated and lyophilized to afford **Example 18** (4.1 mg, 15% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 19** (5.5 mg, 21% yield) as a white solid.

Example 18: ^1H NMR (400 MHz, DMSO- d_6) δ 11.11 (s, 1H), 8.81 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.62 (s, 1H), 7.35 (s, 1H), 4.52-4.58 (m, 1H), 3.74 (s, 3H), 2.82-2.94 (m, 1H), 2.67-2.72 (m, 1H), 1.86 (s, 3H). LC-MS: m/z 527 [M+H] $^+$.

Example 19: ^1H NMR (400 MHz, DMSO- d_6) δ 11.11 (s, 1H), 8.81 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.62 (s, 1H), 7.35 (s, 1H), 4.53-4.58 (m, 1H), 3.74 (s, 3H), 2.82-2.94 (m, 1H), 2.67-2.72 (m, 1H), 1.86 (s, 3H). LC-MS: m/z 527 [M+H] $^+$.

Method A6



Examples 20, 21: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 22, 23: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide, (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole

To a stirred solution of 4-iodo-1H-pyrazole (100 g, 515.5 mmol) in THF (1.2 L) was added NaH (30.9 g, 773.3 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 30 min. 2-(chloromethoxy)ethyl-trimethyl-silane (128.9 g, 773.3 mmol) was added dropwise at 0 °C, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into ice-water (2500 mL) and extracted with ethyl acetate (3x 2500 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:3) to give the title compound (130 g, 73% yield) as a yellow oil. LC-MS: m/z 325 [M+H]⁺.

Step 2: 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-ol

To a stirred mixture of 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (50.1 g, 154.6 mmol) in Et₂O (800 mL) was added n-Butyllithium (61.8 mL, 2.5M in hexane) at -90 °C under nitrogen. The reaction mixture was stirred at -90 °C for 1 h under nitrogen. 6-oxabicyclo[3.1.0]hexane (10 g, 118.9 mmol) and boron trifluoride diethyl etherate (21.9 g, 154.6 mmol) were added at -90 °C, and the mixture was stirred at -78 °C for 1 h under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (100 mL), and the resulting mixture was extracted with ethyl acetate (3x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (2:1) to afford the title compound (9.6 g, 25% yield) as a yellow oil. LC-MS: m/z 283 [M+H]⁺.

Step 3: 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one

In analogy to **Method A1 step 2** but using 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-ol (9.6 g, 34.0 mmol), the title compound was obtained as a yellow oil (6.5 g, 61% yield). LC-MS: m/z 281 [M+H]⁺.

Step 4: 2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one (**A6-4**)

In analogy to **Method A1 step 3** but using 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one (6.5 g, 23.2 mmol), the title compound was obtained as a yellow oil (**A6-4**, 3.4 g, 44% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 (s, 1H), 7.43 (s, 1H), 5.33 (s, 2H), 3.43-3.55 (m, 2H), 2.24-2.34 (m, 3H), 1.76-2.01 (m, 3H), 1.25 (s, 3H), 0.78-0.83 (m, 2H), -0.06 (s, 9H). LC-MS: m/z 295 [M+H]⁺.

Step 5: 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one (3.3 g, 11.2 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethyl-methanedi-
5 amine (4.63 mL, 22.4 mmol) and stirring at 100 °C for 1 h, the crude title compound was obtained as a brown oil (4.5 g) and was used in the next step without further purification. LC-MS: m/z 350 [M+H]⁺.

Step 6: 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**A6-6**)

To a stirred solution of 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one (3.9 g, 8.9 mmol) in toluene (60 mL) were added 3-fluoro-1H-pyrazol-5-amine (1.8 g, 17.9 mmol) and AcOH (6 mL). The resulting mixture was stirred at 90 °C for 16 h. The mixture was allowed to cool to 25 °C and concentrated under reduced pressure. The residue was diluted with water (200 mL). The resulting
15 mixture was extracted with ethyl acetate (2x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:1). The obtained product was further purified by prep-HPLC to give the title compound (**A6-6**), 3 g, 79% yield) as a yellow oil. ¹H NMR (300 MHz, Chloroform-d) δ 8.44 (s, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 6.20 (d, J = 6.0 Hz, 1H), 5.31 (s, 2H), 3.50-3.55 (m, 2H), 3.04-3.21 (m, 2H), 2.61-2.69 (m, 1H), 2.34-2.44 (m, 1H), 1.99 (s, 3H),
20 0.84-0.90 (m, 2H), 0.05 (s, 9H). LC-MS: m/z 388 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

To a stirred solution of 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (4 g, 10.3 mmol) in toluene (20 mL) were added (4*R*)-4-benzyl-2-[1-[(4*R*)-4-benzyl-4,5-dihydrooxazol-2-yl]-1-methyl-ethyl]-4,5-dihydrooxazole (449 mg, 1.2 mmol), acetoxy-copper (255 mg, 2.1 mmol), N-fluorobenzenesulfonimide (4.9 g, 15.5 mmol) and TMS-CN (5.1 g, 51.6 mmol). The mixture was stirred at 25 °C for 16 h under nitrogen. The reaction was quenched by the addition of water (100
30 mL), and the resulting mixture was extracted with ethyl acetate (2x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure.

The residue was purified by prep-HPLC to give the title compound (1.5 g, 26% yield) as a yellow oil. LC-MS: m/z 413 [M+H]⁺.

Step 8: 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

5 A solution of 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (400 mg, 969 μ mol) in AcOH (3 mL) and HCl (12M, 3 mL) was stirred at 90 °C for 15 min. The mixture was allowed to cool to 25 °C. The pH was adjusted to ~6 by careful addition of 2N sodium hydroxide. The mixture was then directly purified by reverse phase flash chromatography to give the title compound (300
10 mg, 77% yield) as a yellow oil. LC-MS: m/z 302 [M+H]⁺.

Step 9: Methyl 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A6-9**)

To a stirred solution of 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (600 mg, 1.9 mmol) in MeOH (10 mL)
15 were added two drops of conc. H₂SO₄. The mixture was stirred at 80 °C for 1 h. The reaction was quenched with water (100 mL), and the resulting mixture was extracted with ethyl acetate (3x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude title compound (**A6-9**, 400 mg, 51% yield) as a yellow oil. LC-MS: m/z 316 [M+H]⁺.

20 Step 10: Methyl 8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (200 mg, 634 μ mol) in ACN (5 mL) were added cesium carbonate (1.0 g, 3.2 mmol) and iodoethane (495 mg, 3.2 mmol). The mixture was
25 stirred at 25 °C for 1 h. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to give the title compound (120 mg, 49% yield) as a yellow oil. LC-MS: m/z 344 [M+H]⁺.

Step 11: 8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

To a stirred solution of methyl 8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (120 mg, 349 μ mol) in MeOH (2 mL) and THF (2 mL) was added LiOH (42 mg, 1.8 mmol) in water (2 mL). The mixture was stirred at 25 °C for 1 h. The pH was adjusted to ~5 with 2M HCl. The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound (100 mg, 78% yield) as a yellow oil. LC-MS: m/z 330 [M+H]⁺.

Step 12: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (100 mg, 304 μ mol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (57 mg, 293 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (60 mg, 37% yield) as a white solid, LC-MS: m/z 507 [M+H]⁺; *cis*-isomer (40 mg, 24% yield) as a white solid, LC-MS: m/z 507 [M+H]⁺.

Step 13: Separation of enantiomers to obtain **Example 20** and **Example 21**

60 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRALPAK IA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 10.081; RT2(min): 18.654; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 20** (25.7 mg, 42% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 21** (22.6 mg, 37% yield) as a white solid.

Example 20: ¹H NMR (300 MHz, Chloroform-d) δ 9.07 (br, 1H), 9.73 (s, 1H), 8.61 (s, 1H), 8.53 (s, 1H), 7.89-7.94 (m, 3H), 7.76 (s, 1H), 6.29 (d, J = 5.1 Hz, 1H), 4.42-4.58 (m, 1H),

4.20-4.28 (m, 2H), 3.06-3.22 (m, 1H), 2.58-2.69 (m, 1H), 2.09 (s, 3H), 1.52 (t, J = 6.9Hz, 3H).
LC-MS: m/z 507 [M+H]⁺.

Example 21: ¹H NMR (300 MHz, Chloroform-d) δ 9.08 (br, 1H), 8.73 (s, 1H), 8.61 (s, 1H), 8.54 (s, 1H), 7.90-7.94 (m, 3H), 7.77 (s, 1H), 6.29 (d, J = 4.8 Hz, 1H), 4.43-4.58 (m, 1H),
5 4.20-4.28 (m, 2H), 3.05-3.22 (m, 1H), 2.58-2.69 (m, 1H), 2.09 (s, 3H), 1.52 (t, J = 6.9 Hz, 3H).
LC-MS: m/z 507 [M+H]⁺.

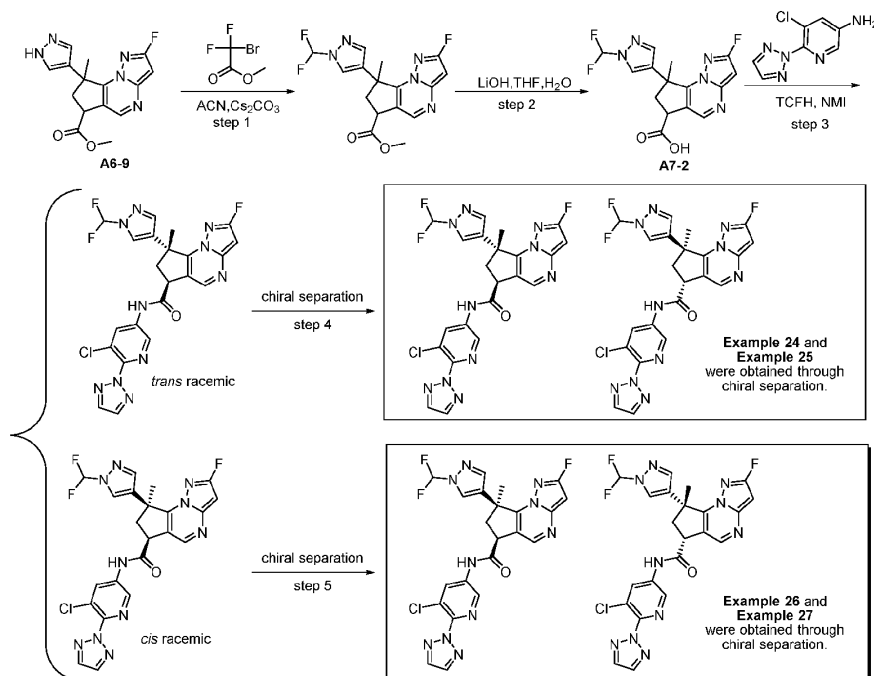
Step 14: Separation of enantiomers to obtain **Example 22** and **Example 23**

40 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-ethyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide
10 was submitted to chiral HPLC purification (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 13.051; RT2(min): 20.088; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 22** (14.1 mg, 35% yield) as a white solid.
15 The first eluting isomer was concentrated and lyophilized to afford **Example 23** (15.7 mg, 39% yield) as a white solid.

Example 22: ¹H NMR (300 MHz, Chloroform-d) δ 8.58 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 7.93 (s, 2H), 7.82 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 6.30 (d, J = 5.1 Hz, 1H), 4.34-4.42 (m, 1H), 4.08-4.17 (m, 2H), 2.83-3.03 (m, 2H), 2.00 (s, 3H), 1.43 (t, J = 6.9 Hz, 3H). LC-MS: m/z 507
20 [M+H]⁺.

Example 23: ¹H NMR (300 MHz, Chloroform-d) δ 8.58 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.05 (s, 1H), 7.92 (s, 2H), 7.64 (s, 1H), 7.52 (s, 1H), 6.29 (d, J = 5.1 Hz, 1H), 4.37-4.43 (m, 1H), 4.08-4.18 (m, 2H), 2.83-3.03 (m, 2H), 1.99 (s, 3H), 1.44 (t, J = 6.9 Hz, 3H). LC-MS: m/z 507 [M+H]⁺.

Method A7



Examples 24, 25: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 26, 27: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A6-9**, 200 mg, 634 μmol) in ACN (6 mL)

was added cesium carbonate (620 mg, 1.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min. and a solution of methyl 2-bromo-2,2-difluoro-acetate (599.3 mg, 3.2 mmol) in ACN (0.5 mL) was added. The mixture was stirred at 25 °C for 16 h. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to give the title compound (120 mg, 46% yield) as a yellow oil. LC-MS (ES, m/z): 366[M+H]⁺.

Step 2: 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**)

To a stirred solution of methyl 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (120 mg, 328 μmol) in MeOH (2 mL) and THF (2 mL) was added LiOH (39 mg, 1.6 mmol) in water (2 mL). The mixture was stirred at 25 °C for 1 h. The pH was adjusted to ~4 with 1M HCl. The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound (**A7-2**, 100 mg, 78% yield) as a yellow oil. LC-MS (ES, m/z): 352[M+H]⁺.

Step 3: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (100 mg, 285 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (210 mg, 1.1 mmol), racemic mixtures of the title compounds were obtained: *trans* isomer (50 mg, 31% yield) as a white solid, LC-MS (ES, m/z): 529[M+H]⁺; *cis*-isomer (50 mg, 31% yield) as a white solid, LC-MS (ES, m/z): 529[M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 24** and **Example 25**

50 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC

purification (Column: CHIRALPAK ID, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.29; RT2(min): 13.952; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 24** (17.3 mg, 34% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 25** (14.5 mg, 29% yield) as a white solid.

Example 24: ^1H NMR (300 MHz, Chloroform- d) δ 8.56-8.70 (m, 4H), 7.93 (s, 2H), 7.86 (s, 1H), 7.68 (s, 1H), 7.12 (t, J = 60.6 Hz, 1H), 6.33 (d, J = 5.1 Hz, 1H), 4.39-4.48 (m, 1H), 3.02-3.06 (m, 1H), 2.73-2.79 (m, 1H), 2.13 (s, 3H). LC-MS (ES, m/z): 529[M+H] $^+$.

Example 25: ^1H NMR (300 MHz, Chloroform- d) δ 8.69 (s, 1H), 8.46-8.62 (m, 2H), 8.14 (s, 1H), 7.94 (s, 2H), 7.83 (s, 1H), 7.66 (s, 1H), 7.13 (t, J = 60.6 Hz, 1H), 6.32 (d, J = 5.1 Hz, 1H), 4.32-4.42 (m, 1H), 3.00-3.05 (m, 1H), 2.73-2.77 (m, 1H), 2.13 (s, 3H). LC-MS (ES, m/z): 529[M+H] $^+$.

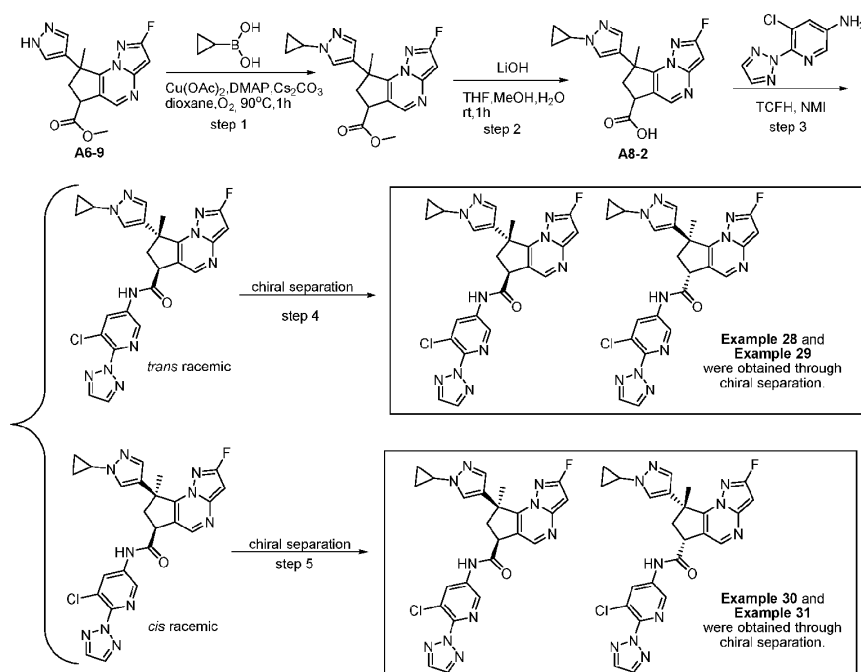
Step 5: Separation of enantiomers to obtain **Example 26** and **Example 27**

50 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.026; RT2(min): 15.277; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 26** (10.6 mg, 21% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 27** (13.6 mg, 27% yield) as a white solid.

Example 26: ^1H NMR (300 MHz, Chloroform- d) δ 8.60 (s, 2H), 8.42 (s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.93 (s, 2H), 7.78 (s, 1H), 7.13 (t, J = 60.3 Hz, 1H), 6.31 (d, J = 5.1 Hz, 1H), 4.37-4.42 (m, 1H), 2.97-3.03 (m, 1H), 2.82-2.90 (m, 1H), 2.00 (s, 3H). LC-MS (ES, m/z): 529[M+H] $^+$.

Example 27: ^1H NMR (300 MHz, Chloroform- d) δ 8.61 (s, 2H), 8.42 (s, 1H), 7.89-7.93 (m, 4H), 7.78 (s, 1H), 7.13 (t, J = 60.6 Hz, 1H), 6.32 (d, J = 4.8 Hz, 1H), 4.36-4.42 (m, 1H), 2.98-3.03 (m, 1H), 2.84-2.91 (m, 1H), 2.01 (s, 3H). LC-MS (ES, m/z): 529[M+H] $^+$.

Method A8



Examples 28, 29: (6*S*,8*R*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 30, 31: (6*S*,8*S*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (6*R*,8*R*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A6-9**, 250 mg, 793 μmol) in dioxane (10 mL) were added cyclopropylboronic acid (136 mg, 1.6 mmol), DMAP (387 mg, 3.2 mmol),

acetoxycopper (158 mg, 793 μ mol) and cesium carbonate (646 mg, 2.0 mmol). The mixture was stirred at 90 °C for 1 h under oxygen atmosphere. The reaction was quenched with water (30 mL), and the resulting mixture was extracted with ethyl acetate (3x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (120 mg, 36% yield) as a yellow oil. LC-MS: m/z 356 [M+H]⁺.

Step 2: 8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A8-2**)

In analogy to **Method A7 step 2** but using methyl 8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (120 mg, 338 μ mol), the crude title compound was obtained as a yellow oil (**A8-2**, 100 mg). LC-MS: m/z 342 [M+H]⁺.

Step 3: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (100 mg, 293 μ mol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (57 mg, 293 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (20 mg, 13% yield) as a white solid, LC-MS: m/z 519 [M+H]⁺; *cis*-isomer (13 mg, 8% yield) as a white solid, LC-MS: m/z 519 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 28** and **Example 29**

20 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 19 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 7.427; RT2(min): 13.024; Sample Solvent: EtOH--HPLC; Injection Volume: 2.5 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 28** (4.7

mg, 23% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 29** (5.5 mg, 27% yield) as a white solid.

Example 28: ¹H NMR (300 MHz, Chloroform-d) δ 9.13 (br, 1H), 8.71 (s, 1H), 8.61 (s, 1H), 8.53 (s, 1H), 7.93 (s, 2H), 7.73 (s, 1H), 6.29 (d, J = 5.1 Hz, 1H), 4.45-4.50 (m, 1H), 3.52-3.60 (m, 1H), 3.09-3.16 (m, 1H), 2.63-2.76 (m, 1H), 2.08 (s, 3H), 1.00-1.11 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Example 29: ¹H NMR (300 MHz, Chloroform-d) δ 9.11 (br, 1H), 8.71 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 7.93 (s, 2H), 7.61-7.71 (m, 2H), 6.29 (d, J = 4.8 Hz, 1H), 4.43-4.49 (m, 1H), 3.51-3.57 (m, 1H), 3.07-3.14 (m, 1H), 2.63-2.70 (m, 1H), 2.08 (s, 3H), 1.00-1.10 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

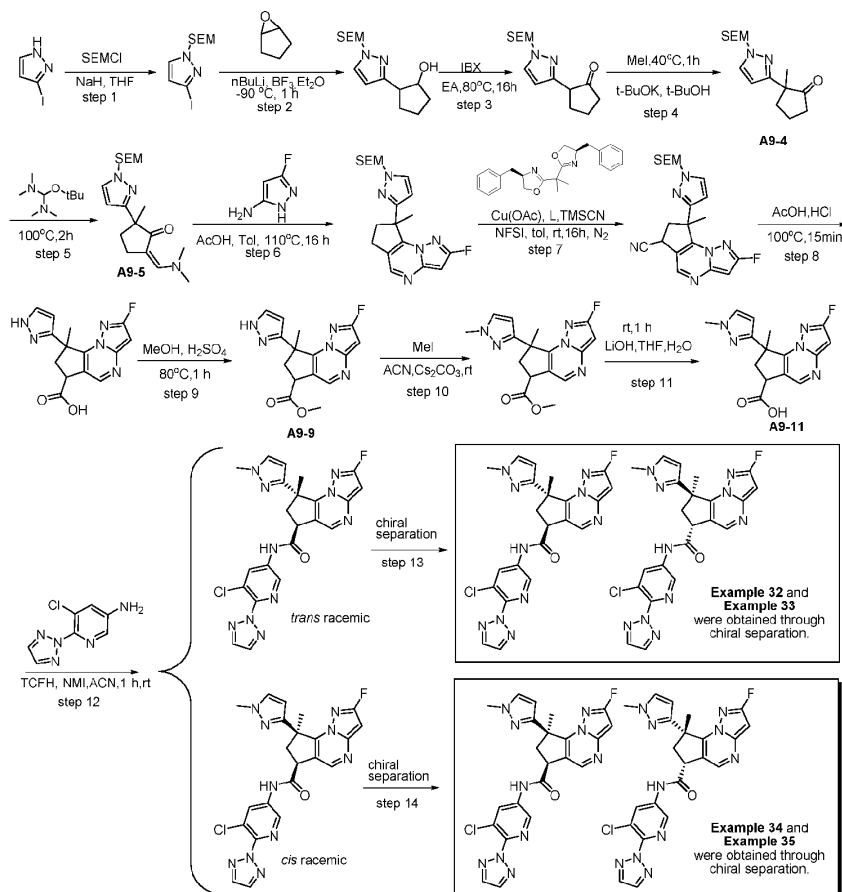
Step 5: Separation of enantiomers to obtain **Example 30** and **Example 31**

13 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 19 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 5.137; RT2(min): 8.122; Sample Solvent: EtOH--HPLC; Injection Volume: 1.8 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 30** (2.1 mg, 16% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 31** (2.5 mg, 18% yield) as a white solid.

Example 30: ¹H NMR (300 MHz, Chloroform-d) δ 8.59 (s, 1H), 8.51 (s, 1H), 8.30-8.42 (m, 2H), 7.92 (s, 2H), 7.59-7.66 (m, 2H), 6.28 (d, J = 5.1 Hz, 1H), 4.39-4.45 (m, 1H), 3.52-3.58 (m, 1H), 2.82-3.03 (m, 2H), 2.01 (s, 3H), 0.99-1.12 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Example 31: ¹H NMR (300 MHz, Chloroform-d) δ 8.59 (s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 8.13 (s, 1H), 7.93 (s, 2H), 7.56-7.64 (m, 2H), 6.30 (d, J = 5.1 Hz, 1H), 4.38-4.45 (m, 1H), 3.51-3.56 (m, 1H), 2.85-3.02 (m, 2H), 2.01 (s, 3H), 0.93-1.09 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Method A9



Examples 32, 33: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 34, 35: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole

In analogy to **Method A6 step 1** but using 3-iodo-1H-pyrazole (100 g, 515.5 mmol), the title compound was obtained as a white solid (130 g, 74% yield). LC-MS: m/z 325 [M+H]⁺.

Step 2: 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-ol

5 To a stirred mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (231.3 g, 713.3 mmol) in Et₂O (4.5 L) was added n-Butyllithium (310 mL, 2.5M in hexane) at -90 °C under nitrogen. The reaction mixture was stirred at -90 °C for 30 min under nitrogen. 6-oxabicyclo[3.1.0]hexane (50 g, 594.4 mmol) and boron trifluoride diethyl etherate (109 g, 772.7 mmol) were added at -90 °C. The reaction mixture was stirred at -90 °C for 1 h under nitrogen. The
10 reaction mixture was quenched with saturated aqueous ammonium chloride (1000 mL), and the resulting mixture was extracted with ethyl acetate (3x 2.0 L). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (60 g, 35% yield) as a yellow oil. LC-MS: m/z 283 [M+H]⁺.

15 Step 3: 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one

In analogy to **Method A1 step 2** but using 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-ol (60 g, 212.4 mmol), the title compound was obtained as a yellow oil (30 g, 31% purity). LC-MS: m/z 281 [M+H]⁺.

20 Step 4: 2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (**A9-4**)

In analogy to **Method A1 step 3** but using 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (23 g, 49.2 mmol) and after purification of the product by prep-HPLC, the title compound was obtained as a yellow oil (**A9-4**, 4.7 g, 32% yield). LC-MS: m/z 295 [M+H]⁺.

25 Step 5: 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (**A9-5**)

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (4.7 g, 15.9 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethyl-methanedi-amine (8.3 g, 47.7 mmol) and stirring at 100 °C for 2 h,
30 the crude title compound was obtained as a yellow oil (**A9-5**, 4.7 g) and was used in the next step without further purification. LC-MS: m/z 350 [M+H]⁺.

Step 6: 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A6 step 6** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (4 g, 11.4 mmol) and stirring at 110 °C for 16 h, the title compound was obtained as a yellow oil (2 g, 45% yield). LC-MS: m/z 388 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A6 step 7** but using 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (2 g, 5.1 mmol) and stirring at 25 °C for 24 h, the title compound was obtained as a yellow oil (420 mg, 11% yield) as a yellow oil. LC-MS: m/z 413 [M+H]⁺.

Step 8: 2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

A solution of 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (700 mg, 1.7 mmol) in AcOH (2.5 mL) and HCl (12M, 2.5 mL) was stirred at 100 °C for 15 min. The mixture was allowed to cool to 25 °C. The reaction mixture was diluted with water (10 mL) and the pH was adjusted to ~7 with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate (3x 15 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The mixture was purified by prep-HPLC to give the title compound (160 mg, 26% yield) as a yellow oil. LC-MS: m/z 302 [M+H]⁺.

Step 9: Methyl 2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A9-9**)

In analogy to **Method A6 step 9** but using 2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (330 mg, 33.2 mmol), the crude title compound was obtained as a yellow oil (**A9-9**, 100 mg). LC-MS: m/z 316 [M+H]⁺.

Step 10: Methyl 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A6 step 10** but using crude methyl 2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (80 mg) and
5 without final purification, the crude title compound was obtained as a yellow oil (50 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.67 (s, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 5.2 Hz, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 4.30-4.46 (m, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 2.83-2.88 (m, 1H), 2.60-2.66 (m, 1H), 1.86 (s, 3H). LC-MS: *m/z* 330 [M+H]⁺.

Step 11: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A9-11**)
10

In analogy to **Method A6 step 11** but using crude methyl 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (50 mg, 142 μmol), the crude title compound was obtained as a yellow oil (**A9-11**, 40 mg). LC-MS: *m/z* 316 [M+H]⁺.

Step 12: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide
15

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A9-11**, 40 mg, 127 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (24 mg, 127 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (23 mg, 37% yield) as a white solid, LC-MS: *m/z* 493 [M+H]⁺; *cis*-isomer (14 mg, 22% yield) as a white solid, LC-MS: *m/z* 493 [M+H]⁺.
20

Step 13: Separation of enantiomers to obtain **Example 32** and **Example 33**
25

23 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow
30 rate: 25 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 28.444; RT2(min): 33.535; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number

Of Runs: 12). The second eluting isomer was concentrated and lyophilized to afford **Example 32** (4 mg, 20% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 33** (2.9 mg, 14% yield) as a white solid.

Example 32: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.14 (s, 1H), 8.76 (d, J = 2.0 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.62 (d, J = 2.0 Hz, 1H), 6.55 (d, J = 5.2 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 4.51-4.56 (m, 1H), 3.73 (s, 3H), 3.00-3.33 (m, 1H), 2.50-2.51 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

Example 33: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.14 (br), 8.75 (d, J = 2.4 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.18 (s, 2H), 7.62 (d, J = 2.0 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 4.52-4.56 (m, 1H), 3.73 (s, 3H), 3.00-3.33 (m, 1H), 2.47-2.50 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

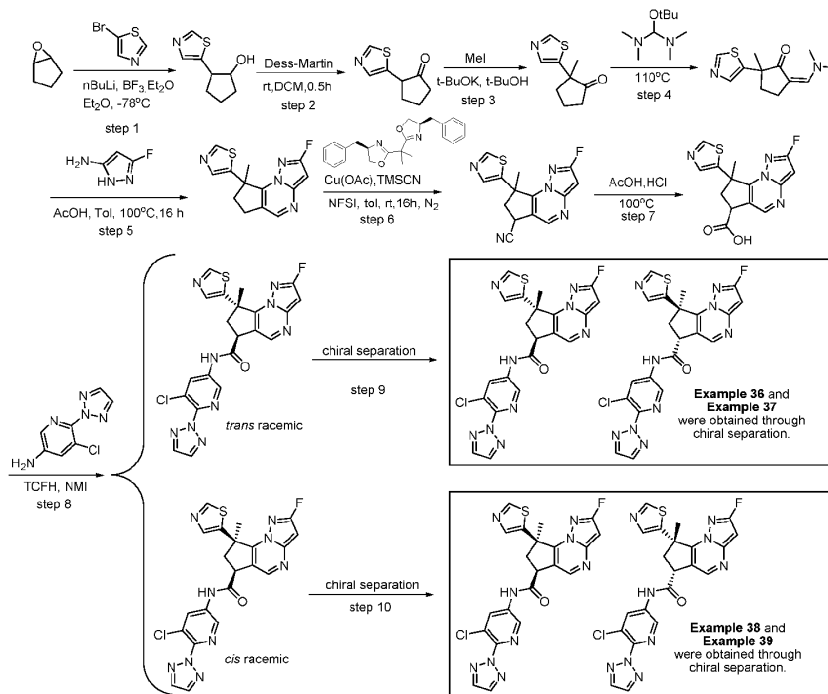
Step 14: Separation of enantiomers to obtain **Example 34** and **Example 35**

14 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide was submitted to chiral HPLC purification. (Column: CHIRALPAK AS-H, 2*25 cm, 5 μm ; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.135; RT2(min): 20.036; Sample Solvent: EtOH--HPLC; Injection Volume: 1.6 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 34** (2.0 mg, 14% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 35** (1.7 mg, 12% yield) as a white solid.

Example 34: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.04 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.69 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.56 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 4.8 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 4.51-4.55 (m, 1H), 3.69 (s, 3H), 2.88-2.92 (m, 1H), 2.74-2.79 (m, 1H), 1.87 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

Example 35: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.02 (s, 1H), 8.72 (d, J = 2.0 Hz, 1H), 8.69 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.56 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 4.8 Hz, 1H), 6.17 (d, J = 2.0 Hz, 1H), 4.51-4.55 (m, 1H), 3.69 (s, 3H), 2.88-2.93 (m, 1H), 2.74-2.79 (m, 1H), 1.87 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

Method A10



Examples 36, 37: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 38, 39: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(thiazol-5-yl)cyclopentan-1-ol

In analogy to Method A1 step 1 but using 5-bromothiazole (11.65 g, 71 mmol), the title compound was obtained as a brown oil (2 g, 20% yield). LC-MS: *m/z* 170 [M+H]⁺.

Step 2: 2-(thiazol-5-yl)cyclopentan-1-one

To a stirred solution of 2-(thiazol-5-yl)cyclopentan-1-ol (1 g, 5.9 mmol) in DCM (100 mL) was added Dess-Martin periodinane (3.76 g, 8.8 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 0.5 h. The reaction was quenched with saturated aqueous NaHSO₃ (200 mL), and the resulting mixture was extracted with DCM (3x 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude title compound (1 g) as a yellow oil. LC-MS: m/z 168 [M+H]⁺.

Step 3: 2-methyl-2-(thiazol-5-yl)cyclopentan-1-one

In analogy to **Method A1 step 3** but using 2-(thiazol-5-yl)cyclopentan-1-one (1.5 g, 5.3 mmol) and purification of the product by silica gel column chromatography eluting with PE/EA (1:1), the title compound was obtained as a yellow oil (270 mg, 28% yield). LC-MS: m/z 182 [M+H]⁺.

Step 4: 5-((dimethylamino)methylene)-2-methyl-2-(thiazol-5-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(thiazol-5-yl)cyclopentan-1-one (530 mg, 2.9 mmol) in 1-*tert*-butoxy-*N,N,N',N'*-tetramethyl-methanediamine (8 mL) and stirring at 110 °C for 1.5 h, the crude title compound was obtained as a yellow oil (230 mg, crude). LC-MS: m/z 237 [M+H]⁺.

Step 5: 5-(2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidin-8-yl)thiazole

To a stirred solution of 5-((dimethylamino)methylene)-2-methyl-2-(thiazol-5-yl)cyclopentan-1-one (520 mg, 2.2 mmol) in toluene (10 mL) were added 5-fluoro-1H-pyrazol-3-amine (445 mg, 4.4 mmol) and AcOH (1 mL) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. The mixture was allowed to cool to 25 °C. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water (50 mL). The pH was adjusted to ~7 with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate (2x 60 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column chromatography and eluted with EA/PE (3:7) to give the title compound (430 mg, 71% yield) as a yellow solid. LC-MS: m/z 275 [M+H]⁺.

Step 6: 2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 5-(2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidin-8-yl)thiazole (430 mg, 1.6 mmol), the title compound was
5 obtained as a white solid (70 mg, 15% yield). LC-MS: m/z 300 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A1 step 7** but using 2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (70 mg, 234 μ mol) and stirring at 90 °C
10 for 1 h, the title compound was obtained as a white solid (55 mg, 74% yield). LC-MS: m/z 319 [M+H]⁺.

Step 8: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-
15 dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (50 mg, 157 μ mol) and 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (31 mg, 157 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (35 mg, 44% yield) as an off-white solid, LC-MS: m/z
20 496 [M+H]⁺; *cis*-isomer (25 mg, 31% yield) as a white solid, LC-MS: m/z 496 [M+H]⁺.

Step 9: Separation of enantiomers to obtain **Example 36** and **Example 37**

35 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase
25 A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 19.03; RT2(min): 41.07; Sample Solvent: Hex(0.1% FA)--HPLC; Injection Volume: 1.1 mL; Number Of Runs: 20). The second eluting isomer was concentrated and lyophilized to afford **Example 36** (5 mg, 28% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 37**
30 (6.7 mg, 38% yield) as a white solid.

Example 36: ¹HNMR (300 MHz, DMSO-d₆) δ: 11.19 (br, 1H), 9.03 (s, 1H), 8.75 (s, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.18 (s, 2H), 7.84 (s, 1H), 6.63 (d, J = 5.1 Hz, 1H), 4.58-4.65 (m, 1H), 2.96-3.01 (m, 1H), 2.68-2.80 (m, 1H), 2.12 (s, 3H). LC-MS: m/z 496 [M+H]⁺.

5 **Example 37:** ¹HNMR (300 MHz, DMSO-d₆) δ: 11.20 (br, 1H), 9.03 (s, 1H), 8.75 (s, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.18 (s, 2H), 7.84 (s, 1H), 6.63 (d, J = 5.1 Hz, 1H), 4.58-4.65 (m, 1H), 2.96-3.01 (m, 1H), 2.68-2.78 (m, 1H), 2.12 (s, 3H). LC-MS: m/z 496 [M+H]⁺.

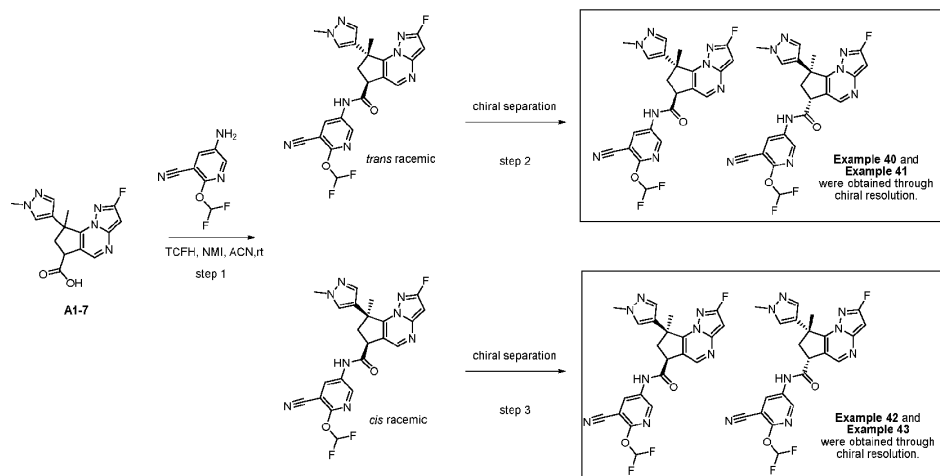
Step 10: Separation of enantiomers to obtain **Example 38** and **Example 39**

10 25 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(thiazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hcx(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 10.14; RT2(min): 12.47; Sample Solvent: EtOH--HPLC; Injection Volume: 0.4 mL; Number Of Runs: 3). The first eluting isomer was concentrated and lyophilized to afford **Example 38** (4.2 mg, 33% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 39** (4.7 mg, 37% yield) as a white solid.

20 **Example 38:** ¹HNMR (300 MHz, DMSO-d₆) δ: 11.22 (br, 1H), 8.99 (s, 1H), 8.77 (s, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.58 (d, J = 2.1 Hz, 1H), 8.18 (s, 2H), 7.82 (s, 1H), 6.61 (d, J = 4.8 Hz, 1H), 4.58-4.64 (m, 1H), 2.95-3.02 (m, 1H), 2.74-2.81 (m, 1H), 2.03 (s, 3H). LC-MS: m/z 496 [M+H]⁺.

25 **Example 39:** ¹HNMR (300 MHz, DMSO-d₆) δ: 11.22 (br, 1H), 8.99 (s, 1H), 8.78 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.82 (s, 1H), 6.61 (d, J = 5.1 Hz, 1H), 4.58-4.64 (m, 1H), 2.95-3.01 (m, 1H), 2.74-2.82 (m, 1H), 2.03 (s, 3H). LC-MS: m/z 496 [M+H]⁺.

Method A11



Examples 40, 41: (6*S*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 42, 43: (6*S*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: *Trans*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 15 a]pyrimidine-6-carboxamide and *cis*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 20 a]pyrimidine-6-carboxylic acid (90 mg, 285 μ mol) and 5-amino-2-(difluoromethoxy)nicotinonitrile (53 mg, 285 μ mol), racemic mixtures of

the title compounds were obtained: *trans* isomer (18 mg, 13% yield) as a white solid, LC-MS: m/z 483 [M+H]⁺; *cis*-isomer (12.4 mg, 9% yield) as a white solid, LC-MS: m/z 483 [M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 40** and **Example 41**

18 mg of *trans*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 10.614; RT2(min): 20.977; Sample Solvent: EtOH--HPLC; Injection Volume: 3 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 40** (4.7 mg, 26% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 41** (2.8 mg 15% yield) as a white solid.

Example 40: ¹H NMR (300 MHz, DMSO-d₆) δ: 10.89 (s, 1H), 8.69 (d, J = 2.7 Hz, 1H), 8.63-8.65 (m, 2H), 7.75 (t, J = 71.7 Hz, 1H), 7.64 (s, 1H), 7.41 (d, J = 0.6 Hz, 1H), 6.57 (d, J = 4.8 Hz, 1H), 4.49-4.52 (m, 1H), 3.75 (s, 3H), 2.84-2.86 (m, 1H), 2.47-2.53 (m, 1H), 1.96 (s, 3H). LC-MS: m/z 483 [M+H]⁺.

Example 41: ¹H NMR (300 MHz, DMSO-d₆) δ: 10.89 (s, 1H), 8.69 (d, J = 2.7 Hz, 1H), 8.63-8.64 (m, 2H), 7.75 (t, J = 71.7 Hz, 1H), 7.64 (s, 1H), 7.41 (d, J = 0.6 Hz, 1H), 6.58 (d, J = 5.1 Hz, 1H), 4.46-4.52 (m, 1H), 3.75 (s, 3H), 2.84-2.91 (m, 1H), 2.47-2.53 (m, 1H), 1.96 (s, 3H). LC-MS: m/z 483 [M+H]⁺.

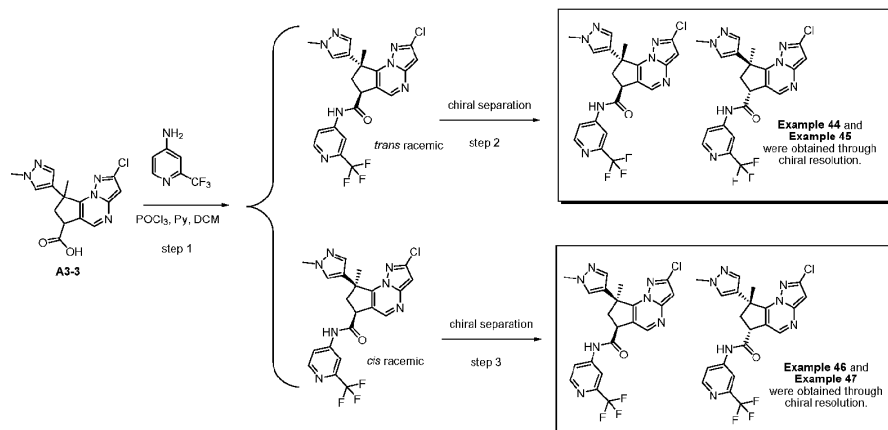
Step 3: Separation of enantiomers to obtain **Example 42** and **Example 43**

12.4 mg of *cis*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.371; RT2(min): 18.431; Sample Solvent: EtOH--HPLC; Injection Volume: 2.5 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 42** (5.4 mg, 28% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 43** (2.6 mg, 13% yield) as a white solid.

Example 42: ^1H NMR (300 MHz, DMSO- d_6) δ : 10.86 (s, 1H), 8.68 (d, J = 2.7 Hz, 1H), 8.67 (s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 7.75 (t, J = 71.4 Hz, 1H), 7.62 (s, 1H), 7.33 (d, J = 0.6 Hz, 1H), 6.54 (d, J = 5.1 Hz, 1H), 4.46-4.51 (m, 1H), 3.75 (s, 3H), 2.66-2.80 (m, 2H), 1.86 (s, 3H). LC-MS: m/z 483 $[\text{M}+\text{H}]^+$.

5 **Example 43:** ^1H NMR (300 MHz, DMSO- d_6) δ : 10.89 (s, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.67 (s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 7.75 (t, J = 71.4 Hz, 1H), 7.62 (s, 1H), 7.33 (d, J = 0.9 Hz, 1H), 6.54 (d, J = 5.1 Hz, 1H), 4.46-4.49 (m, 1H), 3.75 (s, 3H), 2.69-2.79 (m, 2H), 1.86 (s, 3H). LC-MS: m/z 483 $[\text{M}+\text{H}]^+$.

Method A12



10

Examples 44, 45: (6*S*,8*R*)-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

15

Examples 46, 47: (6*S*,8*S*)-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

20

The relative and absolute stereochemistry of each example was not determined.

Step 1: *Trans*-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

To a stirred solution of 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A3-3**, 90 mg, 211 μ mol) in DCM (15 mL) were added pyridine (139 mg, 1.7 mmol) and phosphoryl trichloride (178 mg, 1.2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 25°C for 1 h. 2-(trifluoromethyl)pyridin-4-amine (69 mg, 423 μ mol) was added, and the mixture was stirred at 0°C for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water (10 mL). The resulting mixture was extracted with ethyl acetate (3x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with DCM/MeOH (10:1) to give the crude product, which was further purified by prep-HPLC to afford racemic mixtures of the title compounds: *trans* isomer (19 mg 14% yield) as a white solid, LC-MS: m/z 476 [M+H]⁺; *cis*-isomer (11 mg, 8% yield) as a white solid, LC-MS: m/z 476 [M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 44** and **Example 45**

10 mg of *trans*-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.391; RT2(min): 12.872; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 44** (3.7 mg, 36% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 45** (3.1 mg, 30% yield) as a white solid.

Example 44: ¹H NMR (300 MHz, DMSO-d₆) δ : 11.12 (s, 1H), 8.67 (d, J = 6.3 Hz, 1H), 8.65 (s, 1H), 8.19 (d, J = 1.8 Hz, 1H), 7.80-7.83 (m, 1H), 7.61 (s, 1H), 7.40 (s, 1H), 6.96 (s, 1H), 4.49-4.55 (m, 1H), 3.76 (s, 3H), 2.85-2.92 (m, 1H), 2.47-2.52 (m, 1H), 1.98 (s, 3H). LC-MS: m/z 476 [M+H]⁺.

Example 45: ^1H NMR (300 MHz, DMSO- d_6) δ : 11.11 (s, 1H), 8.67 (d, J = 6.0 Hz, 1H), 8.65 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.80-7.83 (m, 1H), 7.61 (s, 1H), 7.40 (s, 1H), 6.96 (s, 1H), 4.49-4.52 (m, 1H), 3.76 (s, 3H), 2.85-2.92 (m, 1H), 2.48-2.54 (m, 1H), 1.98 (s, 3H). LC-MS: m/z 476 $[\text{M}+\text{H}]^+$.

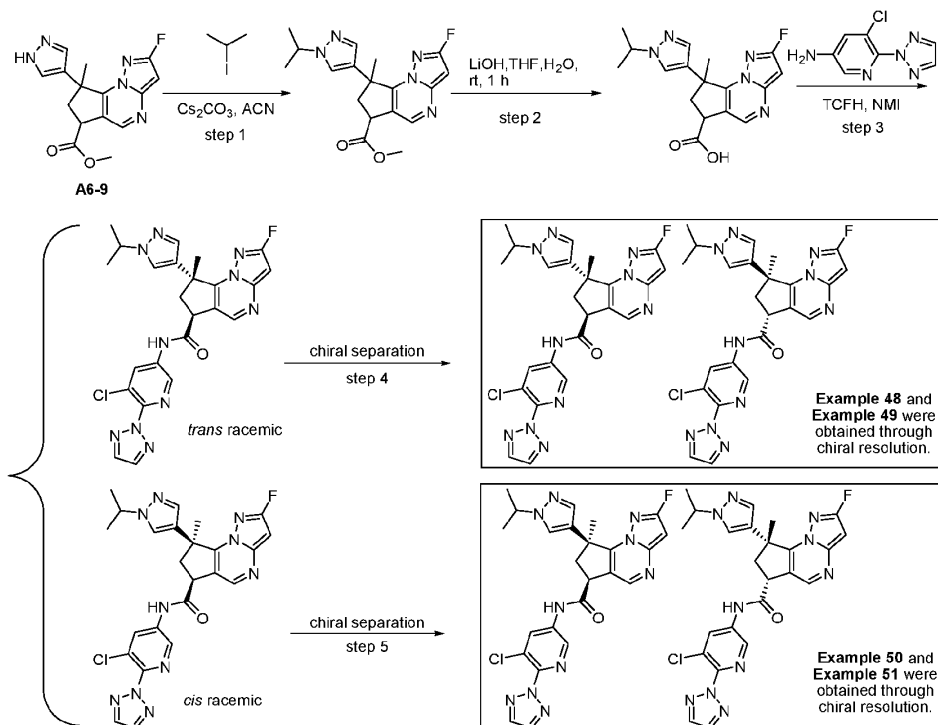
5 Step 10: Separation of enantiomers to obtain **Example 46** and **Example 47**

10 10 mg of *cis*-2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μm ; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 20% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 6.723; RT2(min): 10.474; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 5). The first eluting isomer was concentrated and lyophilized to afford **Example 46** (3.7 mg, 36% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 47** (4.5 mg, 44% yield) as a white solid.

15 **Example 46:** ^1H NMR (300 MHz, DMSO- d_6) δ : 11.12 (s, 1H), 8.70 (s, 1H), 8.65 (d, J = 5.4 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.82-7.84 (m, 1H), 7.59 (s, 1H), 7.31 (d, J = 0.9 Hz, 1H), 6.93(s, 1H), 4.49-4.56 (m, 1H), 3.74 (s, 3H), 2.80-2.87 (m, 1H), 2.62-2.69 (m, 1H), 1.89 (s, 3H). LC-MS: m/z 476 $[\text{M}+\text{H}]^+$.

20 **Example 47:** ^1H NMR (300 MHz, DMSO- d_6) δ : 11.14 (s, 1H), 8.70 (s, 1H), 8.65 (d, J = 5.4 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.81-7.84 (m, 1H), 7.59 (s, 1H), 7.31 (d, J = 0.9 Hz, 1H), 6.93(s, 1H), 4.51-4.53 (m, 1H), 3.74 (s, 3H), 2.80-2.84 (m, 1H), 2.62-2.69 (m, 1H), 1.89 (s, 3H). LC-MS: m/z 476 $[\text{M}+\text{H}]^+$.

Method A13



Examples 48, 49: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1*H*-pyrazol-4-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1*H*-pyrazol-4-yl)-8-methyl-7,8-dihydro-6*H*-
 cyclopenta[*e*]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 50, 51: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1*H*-pyrazol-4-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1*H*-pyrazol-4-yl)-8-methyl-7,8-dihydro-6*H*-
 cyclopenta[*e*]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A6-9**, 180 mg, 571 μ mol) in ACN (5 mL) was added cesium carbonate (372 mg, 1.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min. 2-iodopropane (1.9 g, 11.4 mmol) in ACN (0.5 mL) was added, and the mixture was stirred at 25 °C for 5 h. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with DCM/MeOH (10:1) to give the title compound (80 mg, 27% yield) as a yellow oil. LC-MS (ES, m/z): 358[M+H]⁺.

Step 2: 2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A6 step 11** but using methyl 2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (75 mg, 210 μ mol), the crude title compound was obtained as a yellow oil (80 mg, 70% yield). LC-MS (ES, m/z): 344[M+H]⁺.

Step 3: *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (75 mg, 218 μ mol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (64 mg, 328 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (13.9 mg, 11% yield) as a white solid, LC-MS (ES, m/z): 521[M+H]⁺; *cis*-isomer (6.7 mg, 5% yield) as a white solid, LC-MS (ES, m/z): 521[M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 48** and **Example 49**

12.8 mg of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5

µm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 11.401; RT2(min): 17.85; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 48** (2.6 mg, 20% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 49** (2.0 mg, 15% yield) as a white solid.

Example 48: ¹H NMR (400 MHz, Chloroform-d) δ 8.55-8.77 (m, 4H), 7.94-8.00 (m, 3H), 7.83 (s, 1H), 6.32 (d, J = 5.2 Hz, 1H), 4.48-4.68 (m, 2H), 3.20-3.33 (m, 1H), 2.60-2.72 (m, 1H), 2.12 (s, 3H), 1.56-1.59 (m, 6H). LC-MS (ES, m/z): 521[M+H]⁺.

Example 49: ¹H NMR (400 MHz, Chloroform-d) δ 8.64-8.86 (m, 2H), 8.52-8.67 (m, 2H), 7.96 (s, 2H), 7.67-7.90 (m, 2H), 6.31 (d, J = 5.2 Hz, 1H), 4.43-4.64 (m, 2H), 3.15-3.28 (m, 1H), 2.59-2.74 (m, 1H), 2.12 (s, 3H), 1.51-1.61 (m, 6H). LC-MS (ES, m/z): 521[M+H]⁺.

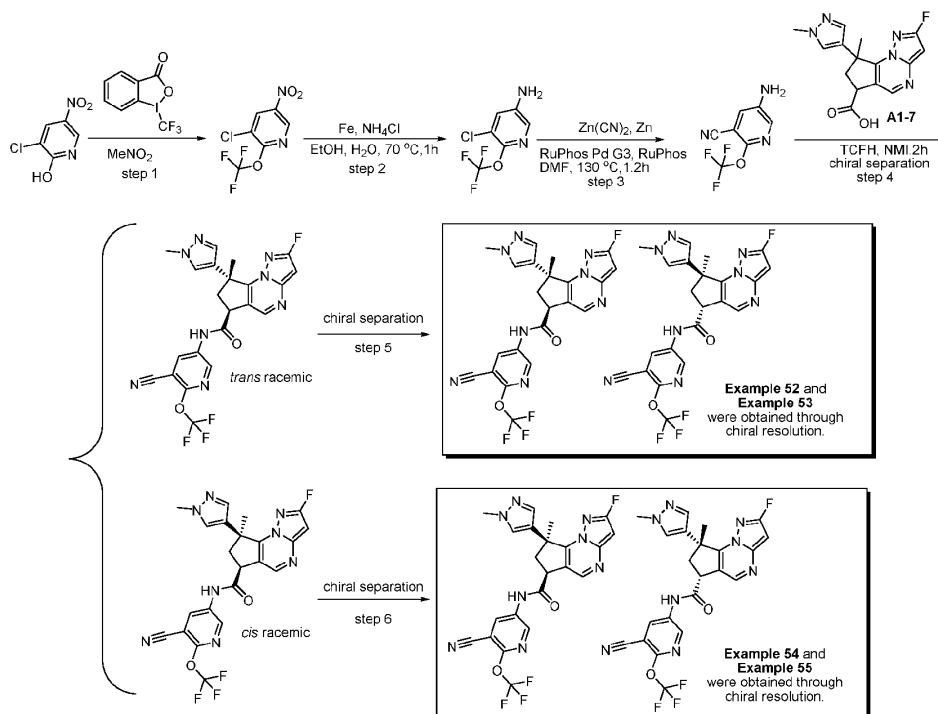
Step 5: Separation of enantiomers to obtain **Example 50** and **Example 51**

5.6 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-(1-isopropyl-1H-pyrazol-4-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 7.898; RT2(min): 14.194; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 50** (1.0 mg, 17% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 51** (1.9 mg, 31% yield) as a white solid.

Example 50: ¹H NMR (400 MHz, Chloroform-d) δ 8.46-8.71 (m, 3H), 7.72-7.99 (m, 4H), 6.32 (d, J = 5.2 Hz, 1H), 4.51-4.74 (m, 2H), 2.83-3.10 (m, 2H), 2.01 (s, 3H), 1.53-1.56 (m, 6H). LC-MS (ES, m/z): 521[M+H]⁺.

Example 51: ¹H NMR (400 MHz, Chloroform-d) δ 8.29-9.05 (m, 4H), 7.64-7.99 (m, 4H), 6.31 (d, J = 5.2 Hz, 1H), 4.49-4.70 (m, 2H), 2.85-3.08 (m, 2H), 2.01 (s, 3H), 1.51-1.57 (m, 6H). LC-MS (ES, m/z): 521[M+H]⁺.

Method A14



Examples 52, 53: (6*S*,8*R*)-*N*-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 54, 55: (6*S*,8*S*)-*N*-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-chloro-5-nitro-2-(trifluoromethoxy)pyridine

15 To a mixture of 3-chloro-5-nitropyridin-2-ol (3 g, 17.2 mmol) in MeNO₂ (30 mL) was added 1-(trifluoromethyl)-1*H*-benzo[*d*][1,2]iodoxol-3(1*H*)-one (10.9 g, 34.4 mmol) in portions at 100 °C. The mixture was stirred at 100 °C for 1 h. The mixture was cooled to room temperature

and poured into water (200 mL) after. The mixture was extracted with EtOAc (3x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:15) to give the title compound (1.3 g, 26% yield) as a yellow oil. LC-MS: m/z 243 [M+H]⁺.

5 Step 2: 5-chloro-6-(trifluoromethoxy)pyridin-3-amine

To a stirred solution of 3-chloro-5-nitro-2-(trifluoromethoxy)pyridine (900 mg, 3.7 mmol) in EtOH/H₂O (3:1, 20 mL) were added iron (1.04 g, 18.5 mmol) and NH₄Cl (6.35 g, 118.7 mmol). The resulting mixture was stirred at 70 °C for 1 h. The mixture was filtered, the filtrate diluted with water (100 mL), and the resulting mixture was extracted with ethyl acetate (3x 100 mL). The
10 combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound (330 mg, 41% yield) as a yellow solid. LC-MS: m/z 213 [M+H]⁺.

Step 3: 5-amino-2-(trifluoromethoxy)nicotinonitrile

To a stirred solution of 5-chloro-6-(trifluoromethoxy)pyridin-3-amine (200 mg, 0.9 mmol) in DMF (8 mL) were added Zn(CN)₂ (221 mg, 1.9 mmol), Zn (6.1 mg, 94 μmol), RuPhos-Pd G3 (43.9 mg, 94 μmol) and RuPhos (76.8 mg, 94 μmol). The resulting mixture was stirred at 130 °C for 1.2 h under nitrogen. The mixture was cooled to 25 °C, and water (100 mL) was added. The resulting mixture was extracted with ethyl acetate (3x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was
20 applied onto a silica gel column and eluted with EtOAc/PE (1:3) to give the title compound (110 mg, 57% yield) as a yellow solid. LC-MS: m/z 204 [M+H]⁺.

Step 4: *trans*-N-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide
25

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A1-7**, 72.4 mg, 229 μmol) and 5-amino-2-(trifluoromethoxy)nicotinonitrile (56 mg, 275 μmol), racemic mixtures
30 of the title compounds were obtained: *trans* isomer (25 mg, 21% yield) as an off-white solid, LC-MS: m/z 501 [M+H]⁺; *cis*-isomer (25 mg, 21% yield) as a white solid, LC-MS: m/z 501 [M+H]⁺.

Step 5: Separation of enantiomers to obtain **Example 52** and **Example 53**

20 mg of *trans*-N-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 6.674; RT2(min): 18.161; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 52** (12.6 mg, 62% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 53** (5.7 mg, 28% yield) as a white solid.

Example 52: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.06 (s, 1H), 8.74-8.76 (m, 2H), 8.62 (s, 1H), 7.64 (s, 1H), 7.41 (s, 1H), 6.56 (d, J = 4.0 Hz, 1H), 4.48-4.52 (m, 1H), 3.75 (s, 3H), 2.84-2.89 (m, 1H), 2.48-2.49 (m, 1H), 1.95 (s, 3H). LC-MS: m/z 501 [M+H] $^+$.

Example 53: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.07 (s, 1H), 8.75-8.76 (m, 2H), 8.62 (s, 1H), 7.64 (s, 1H), 7.41 (s, 1H), 6.56 (d, J = 4.0 Hz, 1H), 4.48-4.53 (m, 1H), 3.75 (s, 3H), 2.84-2.89 (m, 1H), 2.48-2.49 (m, 1H), 1.95 (s, 3H). LC-MS: m/z 501 [M+H] $^+$.

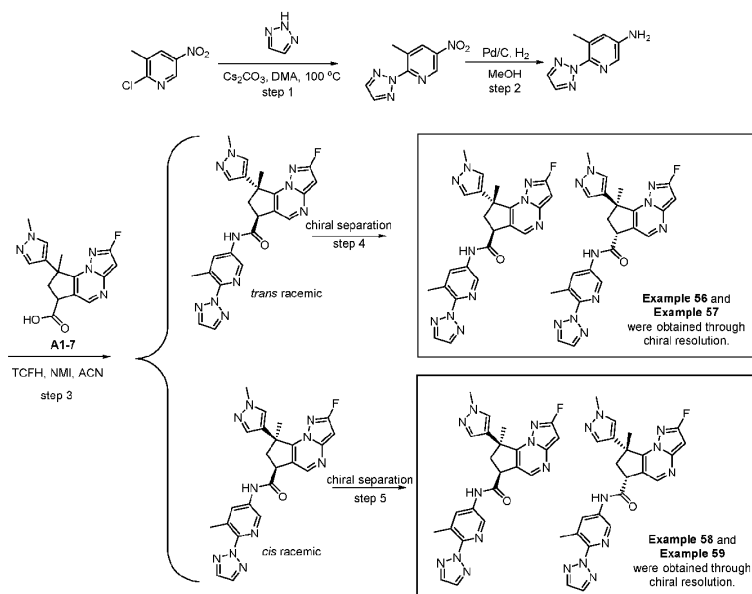
Step 6: Separation of enantiomers to obtain **Example 54** and **Example 55**

20 mg of *cis*-N-(5-cyano-6-(trifluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 4.92; RT2(min): 11.085; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 54** (2.3 mg, 11% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 55** (2.9 mg, 14% yield) as a white solid.

Example 54: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.08 (s, 1H), 8.72-8.76 (m, 2H), 8.67 (s, 1H), 7.61 (s, 1H), 7.32 (s, 1H), 6.54 (d, J = 4.8 Hz, 1H), 4.48-4.52 (m, 1H), 3.75 (s, 3H), 2.77-2.83 (m, 1H), 2.64-2.69 (m, 1H), 1.85 (s, 3H). LC-MS: m/z 501 [M+H] $^+$.

Example 55: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.03 (s, 1H), 8.71-8.75 (m, 2H), 8.67 (s, 1H), 7.61 (s, 1H), 7.32 (s, 1H), 6.54 (d, J = 4.8 Hz, 1H), 4.48-4.51 (m, 1H), 3.75 (s, 3H), 2.78-2.84 (m, 1H), 2.65-2.70 (m, 1H), 1.85 (s, 3H). LC-MS: m/z 501 $[\text{M}+\text{H}]^+$.

Method A15



5

Examples 56, 57: (6*S*,8*R*)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 58, 59: (6*S*,8*S*)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

15

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-methyl-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine

To a stirred mixture of 2-chloro-3-methyl-5-nitropyridine (10.0 g, 57.9 mmol) and 2H-1,2,3-triazole (4.8 g, 69.5 mmol) in acetonitrile (100 mL) was added K_2CO_3 (16.0 g, 115.9 mmol).

The reaction mixture was stirred at 25 °C for 24 h. The resulting mixture was concentrated under reduced pressure. Water (100 mL) was added, and the resulting mixture was extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with water (3x 100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied
5 onto a silica gel column and eluted with EtOAc/PE (5:1) to afford the title compound (10.0 g , 84% yield) as a yellow solid. LC-MS: m/z 206 [M+H]⁺.

Step 2: 5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine

To a stirred solution of 3-methyl-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine (10.0 g, 48.7 mmol) in methanol (50 mL) was added Pd/C (11.8 g, 97.4 mmol). The reaction mixture was
10 degassed and then stirred at 25 °C for 72 h under hydrogen. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (4.0 g, 46% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 (s, 2H), 7.71 (d, *J* = 2.8 Hz, 1H), 6.95 (d, *J* = 2.8, 1H), 5.75 (s, 2H), 1.96 (s, 3H). LC-MS: m/z 176 [M+H]⁺.

Step 3: *trans*-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A1-7**, 80 mg, 254 μmol) and 5-methyl-6-(triazol-2-yl)pyridin-3-amine (44 mg, 254 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (26 mg, 16% yield) as a white solid, LC-MS: m/z 473 [M+H]⁺; *cis*-isomer (22 mg , 15% yield) as a white solid, LC-MS: m/z 473 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 56** and **Example 57**

26 mg of *trans*-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC;
30 Flow rate: 17 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.155; RT2(min): 17.671; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL;

Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 56** (6.4 mg, 24% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 57** (6.7 mg, 25.5% yield) as a white solid.

Example 56: ^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.65 (s, 2H), 8.27 (d, J = 2.4 Hz, 1H), 8.12 (s, 2H), 7.65 (s, 1H), 7.43 (s, 1H), 6.57 (d, J = 4.8 Hz, 1H), 4.53 (t, J = 8.4 Hz, 1H), 3.76 (s, 3H), 2.88-2.93 (m, 1H), 2.50-2.52 (m, 1H), 2.21 (s, 3H), 1.96 (s, 3H). LC-MS: m/z 473 [M+H] $^+$.

Example 57: ^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.65 (s, 2H), 8.27 (d, J = 2.4 Hz, 1H), 8.12 (s, 2H), 7.65 (s, 1H), 7.43 (s, 1H), 6.57 (d, J = 4.8 Hz, 1H), 4.53 (t, J = 8.4 Hz, 1H), 3.76 (s, 3H), 2.88-2.93 (m, 1H), 2.50-2.52 (m, 1H), 2.21 (s, 3H), 1.96 (s, 3H). LC-MS: m/z 473 [M+H] $^+$.

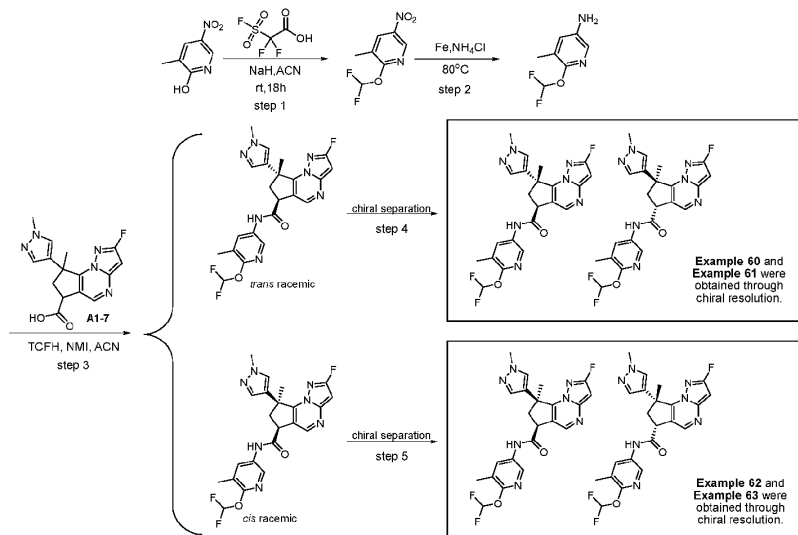
Step 5: Separation of enantiomers to obtain **Example 58** and **Example 59**

22 mg of *cis*-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-N-(5-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm ; Mobile Phase A: MtBE(0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 17 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 7.783; RT2(min): 16.654; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 58** (5.0 mg, 22% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 59** (3.2 mg, 14% yield) as a white solid.

Example 58: ^1H NMR (400 MHz, DMSO- d_6) δ 10.83 (s, 1H), 8.69 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.11 (s, 2H), 7.62 (s, 1H), 7.34 (s, 1H), 6.57 (d, J = 4.9 Hz, 1H), 4.49-4.53 (m, 1H), 3.75 (s, 3H), 2.79-2.85 (m, 1H), 2.66-2.71 (m, 1H), 2.20 (s, 3H), 1.87 (s, 3H). LC-MS: m/z 473 [M+H] $^+$.

Example 59: ^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.69 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.11 (s, 2H), 7.62 (s, 1H), 7.34 (s, 1H), 6.57 (d, J = 4.9 Hz, 1H), 4.49-4.53 (m, 1H), 3.75 (s, 3H), 2.79-2.85 (m, 1H), 2.66-2.71 (m, 1H), 2.20 (s, 3H), 1.87 (s, 3H). LC-MS: m/z 473 [M+H] $^+$.

Method A16



Examples 60, 61: (6*S*,8*R*)-*N*-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 62, 63: (6*S*,8*S*)-*N*-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(difluoromethoxy)-3-methyl-5-nitropyridine

15 To a stirred solution of 3-methyl-5-nitropyridin-2-ol (1 g, 6.5 mmol) in ACN (20 mL) was added NaH (700 mg, 17.5 mmol, 60% in mineral oil) in portions at 0 °C. The mixture was stirred at 25 °C for 1h. 2,2-difluoro-2-(fluorosulfonyl)acetic acid (2.1 g, 11.7 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred at 25 °C for 18 h. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with ethyl acetate (3x 20 mL). The
 20 combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate

and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:5) to give the title compound (800 mg, 60% yield) as a yellow oil. ¹H NMR (300 MHz, Chloroform-d) δ 8.92 (d, J = 2.7 Hz, 1H), 8.36-8.34 (m, 1H), 7.55 (t, J = 71.7 Hz, 1H), 2.39 (s, 3H). LC-MS (ES, m/z): 205 [M+H]⁺.

5 Step 2: 6-(difluoromethoxy)-5-methylpyridin-3-amine

To a stirred solution of 2-(difluoromethoxy)-3-methyl-5-nitropyridine (700 mg, 3.4 mmol) in EtOH (15 mL) and water (5 mL) was added Fe (1.2 g, 20.6 mmol) and NH₄Cl (366.9 mg, 6.9 mmol). The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was applied onto a silica gel
10 column and eluted with EtOAc/PE (1:3) to give the title compound (500 mg, 83% yield) as a yellow oil. LC-MS: m/z 175 [M+H]⁺.

Step 3: *trans*-N-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide
15

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A1-7**, 70 mg, 222 μmol) and 6-(difluoromethoxy)-5-methylpyridin-3-amine (58 mg, 333 μmol) and stirring at 25 °C
20 for 4 h, racemic mixtures of the title compounds were obtained: *trans* isomer (45 mg, 42% yield) as a white solid, LC-MS: m/z 472 [M+H]⁺; *cis*-isomer (25 mg, 23% yield) as a light pink solid, LC-MS: m/z 472 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 60** and **Example 61**

30 mg of *trans*-N-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 5.792; RT2(min): 8.757; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6
30 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford

Example 60 (7.1 mg, 23% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 61** (9.0 mg, 29% yield) as a white solid.

Example 60: ¹HNMR (400 MHz, DMSO-d₆) δ10.51 (s, 1H), 8.59 (s, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.66 (t, J = 73.2 Hz, 1H), 7.63 (s, 1H), 7.41 (s, 1H), 6.55 (d, J = 4.8 Hz, 1H), 4.43-4.48 (m, 1H), 3.75 (s, 3H), 2.83-2.89 (m, 1H), 2.44-2.52 (m, 1H), 2.22 (s, 3H), 1.95 (s, 3H). LC-MS: m/z 472 [M+H]⁺.

Example 61: ¹HNMR (400 MHz, DMSO-d₆) δ10.51 (s, 1H), 8.59 (s, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.66 (t, J = 73.2 Hz, 1H), 7.63 (s, 1H), 7.41 (s, 1H), 6.55 (d, J = 4.8 Hz, 1H), 4.43-4.48 (m, 1H), 3.75 (s, 3H), 2.83-2.89 (m, 1H), 2.44-2.52 (m, 1H), 2.22 (s, 3H), 1.95 (s, 3H). LC-MS: m/z 472 [M+H]⁺.

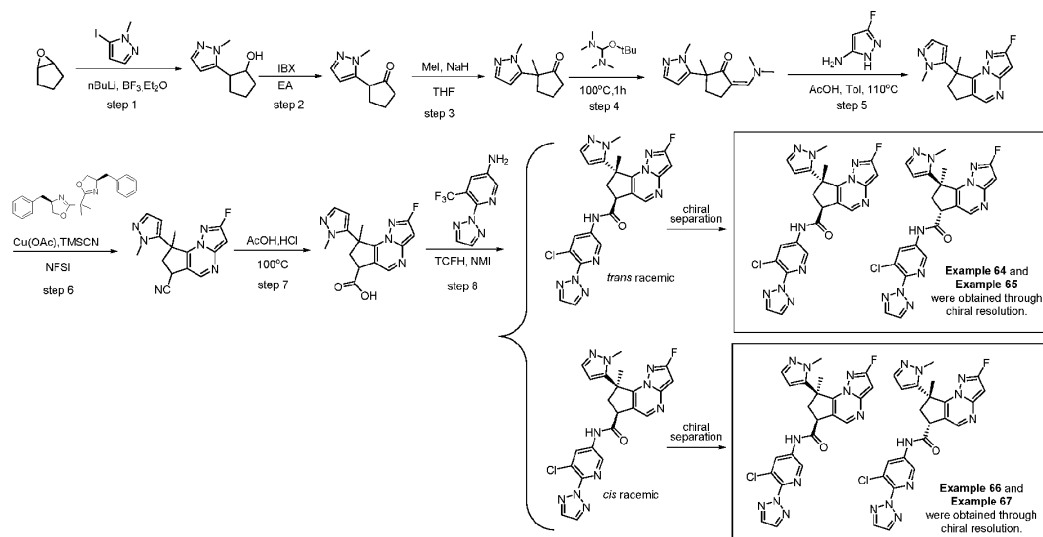
Step 5: Separation of enantiomers to obtain **Example 62** and **Example 63**

20 mg of *cis*-N-(6-(difluoromethoxy)-5-methylpyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 220/254 nm; RT1(min): 9.608; RT2(min): 11.131; Sample Solvent: EtOH--HPLC; Injection Volume: 0.3 mL; Number Of Runs: 4). The first eluting isomer was concentrated and lyophilized to afford **Example 62** (2.8 mg, 13% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 63** (2.6 mg, 12% yield) as a white solid.

Example 62: ¹HNMR (400 MHz, DMSO-d₆) δ10.51 (s, 1H), 8.65 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.65 (t, J = 73.2 Hz, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 6.53 (d, J = 4.8 Hz, 1H), 4.42-4.47 (m, 1H), 3.75 (s, 3H), 2.75-2.81 (m, 1H), 2.63-2.68 (m, 1H), 2.21 (s, 3H), 1.85 (s, 3H). LC-MS: m/z 472 [M+H]⁺.

Example 63: ¹HNMR (400 MHz, DMSO-d₆) δ10.51 (s, 1H), 8.65 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.65 (t, J = 73.2 Hz, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 6.53 (d, J = 4.8 Hz, 1H), 4.42-4.47 (m, 1H), 3.75 (s, 3H), 2.75-2.81 (m, 1H), 2.63-2.68 (m, 1H), 2.21 (s, 3H), 1.85 (s, 3H). LC-MS: m/z 472 [M+H]⁺.

Method A17



Examples 64, 65: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 66, 67: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-5-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(1-methyl-1*H*-pyrazol-5-yl)cyclopentan-1-ol

15 In analogy to **Method A6 step 2** but using 5-iodo-1-methyl-1*H*-pyrazole (10 g, 48.0 mmol), the title compound was obtained as a yellow oil (3.7 g, 46% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 2.0 Hz, 1H), 6.03 (d, *J* = 2.0 Hz, 1H), 4.23 (q, *J* = 6.4 Hz, 1H), 3.85 (s, 3H), 3.02 (m, 1H), 2.27 (m, 2H), 1.94-1.59 (m, 4H). LC-MS: *m/z* 167 [*M*+]⁺.

Step 2: 2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one

In analogy to **Method A10 step 2** but using 2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-ol (7.5 g, 45.1 mmol), stirring for 16 h and purification of the product by silica gel column chromatography eluting with EtOAc/PE (3:2), the title compound was obtained as a yellow oil (6 g, 80% yield). LC-MS: m/z 165 [M+H]⁺.

Step 3: 2-methyl-2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one

To a stirred solution of 2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one (4.6 g, 28.0 mmol) in THF (20 mL) was added NaH (1.3 g, 56.0 mmol, 60% in mineral oil) in portions at 0 °C. The mixture was stirred at 0 °C for 10 min. Iodomethane (2.7 g, 19.6 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred at 80 °C for 16 h. The reaction was quenched with water (50 mL), and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (3:2) to afford the title compound (4 g, 80% yield) as a yellow oil. LC-MS: m/z 179 [M+H]⁺.

Step 4: 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one (4.5 g, 25.2 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethyl-methanediamine (8.8 g, 50.5 mmol) and stirring at 100 °C for 16 h, the crude title compound was obtained as a red oil (5.5 g, 93% yield). LC-MS: m/z 234 [M+H]⁺.

Step 5: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one (5.5 g, 23.5 mmol), the title compound was obtained as a yellow solid (1.8 g, 28% yield). LC-MS: m/z 272 [M+H]⁺.

Step 6: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo [1,5-a]pyrimidine (1.5 g, 5.5 mmol) in chlorobenzene (150 mL), the title compound was obtained as a yellow solid (1.5 g, 91% yield). LC-MS: m/z 297 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A1 step 7** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (1.5 g, 5.0 mmol), stirring at 100 °C for 3 h and purification of the product by prep-HPLC, the title compound was obtained as a yellow solid (380 mg, 23% yield). LC-MS: m/z 316 [M+H]⁺.

Step 8: *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (200 mg, 634 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (124 mg, 634 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (50 mg, 31% yield) as a white solid, LC-MS: m/z 493 [M+H]⁺; *cis*-isomer (70 mg, 44% yield) as a white solid, LC-MS: m/z 493 [M+H]⁺.

Step 9: Separation of enantiomers to obtain **Example 64** and **Example 65**

50 mg of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 7.592; RT2(min): 11.79; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 64** (21.2 mg, 83% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 65** (17.0 mg, 66% yield) as a white solid.

Example 64: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (s, 1H), 8.79 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.17 (s, 2H), 7.32 (d, J = 2.0 Hz, 1H), 6.63 (d, J = 4.8 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 4.56-4.60 (m, 1H), 3.46 (s, 3H), 2.93-2.99 (m, 1H), 2.62-2.67 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 493 [M+H]⁺.

Example 65: ^1H NMR (400 MHz, DMSO- d_6) δ 11.16 (s, 1H), 8.79 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.17 (s, 2H), 7.32 (d, J = 2.0 Hz, 1H), 6.63 (d, J = 4.8 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 4.56-4.60 (m, 1H), 3.46 (s, 3H), 2.93-2.99 (m, 1H), 2.62-2.67 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 493 [M+H] $^+$.

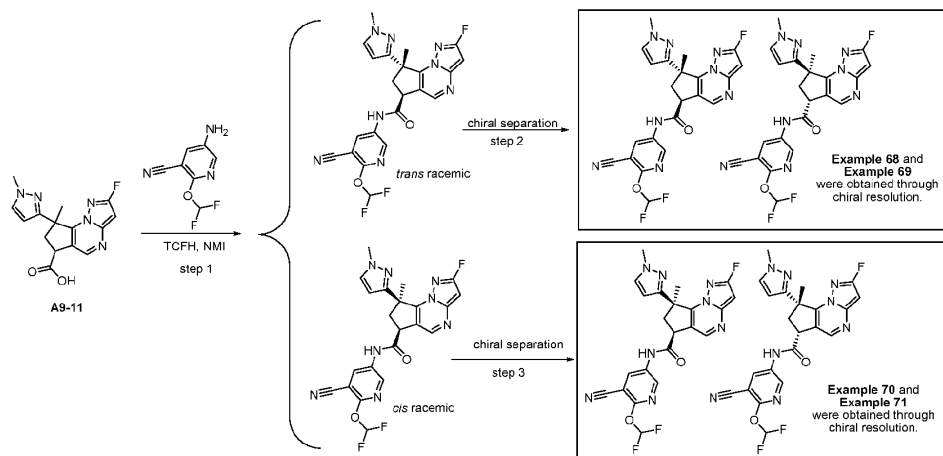
5 Step 10: Separation of enantiomers to obtain **Example 66** and **Example 67**

70 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide was submitted to chiral HPLC purification (Column: CHIRALPAK IF 2*25 cm, 5 μm ; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 6.883; RT2(min): 9.78; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of
10 Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 66** (20.7 mg, 59% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 67** (15.8 mg, 45% yield) as a white solid.

15 **Example 66:** ^1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 8.76 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.38 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 4.8 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 4.63 (t, J = 8.4 Hz, 1H), 3.23 (s, 3H), 2.72-2.81 (m, 2H), 1.89 (s, 3H). LC-MS: m/z 493 [M+H] $^+$.

20 **Example 67:** ^1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 8.76 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.38 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 4.8 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 4.63 (t, J = 8.4 Hz, 1H), 3.23 (s, 3H), 2.72-2.81 (m, 2H), 1.89 (s, 3H). LC-MS: m/z 493 [M+H] $^+$.

Method A18



Examples 68, 69: (6*S*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 5 a]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

Examples 70, 71: (6*S*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 10 a]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: *trans*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 15 a]pyrimidine-6-carboxamide and *cis*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 a]pyrimidine-6-carboxamide

In analogy to Method A1 step 8 but using 2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-
 20 a]pyrimidine-6-carboxylic acid (A9-11, 80 mg, 254 μ mol) and 5-amino-2-(difluoromethoxy)pyridine-3-carbonitrile (94 mg, 507 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (15 mg, 11% yield) as a white solid,

LC-MS: m/z 483 [M+H]⁺; *cis*-isomer (40 mg, 32% yield) as a white solid, LC-MS: m/z 483 [M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 68** and **Example 69**

40 mg of *trans*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IE 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=1: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 5.063; RT2(min): 6.557; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 68** (8.0 mg, 19% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 69** (10.7 mg, 26% yield) as a white solid.

Example 68: ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 2.4 Hz, 1H), 8.54- 8.51 (m, 2H), 8.35 (s, 1H), 7.45 (t, *J* = 71 Hz, 1 H), 7.32 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.25 (d, *J* = 5.2 Hz, 1H), 4.61 (t, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.44-3.49 (m, 1H), 2.48-2.54 (m, 1H), 2.11 (s, 3H). LC-MS: m/z 483 [M+H]⁺.

Example 69: ¹H NMR (400 MHz, Chloroform-*d*) δ 8.60 (d, *J* = 2.4 Hz, 1H), 8.54-8.51 (m, 2H), 8.39 (s, 1H), 7.45 (t, *J* = 72 Hz, 1H), 7.33 (d, *J* = 2 Hz, 1H), 6.65 (d, *J* = 2 Hz, 1H), 6.25 (d, *J* = 5.2 Hz, 1H), 4.63 (t, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.45-3.50 (m, 1H), 2.48-2.54 (m, 1H), 2.09 (s, 3H). LC-MS: m/z 483 [M+H]⁺.

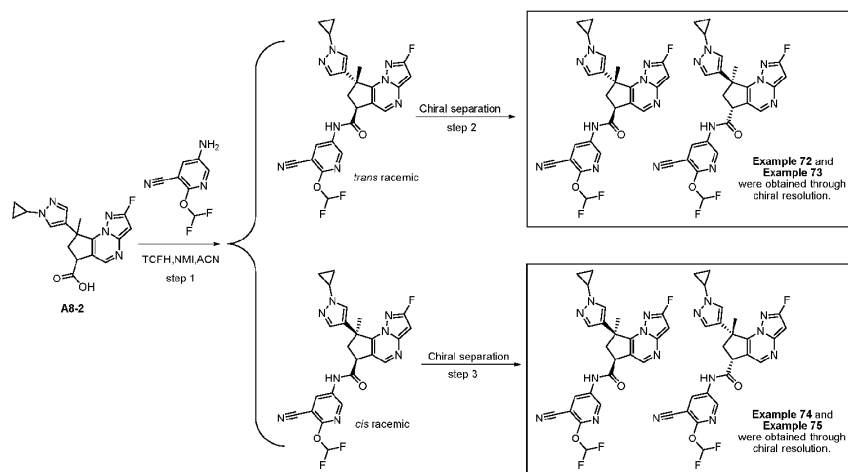
Step 3: Separation of enantiomers to obtain **Example 70** and **Example 71**

15 mg of *cis*-(6S,8R)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 20% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 8.977; RT2(min): 14.167; Sample Solvent: EtOH--HPLC; Injection Volume: 1 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 70** (4.7 mg, 31% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 71** (3.9 mg, 25% yield) as a white solid.

Example 70: ^1H NMR (400 MHz, Chloroform-*d*) δ 10.65 (s, 1H), 8.57 (s, 1H), 8.47 (s, 2H), 7.42 (t, 72 Hz, 1H), 7.41 (s, 1H), 6.73 (d, $J = 2$ Hz, 1H), 6.26 (d, $J = 5.2$ Hz, 1H), 4.47-4.51 (m, 1H), 3.83 (s, 3H), 3.16-3.21 (m, 1H), 2.81-2.87 (m, 1H), 2.07 (s, 3H). LC-MS: m/z 483 $[\text{M}+\text{H}]^+$.

5 **Example 71:** ^1H NMR (400 MHz, Chloroform-*d*) δ 10.65 (s, 1H), 8.57 (s, 1H), 8.48 (s, 2H), 7.43 (t, $J = 68$ Hz, 1H), 7.42 (s, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 6.27 (d, $J = 4.8$ Hz, 1H), 4.48-4.51 (m, 1H), 3.84 (s, 3H), 3.16-3.20 (m, 1H), 2.82-2.88 (m, 1H), 2.07 (s, 3H). LC-MS: m/z 483 $[\text{M}+\text{H}]^+$.

Method A19



10

Examples 72, 73: (6*S*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

15

Examples 74, 75: (6*S*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

20

The relative and absolute stereochemistry of each example was not determined.

Step 1: *trans*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

5 In analogy to **Method A1 step 8** but using 8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A8-2**, 50 mg, 146 μ mol) and 5-amino-2-(difluoromethoxy)pyridine-3-carbonitrile (27 mg, 146 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (20 mg, 26% yield) as a white solid, LC-MS: m/z 509 [M+H]⁺; *cis*-isomer (10 mg, 13% yield) as a white solid, LC-MS: m/z 509
10 [M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 72** and **Example 73**

20 mg of *trans*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2x25 cm, 5
15 μ m; Mobile Phase A: Hex: DCM=1: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.331; RT2(min): 5.782; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2.). The second eluting isomer was concentrated and lyophilized to afford **Example 72** (9.3 mg, 37% yield) as a white solid. The first eluting isomer was concentrated and
20 lyophilized to afford **Example 73** (11.4 mg, 45% yield) as a white solid.

Example 72: ¹H NMR (400 MHz, Chloroform-d) δ 9.61 (s, 1H), 8.62-8.67 (m, 2H), 8.53 (s, 1H), 8.14 (s, 1H), 7.92 (s, 1H), 7.41 (t, *J* = 71.6Hz, 1H), 6.29 (d, *J* = 4.8Hz, 1H), 4.57-4.59 (m, 1H), 3.62-3.63 (m, 1H), 3.29-3.30 (m, 1H), 2.58-2.64 (m, 1H), 2.08 (s, 3H), 1.14-1.17 (m, 4H). LC-MS: m/z 509 [M+H]⁺.

25 **Example 73:** ¹H NMR (400 MHz, Chloroform-d) δ 9.32 (s, 1H), 8.60-8.64 (m, 2H), 8.52 (s, 1H), 7.94 (s, 1H), 7.83 (s, 1H), 7.42 (t, *J* = 71.6Hz, 1H), 6.29 (d, *J* = 4.8Hz, 1H), 4.52-4.54 (m, 1H), 3.57-3.59 (m, 1H), 3.18-3.20 (m, 1H), 2.60-2.65 (m, 1H), 2.07 (s, 3H), 1.09-1.13 (m, 4H). LC-MS: m/z 509 [M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 74** and **Example 75**

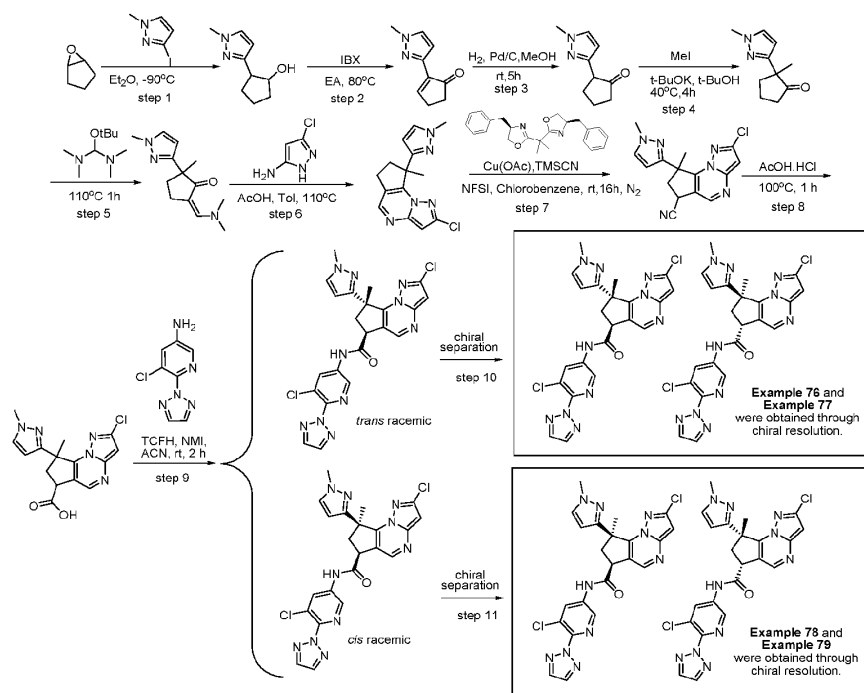
30 10 mg of *cis*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=1: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 6.881; RT2(min): 16.445; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of
 5 Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 74** (3.2 mg, 31% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 75** (2.3 mg, 22% yield) as a white solid.

Example 74: ^1H NMR (400 MHz, Chloroform- d) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 8.00 (s, 1H), 7.60-7.64 (m, 2H), 7.40 (t, $J = 71.6\text{Hz}$, 1H), 6.28 (d, $J = 5.2\text{Hz}$, 1H), 4.40-4.42 (m,
 10 1H), 3.53-3.56 (m, 1H), 2.95-2.98 (m, 1H), 2.82-2.88 (m, 1H), 2.06 (s, 3H), 1.00-1.11 (m, 4H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

Example 75: ^1H NMR (400 MHz, Chloroform- d) δ 8.62 (s, 1H), 8.55 (s, 1H), 8.38-8.42 (m, 2H), 7.70-7.74 (m, 2H), 7.39 (t, $J = 71.6\text{Hz}$, 1H), 6.27 (d, $J = 4.8\text{Hz}$, 1H), 4.48-4.50 (m, 1H), 3.59-3.60 (m, 1H), 2.86-2.99 (m, 2H), 1.98 (s, 3H), 1.08-1.12 (m, 4H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

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Method A20

Examples 76, 77: (6*S*,8*S*)-2-chloro-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-chloro-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 78, 79: (6*S*,8*R*)-2-chloro-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-chloro-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(1-methyl-1*H*-pyrazol-3-yl)cyclopentan-1-ol

To a stirred solution of 3-iodo-1-methyl-1*H*-pyrazole (16.07 g, 77.27 mmol) in Et₂O (500 mL) was added dropwise *n*-Butyllithium (2.5 M, 30.9 mL) at -90 °C under nitrogen. The reaction mixture was stirred at -90 °C for 1 h under nitrogen. 6-oxabicyclo[3.1.0]hexane (5 g, 59.44 mmol) was added dropwise at -90 °C under nitrogen, and the mixture was stirred for 0.5 h at -90 °C. Boron trifluoride diethyl etherate (10.97 g, 77.27 mmol) was added dropwise at -90 °C, and the reaction mixture was stirred at -90 °C for 2 h under nitrogen. The reaction mixture was quenched with saturated aqueous ammonium chloride (500 mL). The resulting mixture was extracted with ethyl acetate (3x 500 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (6 g, 61% yield) as a yellow oil. LC-MS: *m/z* 167 [M+H]⁺.

Step 2: 2-(1-methyl-1*H*-pyrazol-3-yl)cyclopent-2-en-1-one

In analogy to **Method A1 step 2** but using 2-(1-methyl-1*H*-pyrazol-3-yl)cyclopentan-1-ol (15 g, 53.1 mmol), the title compound was obtained as a yellow oil (6 g, 36% yield). LC-MS: *m/z* 163 [M+H]⁺.

Step 3: 2-(1-methyl-1*H*-pyrazol-3-yl)cyclopentan-1-one

To a stirred solution of 2-(1-methyl-1*H*-pyrazol-3-yl)cyclopent-2-en-1-one (6 g, 36.9 mmol) in MeOH (300 mL) was added Pd/C (3.0 g, 2.5 mmol, 10%). The mixture was degassed and then stirred at 25 °C for 5 h under hydrogen atmosphere. The mixture was filtered, and the

filtrate was concentrated under reduced pressure to afford the crude title compound (6 g) as a yellow oil. LC-MS: m/z 165 [M+H]⁺.

Step 4: 2-methyl-2-(1-methyl-1H-pyrazol-3-yl)cyclopentan-1-one

In analogy to **Method A1 step 3** but using 2-(1-methyl-1H-pyrazol-3-yl)cyclopentan-1-one (5.9 g, 25.2 mmol) and after purification of the product by prep-HPLC, the title compound was obtained as a yellow oil (3.3 g, 62% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 2.1 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 3.87 (s, 3H), 2.55-2.66 (m, 1H), 2.29-2.49 (m, 2H), 1.86-2.08 (m, 3H), 1.40 (s, 3H). LC-MS: m/z 179 [M+H]⁺.

Step 5: 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-3-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-methyl-1H-pyrazol-3-yl)cyclopentan-1-one (3.4 g, 19.1 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethyl-methanediamine (6.6 g, 38.2 mmol) and stirring at 110 °C for 1 h, the crude title compound was obtained as a yellow oil (4.2 g). LC-MS: m/z 234 [M+H]⁺.

Step 6: 2-Chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-methyl-1H-pyrazol-3-yl)cyclopentan-1-one (5.9 g, 25.3 mmol) and 3-chloro-1H-pyrazol-5-amine (3.6 g, 30.4 mmol) and after purification of the product by prep-HPLC, the title compound was obtained as a yellow solid (2.5 g, 33% yield). LC-MS: m/z 288 [M+H]⁺.

Step 7: 2-Chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1.5 g, 5.2 mmol) in chlorobenzene (250 mL), the title compound was obtained as a yellow solid (800 mg, 49% yield). LC-MS: m/z 313 [M+H]⁺.

Step 8: 2-Chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A1 step 7** but using 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (1.1 g, 3.5 mmol) and

after purification of the product by prep-HPLC, the title compound was obtained as a yellow solid (800 mg, 68% yield). LC-MS: m/z 332 [M+H]⁺.

Step 9: *trans*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-chloro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (100 mg, 301 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (59 mg, 301 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (30.5 mg, 83% yield) as a white solid, LC-MS: m/z 509 [M+H]⁺; *cis*-isomer (9.9 mg, 6% yield) as a white solid, LC-MS: m/z 509 [M+H]⁺.

Step 10: Separation of enantiomers to obtain **Example 76** and **Example 77**

29 mg of *trans*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=1: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.935; RT2(min): 12.65; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 76** (8.3 mg, 28% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 77** (8.4 mg, 28% yield) as a white solid.

Example 76: ¹H NMR (400 MHz, Chloroform-d) δ 8.77 (s, 1H), 8.70 (d, *J* = 2Hz, 1H), 8.57-8.60 (m, 2H), 7.94 (s, 2H), 7.36 (d, *J* = 2Hz, 1H), 6.73 (s, 1H), 6.68 (s, 1H), 4.69-4.73 (m, 1H), 3.95 (s, 3H), 3.50-3.59 (m, 1H), 2.52-2.58 (m, 1H), 2.14 (s, 3H). LC-MS: m/z 509 [M+H]⁺.

Example 77: ¹H NMR (400 MHz, Chloroform-d) δ 8.70 (d, *J* = 2Hz, 1H), 8.49-8.54 (m, 3H), 7.94 (s, 2H), 7.29 (d, *J* = 2.4Hz, 1H), 6.66 (s, 1H), 6.59 (d, *J* = 2.4Hz, 1H), 4.60-4.64 (m, 1H), 3.85 (s, 3H), 3.43-3.48 (m, 1H), 2.51-2.56 (m, 1H), 2.14 (s, 3H). LC-MS: m/z 509 [M+H]⁺.

Step 11: c **Example 78** and **Example 79**

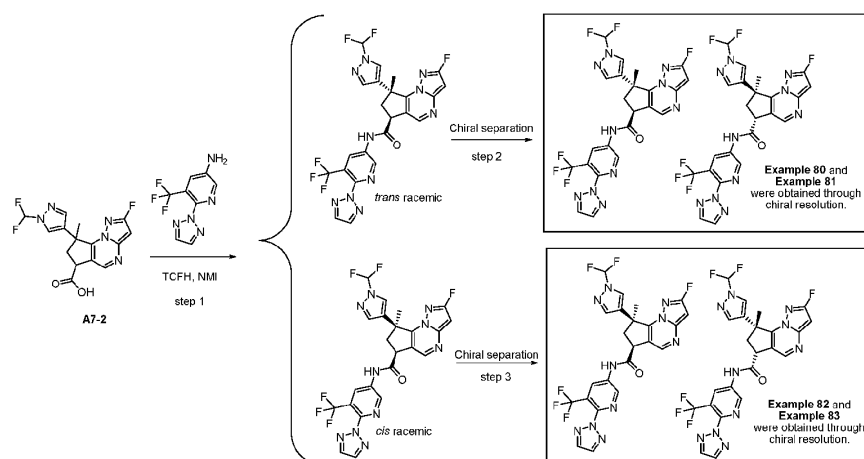
9 mg of *cis*-2-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-

carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=1: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 7% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.355; RT2(min): 9.769; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 3). The first eluting isomer was concentrated and lyophilized to afford **Example 78** (1.8 mg, 19% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 79** (2.1 mg, 23% yield) as a white solid.

Example 78: ^1H NMR (400 MHz, Chloroform- d) δ 10.70 (s, 1H), 8.55-8.62 (m, 3H), 7.92 (s, 2H), 7.40 (d, J = 1.6Hz, 1H), 6.75 (d, J = 2.4Hz, 1H), 6.68 (s, 1H), 4.51-4.54 (m, 1H), 3.86 (s, 3H), 3.26-3.30 (m, 1H), 2.83-2.89 (m, 1H), 2.11 (s, 3H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

Example 79: ^1H NMR (400 MHz, Chloroform- d) δ 10.71 (s, 1H), 8.73 (s, 1H), 8.62-8.67 (m, 2H), 7.91 (s, 2H), 7.48 (s, 1H), 6.77 (d, J = 2.4Hz, 1H), 6.70 (s, 1H), 4.54-4.56 (m, 1H), 3.95 (s, 3H), 3.21-3.27 (m, 1H), 2.89-2.94 (m, 1H), 2.08 (s, 3H). LC-MS: m/z 509 $[\text{M}+\text{H}]^+$.

Method A21



Examples 80, 81: (6*S*,8*R*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 82, 83: (6*S*,8*S*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: *trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**, 230 mg, 655 μ mol) and 6-(triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine (225 mg, 982 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (180 mg, 48% yield) as a yellow solid, LC-MS: *m/z* 563 [*M*+*H*]⁺; *cis*-isomer (120 mg, 32% yield) as a yellow solid, LC-MS: *m/z* 563 [*M*+*H*]⁺.

Step 2: Separation of enantiomers to obtain **Example 80** and **Example 81**

180 mg of *trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.2% TFA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.605; RT2(min): 13.295; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 80** (35.9 mg, 19% yield) as a light-yellow solid. The first eluting isomer was concentrated and lyophilized to afford **Example 81** (18.4 mg, 10% yield) as a white solid.

Example 80: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.22 (s, 1H), 9.02 (d, *J* = 2Hz, 1H), 8.83 (d, *J* = 2.4Hz, 1H), 8.72 (s, 1H), 8.21 (s, 1H), 8.19 (s, 2H), 7.84 (s, 1H), 7.73 (t, *J* = 59.2Hz, 1H),

6.60 (d, $J = 4.8\text{Hz}$, 1H), 4.58 (t, $J = 8\text{Hz}$, 1H), 2.92-2.95 (m, 1H), 2.58-2.63 (m, 1H), 2.00 (s, 3H).
LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

Example 81: ^1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 9.02 (d, $J = 2.4\text{ Hz}$, 1H), 8.83 (d, $J = 2\text{ Hz}$, 1H), 8.72 (s, 1H), 8.21 (s, 1H), 8.19 (s, 2H), 7.84 (s, 1H), 7.73 (t, $J = 59.2\text{Hz}$, 1H), 6.60 (d, $J = 4.8\text{Hz}$, 1H), 4.58 (t, $J = 8\text{Hz}$, 1H), 2.92-2.95 (m, 1H), 2.58-2.63 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

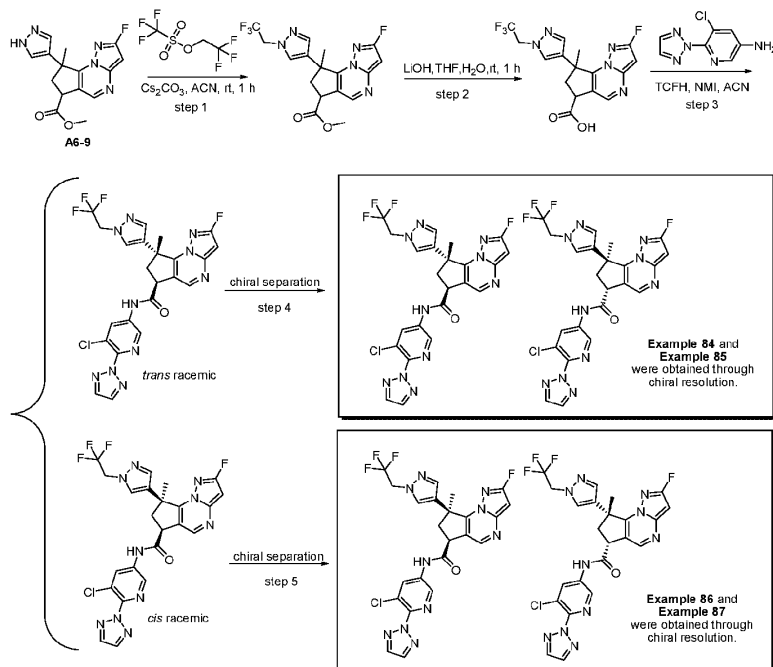
Step 3: Separation of enantiomers to obtain **Example 82** and **Example 83**

120 mg of *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG 2*25 cm, 5 μm ; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220NM nm; RT1(min): 9.392; RT2(min): 10.063; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 82** (21.4 mg, 17% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 83** (12.9 mg, 10% yield) as a white solid.

Example 82: ^1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1H), 9.01 (d, $J = 2.4\text{ Hz}$, 1H), 8.76-8.79 (m, 2H), 8.18-8.19 (m, 3H), 7.77 (s, 1H), 7.72 (t, $J = 59.2\text{Hz}$, 1H), 6.58 (d, $J = 4.8\text{ Hz}$, 1H), 4.59-4.61 (m, 1H), 2.84-2.90 (m, 1H), 2.74-2.80 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

Example 83: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.20 (s, 1H), 9.01 (d, $J = 2\text{Hz}$, 1H), 8.76-8.79 (m, 2H), 8.18-8.19 (m, 3H), 7.77 (s, 1H), 7.72 (t, $J = 59.2\text{Hz}$, 1H), 6.58 (d, $J = 5.2\text{Hz}$, 1H), 4.56-4.60 (m, 1H), 2.84-2.90 (m, 1H), 2.74-2.80 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

Method A22



Examples 84, 85: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 86, 87: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**A6-9**, 225 mg, 711 μ mol) in ACN (10 mL) were added Cesium carbonate (1 g, 3.0 mmol) and 2,2,2-trifluoroethyl

trifluoromethanesulfonate (330 mg, 1.4 mmol). The reaction mixture was stirred at 25 °C for 1 h. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 90% DCM and 10% MeOH as eluent to afford the title compound (170 mg, 54% yield) as a yellow oil. LC-MS: m/z 398 [M+H]⁺.

Step 2: 2-Fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (170 mg, 428 μmol) in THF (1.5 mL) was added LiOH (103 mg, 4.3 mmol) in water (0.5 mL). The reaction mixture was stirred at 25 °C for 1 h. The pH was adjusted to ~6 with 1M HCl, and the resulting mixture was extracted with ethyl acetate (3x10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 90% DCM and 10% MeOH as eluent to afford the title compound (140 mg, 68% yield) as a yellow oil. LC-MS: m/z 384[M+H]⁺.

Step 3: *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (130 mg, 339 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (80 mg, 407 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (57 mg, 29% yield) as a white solid, LC-MS: m/z 561[M+H]⁺; *cis*-isomer (37 mg, 19% yield) as a white solid, LC-MS: m/z 561[M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 84** and **Example 85**

50 mg of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART

Amylose-SA 2x25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220NM nm; RT1(min): 10.463; RT2(min): 15.53; Sample Solvent: EtOH--HPLC; Injection Volume: 3 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 84** (8.1 mg, 16% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 85** (8.6 mg, 17% yield) as a white solid.

Example 84: ^1H NMR (400 MHz, Chloroform-d) δ 9.45 (s, 1H), 8.94 (s, 1H), 8.67-8.70 (m, 2H), 7.91 (s, 2H), 7.68-7.72 (m, 2H), 6.40 (d, J = 4.4Hz, 1H), 4.64-4.70 (m, 3H), 3.08-3.12 (m, 1H), 2.83-2.88 (m, 1H), 2.14 (s, 3H). LC-MS: m/z 561[M+H] $^+$.

Example 85: ^1H NMR (400 MHz, Chloroform-d) δ 9.46 (s, 1H), 8.94 (s, 1H), 8.67-8.74 (m, 2H), 7.92 (s, 2H), 7.68-7.72 (m, 2H), 6.42 (d, J = 4.4Hz, 1H), 4.66-4.71 (m, 3H), 3.08-3.11 (m, 1H), 2.83-2.90 (m, 1H), 2.15 (s, 3H). LC-MS: m/z 561[M+H] $^+$.

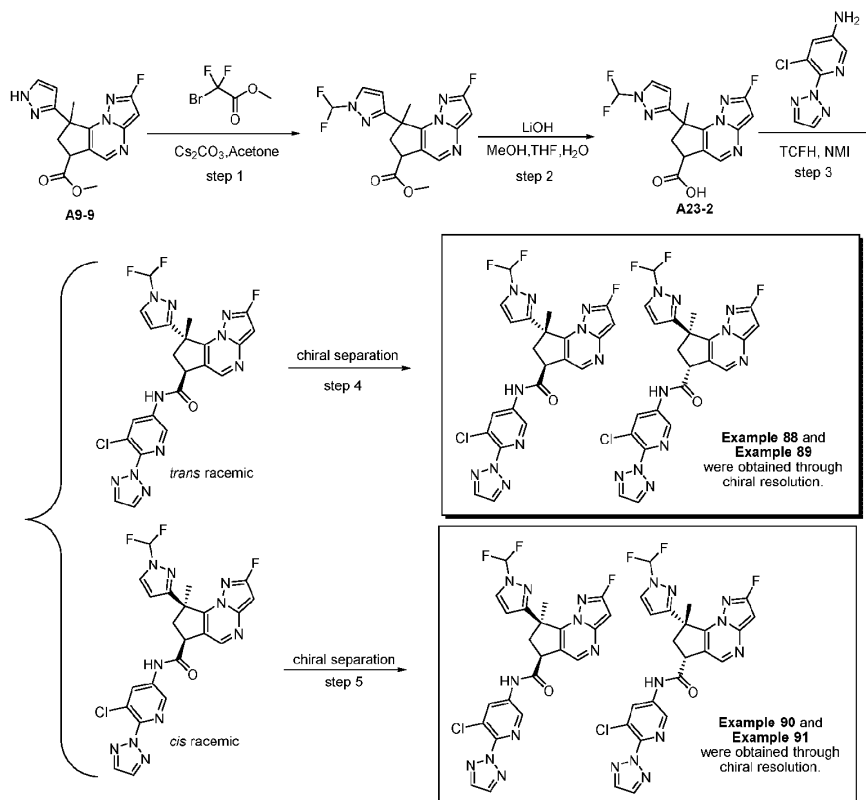
Step 5: Separation of enantiomers to obtain **Example 86** and **Example 87**

30 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA 2x25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220NM nm; RT1(min): 7.245; RT2(min): 8.763; Sample Solvent: EtOH--HPLC; Injection Volume: 2.5 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 86** (4.8 mg, 15% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 87** (4.2 mg, 13% yield) as a white solid.

Example 86: ^1H NMR (400 MHz, Chloroform-d) δ 9.06-9.19 (m, 2H), 8.60-8.68 (m, 2H), 7.90 (s, 2H), 7.78-7.82 (m, 2H), 6.43 (d, J = 5.2Hz, 1H), 4.63-4.70 (m, 3H), 3.14-3.21 (m, 1H), 2.82-2.92 (m, 1H), 2.02 (s, 3H). LC-MS: m/z 561[M+H] $^+$.

Example 87: ^1H NMR (400 MHz, Chloroform-d) δ 8.90 (s, 1H), 8.63 (s, 1H), 8.56 (s, 1H), 7.91 (s, 2H), 7.73-7.75 (m, 2H), 6.38 (d, J = 5.2Hz, 1H), 4.63-4.69 (m, 2H), 4.50-4.54 (m, 1H), 3.10-3.14 (m, 1H), 2.85-2.90 (m, 1H), 2.01 (s, 3H). LC-MS: m/z 561[M+H] $^+$.

Method A23



Examples 88, 89: (6*S*,8*S*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 90, 91: (6*S*,8*R*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A9-9**, 500 mg, 1.6 mmol) in acetone (15 mL) were added cesium carbonate (1.6 g, 4.7 mmol) and methyl 2-bromo-2,2-difluoroacetate (1.5 g, 7.9 mmol). The mixture was stirred at 40 °C for 16 h. The reaction was quenched with water (40 mL). The resulting mixture was extracted with ethyl acetate (3x 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (90 mg, 13% yield) as a yellow oil. LC-MS: m/z 366 [M+H]⁺.

Step 2: 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A23-2**)

In analogy to **Method A7 step 2** but using methyl 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (90 mg, 246 μmol), the crude title compound was obtained as a yellow oil (**A23-2**, 50 mg, 46% yield). LC-MS: m/z 352 [M+H]⁺.

Step 3: *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (150 mg, 427 μmol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (100 mg, 512 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (120 mg, 53% yield) as a white solid, LC-MS: m/z 529 [M+H]⁺; *cis*-isomer (40 mg, 18% yield) as a white solid, LC-MS: m/z 529 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 88** and **Example 89**

120 mg of *trans*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC

purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.826; RT2(min): 9.373; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 5.). The second eluting isomer was concentrated and lyophilized to afford **Example 88** (21.4 mg, 35% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 89** (20.9 mg, 34% yield) as a white solid.

Example 88: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.21 (s, 1H), 7.96 (s, 2H), 7.76 (d, J = 2.4 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.33 (d, J = 5.2 Hz, 1H), 4.58 (t, J = 8.2 Hz, 1H), 3.41-3.46 (m, 1H), 2.67-2.61 (m, 1H), 2.17 (s, 3H). LC-MS: m/z 529 $[\text{M}+\text{H}]^+$.

Example 89: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, J = 1.6 Hz, 2H), 8.61 (s, 1H), 8.39 (s, 1H), 7.96 (s, 2H), 7.76 (d, J = 2.8 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 3.9 Hz, 1H), 4.61 (d, J = 8 Hz, 1H), 3.40-3.45 (m, 1H), 2.66-2.71 (m, 1H), 2.18 (s, 3H). LC-MS: m/z 529 $[\text{M}+\text{H}]^+$.

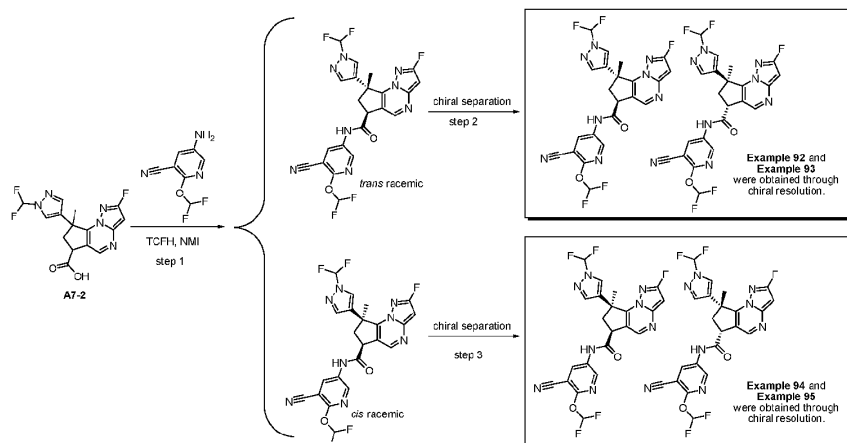
Step 5: Separation of enantiomers to obtain **Example 90** and **Example 91**

40 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 20% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.144; RT2(min): 13.369; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 3.). The second eluting isomer was concentrated and lyophilized to afford **Example 90** (14.2 mg, 71% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 91** (8.9 mg, 44% yield) as a white solid.

Example 90: ^1H NMR (400 MHz, Chloroform-*d*) δ 9.43 (s, 1H), 8.66 (s, 1H), 8.50-8.52 (m, 1H), 8.47 (s, 1H), 7.94 (s, 2H), 7.83 (d, J = 2.4 Hz, 1H), 6.84-7.15 (m, 2H), 6.32 (d, J = 5.2 Hz, 1H), 4.54-4.58 (m, 1H), 3.36-3.41 (m, 1H), 2.86-2.93 (m, 1H), 2.15 (s, 3H). LC-MS: m/z 529 $[\text{M}+\text{H}]^+$.

Example 91: ^1H NMR (400 MHz, Chloroform- d) δ 9.41 (s, 1H), 8.75 (s, 1H), 8.52-8.67 (m, 2H), 7.95 (s, 2H), 7.83 (d, J = 2.4 Hz, 1H), 6.84-7.15 (m, 2H), 6.32 (d, J = 4.4 Hz, 1H), 4.54-4.57 (m, 1H), 3.36-3.41 (m, 1H), 2.86-2.92 (m, 1H), 2.16 (s, 3H). LC-MS: m/z 529 $[\text{M}+\text{H}]^+$.

Method A24



5

Examples 92, 93: (6*S*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 94, 95: (6*S*,8*S*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

15

The relative and absolute stereochemistry of each example was not determined.

Step 1: *trans*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and *cis*-*N*-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

20

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**, 240 mg, 683 μ mol) and 5-amino-2-(difluoromethoxy)pyridine-3-carbonitrile (190 mg, 1.0 mmol), racemic mixtures of the title compounds were obtained: *trans* isomer (60 mg, 16% yield) as a white solid, LC-MS: m/z 519[M+H]⁺; *cis*-isomer (40 mg, 11% yield) as a white solid, LC-MS: m/z 519[M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 92** and **Example 93**

60 mg of *trans*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2x25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.269; RT2(min): 7.473; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 92** (15.0 mg, 24% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 93** (19.4 mg, 32% yield) as a white solid.

Example 92: ¹H NMR (400 MHz, DMSO-d₆) δ 10.88(s, 1H), 8.63-8.68 (m, 3H), 8.20 (s, 1H), 7.57-7.93 (m, 3H), 6.59 (d, J = 4.8 Hz, 1H), 4.48-4.52 (m, 1H), 2.87-2.90 (m, 1H), 2.57-2.60 (m, 1H), 1.98 (s, 3H). LC-MS: m/z 519[M+H]⁺.

Example 93: ¹H NMR (400 MHz, DMSO-d₆) δ 10.89(s, 1H), 8.63-8.68 (m, 3H), 8.20 (s, 1H), 7.57-7.93 (m, 3H), 6.59 (d, J = 4.8 Hz, 1H), 4.48-4.52 (m, 1H), 2.85-2.92 (m, 1H), 2.54-2.60 (m, 1H), 1.98 (s, 3H). LC-MS: m/z 519[M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 94** and **Example 95**

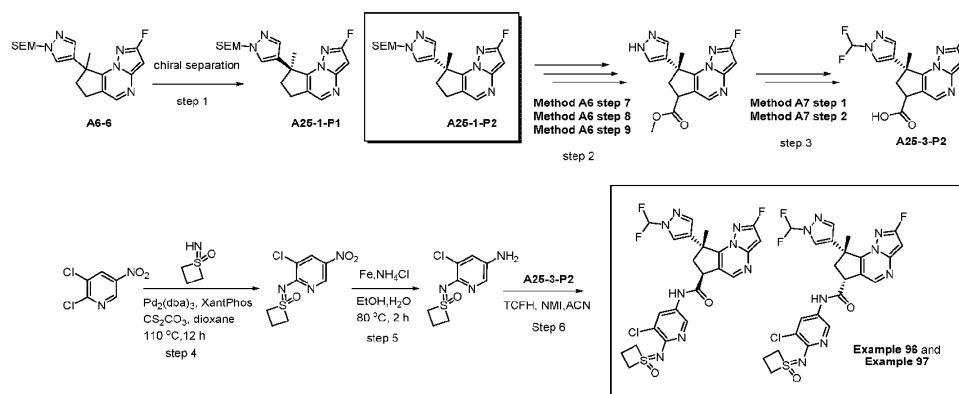
40 mg of *cis*-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2x25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.168; RT2(min): 5.831; Sample Solvent: EtOH--HPLC; Injection Volume: 0.9 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford

Example 94 (10.1 mg, 25% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 95** (12.1 mg, 26% yield) as a white solid.

Example 94: ^1H NMR (400 MHz, DMSO- d_6) δ 10.88 (s, 1H), 8.71 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.59 (d, J = 2.8 Hz, 1H), 8.18 (s, 1H), 7.56-7.92 (m, 3H), 6.57 (d, J = 5.2 Hz, 1H), 4.49-4.52 (m, 1H), 2.80-2.85 (m, 1H), 2.66-2.72 (m, 1H), 1.89 (s, 3H). LC-MS: m/z 519[M+H] $^+$.

Example 95: ^1H NMR (400 MHz, DMSO- d_6) δ 10.88 (s, 1H), 8.71 (s, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.59 (d, J = 2.4Hz, 1H), 8.18 (s, 1H), 7.56-7.92 (m, 3H), 6.57 (d, J = 5.2 Hz, 1H), 4.49-4.51 (m, 1H), 2.80-2.85 (m, 1H), 2.68-2.72 (m, 1H), 1.89 (s, 3H). LC-MS: m/z 519[M+H] $^+$.

Method A25



10

Examples 96, 97: (6*S*,8*R*)-*N*-(5-chloro-6-((1-oxido-1 λ^6 -thietan-1-ylidene)amino)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-((1-oxido-1 λ^6 -thietan-1-ylidene)amino)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

15

The relative and absolute stereochemistry of each example was not determined.

Step 1: (*S*)-2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine (**A25-1-P1**) and (*R*)-2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine (**A25-1-P2**)

20

3 g of 2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine (**A6-6**) were submitted to chiral HPLC

purification (Column: daicel chiral pakia, 250*50 mm, 10 um; Mobile phase A: CO₂, Mobile phase B: IPA (0.1% NH₃H₂O); Flow rate: 200 g/min; Gradient: isocratic 25% Mobile Phase B; Wavelength: 220 nm; Column temperature (°C) : 40 ; System back pressure:100 bar. RT1 (min): 3.68; RT2 (min): 6.71, Sample Solvent: IPA---preparative; Injection Volume: 8.5 mL. Number of
 5 Runs: 6). The first eluting isomer was concentrated and lyophilized to afford **A25-1-P1** (1.3 g) as a light yellow oil, LC-MS: m/z 388 [M+H]⁺. The second eluting isomer was concentrated and lyophilized to afford **A25-1-P2** (1.32 g) as a light yellow oil, LC-MS: m/z 388 [M+H]⁺.

Step 2: Methyl (8*R*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate

10 Using (*R*)-2-fluoro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine (**A25-1-P2**) and following sequentially the reaction conditions described in **Method A6 step 7, step 8 and step 9**, the title compound was obtained as a yellow oil.

Step 3: (8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A25-3-P2**)
 15

Using methyl (8*R*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate and following sequentially the reaction conditions described in **Method A7 step 1 and step 2**, the title compound (**A25-3-P2**) was obtained as a yellow oil.

20 Step 4: 1-((3-chloro-5-nitropyridin-2-yl)imino)-1λ⁶-thietane 1-oxide

To a stirred solution of 2,3-dichloro-5-nitropyridine (200 mg, 1.0 mmol) and 1-imino-1λ⁶-thietane 1-oxide (109 mg, 1.0 mmol) in dioxane (6 mL) were added Pd₂(dba)₃ (95 mg, 104 μmol), XantPhos (120 mg, 207 μmol) and Cs₂CO₃ (1.0 g, 3.1 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 110 °C for 12 h. The mixture was cooled to 25 °C. The reaction
 25 mixture was quenched by the addition of water (20 mL). The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 50% petroleum ether and 50 % ethyl acetate as eluent to afford the title compound (140 mg, 51% yield) as a yellow oil. LC-MS: m/z 262 [M+H]⁺.

Step 5: 1-((5-amino-3-chloropyridin-2-yl)imino)-1 λ^6 -thietane 1-oxide

To a solution of 1-((3-chloro-5-nitropyridin-2-yl)imino)-1 λ^6 -thietane 1-oxide (120 mg, 459 μ mol) in ethanol (7 mL) and water (2 mL) were added Fe (128 mg, 2.3 mmol) and NH₄Cl (123 mg, 2.3 mmol). The resulting mixture was stirred at 80 °C for 2 h. The solids were filtered out.

5 The filtrate was diluted with water (10 mL) and extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title compound (75 mg, 70 % yield) as a brown solid. LC-MS: m/z 232[M+H]⁺.

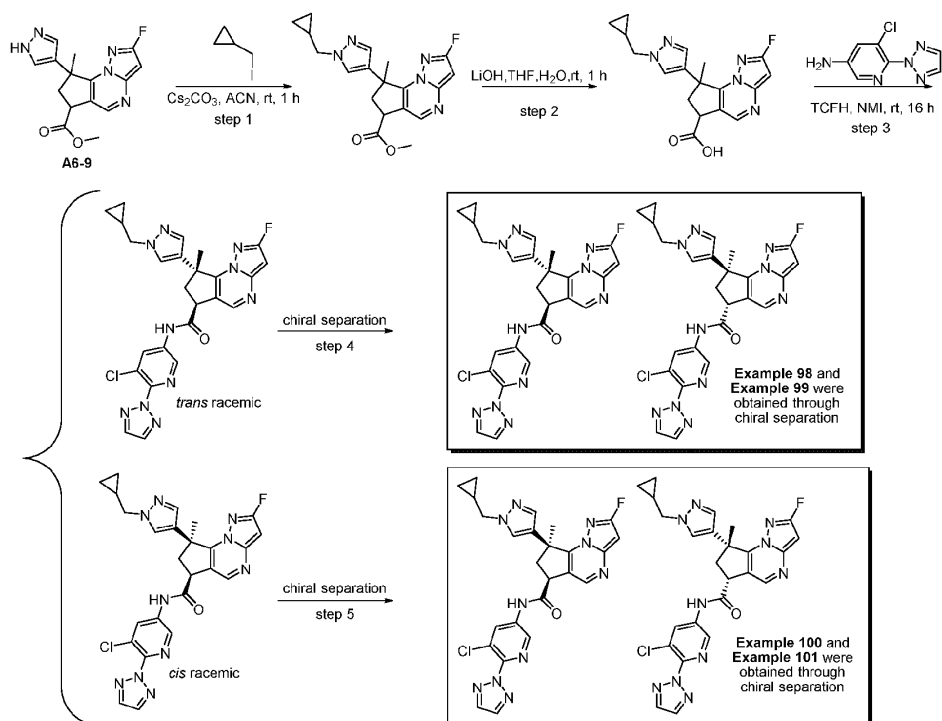
Step 6: **Example 96** and **Example 97**

10 In analogy to **Method A1 step 8** but using (8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A25-3-P2**, 75.8 mg, 215.8 μ mol) and 1-((5-amino-3-chloropyridin-2-yl)imino)-1 λ^6 -thietane 1-oxide (50 mg, 215.8 μ mol), the diastereomeric title compounds were obtained: *trans* isomer **Example 96** (3.1 mg, 2.5% yield) as an off-white solid and *cis*-isomer **Example 97** (3.4 mg, 2.8%
15 yield) as a white solid.

Example 96: ¹HNMR (400 MHz, DMSO-*d*₆) δ : 10.45 (s, 1H), 8.63 (s, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 7.82 (s, 1H), 7.72 (t, *J* = 58.8 Hz, 1H), 6.58 (d, *J* = 4.8 Hz, 1H), 4.28-4.46 (m, 5H), 2.85-2.88 (m, 1H), 2.50-2.55 (m, 1H), 2.23-2.39 (m, 2H), 1.98 (s, 3H). LC-MS: m/z 565 [M+H]⁺.

20 **Example 97:** ¹HNMR (400 MHz, DMSO-*d*₆) δ : 10.44 (s, 1H), 8.69 (s, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 2.4 Hz, 1H), 7.75 (s, 1H), 7.73 (t, *J* = 58.8 Hz, 1H), 6.56 (d, *J* = 5.2 Hz, 1H), 4.31-4.47 (m, 5H), 2.77-2.83 (m, 1H), 2.65-2.70 (m, 1H), 2.23-2.35 (m, 2H), 1.98 (s, 3H). LC-MS: m/z 565 [M+H]⁺.

Method A26



Examples 98, 99: (6*S*,8*R*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 100, 101: (6*S*,8*S*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A6 step 10** but using methyl 2-fluoro-8-methyl-8-(1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (**A6-9**, 225 mg, 711 μ mol), the title compound was obtained as a yellow solid (135 mg, 36% yield). LC-MS (ES, m/z): 370[M+H]⁺.

Step 2: 8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A7 step 2** but using methyl 8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (170 mg, 460 μ mol), the crude title compound was obtained as a yellow oil (100 mg, 57% yield). LC-MS (ES, m/z): 356[M+H]⁺.

Step 3: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (100 mg, 281 μ mol) and 5-chloro-6-(triazol-2-yl)pyridin-3-amine (55 mg, 281 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (48 mg, 30% yield) as a white solid, LC-MS (ES, m/z): 533[M+H]⁺; *cis*-isomer (37 mg, 23% yield) as a white solid, LC-MS (ES, m/z): 533[M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 98** and **Example 99**
40 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: MtBE(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 14 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.463; RT2(min): 12.304; Sample Solvent: EtOH--HPLC; Injection Volume: 2.5 mL; Number Of Runs: 3). The second eluting isomer was

concentrated and lyophilized to afford **Example 98** (8.0 mg, 19% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 99** (8.2 mg, 19% yield) as a white solid.

Example 98: ^1H NMR (400 MHz, Chloroform- d) δ 8.74 (d, J = 1.2 Hz, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 7.88-8.23 (m, 2H), 7.96 (s, 2H), 6.31 (d, J = 4.8 Hz, 1H), 4.56-4.66 (m, 1H), 4.04-4.19 (m, 2H), 3.22-3.43 (m, 1H), 2.61-2.71 (m, 1H), 2.13 (s, 3H), 1.30-1.37 (m, 1H), 0.70-0.76 (m, 2H), 0.44-0.49 (m, 2H). LC-MS (ES, m/z): 533[M+H] $^+$.

Example 99: ^1H NMR (400 MHz, Chloroform- d) δ 8.74 (s, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 7.90-8.26 (m, 2H), 7.96 (s, 2H), 6.31 (d, J = 5.2 Hz, 1H), 4.55-4.70 (m, 1H), 4.04-4.20 (m, 2H), 3.28-3.40 (m, 1H), 2.61-2.71 (m, 1H), 2.13 (s, 3H), 1.30-1.39 (m, 1H), 0.70-0.76 (m, 2H), 0.45-0.49 (m, 2H). LC-MS (ES, m/z): 533[M+H] $^+$.

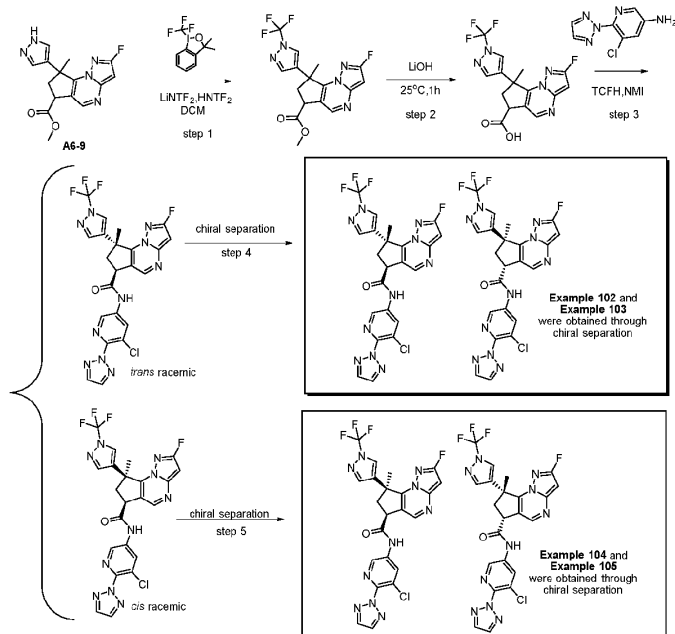
Step 5: Separation of enantiomers to obtain **Example 100** and **Example 101**

30 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μm ; Mobile Phase A: MtBE(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 14 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 6.303; RT2(min): 12.389; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 100** (4.1 mg, 13% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 101** (4.2 mg, 13% yield) as a white solid.

Example 100: ^1H NMR (400 MHz, Chloroform- d) δ 8.62 (s, 1H), 8.53 (s, 1H), 8.37-8.48 (m, 2H), 7.94 (s, 2H), 7.75 (s, 1H), 7.73 (s, 1H), 6.29 (d, J = 5.2 Hz, 1H), 4.45-4.52 (m, 1H), 3.93-4.08 (m, 2H), 2.99-3.07 (m, 1H), 2.85-2.95 (m, 1H), 2.02 (s, 3H), 1.20-1.30 (m, 1H), 0.58-0.68 (m, 2H), 0.32-0.41 (m, 2H). LC-MS (ES, m/z): 533 [M+H] $^+$.

Example 101: ^1H NMR (400 MHz, Chloroform- d) δ 8.80 (s, 1H), 8.65 (s, 1H), 8.46-8.56 (m, 2H), 7.94 (s, 2H), 7.81-7.86 (m, 2H), 6.31 (d, J = 4.8 Hz, 1H), 4.53-4.58 (m, 1H), 4.03-4.10 (m, 2H), 2.87-3.07 (m, 2H), 2.02 (s, 3H), 1.28 (s, 1H), 0.63-0.70 (m, 2H), 0.37-0.43 (m, 2H). LC-MS (ES, m/z): 533 [M+H] $^+$.

Method A27



Examples 102, 103: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 104, 105: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Methyl 2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate

To a stirred solution of methyl 2-fluoro-8-methyl-8-(1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (1.0 g, 3.2 mmol) in DCM (20 mL) was added lithium bis((trifluoromethyl)sulfonyl)amide (91 mg, 317 μmol) and 1,1,1-trifluoro-*N*-

((trifluoromethyl)sulfonyl)methanesulfonamide (892 mg, 3.2 mmol), followed by the addition of 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1 λ^3 -benzo[d][1,2]iodaoxole (1.1 g, 3.2 mmol) in portions. The reaction mixture was stirred at 40 °C for 2 h. The reaction was quenched with water (20 mL). The resulting mixture was extracted with DCM (3x 20 mL). The combined organic layers
5 were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (1:1) to afford the title compound (200 mg, 16% yield) as a yellow solid. LC-MS: m/z 384 [M+H]⁺.

Step 2: 2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

10 In analogy to **Method A7 step 2** but using methyl 2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (210 mg, 547.8 μ mol), the crude title compound was obtained as a yellow oil (90 mg) as a yellow solid. LC-MS: m/z 370 [M+H]⁺.

Step 3: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide
15

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (90 mg, 244 μ mol) and 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (48 mg, 244 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (13.5 mg, 10% yield) as an off-white solid, LC-MS: m/z 547 [M+H]⁺; *cis*-isomer (9.9 mg, 7.4% yield) as a white solid, LC-MS: m/z 547 [M+H]⁺.
20

25 Step 4: Separation of enantiomers to obtain **Example 102** and **Example 103**

13 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.891; RT2(min): 6.658; Sample Solvent: EtOH--HPLC; Injection
30

Volume: 1.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 103** (3.0 mg, 23% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 102** (2.4 mg, 18% yield) as a white solid.

Example 102: ¹HNMR (400 MHz, DMSO-d₆) δ: 11.12 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.72 (s, 1H), 8.60 (d, J = 2.4 Hz, 1H), 8.49 (s, 1H), 8.17 (s, 2H), 8.00 (s, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.55-4.59 (m, 1H), 2.90-2.96 (m, 1H), 2.58-2.63 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 547 [M+H]⁺.

Example 103: ¹HNMR (400 MHz, DMSO-d₆) δ: 11.11 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.49 (s, 1H), 8.17 (s, 2H), 8.00 (s, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.55-4.59 (m, 1H), 2.90-2.96 (m, 1H), 2.58-2.63 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 547 [M+H]⁺.

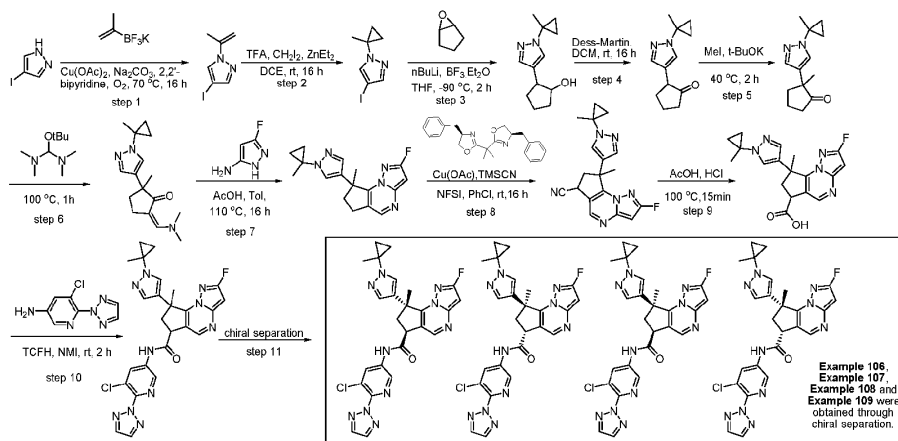
Step 5: Separation of enantiomers to obtain **Example 104** and **Example 105**

9 mg of (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 20% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.175; RT2(min): 4.838; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 105** (1.1 mg, 12% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 104** (2.9 mg, 32% yield) as a white solid.

Example 104: ¹HNMR (400 MHz, DMSO-d₆) δ: 11.09 (s, 1H), 8.76 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.47 (s, 1H), 8.17 (s, 2H), 7.92 (s, 1H), 6.57 (d, J = 4.8 Hz, 1H), 4.55-4.59 (m, 1H), 2.83-2.88 (m, 1H), 2.72-2.77 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 547 [M+H]⁺.

Example 105: ¹HNMR (400 MHz, DMSO-d₆) δ: 11.09 (s, 1H), 8.76 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.47 (s, 1H), 8.17 (s, 2H), 7.92 (s, 1H), 6.57 (d, J = 4.8 Hz, 1H), 4.55-4.58 (m, 1H), 2.83-2.88 (m, 1H), 2.72-2.77 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 547 [M+H]⁺.

Method A28



- Examples 106, 107, 108, 109:** (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-4-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 4-iodo-1-(prop-1-en-2-yl)-1*H*-pyrazole

- To a stirred solution of 4-iodo-1*H*-pyrazole (20 g, 103.1 mmol) in DCE (70 mL) were added diacetoxy copper (18.73 g, 103.1 mmol), 2,2'-bipyridine (32.2 g, 206.2 mmol), sodium carbonate (21.9 g, 206.2 mmol) and potassium trifluoro(prop-1-en-2-yl)borate (30.5 g, 206.2 mmol). The mixture was stirred at 70 °C for 2 h under oxygen atmosphere. The reaction was quenched with water (350 mL). The resulting solution was extracted with DCM (2x 350 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with PE/EtOAc (3:1) to give the title compound (16.6 g, 61% yield) as a yellow oil. LC-MS (ES, *m/z*): 235[*M*+*H*]⁺.

Step 2: 4-iodo-1-(1-methylcyclopropyl)-1H-pyrazole

To a solution of 2,2,2-trifluoroacetic acid (36.5 g, 320.4 mmol) in DCE (200 mL) was added a solution of diethylzinc (1M, 320 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 20 min. A solution of diiodomethane (85.8 g, 320.4 mmol) in DCE (200 mL) was added, and the mixture was stirred at 0 °C for 20 min under nitrogen. A solution of 4-iodo-1-(prop-1-en-2-yl)-1H-pyrazole (15 g, 64.1 mmol) in DCE (200 mL) was added, and the mixture was stirred at 25 °C for 16 h under nitrogen. The reaction was quenched with water (50 mL). The resulting mixture was extracted with DCM (2x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with PE/EtOAc (3:1) to give the title compound (7.5 g, 47% yield) as a yellow oil. LC-MS (ES, m/z): 249[M+H]⁺.

Step 3: 2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-ol

In analogy to **Method A6 step 2** but using 4-iodo-1-(1-methylcyclopropyl)-1H-pyrazole (7.9 g, 31.8 mmol), the title compound was obtained as a yellow oil (0.9 g, 13% yield) as a yellow oil. LC-MS: m/z 207 [M+H]⁺.

Step 4: 2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one

In analogy to **Method A10 step 2** but using 2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-ol (1.8 g, 8.7 mmol) purification of the product by prep-HPLC, the title compound was obtained as a yellow oil (880 mg, 49 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ: 7.61 (s, 1H), 7.28 (s, 1H), 3.20-3.25 (m, 1H), 2.13-2.38 (m, 3H), 1.78-2.01 (m, 3H), 1.52 (s, 3H), 1.10-1.14 (m, 2H), 0.82-0.88 (m, 2H). LC-MS: m/z 205 [M+H]⁺.

Step 5: 2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one

In analogy to **Method A1 step 3** but using 2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one (830 mg, 4.1 mmol), and purification of the product by silica gel column chromatography eluting with PE/EA (1:1), the title compound was obtained as a yellow oil (500 mg, 39% yield). ¹H NMR (400 MHz, DMSO-d₆) δ: 7.61 (s, 1H), 7.29 (s, 1H), 2.19-2.35 (m, 3H), 1.79-2.01 (m, 3H), 1.51 (s, 3H), 1.22 (s, 3H), 1.08-1.16 (m, 2H), 0.81-0.87 (m, 2H). LC-MS: m/z 219 [M+H]⁺.

Step 6: 5-((dimethylamino)methylene)-2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one (450 mg, 2.1 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanediamine (719 mg, 4.2 mmol) and stirring at 100 °C for 1, the crude title compound was obtained as a yellow oil (500 mg, 88% yield) was used in the next step without further purification. LC-MS: m/z 274 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)cyclopentan-1-one (500 mg, 1.8 mmol), the title compound was obtained as a yellow oil (480 mg, 84% yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.28 (s, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 6.12 (d, J = 4.8 Hz, 1H), 2.89-3.02 (m, 2H), 2.47-2.61 (m, 1H), 2.19-2.33 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.16-1.25 (m, 2H), 0.82-0.90 (m, 2H). LC-MS: m/z 312 [M+H]⁺.

Step 8: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (520 mg, 1.7 mmol) in chlorobenzene (50 mL), the title compound was obtained as a yellow solid (150 mg, 17% yield). LC-MS: m/z 337 [M+H]⁺.

Step 9: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A9 step 8** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (90 mg, 268 μmol), the title compound was obtained as a yellow solid (80 mg, 84% yield). LC-MS: m/z 356 [M+H]⁺.

Step 10: N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (60 mg, 169 μ mol) and 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (40 mg, 203 μ mol), a mixture of all stereoisomers of the title compound (27 mg, 30% yield) was obtained as a white solid. LC-MS: m/z 533 [M+H]⁺.

Step 11: Separation of enantiomers to obtain **Example 106**, **Example 107**, **Example 108**, and **Example 109**

27 mg of N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.153; RT2(min): 7.491; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 3). The fourth eluting isomer was concentrated and lyophilized to afford **Example 106** (7.1 mg, 26% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 109** (1.2 mg, 4% yield) as a white solid. The third eluting isomer and the second eluting isomer was concentrated and lyophilized to afford a mixture, which was submitted to chiral HPLC purification (Column: CHIRALPAK ID, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 70% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.131; RT2(min): 5.522; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 107** (4.7 mg, 17% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 108** (1.2 mg, 4% yield) as a white solid.

Example 106: ¹H NMR (400 MHz, Chloroform-d) δ : 8.84 (s, 1H), 8.75 (s, 1H), 8.58 (s, 1H), 8.18 (s, 1H), 7.95 (s, 2H), 6.32 (d, J = 5.2 Hz, 1H), 4.69-4.84 (m, 1H), 3.38-3.66 (m, 1H), 2.52-2.63 (m, 1H), 2.10 (s, 3H), 1.74 (s, 3H), 1.35-1.39 (m, 2H), 1.10-1.25 (m, 2H). LC-MS (ES, m/z): 533[M+H]⁺.

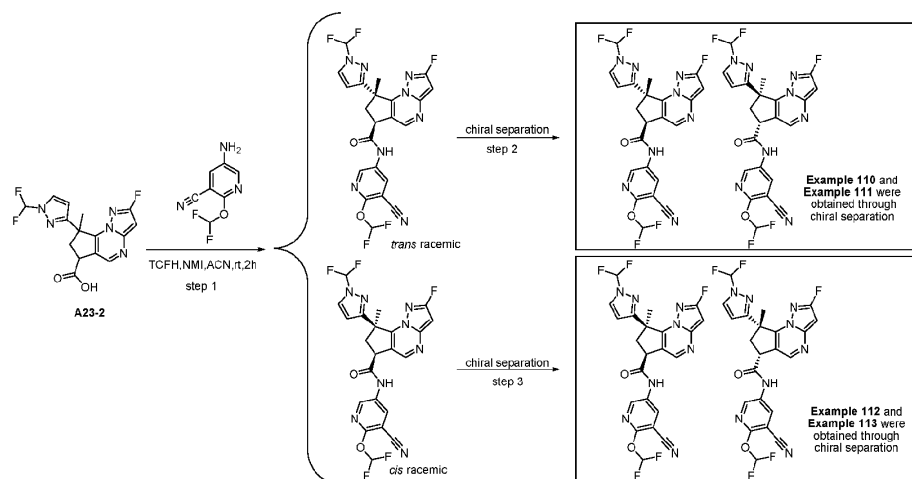
Example 107: ¹H NMR (400 MHz, Chloroform-d) δ : 9.05 (s, 1H), 8.68 (s, 1H), 8.50-8.56 (m, 2H), 7.95 (s, 2H), 7.63 (s, 1H), 7.44 (s, 1H), 6.29 (d, J = 4.8 Hz, 1H), 4.38-4.43 (m, 1H), 3.00-

3.04 (m, 1H), 2.65-2.72 (m, 1H), 2.08 (s, 3H), 1.55 (s, 3H), 1.12-1.23 (m, 2H), 0.82-0.94 (m, 2H).
LC-MS (ES, m/z): 533[M+H]⁺.

Example 108: ¹H NMR (400 MHz, Chloroform-d) δ: 8.35-8.67 (m, 4H), 7.94 (s, 2H), 7.69-7.81 (m, 2H), 6.31 (d, J = 4.0 Hz, 1H), 4.50-4.56 (m, 1H), 2.74-3.21 (m, 2H), 2.02 (s, 3H), 1.60 (s, 3H), 1.25-1.30 (m, 2H), 0.90-0.98 (m, 2H). LC-MS (ES, m/z): 533[M+H]⁺.

Example 109: ¹H NMR (400 MHz, Chloroform-d) δ: 8.66 (s, 1H), 8.52-8.56 (m, 2H), 7.79-7.99 (m, 3H), 7.75 (s, 1H), 6.32 (d, J = 4.8 Hz, 1H), 4.50-4.56 (m, 1H), 2.82-3.06 (m, 2H), 1.99 (s, 3H), 1.61 (s, 3H), 1.20-1.33 (m, 2H), 0.94-1.01 (m, 2H). LC-MS (ES, m/z): 533[M+H]⁺.

Method A29



Examples 110, 111: Single enantiomers obtained from a racemic mixture containing (6*S*,8*S*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 112, 113: Single enantiomers obtained from a racemic mixture containing (6*S*,8*R*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-

1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: (*trans*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (110 mg, 313 μ mol) and 5-amino-2-(difluoromethoxy)nicotinonitrile (116 mg, 626 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (35 mg, 21% yield) as a white solid, LC-MS (ES, m/z): 519[M+H]⁺; *cis*-isomer (20 mg, 10% yield) as a white solid, LC-MS (ES, m/z): 519[M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 110** and **Example 111**

35 mg of (*trans*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm; RT1(min): 3.654; RT2(min): 4.387; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 110** (11.4 mg, 37% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 111** (14.9 mg, 47% yield) as a white solid.

Example 110: ¹H NMR (400 MHz, Chloroform-d) δ 8.59-8.62 (m, 2H), 8.54 (s, 1H), 7.85 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.47 (t, J = 71.6 Hz, 1H), 7.05 (t, J = 60.8 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 4.8 Hz, 1H), 4.50-4.56 (m, 1H), 3.39-3.44 (m, 1H), 2.58-2.63 (m, 1H), 2.16 (s, 3H). LC-MS (ES, m/z): 519[M+H]⁺.

Example 111: ¹H NMR (400 MHz, Chloroform-d) δ 8.61 (d, J = 2.4 Hz, 1H), 8.57 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 7.83 (s, 1H), 7.75 (d, J = 2.8 Hz, 1H), 7.47 (t, J = 71.6 Hz, 1H), 7.05 (t, J

= 60.8 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.30 (d, J = 5.2 Hz, 1H), 4.48-4.53 (m, 1H), 3.39-3.45 (m, 1H), 2.57-2.62 (m 1H), 2.16 (s, 3H). LC-MS (ES, m/z): 519[M+H]⁺.

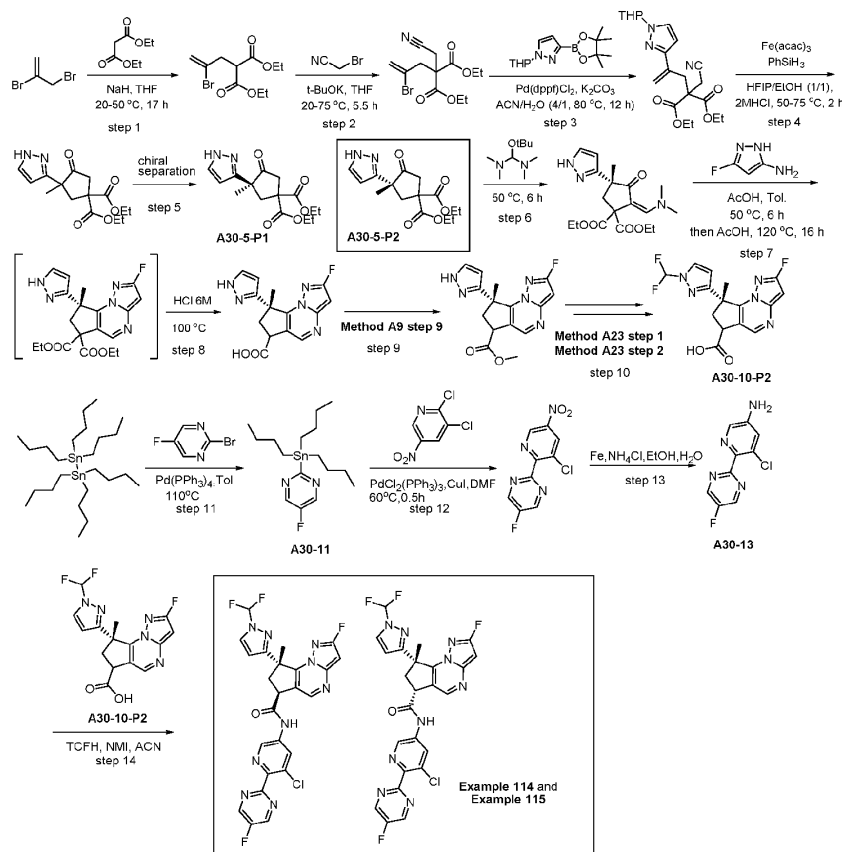
Step 3: Separation of enantiomers to obtain **Example 112** and **Example 113**

20 mg of (*cis*)-N-(5-cyano-6-(difluoromethoxy)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.302; RT2(min): 5.481; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 112** (6.7 mg, 33% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 113** (6.2 mg, 30% yield) as a white solid.

Example 112: ¹H NMR (400 MHz, Chloroform-d) δ 9.52 (s, 1H), 8.63 (s, 1H), 8.39-8.40 (m, 1H), 8.35-8.36 (m, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.46 (t, J = 71.6 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H), 6.96 (t, J = 60.4 Hz, 1H), 6.31 (d, J = 4.8 Hz, 1H), 4.52-4.55 (m, 1H), 3.33-3.38 (m, 1H), 2.84-2.90 (m, 1H), 2.15 (s, 3H). LC-MS (ES, m/z): 519[M+H]⁺.

Example 113: ¹H NMR (400 MHz, Chloroform-d) δ 9.52 (s, 1H), 8.63 (s, 1H), 8.39-8.40 (m, 1H), 8.35-8.36 (m, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.46 (t, J = 71.6 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H), 6.96 (t, J = 60.4 Hz, 1H), 6.31 (d, J = 4.8 Hz, 1H), 4.52-4.55 (m, 1H), 3.33-3.38 (m, 1H), 2.84-2.90 (m, 1H), 2.15 (s, 3H). LC-MS (ES, m/z): 519[M+H]⁺.

Method A30



Examples 114, 115: (6S,8S)-N-(5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6R,8S)-N-(5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: Diethyl 2-(2-bromoallyl)propanedioate

- 10 To a mixture of NaH (1.25 g, 32.5 mmol, 60% in mineral oil) in THF (35.0 mL) was added diethyl propanedioate (6.0 g, 37.5 mmol) at 20 °C, and the mixture was stirred at 20 °C for 1 hr. The mixture was cooled to 0 °C, and 2,3-dibromoprop-1-ene (5.0 g, 25.0 mmol) was added. The mixture was stirred at 50 °C for 16 h. The mixture was poured into sat. NH₄Cl (50 mL), and it was extracted with EtOAc (2x 30 mL). The combined organic layers were washed with brine (20 mL),

dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 10/1) to give the title compound (2.00 g, 7.17 mmol) as a colorless oil.

Step 2: Diethyl 2-(2-bromoallyl)-2-(cyanomethyl)propanedioate

5 To a solution of diethyl 2-(2-bromoallyl)propanedioate (10.0 g, 35.8 mmol) in THF (70.0 mL) was added *t*-BuOK (4.82 g, 42.9 mmol) at 20 °C and the mixture was stirred at 20 °C for 0.5 h. 2-bromoacetonitrile (5.16 g, 42.9 mmol) was added and the mixture was stirred at 75 °C for 5 h. The mixture was poured into H₂O (100 mL), and it was extracted with EtOAc (2x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered
10 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 5/1) to give the title compound (8.90 g, 27.9 mmol) as a colorless oil.

Step 3: Diethyl 2-(cyanomethyl)-2-[2-(1-tetrahydropyran-2-ylpyrazol-3-yl)allyl]propanedioate

15 To a mixture of diethyl 2-(2-bromoallyl)-2-(cyanomethyl)propanedioate (10.0 g, 31.4 mmol) and 1-tetrahydropyran-2-yl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (17.4 g, 62.8 mmol) in dioxane (80.0 mL) and H₂O (20.0 mL) were added Pd(dppf)Cl₂ (2.30 g, 3.14 mmol) and K₂CO₃ (8.69 g, 62.8 mmol) under N₂. The mixture was stirred at 100 °C for 16 h under N₂. The mixture was poured into H₂O (100 mL), and it was extracted with EtOAc (2x 100 mL).
20 The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1 to 1/1) to obtain the title compound (2.30 g, 5.91mmol, 18.7% yield) as a colorless oil. LC-MS: *m/z* 390 [M+H]⁺.

Step 4: Diethyl 3-methyl-4-oxo-3-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate

25 A solution of PhSiH₃ (3.75 g, 34.6 mmol) in HFIP (22.5 mL) and EtOH (22.5 mL) was added to a flask containing diethyl 2-(cyanomethyl)-2-(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)allyl)malonate (4.50 g, 11.5 mmol) and Fe(acac)₃ (2.04 g, 5.78 mmol) under N₂. The reaction mixture was stirred at 50 °C for 1 h under N₂. HCl (2M, 45 mL) was added, and the reaction mixture was stirred at 75 °C for 1 h under N₂. The reaction mixture was poured into H₂O
30 (10 mL), and it was extracted with EtOAc (2x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The

residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 0/1) to obtain a racemic mixture of the title compound (1.20 g) as a yellow oil. LC-MS: m/z 309 [M+H]⁺.

Step 5: Separation of enantiomers to obtain diethyl (*S*)-3-methyl-4-oxo-3-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate (**A30-5-P1**) and diethyl (*R*)-3-methyl-4-oxo-3-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate (**A30-5-P2**)

Diethyl 3-methyl-4-oxo-3-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate (1.20 g) was submitted to chiral SFC (Column: DAICEL CHIRALCEL OJ(250mm*30mm,10um); Mobile phase: A for CO₂ and B for IPA(0.1%NH₃H₂O); Gradient: isocratic 25% Mobile Phase B; Flow rate: 54g/min; Wavelength:220nm; Column temperature: 35 °C System back pressure: 100 bar.RT1(min)3.7;RT2(min)5.3.Sample Solvent:IPA-Preparative;Injection Volume:2 mL;Number Of Runs:40). The first eluting isomer was lyophilized to afford **A30-5-P1** (430 mg) as a yellow oil, LC-MS: m/z 309 [M+H]⁺. The second eluting isomer was lyophilized to afford **A30-5-P2** (440 mg) as a yellow oil, LC-MS: m/z 309 [M+H]⁺.

Step 6: Diethyl (*R*)-2-((dimethylamino)methylene)-4-methyl-3-oxo-4-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate

A solution of diethyl (*R*)-3-methyl-4-oxo-3-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate (**A30-5-P2**, 3.80 g, 12.3 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanediamine (6.44 g, 36.9 mmol) was stirred at 50 °C for 6 h. The reaction mixture was concentrated under reduced pressure to give the crude title compound (4.60 g), which was used in the next step without further purification. LC-MS: m/z 364 [M+H]⁺.

Step 7: Diethyl (*S*)-2-fluoro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6,6-dicarboxylate

To a solution of diethyl (*R*)-2-((dimethylamino)methylene)-4-methyl-3-oxo-4-(1H-pyrazol-3-yl)cyclopentane-1,1-dicarboxylate (4.60 g, 12.6 mmol) in AcOH (5 mL) and toluene (50 mL) was added 3-fluoro-1H-pyrazol-5-amine (1.54 g, 15.1 mmol). The mixture was stirred at 50 °C for 6 h. Ice-water (50 mL) was added, and it was extracted with EtOAc (2x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. AcOH (50 mL) was added, and it was stirred at 120 °C for 16 h. The reaction mixture was concentrated under reduced pressure until the remaining volume

of AcOH was approximately 5 mL. This crude solution of the title compound in AcOH (~5 mL) was directly used in the next step. LC-MS: m/z 402 [M+H]⁺.

Step 8: (8*S*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid

5 To a solution of diethyl (8*S*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6,6-dicarboxylate in AcOH (~5 mL), which was obtained from the previous step 7, was added HCl (6*M*, 50 mL) at 25 °C. The reaction mixture was stirred at 100 °C and for 3 h. The mixture was cooled and concentrated under reduced pressure to give the crude title compound (3.30 g) as a yellow oil, which was used in the next step without further
10 purification. LC-MS: m/z 302 [M+H]⁺.

Step 9: Methyl (8*S*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate

Using crude (8*S*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (3.30 g) and following the reaction
15 conditions described in **Method A9 step 9**, the crude title compound (3.00 g) was obtained as a yellow oil, which was used in the next step without purification. LC-MS: m/z 316 [M+H]⁺.

Step 10: Methyl (8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A30-10-P2**)

Using methyl (8*S*)-2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate, and following sequentially the reaction
20 conditions described in **Method A23 step 1** and **step 2**, the title compound (**A30-10-P2**) was obtained as a yellow oil. LC-MS: m/z 352 [M+H]⁺.

Step 11: 5-fluoro-2-(tributylstannyl)pyrimidine (**A30-11**)

To a stirred solution of 2-bromo-5-fluoropyrimidine (4.9 g, 27.6 mmol) in toluene (85 mL)
25 was added 1,1,1,2,2,2-hexabutyldistannane (32 g, 55.2 mmol) and Pd(PPh₃)₄ (3.2 g, 2.8 mmol). The resulting mixture was stirred at 110 °C for 24 h. The reaction was quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (3x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 85% petroleum ether and 15%
30 ethyl acetate as eluent to afford the title compound (**A30-11**, 4.6 g, 35% yield) as a yellow solid. LC-MS: m/z 389 [M+H]⁺.

Step 12: 2-(3-chloro-5-nitropyridin-2-yl)-5-fluoropyrimidine

To a stirred solution of 5-fluoro-2-(tributylstannyl)pyrimidine (1.7 g, 4.4 mmol) in DMF (16 mL) were added 2,3-dichloro-5-nitropyridine (932 mg, 4.8 mmol), PdCl₂(PPh₃)₂ (616 mg, 878 μmol) and CuI (167 mg, 878 μmol). The resulting mixture was stirred at 60 °C for 0.5 h under nitrogen atmosphere. The mixture was allowed to cool to 25 °C and quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 50% petroleum ether and 50% ethyl acetate as eluent to afford the title compound (340 mg, 24% yield) as a yellow solid. LC-MS: m/z 255 [M+H]⁺.

Step 13: 5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-amine (**A30-13**)

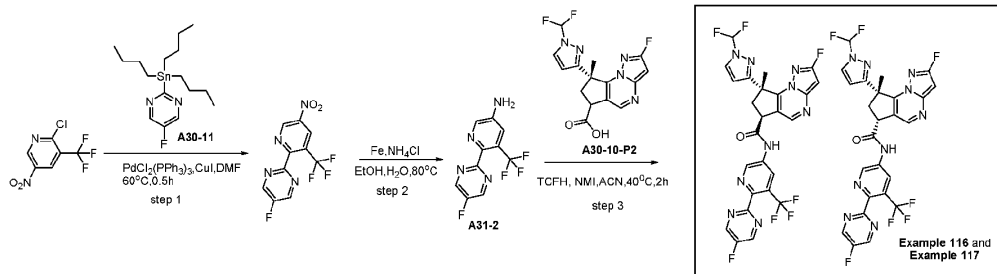
To a stirred mixture of 2-(3-chloro-5-nitropyridin-2-yl)-5-fluoropyrimidine (300 mg, 1.2 mmol) in EtOH (5 mL) and water (1 mL) were added Fe (197 mg, 3.5 mmol) and NH₄Cl (315 mg, 5.9 mmol). The resulting mixture was stirred at 80 °C for 1 h. The solids were filtered out. The filtrate was diluted with water (20 mL) and extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography to afford the title compound (**A30-13**, 80 mg, 28% yield) as a yellow solid. LC-MS: m/z 225 [M+H]⁺.

Step 14: **Example 114** and **Example 115**

In analogy to **Method A1 step 8** but using (8S)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A30-10-P2**, 41 mg, 116 μmol) and 5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-amine (39 mg, 174 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 114** (2.8 mg, 4% yield) as a white solid and *cis*-isomer **Example 115** (1.1 mg, 2% yield) as a white solid.

Example 114: ¹H NMR (400 MHz, DMSO-d₆) δ 11.01 (s, 1H), 9.08 (s, 2H), 8.80 (s, 1H), 8.72 (s, 1H), 8.47 (s, 1H), 8.21 (d, J = 2.8 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.48-4.54 (m, 1H), 3.00-3.07 (m, 1H), 2.49-2.60 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 558 [M+H]⁺.

Example 115: ¹H NMR (400 MHz, DMSO-d₆) δ 10.93 (s, 1H), 9.08 (s, 2H), 8.78 (s, 1H), 8.73 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 7.71 (t, J = 59.2 Hz, 1H), 6.59 (d, J = 4.4 Hz, 1H), 6.48 (s, 1H), 4.55-4.59 (m, 1H), 2.82-2.87 (m, 2H), 1.92 (s, 3H). LC-MS: m/z 558 [M+H]⁺.

Method A31

Examples 116, 117: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 5-fluoro-2-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine

In analogy to **Method A30 step 12** but using 2-chloro-5-nitro-3-(trifluoromethyl)pyridine (966 mg, 4.3 mmol), the title compound was obtained as a yellow solid (451 mg, 34% yield). LC-MS: *m/z* 289[M+H]⁺.

Step 2: 6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A31-2**)

In analogy to **Method A30 step 13** but using 5-fluoro-2-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine (190 mg, 659 μmol), the title compound was obtained as a yellow solid (**A31-2**, 95 mg, 53% yield). LC-MS: *m/z* 259 [M+H]⁺.

Step 3: Example 116 and Example 117

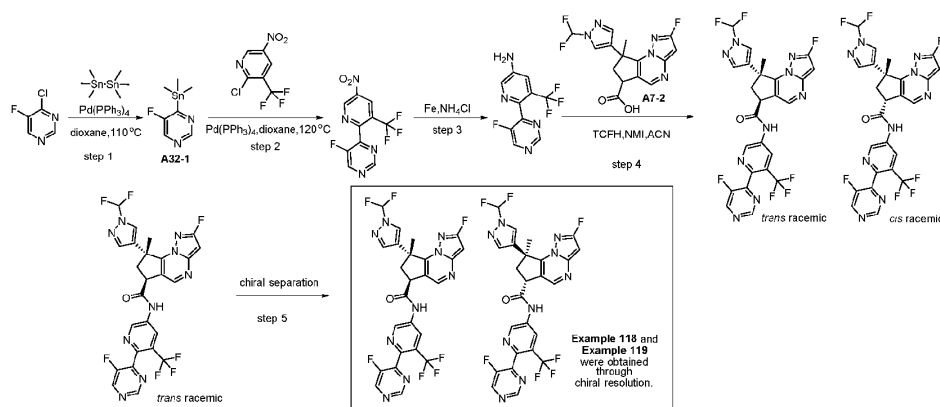
In analogy to **Method A1 step 8** but using (8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A30-10-P2**, 40 mg, 114 μmol) and 6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (35 mg, 136 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 116** (7.6 mg, 11% yield) as a white solid and *cis*-isomer **Example 117** (5.2 mg, 8% yield) as a white solid.

Example 116: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.14 (s, 1H), 9.08 (s, 2H), 9.07 (s, 1H), 8.75 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 7.70 (t, *J* = 59.2 Hz, 1H), 6.63 (d,

J = 2.8 Hz, 1H), 6.59 (d, J = 4.8 Hz, 1H), 4.51-4.56 (t, J = 8.1 Hz, 1H), 3.00-3.08 (m, 1H), 2.57-2.63 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 592 [M+H]⁺.

Example 117: ¹H NMR (400 MHz, DMSO-d₆) δ 11.05 (s, 1H), 9.08 (s, 2H), 9.05 (s, 1H), 8.75 (s, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.69 (t, J = 59.2 Hz, 1H), 6.57 (d, J = 4.8 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 4.59 (t, J = 7.7 Hz, 1H), 2.90-2.95 (m, 1H), 2.81-2.86 (m, 1H), 1.93 (s, 3H). LC-MS: m/z 592 [M+H]⁺.

Method A32



Examples 118, 119: (6*S*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 5-fluoro-4-(trimethylstannyl)pyrimidine (**A32-1**)

To a stirred mixture of 4-chloro-5-fluoropyrimidine (1 g, 7.6 mmol) in dioxane (15 mL) were added Pd(PPh₃)₄ (875 mg, 757 μmol) and 1,1,1,2,2,2-hexamethyldistannane (3.7 g, 11.3 mmol). The resulting mixture was stirred at 110 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool to 25 °C. The solids were filtered out and the filtrate was concentrated under reduced pressure to afford the crude title compound (**A32-1**, 1 g). LC-MS: m/z 263 [M+H]⁺.

Step 2: 5-fluoro-4-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine

To a stirred mixture of 2-chloro-5-nitro-3-(trifluoromethyl)pyridine (2 g, 8.8 mmol) in dioxane (10 mL) were added 5-fluoro-4-(trimethylstannyl)pyrimidine (1 g, 3.8 mmol),

PdCl₂(PPh₃)₂ (532 mg, 758 μmol) and CuI (144 mg, 756 μmol). The resulting mixture was stirred at 110°C for 1h under nitrogen atmosphere. The mixture was allowed to cool down to 25 °C. The solids were filtered out. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 80% petroleum ether and 20% ethyl acetate as eluent to afford the title compound (400 mg, 31% yield) as a yellow solid. LC-MS: m/z 289 [M+H]⁺.

Step 3: 6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-amine

In analogy to **Method A30 step 13** but using 5-fluoro-4-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine (0.2 g, 694 μmol), the title compound was obtained as a yellow solid (150 mg, 77% yield). LC-MS: m/z 259 [M+H]⁺.

Step 4: (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-N-(6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-N-(6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**, 100 mg, 285 μmol) and 6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-amine (88 mg, 341 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (13.6 mg, 8% yield) as a white solid, LC-MS: m/z 592 [M+H]⁺; *cis*-isomer (6.9 mg, 4% yield) as a white solid, LC-MS: m/z 592 [M+H]⁺.

Step 5: Separation of enantiomers to obtain **Example 118** and **Example 119**

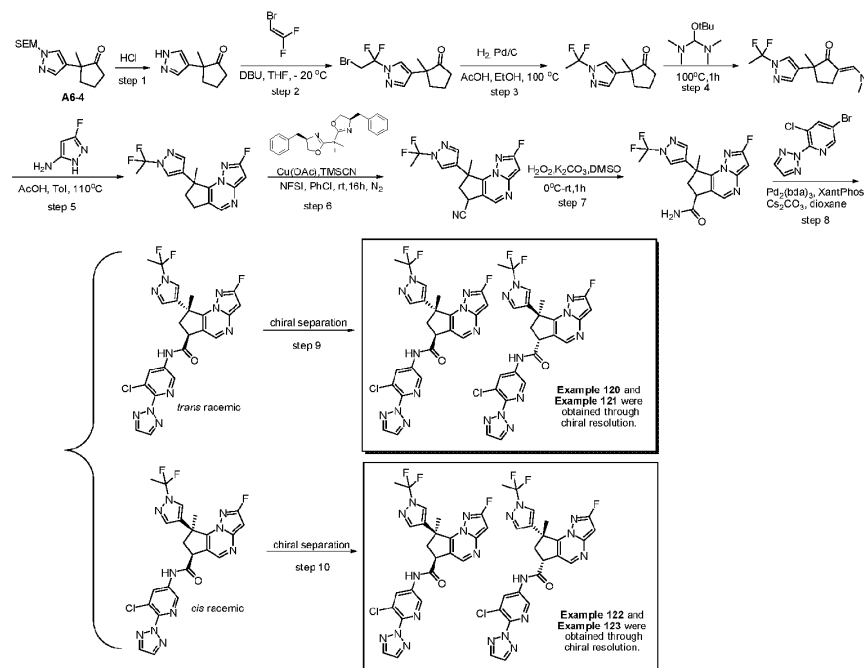
13 mg of (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-N-(6-(5-fluoropyrimidin-4-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 3.421; RT2(min): 6.738; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 30 1). The first eluting isomer was concentrated and lyophilized to afford **Example 118** (2.7 mg, 22%

yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 119** (3.8 mg, 32% yield) as a white solid.

Example 118: ^1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 9.22 (d, J = 2.8 Hz, 1H), 9.16 (d, J = 2.0 Hz, 1H), 9.13 (d, J = 2.4 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H), 8.75 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.71 (t, J = 58.8 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 4.8 Hz, 1H), 4.54 (t, J = 8.1 Hz, 1H), 3.04 (dd, J = 12.8, 8.4 Hz, 1H), 2.60 (dd, J = 12.8, 7.6 Hz, 1H), 2.04 (s, 3H). LC-MS: m/z 592 $[\text{M}+\text{H}]^+$.

Example 119: ^1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 9.22 (d, J = 2.8 Hz, 1H), 9.16 (d, J = 1.6 Hz, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H), 8.75 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.71 (t, J = 58.8 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 4.8 Hz, 1H), 4.54 (t, J = 8.1 Hz, 1H), 3.04 (dd, J = 13.0, 8.4 Hz, 1H), 2.60 (dd, J = 13.0, 7.9 Hz, 1H), 2.04 (s, 3H). LC-MS: m/z 592 $[\text{M}+\text{H}]^+$.

Method A33



Examples 120, 121: (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-

triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 122, 123: (6*S*,8*S*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-methyl-2-(1H-pyrazol-4-yl)cyclopentan-1-one

10 A solution of 2-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)cyclopentan-1-one (**A6-4**, 2 g, 6.8 mmol) in HCl (200 mL, 4M in MeOH) was stirred at 80 °C for 1 h. The mixture was cooled to room temperature, and the pH was adjusted to 7-8 with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate (3x 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, 15 filtered and concentrated under reduced pressure to give the title compound (1 g, 6.1 mmol) as a yellow oil. LC-MS: *m/z* 165 [M+H]⁺.

Step 2: 2-(1-(2-bromo-1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-methylcyclopentan-1-one

To a stirred solution of 2-methyl-2-(1H-pyrazol-4-yl)cyclopentan-1-one (2 g, 12.2 mmol) and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]zepine (1.9 g, 12.2 mmol) in THF (200 mL) was 20 added slowly 2-bromo-1,1-difluoroethene (1.7 g, 12.2 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 3 h. The reaction was quenched with water (200 mL). The resulting mixture was extracted with ethyl acetate (3x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EtOAc/PE (4:1) to afford the title compound (900 mg, 24% 25 yield) as a colorless oil. LC-MS: *m/z* 307 [M+H]⁺.

Step 3: 2-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-methylcyclopentan-1-one

To a solution of 2-(1-(2-bromo-1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-methylcyclopentan-1-one (900 mg, 2.9 mmol) in EtOH (20 mL) and AcOH (1 mL) was added Pd/C (125 mg, 10%). The reaction mixture was degassed and then stirred at 100 °C for 16 h under hydrogen atmosphere. 30 The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue

was purified by reverse phase chromatography to afford the title compound (600 mg, 89% yield) as a yellow oil. LC-MS: m/z 229 [M+H]⁺.

Step 4: 2-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-5-((dimethylamino)methylene)-2-methylcyclopentan-1-one

5 In analogy to **Method A1 step 4** but using 2-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-methylcyclopentan-1-one (600 mg, 2.6 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanediamine (1.4 g, 7.9 mmol) and stirring at 100 °C for 1, the crude title compound was obtained as a red oil (600 mg). LC-MS: m/z 284 [M+H]⁺.

Step 5: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 2-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-5-((dimethylamino)methylene)-2-methylcyclopentan-1-one (600 mg, 2.1 mmol), the title compound was obtained as a yellow solid (600 mg, 75% yield). LC-MS: m/z 322 [M+H]⁺.

Step 6: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (600 mg, 1.9 mmol) in chlorobenzene (60 mL), the title compound was obtained as a yellow oil (320 mg, 44% yield). LC-MS: m/z 347 [M+H]⁺.

Step 7: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

To a stirred mixture of 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (300 mg, 866 μmol) and K₂CO₃ (359 mg, 2.6 mmol) in DMSO (7 mL) was added H₂O₂ (7 mL, 30% in water) dropwise at 25 °C. The mixture was stirred at 25 °C for 30 min. The reaction was quenched with saturated sodium thiosulfate solution (10 mL) and diluted with water (30 mL). The resulting mixture was extracted with ethyl acetate (2x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase chromatography and the collected fractions were concentrated under reduced pressure to afford the title compound (180 mg, 48% yield) as a yellow oil. LC-MS: m/z 365 [M+H]⁺.

Step 8: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

To a stirred solution of 8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (170 mg, 467 μ mol) in dioxane (20 mL) were added 5-bromo-3-chloro-2-(triazol-2-yl)pyridine (121 mg, 467 μ mol), Pd₂(dba)₃ (48 mg, 47 μ mol), Xantphos (54 mg, 93 μ mol) and Cs₂CO₃ (456 mg, 1.4 mmol). The mixture was stirred at 110 °C for 1 h under nitrogen atmosphere. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (2x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reversed phase column chromatography. The obtained product was further purified by prep-achiral SFC to afford racemic mixtures of the title compounds: *trans* isomer (50 mg, 18% yield) as a white solid, LC-MS: m/z 543 [M+H]⁺; *cis*-isomer (30 mg, 11% yield) as a white solid, LC-MS: m/z 543 [M+H]⁺.

Step 9: Separation of enantiomers to obtain **Example 120** and **Example 121**

trans-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (50 mg, 92 μ mol) was submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.436; RT2(min): 18.731; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2) The first eluting isomer was concentrated and lyophilized to afford **Example 120** (18.4 mg, 36% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 121** (21.1 mg, 42% yield) as a white solid.

Example 120: ¹H NMR (400 MHz, Chloroform-d) δ 8.70 (s, 1H), 8.61 (s, 1H), 8.55 (s, 1H), 8.18 (s, 1H), 7.96 (s, 2H), 7.83 (s, 1H), 7.65 (s, 1H), 6.34 (d, *J* = 4.4 Hz, 1H), 4.40-4.45 (m, 1H), 3.01-3.06 (m, 1H), 2.73-2.78 (m, 1H), 2.26 (t, *J* = 16.0 Hz, 3H), 2.15 (s, 3H). LC-MS: m/z 543 [M+H]⁺.

Example 121: ^1H NMR (400 MHz, Chloroform- d) δ 8.71 (s, 1H), 8.67 (s, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 7.95 (s, 2H), 7.85 (s, 1H), 7.66 (s, 1H), 6.35 (d, J = 4.8 Hz, 1H), 4.43-4.49 (m, 1H), 3.01-3.08 (m, 1H), 2.74-2.82 (m, 1H), 2.25 (t, J = 16.0 Hz, 3H), 2.15 (s, 3H). LC-MS: m/z 543 $[\text{M}+\text{H}]^+$.

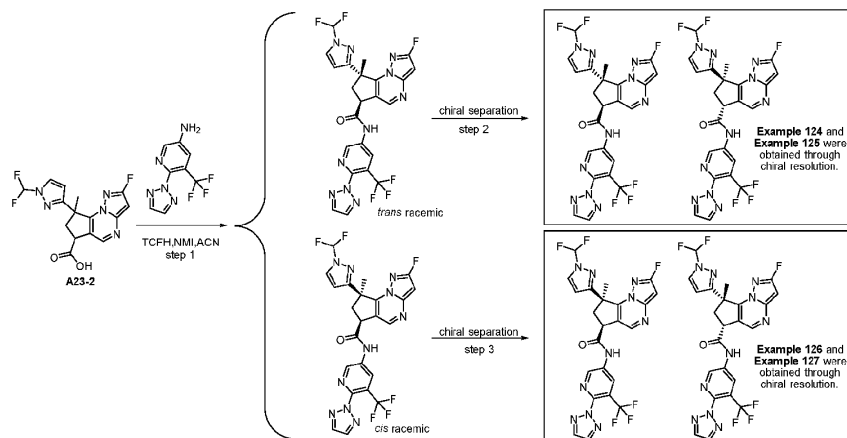
5 Step 10: Separation of enantiomers to obtain **Example 122** and **Example 123**

cis-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (30 mg, 55 μmol) was submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm ; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile
10 Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.855; RT2(min): 11.409; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 2) The first eluting isomer was concentrated and lyophilized to afford **Example 122** (14.3 mg, 46% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 123** (11.8 mg, 39% yield) as a white
15 solid.

Example 122 : ^1H NMR (400 MHz, Chloroform- d) δ 8.72 (s, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 7.94-7.98 (m, 4H), 7.75 (s, 1H), 6.37 (d, J = 5.2 Hz, 1H), 4.43-4.47 (m, 1H), 3.04-3.08 (m, 1H), 2.88-2.94 (m, 1H), 2.25 (t, J = 16.0 Hz, 3H), 2.04 (s, 3H). LC-MS: m/z 543 $[\text{M}+\text{H}]^+$.

Example 123: ^1H NMR (400 MHz, Chloroform- d) δ 8.68 (s, 1H), 8.59 (s, 1H), 8.44 (s, 20 1H), 7.90-7.96 (m, 4H), 7.75 (s, 1H), 6.35 (d, J = 4.8 Hz, 1H), 4.40-4.46 (m, 1H), 3.02-3.08 (m, 1H), 2.87-2.94 (m, 1H), 2.25 (t, J = 16.0 Hz, 3H), 2.03 (s, 3H). LC-MS: m/z 543 $[\text{M}+\text{H}]^+$.

Method A34



Examples 124, 125: (6*S*,8*S*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 126, 127: (6*S*,8*R*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*S*,8*R*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: (*trans*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A23-2**, 70 mg, 199 μ mol) and 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine (68.5 mg, 299 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (30 mg, 26%

yield) as a white solid, LC-MS (ES, m/z): 563[M+H]⁺; *cis*-isomer (20 mg, 16% yield) as a white solid, LC-MS (ES, m/z): 563[M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 124** and **Example 125**

30 mg of (*trans*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.954; 10 RT2(min): 13.761; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 124** (10.0 mg, 33% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 125** (12.6 mg, 40% yield) as a white solid.

Example 124: ¹H NMR (400 MHz, DMSO-d₆) δ 11.28 (s, 1H), 9.03 (d, J = 2.4 Hz, 1H), 15 8.83 (d, J = 2.8 Hz, 1H), 8.74 (s, 1H), 8.20 (d, J = 2.8 Hz, 2H), 8.19 (s, 2H), 7.70 (t, J = 59.2 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 5.2 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 3.02-3.07 (m, 1H), 2.57-2.62 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 563 [M+H]⁺.

Example 125: ¹H NMR (400 MHz, DMSO-d₆) δ 11.28 (s, 1H), 9.03 (d, J = 2.4 Hz, 1H), 8.84 (d, J = 2.8 Hz, 1H), 8.74 (s, 1H), 8.20 (d, J = 2.8 Hz, 3H), 8.19 (s, 2H), 7.70 (t, J = 59.2 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 5.2 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 3.02-3.07 (m, 1H), 2.57-2.62 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 563 [M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 126** and **Example 127**

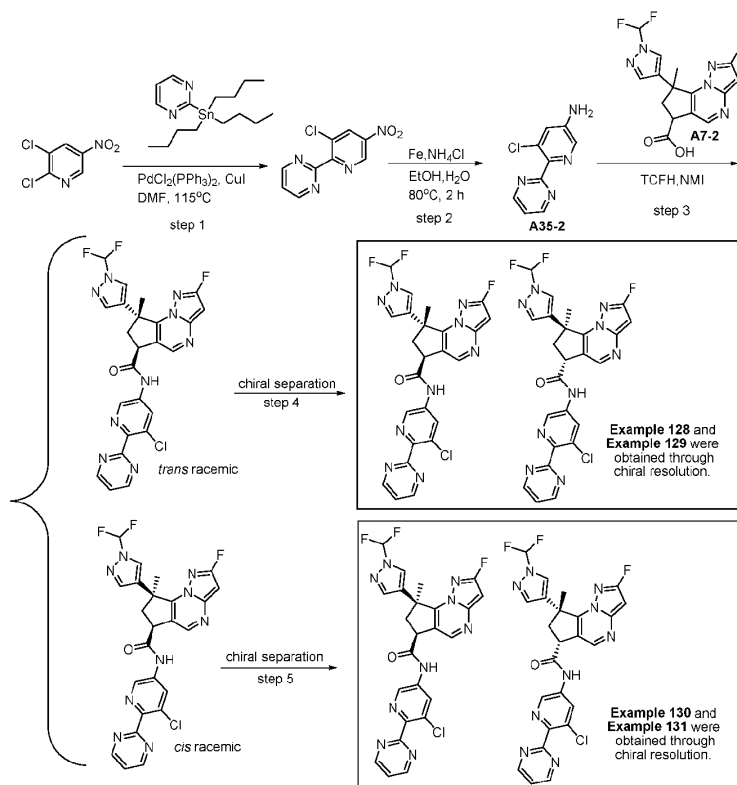
20 mg of (*cis*)-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 20% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.056; RT2(min): 8.952; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 30 3). The second eluting isomer was concentrated and lyophilized to afford **Example 126** (4.7 mg,

23% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 127** (6.2 mg, 30% yield) as a white solid.

Example 126: ^1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 9.00 (d, J = 2.4 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H), 8.74 (s, 1H), 8.19 (s, 2H), 8.14 (d, J = 2.8 Hz, 1H), 7.68 (t, J = 59.2 Hz, 1H), 6.57 (d, J = 4.8 Hz, 1H), 6.50 (d, J = 2.8 Hz, 1H), 4.58-4.62 (m, 1H), 2.91-2.96 (m, 1H), 2.80-2.86 (m, 1H), 1.92 (s, 3H). LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

Example 127: ^1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 9.00 (d, J = 2.4 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H), 8.74 (s, 1H), 8.19 (s, 2H), 8.14 (d, J = 2.8 Hz, 1H), 7.68 (t, J = 59.2 Hz, 1H), 6.57 (d, J = 4.8 Hz, 1H), 6.50 (d, J = 2.8 Hz, 1H), 4.58-4.62 (m, 1H), 2.91-2.96 (m, 1H), 2.80-2.86 (m, 1H), 1.92 (s, 3H). LC-MS: m/z 563 $[\text{M}+\text{H}]^+$.

Method A35



Examples 128, 129: (6*S*,8*R*)-*N*-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(5-chloro-6-(pyrimidin-

2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 130, 131: (6*S*,8*S*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(3-chloro-5-nitro-2-pyridyl)pyrimidine

To a stirred mixture of 2,3-dichloro-5-nitro-pyridine (600 mg, 3.1 mmol) and tributyl(pyrimidin-2-yl)stannane (1.3 g, 3.4 mmol) in DMF (10 mL) was added iodocopper (118 mg, 622 μ mol) and bis(triphenylphosphine)palladium(II) chloride (436 mg, 622 μ mol). The resulting mixture was stirred at 120 °C for 16 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography to afford the title compound (410 mg, 55% yield) as a yellow solid. LC-MS: *m/z* 237 [M+H]⁺.

Step 2: 5-chloro-6-pyrimidin-2-yl-pyridin-3-amine (**A35-2**)

In analogy to **Method A30 step 13** but using 2-(3-chloro-5-nitro-2-pyridyl)pyrimidine (390 mg, 1.6 mmol), the title compound was obtained as a yellow solid (**A35-2**, 100 mg, 29% yield) as a yellow solid. LC-MS: *m/z* 207 [M+H]⁺.

Step 3: *trans*-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 5-chloro-6-pyrimidin-2-yl-pyridin-3-amine (**A35-2**, 80 mg, 387 μ mol) and 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**, 136 mg, 387 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (20 mg, 16% yield) as a white solid, LC-MS: *m/z* 540 [M+H]⁺; *cis*-isomer (20 mg, 16% yield), LC-MS: *m/z* 540 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 128** and **Example 129**

Trans-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (20 mg, 37 μ mol) was submitted to chiral HPLC purification (Column: CHIRALPAK ID, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.83; RT2(min): 9.43; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 128** (6.0 mg, 29% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 129** (4.3 mg, 21% yield) as a white solid.

Example 128: ^1H NMR (400 MHz, DMSO- d_6) δ 10.96 (s, 1H), 8.98 (d, J = 5.2 Hz, 2H), 8.79 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 7.84 (s, 1H), 7.73 (t, J = 58.8 Hz, 1H), 7.62 (t, J = 5.2 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.56 (t, J = 8.4 Hz, 1H), 2.92-2.98 (m, 1H), 2.55-2.60 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 540 [M+H] $^+$.

Example 129: ^1H NMR (400 MHz, DMSO- d_6) δ 10.94 (s, 1H), 8.98 (d, J = 5.2 Hz, 2H), 8.79 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.21 (s, 1H), 7.84 (s, 1H), 7.73 (t, J = 58.8 Hz, 1H), 7.62 (t, J = 4.8 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.55 (t, J = 8.4 Hz, 1H), 2.92-2.98 (m, 1H), 2.55-2.60 (m, 1H), 2.00 (s, 3H).. LC-MS: m/z 540 [M+H] $^+$.

Step 5: Separation of enantiomers to obtain **Example 130** and **Example 131**

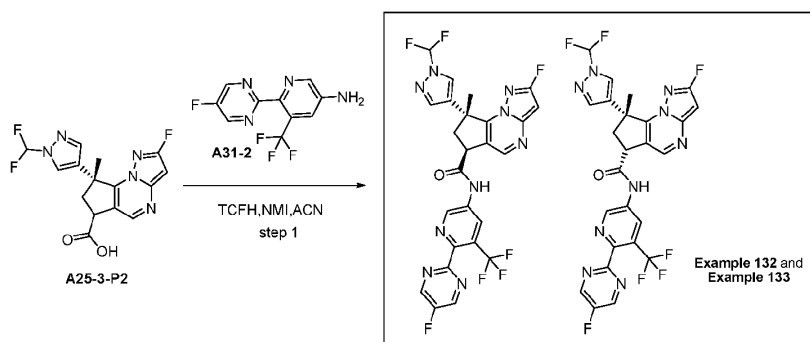
Cis-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (20 mg, 37 μ mol) was submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 9.18; RT2(min): 19.56; Sample Solvent: EtOH--HPLC; Injection Volume: 1.8 mL; Number Of Runs: 1). The first eluting isomer was concentrated and lyophilized to afford **Example 130** (2.0 mg, 10% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 131** (2.0 mg, 10% yield) as a white solid.

Example 130: ^1H NMR (400 MHz, DMSO- d_6) δ 10.98 (s, 1H), 8.98 (d, J = 5.2 Hz, 2H), 8.78 (d, J = 2.0 Hz, 1H), 8.75 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 7.77 (s, 1H), 7.74 (t,

$J = 58.8$ Hz, 1H), 7.61 (t, $J = 4.8$ Hz, 1H), 6.58 (d, $J = 4.8$ Hz, 1H), 4.53-4.58 (m, 1H), 2.82-2.90 (m, 1H), 2.71-2.78 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 540 $[M+H]^+$.

Example 131: ^1H NMR (400 MHz, DMSO- d_6) δ 10.94 (s, 1H), 8.98 (d, $J = 5.2$ Hz, 2H), 8.78 (d, $J = 2.0$ Hz, 1H), 8.75 (s, 1H), 8.42 (d, $J = 2.0$ Hz, 1H), 8.19 (s, 1H), 7.77 (s, 1H), 7.74 (t, $J = 58.8$ Hz, 1H), 7.60 (t, $J = 4.8$ Hz, 1H), 6.58 (d, $J = 4.8$ Hz, 1H), 4.53-4.58 (m, 1H), 2.82-2.90 (m, 1H), 2.71-2.78 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 540 $[M+H]^+$.

Method A36



Examples 132, 133: (6*S*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-*N*-(6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

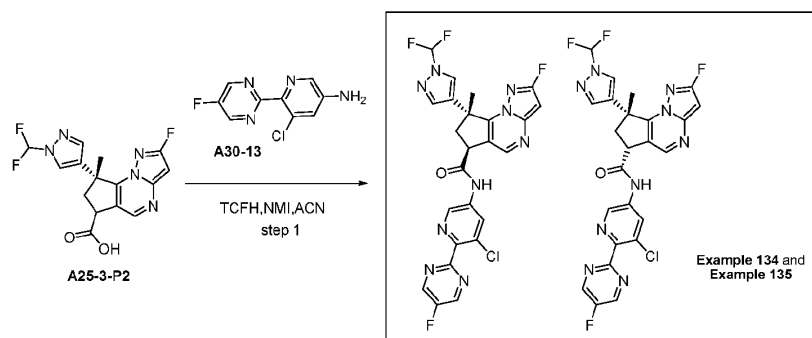
Step 1: Example 132 and Example 133

In analogy to **Method A1 step 8** but using 6-(5-fluoropyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A31-2**, 80 mg, 310 μmol) and (8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A25-3-P2**, 91 mg, 259 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 132** (11.5 mg, 7% yield) as a white solid and *cis*-isomer **Example 133** (15.7 mg, 10% yield) as a white solid.

Example 132: ^1H NMR (400 MHz, DMSO- d_6) δ 11.11 (s, 1H), 9.08 (s, 3H), 8.71-8.73 (m, 2H), 8.21 (s, 1H), 7.84 (s, 1H), 7.73 (t, $J = 58.8$ Hz, 1H), 6.59 (d, $J = 5.2$ Hz, 1H), 4.58 (t, $J = 8.2$ Hz, 1H), 2.92-2.98 (m, 1H), 2.58-2.63 (m, 1H), 2.01 (s, 3H). LC-MS: m/z 592 $[M+H]^+$.

Example 133: ^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1H), 9.08 (s, 3H), 8.77 (s, 1H), 8.66 (s, 1H), 8.18 (s, 1H), 7.78 (s, 1H), 7.73 (t, J = 58.8 Hz, 1H), 6.59 (d, J = 4.8 Hz, 1H), 4.58 (t, J = 8.2 Hz, 1H), 2.84-2.90 (m, 1H), 2.75-2.80 (m, 1H), 1.92 (s, 3H). LC-MS: m/z 592 $[\text{M}+\text{H}]^+$.

Method A37



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Examples 134, 135: (6*S*,8*R*)-*N*-(5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide, (6*R*,8*R*)-*N*-(5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

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The relative and absolute stereochemistry of each example was not determined.

Step 1: Example 134 and Example 135

In analogy to **Method A1 step 8** but using 5-chloro-6-(5-fluoropyrimidin-2-yl)pyridin-3-amine (**A30-13**, 90 mg, 401 μmol) and (8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A25-3-P2**, 94 mg, 267 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 134** (5.9 mg, 4% yield) as an off-white solid and *cis*-isomer **Example 135** (4.8 mg, 3% yield) as an off-white solid.

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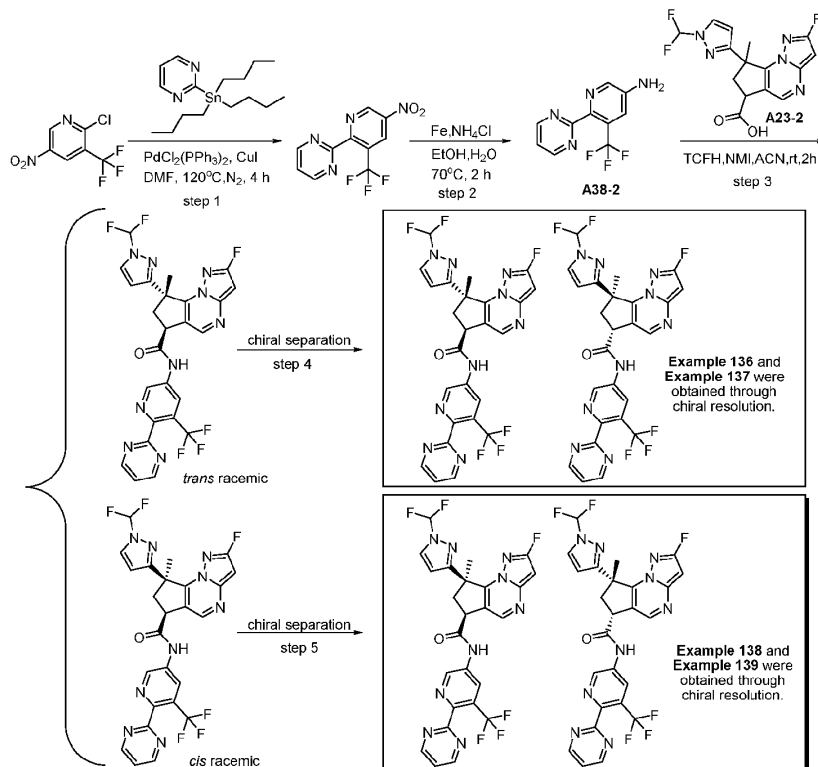
Example 134: ^1H NMR (400 MHz, DMSO- d_6) 10.98 (s, 1H), 9.08 (s, 2H), 8.79 (d, J = 2.4 Hz, 1H), 8.75 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.19 (s, 1H), 7.77 (s, 1H), 7.74 (t, J = 59.2 Hz, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.57 (t, J = 8.2 Hz, 1H), 2.83-2.89 (m, 1H), 2.72-2.78 (m, 1H), 1.91 (s, 3H). LC-MS: m/z 558 $[\text{M}+\text{H}]^+$.

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Example 135: ^1H NMR (400 MHz, DMSO- d_6) δ 11.05 (s, 1H), 9.08 (s, 2H), 8.80 (d, J = 2.0 Hz, 1H), 8.70 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.84 (s, 1H), 7.73 (t, J = 59.2 Hz,

1H), 6.59 (d, J = 4.8 Hz, 1H), 4.57 (t, J = 8.2 Hz, 1H), 2.91-2.98 (m, 1H), 2.55-2.61 (m, 1H), 2.00 (s, 3H). LC-MS: m/z 558 [M+H]⁺.

Method A38



5 **Examples 136, 137:** (6*S*,8*S*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide, (6*R*,8*R*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

10 **Examples 138, 139:** (6*S*,8*R*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide, (6*R*,8*S*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

15 The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine

In analogy to **Method A35 step 1** but using 2-chloro-5-nitro-3-(trifluoromethyl)pyridine (1.2 g, 5.2 mmol) and stirring at 120 °C for 3 h, the title compound was obtained as a yellow solid (740 mg, 47% yield). LC-MS (ES, m/z): 271 [M+H]⁺.

5 Step 2: 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**)

To a stirred solution of a mixture of 2-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyrimidine (900 mg, 3.3 mmol) in EtOH (45 mL) and water (45 mL) was added Fe (744 mg, 13.3 mmol) and NH₄Cl (713 mg, 13.3 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was
10 purified by prep-HPLC to afford the title compound (**A38-2**, 580 mg, 71% yield) as a yellow solid. LC-MS: m/z 241 [M+H]⁺.

Step 3: (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide
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In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A23-2**, 150 mg, 427 μmol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**,
20 123 mg, 512 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (30 mg, 11% yield) as a white solid, LC-MS (ES, m/z): 574[M+H]⁺; *cis*-isomer (20 mg, 7% yield) as a white solid, LC-MS (ES, m/z): 574[M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 136** and **Example 137**

30 mg of (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 70% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.369; RT2(min): 6.209; Sample Solvent: EtOH--HPLC; Injection
30 Volume: 0.9 mL; Number Of Runs: 3). The second eluting isomer was concentrated and

lyophilized to afford **Example 136** (10.2 mg, 32% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 137** (13.3 mg, 42% yield) as a white solid.

Example 136: ^1H NMR (400 MHz, Chloroform- d) δ 9.20 (s, 1H), 9.05 (s, 1H), 8.96 (d, J = 4.8 Hz, 2H), 8.65 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.44 (t, J = 4.8 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 5.2 Hz, 1H), 4.64 (t, J = 7.2 Hz, 1H), 3.41-3.46 (m, 1H), 2.64-2.69 (m, 1H), 2.17 (s, 3H). LC-MS (ES, m/z): 574[M+H] $^+$.

Example 137: ^1H NMR (400 MHz, Chloroform- d) δ 9.00 (s, 1H), 8.95 (d, J = 5.2 Hz, 2H), 8.85 (s, 1H), 8.59 (s, 1H), 8.26 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.43 (t, J = 4.8 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 5.2 Hz, 1H), 4.56 (t, J = 8.4 Hz, 1H), 3.42-3.47 (m, 1H), 2.60-2.66 (m, 1H), 2.16 (s, 3H). LC-MS (ES, m/z): 574[M+H] $^+$.

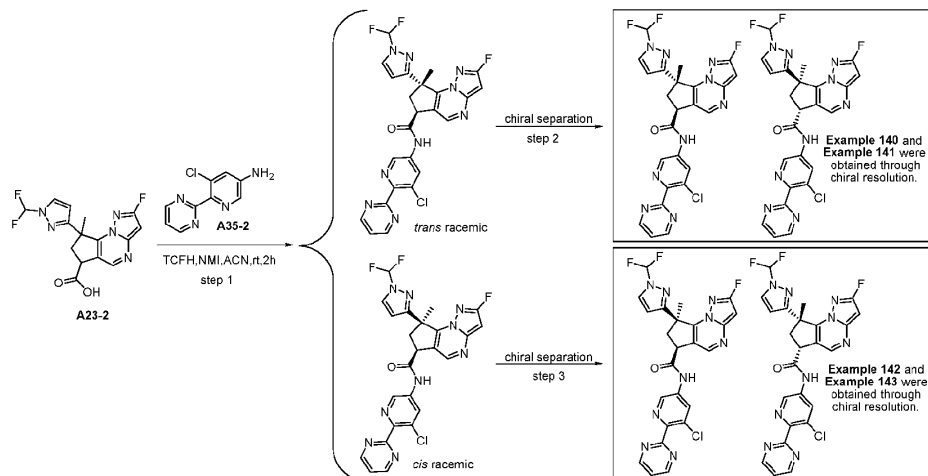
Step 5: Separation of enantiomers to obtain **Example 138** and **Example 139**

20 mg of (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm ; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 11.491; RT2(min): 16.05; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 3). The first eluting isomer was concentrated and lyophilized to afford **Example 138** (5.5 mg, 27% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 139** (4.7 mg, 23% yield) as a white solid.

Example 138: ^1H NMR (400 MHz, Chloroform- d) δ 9.62 (s, 1H), 9.01 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.68 (s, 1H), 8.61 (s, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.41 (t, J = 4.8 Hz, 1H), 6.99 (t, J = 60.8 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 5.2 Hz, 1H), 4.58-4.61 (m, 1H), 3.38-3.43 (m, 1H), 2.87-2.94 (m, 1H), 2.15 (s, 3H). LC-MS (ES, m/z): 574[M+H] $^+$.

Example 139: ^1H NMR (400 MHz, Chloroform- d) δ 10.09 (s, 1H), 9.18 (s, 1H), 8.96 (d, J = 4.8 Hz, 2H), 8.82 (s, 1H), 8.70 (s, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.44 (t, J = 4.4 Hz, 1H), 7.00 (t, J = 60.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 5.2 Hz, 1H), 4.62-4.66 (m, 1H), 3.38-3.42 (m, 1H), 2.88-2.94 (m, 1H), 2.12 (s, 3H). LC-MS (ES, m/z): 574[M+H] $^+$.

Method A39



Examples 140, 141: (6*S*,8*S*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 142, 143: (6*S*,8*R*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: (*trans*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

In analogy to Method A1 step 8 but using 8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (A23-2, 150 mg, 427 μ mol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (A35-2, 132 mg, 640 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (45 mg,

19% yield) as a white solid, LC-MS (ES, m/z): 540[M+H]⁺; *cis*-isomer (10 mg, 4% yield) as a white solid, LC-MS (ES, m/z): 540[M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 140** and **Example 141**

45 mg of (*trans*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 60% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 4.274; RT2(min): 6.805; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 5). The second eluting isomer was concentrated and lyophilized to afford **Example 140** (8.2 mg, 17% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 141** (10.1 mg, 20% yield) as a white solid.

Example 140: ¹H NMR (400 MHz, Chloroform-d) δ 8.97 (d, J = 5.2 Hz, 2H), 8.76 (s, 1H), 8.71 (s, 1H), 8.58 (s, 1H), 8.29 (s, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.40 (t, J = 4.8 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 5.2 Hz, 1H), 4.55 (t, J = 8.4 Hz, 1H), 3.44-3.45 (m, 1H), 2.59-2.64 (m, 1H), 2.16 (s, 3H). LC-MS (ES, m/z): 540[M+H]⁺.

Example 141: ¹H NMR (400 MHz, Chloroform-d) δ 8.97 (d, J = 4.8 Hz, 2H), 8.77 (s, 1H), 8.73 (s, 1H), 8.59 (s, 1H), 8.26 (s, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.40 (t, J = 4.8 Hz, 1H), 7.06 (t, J = 60.8 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 4.8 Hz, 1H), 4.56 (t, J = 8.4 Hz, 1H), 3.40-3.46 (m, 1H), 2.59-2.65 (m, 1H), 2.16 (s, 3H). LC-MS (ES, m/z): 540[M+H]⁺.

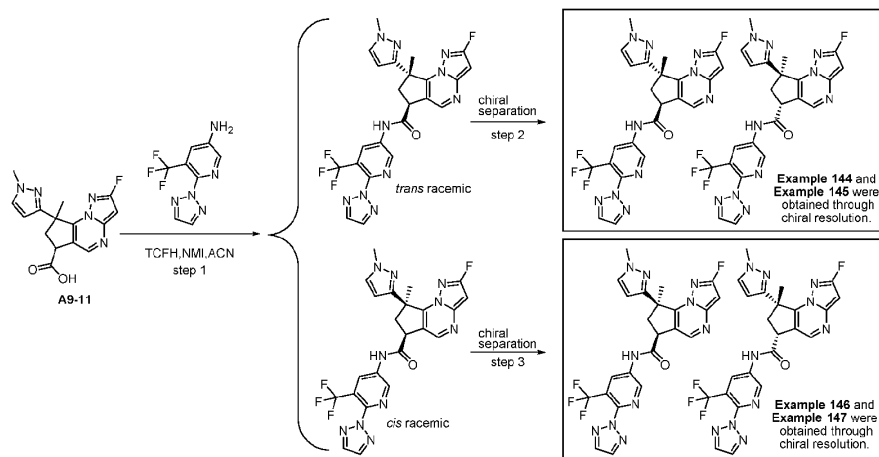
Step 3: Separation of enantiomers to obtain **Example 142** and **Example 143**

20 mg of (*cis*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.321; RT2(min): 10.659; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 142** (2.8 mg, 27% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 143** (2.4 mg, 23% yield) as a white solid.

Example 142: ^1H NMR (400 MHz, Chloroform- d) δ 9.57 (s, 1H), 8.96 (d, J = 4.8 Hz, 2H), 8.69 (s, 1H), 8.66 (s, 1H), 8.53 (s, 1H), 7.81 (d, J = 2.8 Hz, 1H), 7.39 (t, J = 4.8 Hz, 1H), 7.01 (t, J = 60.8 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.30 (d, J = 5.2 Hz, 1H), 4.54-4.60 (m, 1H), 3.35-3.40 (m, 1H), 2.86-2.92 (m, 1H), 2.13 (s, 3H). LC-MS (ES, m/z): 540 $[M+H]^+$.

5 **Example 143:** ^1H NMR (400 MHz, Chloroform- d) δ 10.23 (s, 1H), 8.92-8.99 (m, 3H), 8.78 (s, 1H), 8.67 (s, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.42 (t, J = 4.8 Hz, 1H), 7.02 (t, J = 60.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.29 (d, J = 5.2 Hz, 1H), 4.59-4.66 (m, 1H), 3.34-3.38 (m, 1H), 2.88-2.94 (m, 1H), 2.10 (s, 3H). LC-MS (ES, m/z): 540 $[M+H]^+$.

Method A40



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Examples 144, 145: (6*S*,8*S*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide, (6*R*,8*R*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

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Examples 146, 147: (6*S*,8*R*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-*N*-(6-(2*H*-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

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The relative and absolute stereochemistry of each example was not determined.

Step 1: *Trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A9-11**, 85 mg, 270 μ mol) and 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine (124 mg, 539 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (20 mg, 14% yield) as a white solid, LC-MS: m/z 527 $[M+H]^+$; *cis*-isomer (6 mg, 4% yield) as a white solid, LC-MS: m/z 527 $[M+H]^+$.

Step 2: Separation of enantiomers to obtain **Example 144** and **Example 145**

20 mg of *trans*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.22; RT2(min): 7.789; Sample Solvent: EtOH--HPLC; Sample concentration: mg/mL; Injection Volume: 2.0 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 144** (7.6 mg, 38% yield) as a white solid. The first second eluting isomer was concentrated and lyophilized to afford **Example 145** (6.6 mg, 33% yield) as a white solid.

Example 144: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, J = 2.4 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.57 (s, 1H), 8.29 (s, 1H), 7.97 (s, 2H), 7.31 (d, J = 2.4 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 5.2 Hz, 1H), 4.65 (t, J = 8.6 Hz, 1H), 3.87 (s, 3H), 3.47-3.52 (m, 1H), 2.54-2.59 (m, 1H), 2.14 (s, 3H). LC-MS: m/z 527 $[M+H]^+$.

Example 145: ^1H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, J = 2.4 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.57 (s, 1H), 8.30 (s, 1H), 7.97 (s, 2H), 7.32 (d, J = 2.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 5.2 Hz, 1H), 4.64-4.68 (m, 1H), 3.88 (s, 3H), 3.47-3.52 (m, 1H), 2.54-2.69 (m, 1H), 2.14 (s, 3H). LC-MS: m/z 527 $[M+H]^+$.

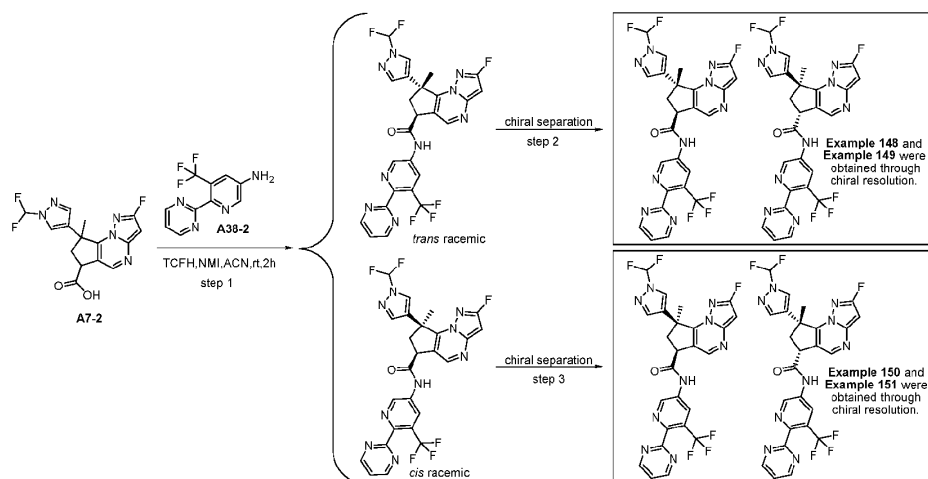
Step 3: Separation of enantiomers to obtain **Example 146** and **Example 147**

6 mg of *cis*-N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-2-fluoro-8-methyl-8-(1-methyl-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 10% Mobile Phase B; Wave Length: 254/220nm; RT1(min): 8.881; RT2(min): 11.324; Sample Solvent: EtOH--HPLC; Sample concentration: mg/mL; Injection Volume: 2.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 146** (2.4 mg, 39% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 147** (2.1 mg, 35% yield) as a white solid.

Example 146: ^1H NMR (400 MHz, Chloroform-*d*) δ 10.80 (s, 1H), 8.88 (d, *J* = 2.0 Hz, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.63 (s, 1H), 7.94 (s, 2H), 7.40 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 5.2 Hz, 1H), 4.55-4.58 (m, 1H), 3.85 (s, 3H), 3.27-3.32 (m, 1H), 2.85-2.91 (m, 1H), 2.13 (s, 3H). LC-MS: *m/z* 527 [M+H] $^+$.

Example 147: ^1H NMR (400 MHz, Chloroform-*d*) δ 10.80 (s, 1H), 8.87 (d, *J* = 2 Hz, 1H), 8.73 (d, *J* = 2 Hz, 1H), 8.63 (s, 1H), 7.94 (s, 2H), 7.39 (d, *J* = 2 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 4.8 Hz, 1H), 4.55-4.58 (m, 1H), 3.84 (s, 3H), 3.28-3.30 (m, 1H), 2.84-2.91 (m, 1H), 2.13 (s, 3H). LC-MS: *m/z* 527 [M+H] $^+$.

Method A41



Examples 148, 149: (6*S*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 150, 151: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: *Trans*-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and *cis*-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A7-2**, 120 mg, 342 μ mol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**, 123 mg, 512 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (20 mg, 10%

yield) as an off-white solid, LC-MS: m/z 574 [M+H]⁺; *cis*-isomer (18 mg, 9% yield) as an off-white solid, LC-MS: m/z 574 [M+H]⁺.

Step 2: Separation of enantiomers to obtain **Example 148** and **Example 149**

17 mg of *trans*-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK ID, 2*25 cm, 5 µm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.34; RT2(min): 14.14; Sample Solvent: EtOH--HPLC; Injection Volume: 1.55 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 148** (2.6 mg, 15% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 149** (2.0 mg, 11% yield) as a white solid.

Example 148: ¹H NMR (400 MHz, DMSO-d₆) δ 11.12 (s, 1H), 9.07 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 4.8 Hz, 2H), 8.73 (s, 1H), 8.71 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.84 (s, 1H), 7.73 (t, J = 59.2 Hz, 1H), 7.64 (t, J = 5.2 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.58 (t, J = 8.2 Hz, 1H), 2.96 (dd, J = 13.2, 8.0 Hz, 1H), 2.61 (dd, J = 13.2, 8.0 Hz, 1H), 2.00 (s, 3H). LC-MS: m/z 574 [M+H]⁺.

Example 149: ¹H NMR (400 MHz, DMSO-d₆) δ 11.16 (s, 1H), 9.07 (d, J = 2.3 Hz, 1H), 8.97 (d, J = 5.2 Hz, 2H), 8.73 (s, 1H), 8.71 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.85 (s, 1H), 7.73 (t, J = 59.2 Hz, 1H), 7.64 (t, J = 5.2 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.59 (t, J = 8.0 Hz, 1H), 2.96 (dd, J = 13.2, 8.0 Hz, 1H), 2.61 (dd, J = 13.2, 8.0 Hz, 1H), 2.01 (s, 3H). LC-MS: m/z 574 [M+H]⁺.

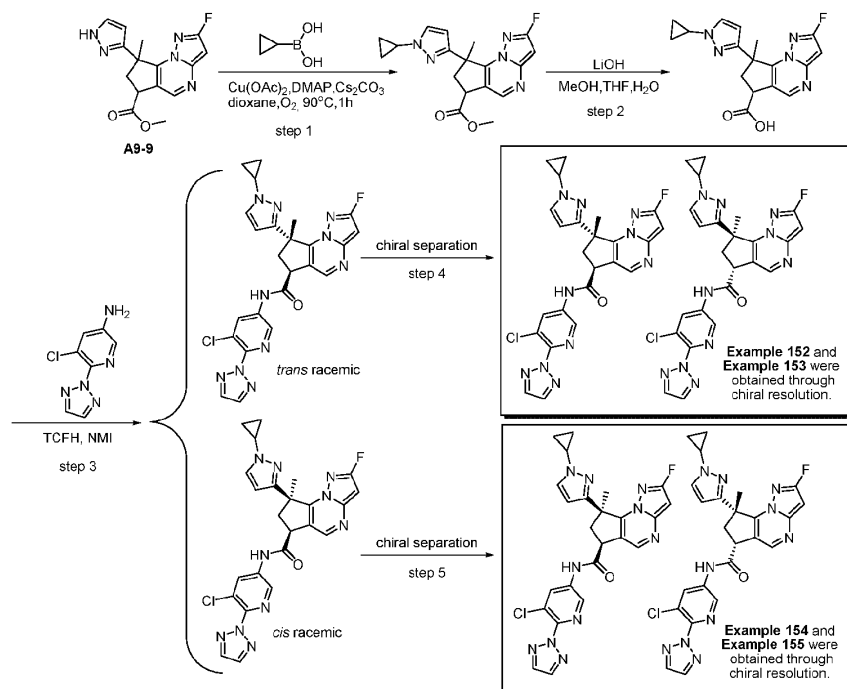
Step 3: Separation of enantiomers to obtain **Example 150** and **Example 151**

18 mg of *cis*-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose SC, 2*25 cm, 5 µm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.44; RT2(min): 10.21; Sample Solvent: EtOH--HPLC; Injection Volume: 0.9 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 150** (2.2 mg, 12% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 151** (2.3 mg, 12% yield) as a white solid.

Example 150: ^1H NMR (400 MHz, DMSO- d_6) δ 11.09 (s, 1H), 9.06 (d, $J = 2.3$ Hz, 1H), 8.97 (d, $J = 4.8$ Hz, 2H), 8.77 (s, 1H), 8.67 (d, $J = 2.3$ Hz, 1H), 8.19 (s, 1H), 7.78 (s, 1H), 7.73 (t, $J = 59.2$ Hz, 1H), 7.64 (t, $J = 4.8$ Hz, 1H), 6.59 (d, $J = 4.4$ Hz, 1H), 4.55-4.60 (m, 1H), 2.84-2.90 (m, 1H), 2.74-2.80 (m, 1H), 1.92 (s, 3H). LC-MS: m/z 574 $[\text{M}+\text{H}]^+$.

5 **Example 151:** ^1H NMR (400 MHz, DMSO- d_6) δ 11.09 (s, 1H), 9.06 (d, $J = 2.3$ Hz, 1H), 8.97 (d, $J = 5.2$ Hz, 2H), 8.77 (s, 1H), 8.66 (d, $J = 2.3$ Hz, 1H), 8.19 (s, 1H), 7.79 (s, 1H), 7.73 (t, $J = 59.2$ Hz, 1H), 7.64 (t, $J = 4.8$ Hz, 1H), 6.58 (d, $J = 4.8$ Hz, 1H), 4.56-4.60 (m, 1H), 2.84-2.88 (m, 1H), 2.74-2.80 (m, 1H), 1.92 (s, 3H). LC-MS: m/z 574 $[\text{M}+\text{H}]^+$.

Method A42



10 **Examples 152, 153:** (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

15 **Examples 154, 155:** (6*S*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

a]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

5 Step 1: Methyl 8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate

In analogy to **Method A8 step 1** but using methyl 2-fluoro-8-methyl-8-(1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**A9-9**, 280 mg, 622 μ mol), the title compound was obtained as a white solid (90 mg, 41% yield). LC-MS: *m/z* 356
10 [M+H]⁺.

Step 2: 8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid

In analogy to **Method A7 step 2** but using methyl 8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (90 mg, 253 μ mol), the crude title compound was obtained as a white solid (75 mg, 86% yield). LC-MS:
15 *m/z* 342 [M+H]⁺.

Step 3: *Trans*-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide
20

In analogy to **Method A1 step 8** but using 8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (75 mg, 131.8 mmol) and 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine (31 mg, 158 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (40 mg, 58% yield) as a white solid, LC-MS: *m/z* 519 [M+H]⁺; *cis*-isomer (20 mg, 29% yield) as a white solid, LC-MS: *m/z* 519
25 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 152** and **Example 153**

40 mg of *trans*-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5
30

µm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 18ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.56; RT2(min): 12.048; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford

5 **Example 152** (17.2 mg, 43% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 153** (17.3 mg, 43% yield) as a white solid.

Example 152: ¹H NMR (400 MHz, DMSO-d₆) δ: 11.13 (s, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.17 (s, 2H), 7.67 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 4.50-4.54 (m, 1H), 3.52-3.62 (m, 1H), 3.01-3.10 (m, 1H), 2.43-2.51
10 (m, 1H), 1.98 (s, 3H), 0.82-0.97 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Example 153: ¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (s, 2H), 7.67 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 4.48-4.57 (m, 1H), 3.52-3.62 (m, 1H), 3.00-3.11 (m, 1H), 2.43-2.52
(m, 1H), 1.99 (s, 3H), 0.82-0.97 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

15 Step 5: Separation of enantiomers to obtain **Example 154** and **Example 155**

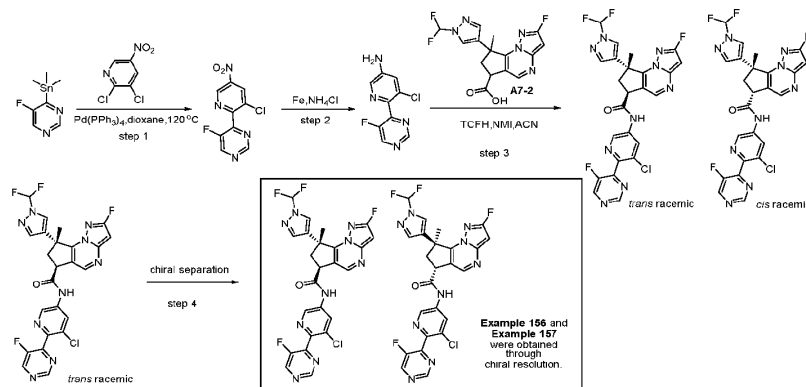
20 mg of *cis*-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-cyclopropyl-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 µm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow
20 rate: 20ML/MIN mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.556; RT2(min): 10.156; Sample Solvent: EtOH--HPLC; Injection Volume: 0.7 mL; Number Of Runs: 5). The first eluting isomer was concentrated and lyophilized to afford **Example 154** (5.8 mg, 29% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 155** (4.5 mg, 22% yield) as a white solid.

25 **Example 154:** ¹H NMR (400 MHz, DMSO-d₆) δ 10.96 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.67 (s, 1H), 8.58 (d, J = 2.4 Hz, 1H), 8.17 (s, 2H), 7.62 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 4.8 Hz, 1H), 6.20 (d, J = 2.0 Hz, 1H), 4.51-4.55 (m, 1H), 3.47-3.57 (m, 1H), 2.95-3.05 (m, 1H), 2.70-2.80 (m, 1H), 1.88 (s, 3H), 0.72-0.88 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Example 155: ¹H NMR (400 MHz, DMSO-d₆) δ: 10.96 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H),
30 8.67 (s, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.17 (s, 2H), 7.62 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 5.2 Hz,

1H), 6.20 (d, J = 2.4 Hz, 1H), 4.49-4.57 (m, 1H), 3.47-3.58 (m, 1H), 2.95-3.04 (m, 1H), 2.70-2.80 (m, 1H), 1.88 (s, 3H), 0.72-0.89 (m, 4H). LC-MS: m/z 519 [M+H]⁺.

Method A43



- 5 **Examples 156, 157: (6*S*,8*R*)-N-(5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide**

10 The relative and absolute stereochemistry of each example was not determined.

Step 1: 4-(3-chloro-5-nitropyridin-2-yl)-5-fluoropyrimidine

In analogy to **Method A32 step 2** but using 2,3-dichloro-5-nitropyridine (3.4 g, 17.6 mmol) in dioxane (20 mL) and 5-fluoro-4-(trimethylstannyl)pyrimidine (**A32-1**, 2 g, 7.7 mmol), the title compound was obtained as a yellow solid (1.3 g, 61% yield). LC-MS: m/z 255 [M+H]⁺.

15 Step 2: 5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-amine

In analogy to **Method A30 step 13** but using 4-(3-chloro-5-nitropyridin-2-yl)-5-fluoropyrimidine (0.2 g, 785 μmol), the title compound was obtained as a yellow solid (150 mg, 79% yield). LC-MS: m/z 225 [M+H]⁺.

20 Step 3: *Trans*-N-(5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*c*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and *cis*-N-(5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A7-2**, 90 mg, 256 μ mol) and 5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-amine (69 mg, 307 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (8.5 mg, 5% yield) as a white solid, LC-MS: m/z 558 [M+H]⁺; *cis*-isomer (2.8 mg, 2% yield) as a white solid, LC-MS: m/z 558 [M+H]⁺.

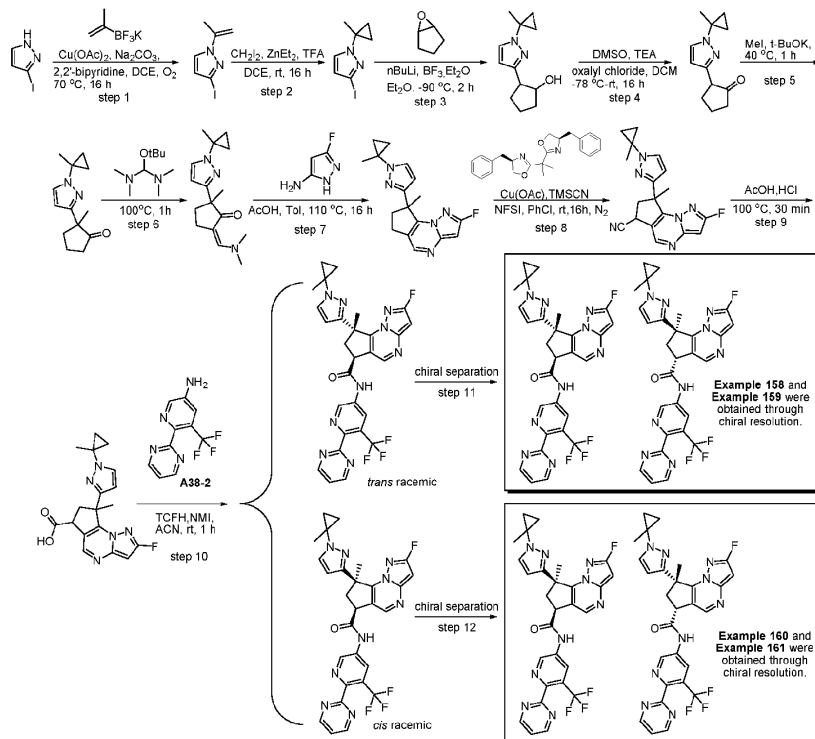
Step 4: Separation of enantiomers to obtain **Example 156** and **Example 157**

7 mg of *trans*-N-(5-chloro-6-(5-fluoropyrimidin-4-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 8.17; RT2(min): 9.948; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 156** (2.5 mg, 33% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 157** (2.2 mg, 31% yield) as a white solid.

Example 156: ¹H NMR (400 MHz, DMSO-d₆) δ 11.09 (s, 1H), 9.24 (d, J = 2.8 Hz, 1H), 9.13 (d, J = 1.8 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 8.72 (s, 1H), 8.53 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 2.7 Hz, 1H), 7.70 (t, J = 59.1 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 4.9 Hz, 1H), 4.52 (t, J = 8.1 Hz, 1H), 3.00-3.06 (m, 1H), 2.55-2.60 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 558 [M+H]⁺.

Example 157: ¹H NMR (400 MHz, DMSO-d₆) δ 11.09 (s, 1H), 9.24 (d, J = 2.9 Hz, 1H), 9.13 (d, J = 1.8 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 8.72 (s, 1H), 8.53 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 2.7 Hz, 1H), 7.70 (t, J = 59.1 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 4.9 Hz, 1H), 4.52 (t, J = 8.1 Hz, 1H), 3.00-3.06 (m, 1H), 2.55-2.61 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 558 [M+H]⁺.

Method A44



Examples 158, 159: (6*S*,8*S*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 160, 161: (6*S*,8*R*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-iodo-1-(prop-1-en-2-yl)-1*H*-pyrazole

In analogy to Method A28 step 1 but using 3-iodo-1*H*-pyrazole (20 g, 103.1 mmol) and stirring at 70 °C for 16 h, the title compound was obtained as a yellow oil (7.3 g, 30% yield). ¹H

NMR (400 MHz, DMSO-d₆) δ : 8.02 (d, J = 2.8 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 5.37 (s, 1H), 4.71-4.76 (m, 1H), 2.18-2.23 (m, 3H). LC-MS (ES, m/z): 235[M+H]⁺.

Step 2: 3-iodo-1-(1-methylcyclopropyl)-1H-pyrazole

In analogy to **Method A28 step 2** but using 3-iodo-1-(prop-1-en-2-yl)-1H-pyrazole (7.3 g, 31.2 mmol), the title compound was obtained as a yellow solid (4.3 g, 55% yield). ¹H NMR (400 MHz, DMSO-d₆) δ : 7.71 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H), 1.53 (s, 3H), 1.12-1.17 (m, 2H), 0.86-0.91 (m, 2H). LC-MS (ES, m/z): 249[M+H]⁺.

Step 3: 2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-ol

In analogy to **Method A6 step 2** but using 3-iodo-1-(1-methylcyclopropyl)-1H-pyrazole (4.3 g, 17.3 mmol), the title compound was obtained as a yellow oil (0.6 g, 18% yield). LC-MS: m/z 207 [M+H]⁺.

Step 4: 2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one

To a stirred solution of oxalyl chloride (2.1 g, 17.0 mmol) in DCM (15 mL) was added DMSO (2.6 g, 33.9 mmol) in DCM (15 mL) under nitrogen at -78 °C. The resulting mixture was stirred at -78 °C for 0.5 h. A solution of 2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-ol (1.8 g, 8.5 mmol) in DCM (15 mL) was added slowly at -78 °C under nitrogen, and it was stirred at -78 °C for 30 min. Triethylamine (4.3 g, 42.4 mmol) was added dropwise at -78 °C under nitrogen. The mixture was allowed to warm to 25 °C and was stirred for 16 h. The reaction was quenched with water (30 mL), and the resulting mixture was extracted with DCM (3x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound (1.8 g) as a yellow oil, which was used in the next step without further purification. LC-MS: m/z 205 [M+H]⁺.

Step 5: 2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one

In analogy to **Method A1 step 3** but using 2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one (370 mg, 1.8 mmol) and purification of the product by reverse phase column chromatography, the title compound was obtained as a yellow oil (220 mg, 55% yield). LC-MS: m/z 219 [M+H]⁺.

Step 6: 5-((dimethylamino)methylene)-2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one (1.2 g, 5.5 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethyl-

methanediamine (1.9 g, 11.0 mmol) and stirring at 100 °C for 1, the crude title compound was obtained as a yellow oil (1.2 g, 79% yield), which was used in the next step without further purification. LC-MS: m/z 274 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)cyclopentan-1-one (1.2 g, 4.4 mmol), the title compound was obtained as a yellow solid (1 g, 73% yield). ¹H NMR (400 MHz, DMSO-d₆) δ: 8.59 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 4.8 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 3.01-3.10 (m, 2H), 2.58-2.69 (m, 1H), 2.20-2.32 (m, 1H), 1.86 (s, 3H), 1.44 (s, 3H), 1.01-1.06 (m, 2H), 0.75-0.83 (m, 2H). LC-MS: m/z 312 [M+H]⁺.

Step 8: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1.2 g, 3.8 mmol) in chlorobenzene (125 mL), the title compound was obtained as a yellow solid (340 mg, 13% yield). LC-MS: m/z 337 [M+H]⁺.

Step 9: 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A9 step 8** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (340 mg, 505 μmol), the title compound was obtained as a yellow oil (160 mg, 82% yield). LC-MS: m/z 356 [M+H]⁺.

Step 10: (*trans*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (150 mg, 422 μmol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**, 112 mg,

464 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (75 mg, 30% yield) as an off-white solid, LC-MS: m/z 578 $[M+H]^+$; *cis*-isomer (30 mg, 12% yield) as an off-white solid, LC-MS: m/z 578 $[M+H]^+$.

Step 11: Separation of enantiomers to obtain **Example 158** and **Example 159**

5 27 mg of (*trans*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 60% Mobile Phase B; Wave Length: 254/220
10 nm; RT1(min): 4.753; RT2(min): 7.829; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 158** (22.5 mg, 29% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 159** (30.2 mg, 40% yield) as a white solid.

Example 158: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.11 (s, 1H), 9.09 (d, J = 2.0 Hz, 1H),
15 8.98 (d, J = 4.8 Hz, 2H), 8.73 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.56 (d, J = 4.8 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 4.53 (t, J = 8.4 Hz, 1H), 3.11 (dd, J = 12.4, 8.0 Hz, 1H), 2.52-2.55 (m, 1H), 1.99 (s, 3H), 1.47 (s, 3H), 1.01-1.12 (m, 2H), 0.78-0.88 (m, 2H). LC-MS (ES, m/z): 578 $[M+H]^+$.

Example 159: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.11 (s, 1H), 9.10 (d, J = 2.0 Hz, 1H),
20 8.98 (d, J = 5.2 Hz, 2H), 8.73 (d, J = 2.4 Hz, 1H), 8.71 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.56 (d, J = 5.2 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 4.53 (t, J = 8.0 Hz, 1H), 3.11 (dd, J = 12.4, 8.0 Hz, 1H), 2.52-2.55 (m, 1H), 1.99 (s, 3H), 1.47 (s, 3H), 1.01-1.12 (m, 2H), 0.78-0.88 (m, 2H). LC-MS (ES, m/z): 578 $[M+H]^+$.

Step 12: Separation of enantiomers to obtain **Example 160** and **Example 161**

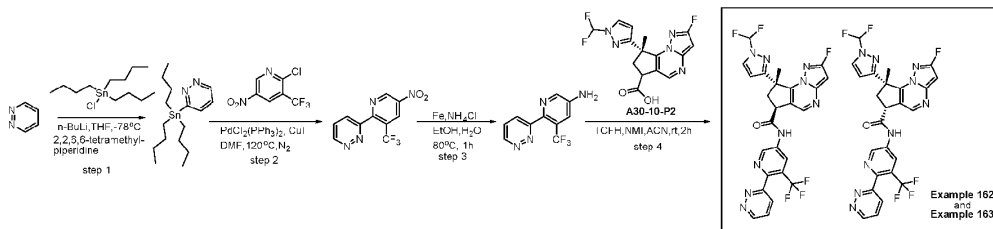
25 30 mg of (*cis*)-2-fluoro-8-methyl-8-(1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SZ, 3*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length:
30 254/220 nm; RT1(min): 9.733; RT2(min): 14.084; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized

to afford **Example 160** (11.7 mg, 38% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 161** (6.8 mg, 22% yield) as a white solid.

Example 160: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 10.93 (s, 1H), 9.07 (d, $J = 1.6$ Hz, 1H), 8.97 (d, $J = 5.2$ Hz, 2H), 8.72 (d, $J = 2.4$ Hz, 1H), 8.69 (s, 1H), 7.62-7.65 (m, 2H), 6.54 (d, $J = 4.8$ Hz, 1H), 6.24 (d, $J = 2.0$ Hz, 1H), 4.54 (dd, $J = 9.2, 4.8$ Hz, 1H), 3.13 (dd, $J = 13.2, 5.2$ Hz, 1H), 2.76 (dd, $J = 13.2, 9.6$ Hz, 1H), 1.89 (s, 3H), 1.35 (s, 3H), 0.88-1.01 (m, 2H), 0.58-0.70 (m, 2H). LC-MS (ES, m/z): 578 $[\text{M}+\text{H}]^+$.

Example 161: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 10.94 (s, 1H), 9.07 (s, 1H), 8.98 (d, $J = 4.8$ Hz, 2H), 8.72 (s, 1H), 8.69 (s, 1H), 7.60-7.67 (m, 2H), 6.54 (d, $J = 4.8$ Hz, 1H), 6.24 (d, $J = 2.0$ Hz, 1H), 4.54 (dd, $J = 9.2, 5.2$ Hz, 1H), 3.13 (dd, $J = 12.8, 4.8$ Hz, 1H), 2.76 (dd, $J = 13.2, 9.6$ Hz, 1H), 1.89 (s, 3H), 1.35 (s, 3H), 0.88-1.01 (m, 2H), 0.58-0.70 (m, 2H). LC-MS (ES, m/z): 578 $[\text{M}+\text{H}]^+$.

Method A45



Examples 162, 163: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(6-(pyridazin-3-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(6-(pyridazin-3-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-(tributylstannyl)pyridazine

To a solution of 2,2,6,6-tetramethylpiperidine (1.94 g, 13.7 mmol, 2.32 mL) in THF (80 mL) was added *n*-Butyllithium (5.5 mL, 2.5 M in hexanes) at -30°C . The mixture was stirred at 0°C for 30 min. A solution of pyridazine (1 g, 12.5 mmol) in THF (20 mL) and a solution of tributylchlorostannane (4.1 g, 12.5 mmol) in THF (20 mL) were added simultaneously at -78°C , and the mixture was stirred at -78°C for 4 h. The mixture was allowed to warm to 25°C and

quenched with aqueous saturated ammonium chloride (20 ml). The mixture was diluted with water (200 mL) and extracted with DCM (3x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with EA/PE (1:1) to afford the title compound (2.1 g, 45% yield) as a yellow oil. LC-MS (ES, m/z): 371 [M+H]⁺.

Step 2: 3-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyridazine

In analogy to **Method A30 step 12** but using 3-(tributylstannyl)pyridazine (1 g, 2.7 mmol) and 2-chloro-5-nitro-3-(trifluoromethyl)pyridine (614 mg, 2.7 mmol) and stirring at 120 °C for 1 h, the title compound was obtained as a yellow oil (120 mg, 16% yield). LC-MS (ES, m/z): 271 [M+H]⁺.

Step 3: 6-(pyridazin-3-yl)-5-(trifluoromethyl)pyridin-3-amine

In analogy to **Method A30 step 13** but using 3-(5-nitro-3-(trifluoromethyl)pyridin-2-yl)pyridazine (110 mg, 407 μmol), the title compound was obtained as a yellow oil (45 mg, 46% yield). LC-MS (ES, m/z): 241 [M+H]⁺.

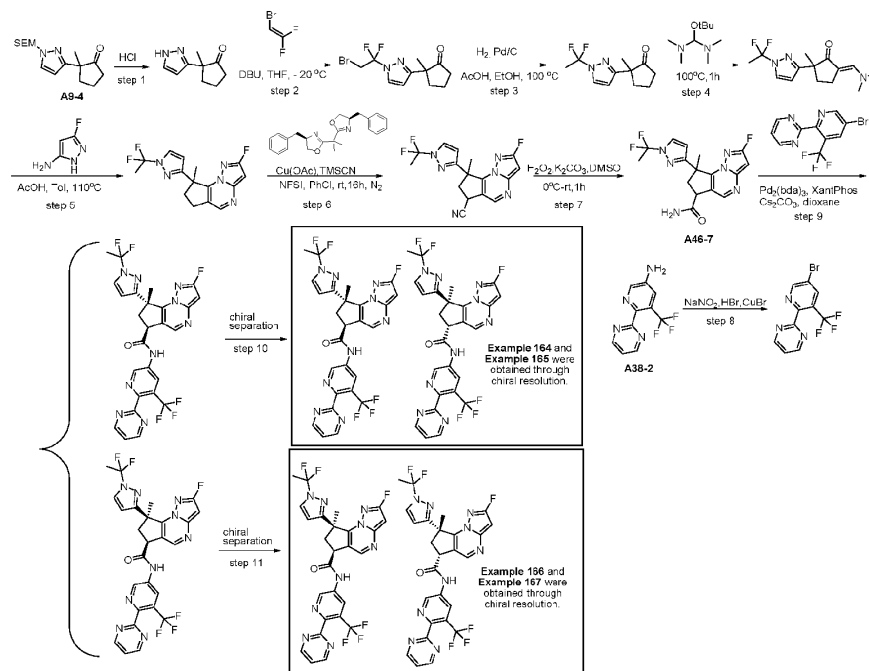
Step 4: **Example 162** and **Example 163**

In analogy to **Method A1 step 8** but using (8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A30-10-P2**, 44 mg, 125 μmol) and 6-(pyridazin-3-yl)-5-(trifluoromethyl)pyridin-3-amine (30 mg, 125 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 162** (14.0 mg, 19% yield) as a white solid and *cis*-isomer **Example 163** (6.0 mg, 8% yield) as a white solid.

Example 162: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 9.31-9.37 (m, 1H), 9.14 (d, *J* = 2.0 Hz, 1H), 8.77 (d, *J* = 2.4 Hz, 1H), 8.75 (s, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 8.02-8.06 (m, 1H), 7.86-7.92 (m, 1H), 7.71 (t, *J* = 59.2 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 6.59 (d, *J* = 4.8 Hz, 1H), 4.50-4.58 (m, *J* = 8.0 Hz, 1H), 3.00-3.09 (m, 1H), 2.55-2.65 (m, 1H), 2.04 (s, 3H). LC-MS (ES, m/z): 574[M+H]⁺.

Example 163: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 9.31-9.37 (m, 1H), 9.11 (d, *J* = 2.0 Hz, 1H), 8.75 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 2H), 8.14 (d, *J* = 2.8 Hz, 1H), 8.00-8.06 (m, 1H), 7.86-7.93 (m, 1H), 7.70 (t, *J* = 59.2 Hz, 1H), 6.57 (d, *J* = 4.8 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 4.54-4.63 (m, 1H), 2.79-2.96 (m, 2H), 1.93 (s, 3H). LC-MS (ES, m/z): 574[M+H]⁺.

Method A46



Examples 164, 165: (6*S*,8*S*)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 166, 167: (6*S*,8*R*)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-methyl-2-(1*H*-pyrazol-3-yl)cyclopentan-1-one

In analogy to Method A33 step 1 but using 2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)cyclopentan-1-one (A9-4, 31.0 g, 105 mmol), the title compound was obtained as a yellow oil (9.0 g, 52% yield). LC-MS: *m/z* 165 [M+H]⁺.

Step 2: 2-(1-(2-bromo-1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-methylcyclopentan-1-one

To a stirred solution of 2-methyl-2-(1H-pyrazol-3-yl)cyclopentan-1-one (4.5 g, 27 mmol) in THF (200 mL) were added DBU (8.3 g, 54 mmol) and 2-bromo-1,1-difluoroethene (50.0 g, 349 mmol) at -40 °C. The reaction mixture was warmed to 50 °C and stirred for 16 h. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with brine (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase column to afford the title compound (2.3 g, 27% yield) as a yellow oil. LC-MS: m/z 307[M+H]⁺.

Step 3: 2-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-methylcyclopentan-1-one

To a solution of 2-(1-(2-bromo-1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-methylcyclopentan-1-one (4.5 g, 14 mmol) in EtOH (200 mL) were added Pd(OH)₂/C (4.1 g, 1 mmol, 10%) and Pd/C (3.5 g, 1 mmol, 10%). The mixture was degassed and then stirred at 120 °C for 48 h under hydrogen pressure [30 atm]. The solids were filtered out, and the filtrate was concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with PE/EtOAc (10:1) to afford the title compound (1.8 g, 37% yield) as a yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.75 (d, J = 2.8 Hz, 1H), 6.36 (d, J = 2.8 Hz, 1H), 2.67-2.76 (m, 1H), 2.34-2.44 (m, 1H), 2.26 (t, J = 16.0 Hz, 3H), 1.92-2.12 (m, 4H), 1.43 (s, 3H). LC-MS: m/z 229 [M+H]⁺.

Step 4: 2-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-5-((dimethylamino)methylene)-2-methylcyclopentan-1-one

In analogy to **Method A1 step 4** but using 2-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-methylcyclopentan-1-one (100 mg, 440 μmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanediamine (382 mg, 2.2 mmol) and stirring at 100 °C for 1 h, the crude title compound was obtained as a red oil (100 mg). LC-MS: m/z 284 [M+H]⁺.

Step 5: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A1 step 5** but using 2-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-5-((dimethylamino)methylene)-2-methylcyclopentan-1-one (100 mg, 353 μmol) and 3-fluoro-1H-pyrazol-5-amine (36 mg, 353 μmol) in EtOH (5 mL) and HCl (0.5 mL, 4M in dioxane) and stirring at 100 °C for 1 h, the title compound was obtained as a yellow solid (50 mg, 44% yield). LC-MS: m/z 322 [M+H]⁺.

Step 6: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A1 step 6** but using 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (400 mg, 1.2 mmol) in chlorobenzene (40 mL), the title compound was obtained as a yellow solid (200 mg, 23% yield). LC-MS: m/z 347 [M+H]⁺.

Step 7: 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (**A46-7**)

In analogy to **Method A33 step 7** but using 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (65 mg, 187 μmol), the title compound was obtained as a yellow oil (**A46-7**, 30 mg, 44% yield). LC-MS: m/z 365 [M+H]⁺.

Step 8: 2-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)pyrimidine

To a stirred mixture of 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**, 260 mg, 1.1 mmol) in HBr (2 mL, 33% in acetic acid) was added a solution of NaNO₂ (224 mg, 3.3 mmol) in water (2 mL) dropwise at 0 °C, and it was stirred at 0 °C for 30 min. CuBr (202 mg, 1.4 mmol) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (3x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column and eluted with PE/EtOAc (3:1) to afford the title compound (210 mg, 64% yield) as a yellow solid. LC-MS: m/z 304 [M+H]⁺.

Step 9: (*trans*)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A33 step 8** but using 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (30 mg, 82 μmol) and 2-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)pyrimidine (30 mg, 98 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (12 mg, 21% yield) as a white solid,

LC-MS: m/z 588 [M+H]⁺; *cis*-isomer (6 mg, 10% yield) as a white solid, LC-MS: m/z 588 [M+H]⁺.

Step 10: Separation of enantiomers to obtain **Example 164** and **Example 165**

25 mg of (*trans*)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRALPAK IF, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.47; RT2(min): 10.61; Sample Solvent: EtOH--HPLC; Injection Volume: 1.3 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 164** (5.4 mg, 21% yield) as an off-white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 165** (11.6 mg, 44% yield) as a light-yellow solid.

Example 164: ¹H NMR (400 MHz, DMSO-d₆) δ: 11.13(s, 1H), 9.08 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 4.8 Hz, 2H), 8.74 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.57-6.59 (m, 2H), 4.55 (t, J = 8.4 Hz, 1H), 3.05-3.11 (m, 1H), 2.56-2.61 (m, 1H), 2.20 (t, J = 16.4 Hz, 3H), 2.03 (s, 3H). LC-MS: m/z 588 [M+H]⁺.

Example 165: ¹H NMR (400 MHz, DMSO-d₆) δ: 11.10(s, 1H), 9.08 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 4.8 Hz, 2H), 8.74 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.57-6.59 (m, 2H), 4.55 (t, J = 8.4 Hz, 1H), 3.05-3.11 (m, 1H), 2.56-2.61 (m, 1H), 2.21 (t, J = 16.4 Hz, 3H), 2.03 (s, 3H). LC-MS: m/z 588 [M+H]⁺.

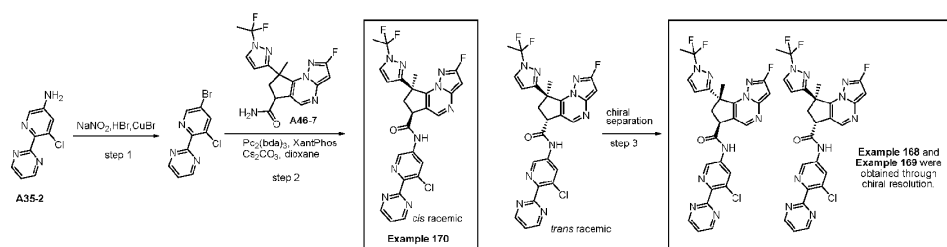
Step 11: Separation of enantiomers to obtain **Example 166** and **Example 167**

23 mg of (*cis*)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRALPAK IG, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.17; RT2(min): 10.41; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number Of Runs: 4). The second eluting isomer was concentrated and lyophilized to afford **Example 166** (2.7 mg, 11% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 167** (1.3 mg, 5% yield) as a white solid.

Example 166: ^1H NMR (400 MHz, DMSO- d_6) δ : 11.00 (s, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.96 (d, J = 4.8 Hz, 2H), 8.73 (s, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.63 (t, J = 4.8 Hz, 1H), 6.57 (d, J = 5.2 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.56-4.60 (m, 1H), 2.99-3.03 (m, 1H), 2.78-2.85 (m, 1H), 2.09 (t, J = 16.4 Hz, 3H), 1.93 (s, 3H). LC-MS: m/z 588 $[\text{M}+\text{H}]^+$.

5 **Example 167:** ^1H NMR (400 MHz, DMSO- d_6) δ : 11.01 (s, 1H), 9.05 (d, J = 2.4 Hz, 1H), 8.96 (d, J = 4.8 Hz, 2H), 8.73 (s, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.63 (t, J = 4.8 Hz, 1H), 6.57 (d, J = 4.8 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.56-4.60 (m, 1H), 2.99-3.03 (m, 1H), 2.78-2.85 (m, 1H), 2.09 (t, J = 16.4 Hz, 3H), 1.93 (s, 3H). LC-MS: m/z 588 $[\text{M}+\text{H}]^+$.

Method A47



Examples 168, 169: (6*S*,8*S*)-*N*-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide, (6*R*,8*R*)-*N*-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

15

Example 170: (*cis*)-*N*-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

20 Step 1: 2-(5-bromo-3-chloropyridin-2-yl)pyrimidine

In analogy to **Method A46 step 8** but using 5-chloro-6-(pyrimidin-2-yl)pyridin-3-amine (**A35-2**, 120 mg, 581 μmol), the title compound was obtained as a yellow solid (110 mg, 70% yield). LC-MS: m/z 270 $[\text{M}+\text{H}]^+$.

25 Step 2: (*trans*)-*N*-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide and **Example 170**

In analogy to **Method A33 step 8** but using 8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (**A46-7**, 30 mg, 82 μ mol) and 2-(5-bromo-3-chloropyridin-2-yl)pyrimidine (26.7 mg, 98 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (1.3 mg, 2% yield) as a white solid, LC-MS: m/z 554 [M+H]⁺; **Example 170** (1.2 mg, 2% yield) as a white solid.

Example 170: ¹H NMR (400 MHz, DMSO-d₆) δ : 10.89(s, 1H), 8.97 (d, J = 4.8 Hz, 2H), 8.77 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.41 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.61 (t, J = 4.8 Hz, 1H), 6.56 (d, J = 4.8 Hz, 1H), 6.46 (d, J = 2.8 Hz, 1H), 4.54-4.58 (m, 1H), 2.93-2.98 (m, 1H), 2.78-2.84 (m, 1H), 2.12 (t, J = 16.4 Hz, 3H), 1.92 (s, 3H). LC-MS: m/z 554 [M+H]⁺.

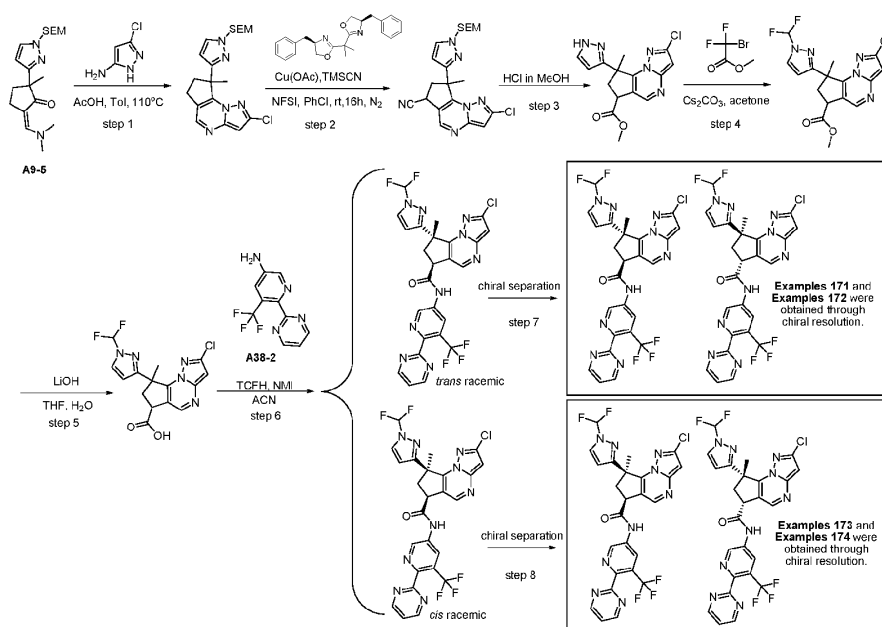
10 Step 3: Separation of enantiomers to obtain **Example 168** and **Example 169**

5.8 mg of (*trans*)-N-(5-chloro-6-(pyrimidin-2-yl)pyridin-3-yl)-8-(1-(1,1-difluoroethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification. (Column: CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 60% Mobile Phase B; Wave Length: 254/220nm; RT1(min): 6.138; RT2(min): 12.152; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 168** (1.8 mg, 31% yield) as an off-white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 169** (1.3 mg, 22% yield) as a white solid.

20 **Example 168:** ¹H NMR (400 MHz, DMSO-d₆) δ : 10.97 (s, 1H), 8.98 (d, J = 4.8 Hz, 2H), 8.80 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.61 (t, J = 4.8 Hz, 1H), 6.56-6.59 (m, 2H), 4.51-4.55 (m, 1H), 3.05-3.10 (m, 1H), 2.56-2.67 (m, 1H), 2.20 (t, J = 16.4 Hz, 3H), 2.03 (s, 3H). LC-MS: m/z 554 [M+H]⁺.

25 **Example 169:** ¹H NMR (400 MHz, DMSO-d₆) δ : 10.97(s, 1H), 8.98 (d, J = 4.8 Hz, 2H), 8.80 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.62 (t, J = 4.8 Hz, 1H), 6.56-6.59 (m, 2H), 4.51-4.55 (m, 1H), 3.04-3.10 (m, 1H), 2.56-2.67 (m, 1H), 2.20 (t, J = 16.4 Hz, 3H), 2.03 (s, 3H). LC-MS: m/z 554 [M+H]⁺.

Method A48



Examples 171, 172: (6*S*,8*S*)-2-chloro-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-8-methyl-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-2-chloro-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-8-methyl-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 173, 174: (6*S*,8*R*)-2-chloro-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-8-methyl-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-2-chloro-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-8-methyl-*N*-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-chloro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine

In analogy to **Method A6 step 6** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)cyclopentan-1-one (6 g, 17 mmol) and 3-chloro-

1H-pyrazol-5-amine (2 g, 17 mmol), stirring at 110 °C for 1 h, the title compound was obtained (2.9 g, 41% yield) as a red solid. LC-MS: m/z 404 [M+H]⁺.

Step 2: 2-chloro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

5 In analogy to **Method A6 step 7** but using 2-chloro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1.1 g, 3 mmol) in chlorobenzene (20 mL), the title compound was obtained as a yellow oil (200 mg, 17% yield) as a yellow oil. LC-MS: m/z 429 [M+H]⁺.

Step 3: Methyl 2-chloro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate
10

A solution of 2-chloro-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (400 mg, 932 μmol) in HCl (10 mL, 4M in MeOH) was stirred at 80 °C for 2 h. The mixture was concentrated under reduced pressure to give the title compound (200 mg, 65% yield) as a yellow oil, which was used
15 directly in the next step. LC-MS: m/z 332 [M+H]⁺.

Step 4: Methyl 2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A23 step 1** but using methyl 2-chloro-8-methyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (200 mg, 602 μmol)
20 and stirring at 60 °C for 16 h, the title compound was obtained as a yellow oil (200 mg, 87% yield). LC-MS: m/z 382 [M+H]⁺.

Step 5: 2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A7 step 2** but using methyl 2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate
25 (200 mg, 524 μmol) in THF (10 mL) and purification of the product by reverse phase column chromatography, the title compound was obtained as a yellow oil (130 mg, 67% yield). LC-MS: m/z 368 [M+H]⁺.

Step 6: (*trans*)-2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (120 mg, 326 μ mol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**, 78 mg, 326 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (24 mg, 25% yield) as a pink solid, LC-MS: m/z 590[M+H]⁺; *cis*-isomer (19 mg, 19% yield) as a white solid, LC-MS: m/z 590[M+H]⁺.

Step 7: Separation of enantiomers to obtain **Example 171** and **Example 172**

(*trans*)-2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (24 mg, 40 μ mol) was submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 5.732; RT2(min): 13.43; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 171** (5 mg, 40% yield) as a pink solid. The first eluting isomer was concentrated and lyophilized to afford **Example 172** (9 mg, 72% yield) as a yellow solid.

Example 171: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 9.07 (d, *J* = 2.4 Hz, 1H), 8.98 (d, *J* = 4.8 Hz, 2H), 8.76 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 2.8 Hz, 1H), 7.71 (t, *J* = 59.2 Hz, 1H), 7.64 (t, *J* = 4.8 Hz, 1H), 6.97 (s, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 4.51-4.56 (m, 1H), 3.01-3.08 (m, 1H), 2.55-2.63 (m, 1H), 2.07 (s, 3H). LC-MS: m/z 590[M+H]⁺.

Example 172: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 9.07 (d, *J* = 2.0 Hz, 1H), 8.98 (d, *J* = 4.8 Hz, 2H), 8.76 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 2.8 Hz, 1H), 7.71 (t, *J* = 59.2 Hz, 1H), 7.64 (t, *J* = 4.8 Hz, 1H), 6.97 (s, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 4.51-4.57 (m, 1H), 3.00-3.08 (m, 1H), 2.55-2.63 (m, 1H), 2.07 (s, 3H). LC-MS: m/z 590[M+H]⁺.

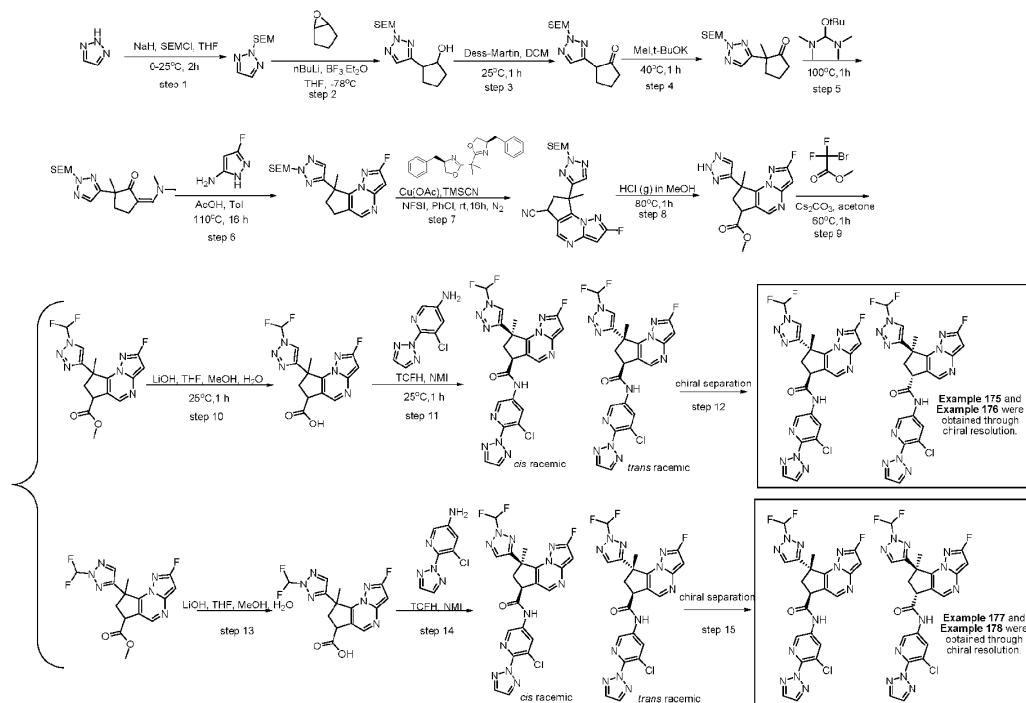
Step 8: Separation of enantiomers to obtain **Example 173** and **Example 174**

(*cis*)-2-chloro-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-8-methyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (19 mg, 32 μ mol) was submitted to chiral HPLC purification (Column: 5 CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 12.948; RT2(min): 18.039; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 173** (6 mg, 63% yield) as a white solid. The first 10 eluting isomer was concentrated and lyophilized to afford **Example 174** (5 mg, 8 μ mol, 52% yield,) as a white solid.

Example 173: ^1H NMR (400 MHz, DMSO- d_6) δ 11.03 (s, 1H), 9.04 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 4.8 Hz, 2H), 8.77 (s, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.69 (t, J = 59.2 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.95 (s, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.56-4.62 (m, 1H), 15 2.81-2.97 (m, 2H), 1.95 (s, 3H). LC-MS: m/z 590[M+H] $^+$.

Example 174: ^1H NMR (400 MHz, DMSO- d_6) δ 11.02 (s, 1H), 9.04 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 4.8Hz, 2H), 8.77 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 7.64 (t, J = 4.8 Hz, 1H), 6.95 (s, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.57-4.62 (m, 1H), 2.81-2.95 (m, 2H), 1.95 (s, 3H). LC-MS: m/z 590[M+H] $^+$.

Method A49



Examples 175, 176: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 177, 178: (6*S*,8*S*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(2-(difluoromethyl)-2*H*-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(2-(difluoromethyl)-2*H*-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazole

In analogy to **Method A6 step 1** but using 2H-triazole (30 g, 434.4 mmol), the title compound was obtained as a yellow oil (46 g, 45% yield). LC-MS: m/z 200 [M+H]⁺.

Step 2: 2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-ol

5 In analogy to **Method A1 step 1** but using 2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazole (50 g, 250.9 mmol), the title compound was obtained as a yellow oil (33.5 g, 42% yield). LC-MS: m/z 284 [M+H]⁺.

Step 3: 2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one

10 In analogy to **Method A10 step 2** but using 2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-ol (15 g, 52.9 mmol) and after purification by reverse phase column chromatography, the title compound was obtained as a yellow oil (15 g, 90% yield). LC-MS: m/z 282 [M+H]⁺.

Step 4: 2-methyl-2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one

15 In analogy to **Method A1 step 3** but using 2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one (10 g, 35.5 mmol), the title compound was obtained as a colorless oil (4.1 g, 36% yield). LC-MS: m/z 296 [M+H]⁺.

Step 5: 5-((dimethylamino)methylene)-2-methyl-2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one

20 In analogy to **Method A1 step 4** but using 2-methyl-2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one (3.9 g, 13.2 mmol) in 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanedi-amine (4.6 g, 26.4 mmol) and stirring at 100 °C for 1 h, the crude title compound was obtained as a brown oil (4.2 g) and was used in the next step without further purification. LC-MS: m/z 351 [M+H]⁺.

25 Step 6: 2-fluoro-8-methyl-8-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

30 In analogy to **Method A1 step 5** but using 5-((dimethylamino)methylene)-2-methyl-2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)cyclopentan-1-one (1 g, 2.9 mmol) and after purification by reverse phase column chromatography, the title compound was obtained as a yellow oil (250 mg, 23% yield). LC-MS: m/z 389 [M+H]⁺.

Step 7: 2-fluoro-8-methyl-8-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

In analogy to **Method A6 step 7** but using 2-fluoro-8-methyl-8-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (1 g, 2.6 mmol) in Chlorobenzene (20 mL), the title compound was obtained as a yellow oil (90 mg, 8% yield). LC-MS: m/z 414 [M+H]⁺.

Step 8: Methyl 2-fluoro-8-methyl-8-(2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A48 step 3** but using 2-fluoro-8-methyl-8-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (90 mg, 185 μmol), the title compound was obtained as a yellow oil (50 mg, 85% yield). LC-MS: m/z 317 [M+H]⁺.

Step 9: Methyl 8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate and Methyl 8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A23 step 1** but using 2-fluoro-8-methyl-8-(2H-1,2,3-triazol-4-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (50 mg, 158 μmol) and stirring at 60 °C for 1 h and after purification by prep-HPLC methyl 8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (35 mg, 60% yield), LC-MS: m/z 367 [M+H]⁺ and methyl 8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (20 mg, 35% yield), LC-MS: m/z 367 [M+H]⁺ were both obtained as white solids.

Step 10: 8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A7 step 2** but using 8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (33 mg, 90.1 μmol), the crude title compound was obtained as a yellow oil (28 mg, 88% yield). LC-MS: m/z 353 [M+H]⁺.

Step 11: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (26 mg, 74 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (10.4 mg, 26% yield) as a white solid; *cis*-isomer (5.6 mg, 14% yield) as a white solid.

Cis isomer: ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 8.79 (s, 1H), 8.77 (s, 1H), 8.72 (d, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 8.25 (t, *J* = 58.0 Hz, 1H), 8.18 (s, 2H), 6.58 (d, *J* = 4.8 Hz, 1H), 4.61 (t, *J* = 8.0 Hz, 1H), 2.82-2.97 (m, 2H), 1.95 (s, 3H). LC-MS: *m/z* 530 [M+H]⁺.

Step 12: Separation of enantiomers to obtain **Example 175** and **Example 176**

9 mg of (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (9 mg, 17 μ mol) were submitted to chiral HPLC purification (Column: CHIRALPAK IF, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 9.704; RT2(min): 12.258; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number Of Runs: 3). The second eluting isomer was concentrated and lyophilized to afford **Example 175** (2.8 mg, 31% yield) as an off-white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 176** (3.9 mg, 43% yield) as an off-white solid.

Example 175: ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 8.88 (s, 1H), 8.78 (s, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.23 (t, *J* = 58.0, 1H), 8.18 (s, 2H), 6.60 (d, *J* = 4.8 Hz, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 3.01-3.09 (m, 1H), 2.64-2.69 (m, 1H), 2.07 (s, 3H). LC-MS: *m/z* 530 [M+H]⁺.

Example 176: ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 1H), 8.88 (s, 1H), 8.77 (s, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.23 (t, *J* = 58.0, 1H), 8.18 (s, 2H), 6.60 (d, *J* = 4.8 Hz, 1H), 4.67 (t, *J* = 8.0 Hz, 1H), 3.00-3.10 (m, 1H), 2.61-2.69 (m, 1H), 2.07 (s, 3H). LC-MS: *m/z* 530 [M+H]⁺.

Step 13: 8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A7 step 2** but using methyl 8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (30 mg, 82 μ mol), the crude title compound was obtained as a yellow oil (20 mg, 69% yield). LC-MS (ES, m/z): 353[M+H]⁺.

Step 14: (*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (15 mg, 43 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (7 mg, 31% yield) as a white solid; *cis*-isomer (3 mg, 13% yield) as a white solid.

Cis isomer: ¹H NMR (400 MHz, DMSO-d₆) δ 11.15 (br, 1H), 8.79 (s, 1H), 8.72 (d, J = 1.6 Hz, 1H), 8.56 (d, J = 1.6 Hz, 1H), 8.23 (s, 1H), 8.18 (s, 2H), 8.07 (t, J = 57.6 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 4.63 (t, J = 7.6 Hz, 1H), 2.83-2.93 (m, 2H), 1.97 (s, 3H). LC-MS: m/z 530 [M+H]⁺.

Step 15: Separation of enantiomers to obtain **Example 177** and **Example 178**

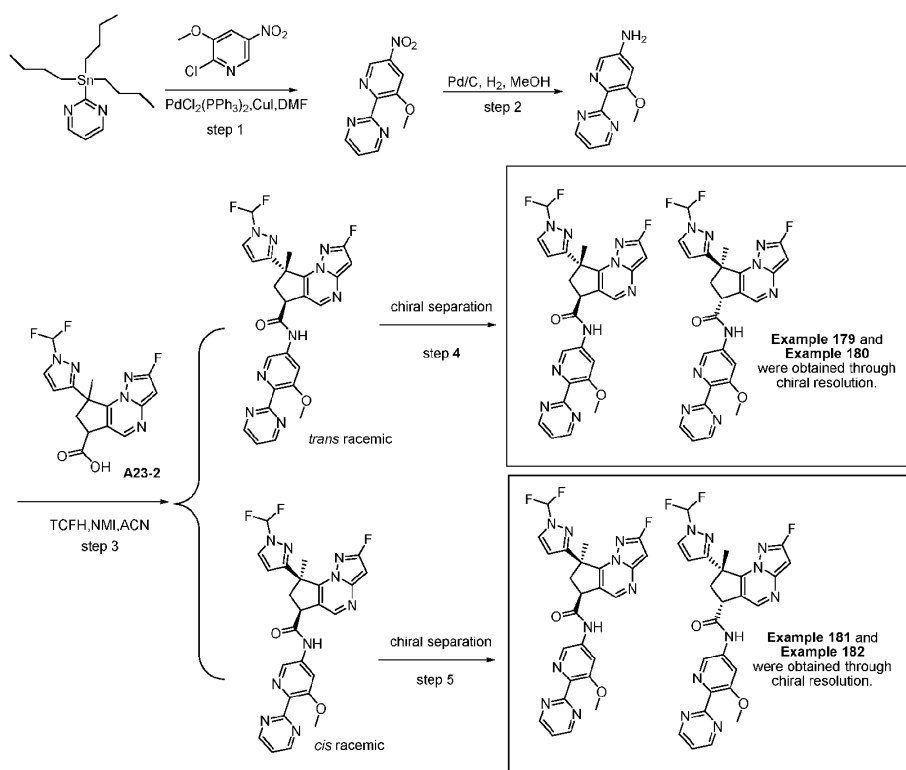
(*trans*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-8-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide (7 mg, 13 μ mol) was submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 6.412; RT2(min): 10.459; Injection Volume: 2 mL; Number Of Runs: 1). The second eluting isomer was concentrated and lyophilized to afford **Example 177** (2.2 mg, 31% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 178** (2.8 mg, 37% yield) as a white solid.

Example 177: ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.78 (s, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.33 (s, 1H), 8.18 (s, 2H), 8.07 (t, J = 57.2 Hz, 1H), 6.61 (d,

J = 4.8 Hz, 1H), 4.54-4.63 (m, 1H), 2.97-3.06 (m, 1H), 2.66-2.72 (m, 1H), 2.09 (s, 3H). LC-MS (ES, m/z): 530[M+H]⁺.

Example 178: ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.78 (s, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.33 (s, 1H), 8.18 (s, 2H), 8.07 (t, J = 57.2 Hz, 1H), 6.61 (d, J = 5.2 Hz, 1H), 4.51-4.64 (m, 1H), 2.97-3.10 (m, 1H), 2.66-2.72 (m, 1H), 2.09 (s, 3H). LC-MS (ES, m/z): 530[M+H]⁺.

Method A50



Example 179, 180: (6*S*,8*S*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-N-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-N-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 181, 182: (6*S*,8*R*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-N-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-N-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

5 Step 1: 2-(3-methoxy-5-nitropyridin-2-yl)pyrimidine

In analogy to **Method A35 step 1** but using 2-chloro-3-methoxy-5-nitro-pyridine (1 g, 5.3 mmol), the title compound was obtained as a yellow solid (520 mg, 42% yield). LC-MS: *m/z* 233 [M+H]⁺.

Step 2: 5-methoxy-6-(pyrimidin-2-yl)pyridin-3-amine

10 In analogy to **Method A15 step 2** but using 2-(3-methoxy-5-nitropyridin-2-yl)pyrimidine (150 mg, 581 μmol), the title compound was obtained as a yellow oil (83 mg, 71% yield). LC-MS: *m/z* 203 [M+H]⁺.

Step 3: (*trans*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

15 In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (55 mg, 157 μmol) and 5-methoxy-6-(pyrimidin-2-yl)pyridin-3-amine (38 mg, 188 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (23 mg, 26% yield) as an off-white solid, LC-MS: *m/z* 536 [M+H]⁺; *cis*-isomer (15 mg, 17% yield) as an off white solid, LC-MS: *m/z* 536 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 179** and **Example 180**

25 23 mg of (*trans*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-*N*-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 70% Mobile Phase B; Wave Length: 254/220nm; RT1(min): 5.344; RT2(min): 10.928; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 1). The first eluting isomer was concentrated and lyophilized to afford

Example 179 (6.1 mg, 26% yield) as an off white solid. The second eluting isomer was concentrated and lyophilized to afford **Example 180** (4.8 mg, 21% yield) as an off white solid.

Example 179: ¹HNMR (400 MHz, CDCl₃) δ: 8.94 (d, J = 4.8 Hz, 2H), 8.73 (br, 1H), 8.60 (s, 1H), 8.57 (s, 1H), 8.46 (s, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.08 (t, J = 60.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.27 (d, J = 4.8 Hz, 1H), 4.60 (t, J = 8.0 Hz, 1H), 4.00 (s, 3H), 3.37-3.47 (m, 1H), 2.59-2.69 (m, 1H), 2.16 (s, 3H). LC-MS: m/z 536 [M+H]⁺.

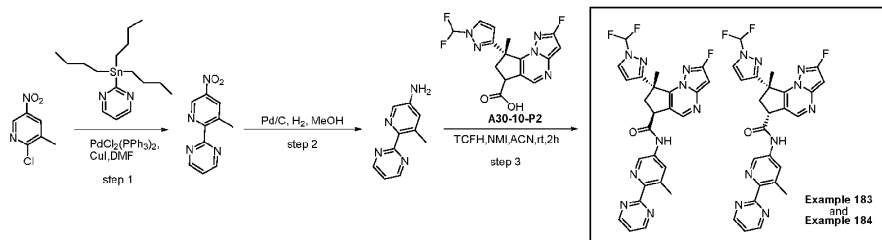
Example 180: ¹HNMR (400 MHz, CDCl₃) δ: 8.94 (d, J = 4.8 Hz, 2H), 8.65 (br, 1H), 8.60 (s, 1H), 8.55 (s, 1H), 8.44 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.08 (t, J = 60.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 4.8 Hz, 1H), 4.59 (t, J = 8.0 Hz, 1H), 4.00 (s, 3H), 3.38-3.47 (m, 1H), 2.60-2.66 (m, 1H), 2.16 (s, 3H). LC-MS: m/z 536 [M+H]⁺.

Step 5: Separation of enantiomers to obtain **Example 181** and **Example 182**

15 mg of (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-N-(5-methoxy-6-(pyrimidin-2-yl)pyridin-3-yl)-8-methyl-7,8-dihydro-6H-cyclopenta[c]pyrazolo[1,5-a]pyrimidine-6-carboxamide was submitted to chiral HPLC purification (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: IPA: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 80% Mobile Phase B; Wave Length: 254/220nm nm; RT1(min): 7.973; RT2(min): 11.305; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 181** (3.5 mg, 24% yield) as a light pink solid. The second eluting isomer was concentrated and lyophilized to afford **Example 182** (2.6 mg, 18% yield) as an off white solid.

Example 181: ¹HNMR (400 MHz, CDCl₃) δ: 9.47 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.68 (s, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 7.81 (d, J = 2.8 Hz, 1H), 7.32 (d, J = 4.8 Hz, 1H), 7.02 (t, J = 60.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.30 (d, J = 5.1 Hz, 1H), 4.52-4.60 (m, 1H), 3.97 (s, 3H), 3.35-3.45 (m, 1H), 2.84-2.94 (m, 1H), 2.12 (s, 3H). LC-MS: m/z 536 [M+H]⁺.

Example 182: ¹HNMR (400 MHz, CDCl₃) δ: 9.86 (s, 1H), 8.95 (d, J = 4.8 Hz, 2H), 8.68 (s, 1H), 8.42-8.46 (m, 2H), 7.80 (d, J = 2.8 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.03 (t, J = 60.4 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.29 (d, J = 5.1 Hz, 1H), 4.58-4.65 (m, 1H), 3.99 (s, 3H), 3.35-3.45 (m, 1H), 2.85-2.96 (m, 1H), 2.11 (s, 3H). LC-MS: m/z 536 [M+H]⁺.

Method A51

Examples 183, Example 184: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(5-methyl-6-(pyrimidin-2-yl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(5-methyl-6-(pyrimidin-2-yl)pyridin-3-yl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-(3-methyl-5-nitropyridin-2-yl)pyrimidine

In analogy to **Method A30 step 12** but using 2-(tributylstannyl)pyrimidine (2.6 g, 6.9 mmol) and 2-chloro-3-methyl-5-nitropyridine (1 g, 5.8 mmol) and stirring at 120 °C for 1 h, the title compound was obtained as a white solid (600 mg, 45% yield). LC-MS: *m/z* 217 [*M*+*H*]⁺.

Step 2: 5-methyl-6-(pyrimidin-2-yl)pyridin-3-amine

In analogy to **Method A15 step 2** but using 2-(3-methyl-5-nitropyridin-2-yl)pyrimidine (500 mg, 2.3 mmol) and without further purification, the crude title compound was obtained as a brown solid (435 mg). LC-MS: *m/z* 187 [*M*+*H*]⁺.

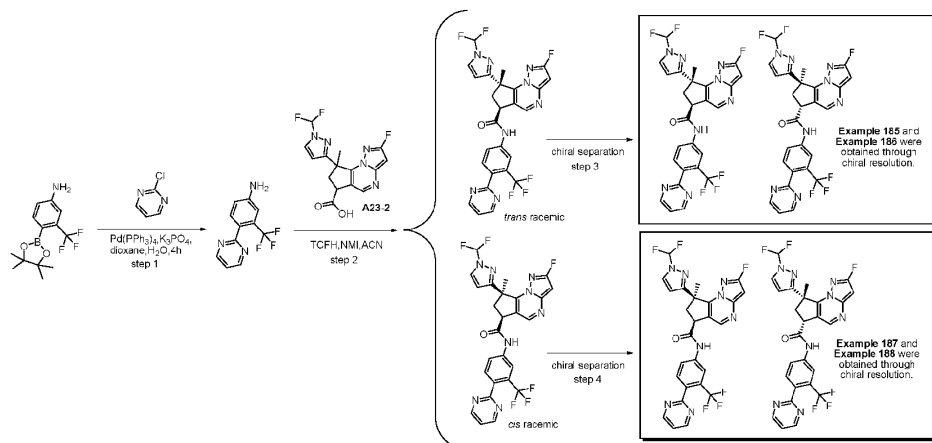
Step 3: **Example 183 and Example 184**

In analogy to **Method A1 step 8** but using (8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**A30-10-P2**, 50 mg, 142 μmol) and 5-methyl-6-(pyrimidin-2-yl)pyridin-3-amine (32 mg, 169.7 μmol), the diastereomeric title compounds were obtained: *trans* isomer **Example 183** (16.5 mg, 41% yield) as a light pink solid and *cis*-isomer **Example 184** (10.2 mg, 24% yield) as a light pink solid.

Example 183: ¹HNMR (400 MHz, CDCl₃) δ: 9.00 (br, 1H), 8.93 (d, *J* = 4.8 Hz, 2H), 8.90 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 7.73 (d, *J* = 2.8 Hz, 1H), 7.34 (t, *J* = 4.8 Hz, 1H), 7.08 (t, *J* = 60.8 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 4.8 Hz, 1H), 4.63 (t, *J* = 8.0 Hz, 1H), 3.35-3.45 (m, 1H), 2.71 (s, 3H), 2.63-2.68 (m, 1H), 2.16 (s, 3H). LC-MS: *m/z* 520 [*M*+*H*]⁺.

Example 184: ^1H NMR (400 MHz, CDCl_3) δ : 9.38 (s, 1H), 8.93 (d, $J = 4.8$ Hz, 2H), 8.68 (s, 1H), 8.65 (s, 1H), 8.21 (s, 1H), 7.81 (d, $J = 2.4$ Hz, 1H), 7.33 (t, $J = 4.8$ Hz, 1H), 7.01 (t, $J = 60.4$ Hz, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 6.30 (d, $J = 4.8$ Hz, 1H), 4.54-4.58 (m, 1H), 3.34-3.42 (m, 1H), 2.84-2.92 (m, 1H), 2.62 (s, 3H), 2.12 (s, 3H). LC-MS: m/z 520 $[\text{M}+\text{H}]^+$.

5

Method A52

Examples 185, 186: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

Examples 187, 188: (6*S*,8*R*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-*N*-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 4-(pyrimidin-2-yl)-3-(trifluoromethyl)aniline

To a stirred mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)aniline (220 mg, 766 μmol) in 1,4-dioxane (10 mL) and water (2 mL) were added 2-chloropyrimidine (105 mg, 919 μmol), $\text{Pd}(\text{PPh}_3)_4$ (88 mg, 77 μmol) and tripotassium phosphate (487 mg, 2.3 mmol) at 25 $^\circ\text{C}$ under nitrogen atmosphere. The resulting mixture was stirred at 80

°C for 4 h under nitrogen atmosphere. The mixture was allowed to cool to 25 °C, quenched with water (50 mL), and the resulting mixture was extracted with ethyl acetate (3x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase column to afford the title compound (150 mg, 75% yield) as a yellow solid. LC-MS (ES, m/z): 240[M+H]⁺.

Step 2: (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A23-2**, 50 mg, 142 μmol) and 4-(pyrimidin-2-yl)-3-(trifluoromethyl)aniline (37 mg, 156 μmol), racemic mixtures of the title compounds were obtained: *trans* isomer (25 mg, 29% yield) as a white solid, LC-MS (ES, m/z): 573[M+H]⁺; *cis*-isomer (15 mg, 17% yield) as a white solid, LC-MS (ES, m/z): 573[M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 185** and **Example 186**

25 mg of (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2x25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1-HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 3.573; RT2(min): 6.164; Sample Solvent: EtOH--HPLC; Injection Volume: 1.1 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 185** (8.5 mg, 32% yield) as an off-white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 186** (12.1 mg, 46% yield) as a white solid.

Example 185: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.87 (s, 1H), 8.93 (d, J = 4.8 Hz, 2H), 8.71 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.98-8.01 (m, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 7.53-7.56 (m, 1H), 6.62 (d, J = 2.8 Hz, 1H), 6.58 (d, J = 5.1 Hz, 1H), 4.49 (t, J = 8.4 Hz, 1H), 2.99-3.05 (m, 1H), 2.53-2.58 (m, 1H), 2.03 (s, 3H). LC-MS (ES, m/z): 573 [M+H]⁺.

Example 186: ^1H NMR (400 MHz, DMSO- d_6) δ 10.88 (s, 1H), 8.93 (d, J = 4.8 Hz, 2H), 8.71 (s, 1H), 8.28 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.98-8.02 (m, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 7.53-7.56 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 5.1 Hz, 1H), 4.49 (t, J = 8.0 Hz, 1H), 2.99-3.06 (m, 1H), 2.53-2.59 (m, 1H), 2.03 (s, 3H). LC-MS (ES, m/z): 573 $[\text{M}+\text{H}]^+$.

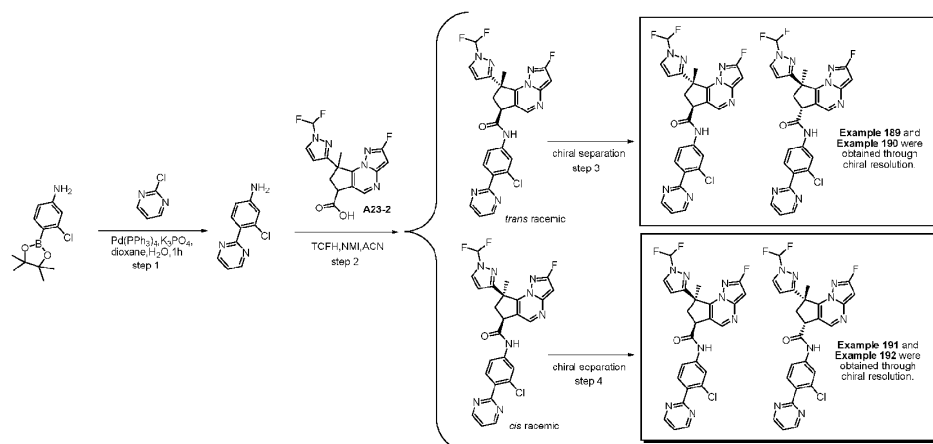
Step 4: Separation of enantiomers to obtain **Example 187** and **Example 188**

15 mg of (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-N-(4-(pyrimidin-2-yl)-3-(trifluoromethyl)phenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2x25 cm, 5 μm ; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 7.104; RT2(min): 9.999; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 187** (4.4 mg, 29% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 188** (4.0 mg, 25% yield) as a white solid.

Example 187: ^1H NMR (400 MHz, DMSO- d_6) δ 10.81 (s, 1H), 8.93 (d, J = 4.8 Hz, 2H), 8.72 (s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.96-7.99 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 59.2 Hz, 1H), 7.53 (t, J = 4.8 Hz, 1H), 6.55 (d, J = 5.1 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 4.55 (t, J = 8.0 Hz, 1H), 2.83 (d, J = 8.0 Hz, 2H), 1.91 (s, 3H). LC-MS (ES, m/z): 573 $[\text{M}+\text{H}]^+$.

Example 188: ^1H NMR (400 MHz, DMSO- d_6) δ 10.81 (s, 1H), 8.93 (d, J = 4.8 Hz, 2H), 8.72 (s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.96-7.98 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 59.2 Hz, 1H), 7.53 (t, J = 4.8 Hz, 1H), 6.55 (d, J = 5.1 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 4.55 (t, J = 8.0 Hz, 1H), 2.83 (d, J = 8.0 Hz, 2H), 1.91 (s, 3H). LC-MS (ES, m/z): 573 $[\text{M}+\text{H}]^+$.

Method A53



Examples 189, 190: (6*S*,8*S*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*R*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

Examples 191, 192: (6*S*,8*R*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (6*R*,8*S*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: 3-chloro-4-(pyrimidin-2-yl)aniline

In analogy to **Method A52 step 1** but using 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (520 mg, 2.1 mmol), the title compound was obtained as a yellow solid (290 mg, 64% yield). LC-MS (ES, m/z): 206[$\text{M}+\text{H}$] $^+$.

Step 2: (*trans*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide and (*cis*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**A23-2**, 50 mg, 142 μ mol) and 3-chloro-4-(pyrimidin-2-yl)aniline (32 mg, 156 μ mol), racemic mixtures of the title compounds were obtained: *trans* isomer (35 mg, 43% yield) as a white solid, LC-MS (ES, m/z): 539 [M+H]⁺; *cis*-isomer (20 mg, 24% yield) as a white solid, LC-MS (ES, m/z): 539 [M+H]⁺.

Step 3: Separation of enantiomers to obtain **Example 189** and **Example 190**

30 mg of (*trans*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2x25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1-HPLC; Flow rate: 20 mL/min; Gradient: isocratic 60% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 3.846; RT2(min): 6.992; Sample Solvent: EtOH--HPLC; Injection Volume: 3.0 mL; Number Of Runs: 2). The second eluting isomer was concentrated and lyophilized to afford **Example 189** (10.5 mg, 33% yield) as a white solid. The first eluting isomer was concentrated and lyophilized to afford **Example 190** (15.2 mg, 48% yield) as an off-white solid.

Example 189: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 8.95 (d, J = 4.8 Hz, 2H), 8.69 (s, 1H), 8.21 (d, J = 2.8 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 7.67-7.70 (m, 1H), 7.52 (t, J = 4.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.48 (t, J = 8.0 Hz, 1H), 2.97-3.04 (m, 1H), 2.52-2.61 (m, 1H), 2.04 (s, 3H). LC-MS (ES, m/z): 539 [M+H]⁺.

Example 190: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 8.95 (d, J = 4.8 Hz, 2H), 8.69 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 59.2 Hz, 1H), 7.67-7.70 (m, 1H), 7.52 (t, J = 4.8 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 4.8 Hz, 1H), 4.48 (t, J = 8.0 Hz, 1H), 2.97-3.05 (m, 1H), 2.51-2.61 (m, 1H), 2.04 (s, 3H). LC-MS (ES, m/z): 539 [M+H]⁺.

Step 4: Separation of enantiomers to obtain **Example 191** and **Example 192**

20 mg of (*cis*)-N-(3-chloro-4-(pyrimidin-2-yl)phenyl)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide were submitted to chiral HPLC purification (Column: CHIRALPAK IG, 2x25 cm, 5 μ m; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20

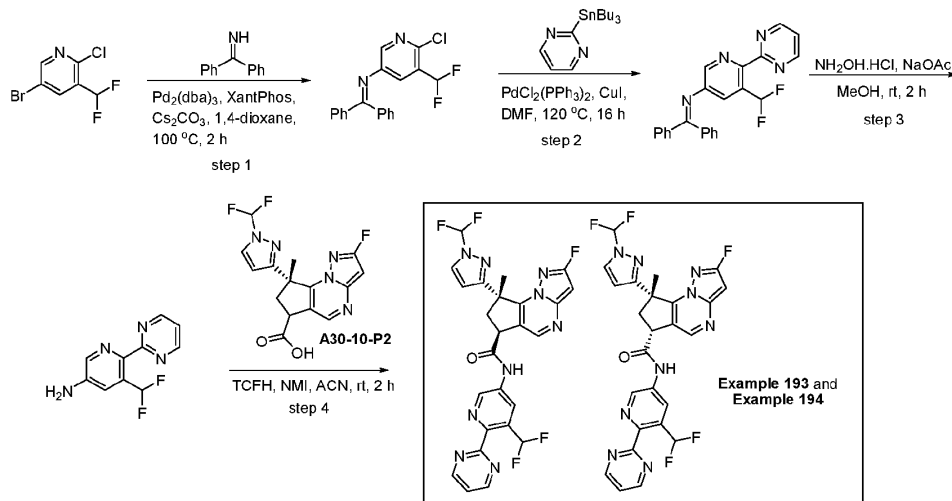
mL/min; Gradient: isocratic 40% Mobile Phase B; Wave Length: 254/220 nm; RT1(min): 6.883; RT2(min): 9.731; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2). The first eluting isomer was concentrated and lyophilized to afford **Example 191** (5.2 mg, 26% yield) as a white solid. The second eluting isomer was concentrated and lyophilized to afford

Example 192 (5.0 mg, 24% yield) as a white solid.

Example 191: ^1H NMR (400 MHz, DMSO- d_6) δ 10.68 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.71 (s, 1H), 8.15 (d, J = 2.8 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 59.2 Hz, 1H), 7.64-7.68 (m, 1H), 7.51 (t, J = 4.8 Hz, 1H), 6.55 (d, J = 5.1 Hz, 1H), 6.46 (d, J = 2.8 Hz, 1H), 4.54 (t, J = 8.0 Hz, 1H), 2.79-2.84 (m, 2H), 1.91 (s, 3H). LC-MS (ES, m/z): 539 $[\text{M}+\text{H}]^+$.

Example 192: ^1H NMR (400 MHz, DMSO- d_6) δ 10.68 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.71 (s, 1H), 8.15 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 59.2 Hz, 1H), 7.64-7.69 (m, 1H), 7.51 (t, J = 4.8 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 6.46 (d, J = 2.8 Hz, 1H), 4.54 (t, J = 8.0 Hz, 1H), 2.79-2.84 (m, 2H), 1.91 (s, 3H). LC-MS (ES, m/z): 539 $[\text{M}+\text{H}]^+$.

Method A54



Examples 193, 194: (6*S*,8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-*N*-(5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-6-carboxamide; (6*R*,8*S*)-8-(1-(difluoromethyl)-1*H*-

pyrazol-3-yl)-N-(5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

The relative and absolute stereochemistry of each example was not determined.

Step 1: N-(6-chloro-5-(difluoromethyl)pyridin-3-yl)-1,1-diphenylmethanimine

5 To a solution of 5-bromo-2-chloro-3-(difluoromethyl)pyridine (1 g, 4.1 mmol) in 1,4-dioxane (10 mL) were added diphenylmethanimine (822 mg, 4.5 mmol), cesium carbonate (2.7 g, 8.3 mmol), Xantphos (477 mg, 825 μ mol) and Pd₂(dba)₃ (755 mg, 825 μ mol). The reaction was stirred at 100 °C for 2 h under nitrogen. The reaction was cooled to 25 °C and diluted with water (10 mL). The resulting mixture was extracted with ethyl acetate (2x 10 mL). The combined organic
10 layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE: EA (9:1) to afford the title compound (420 mg, 28% yield) as a yellow oil. LC-MS: m/z 343 [M+H]⁺.

Step 2: N-(5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-yl)-1,1-diphenylmethanimine

In analogy to **Method A32 step 2** but using N-(6-chloro-5-(difluoromethyl)pyridin-3-yl)-
15 1,1-diphenylmethanimine (400 mg, 1.2 mmol) and 2-(tributylstannyl)pyrimidine (2.2 g, 5.8 mmol) and stirring at 120 °C for 16 h, the title compound was obtained as a yellow oil (130 mg, 28% yield). LC-MS: m/z 387 [M+H]⁺.

Step 3: 5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-amine

To a solution of N-(5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-yl)-1,1-
20 diphenylmethanimine (120 mg, 311 μ mol) in MeOH (10 mL) was added hydroxylamine hydrochloride (108 mg, 1.6 mmol) and sodium acetate (127 mg, 1.6 mmol). The reaction was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase column to afford the title compound (25 mg, 36% yield) as a yellow solid. LC-MS: m/z 223 [M+H]⁺.

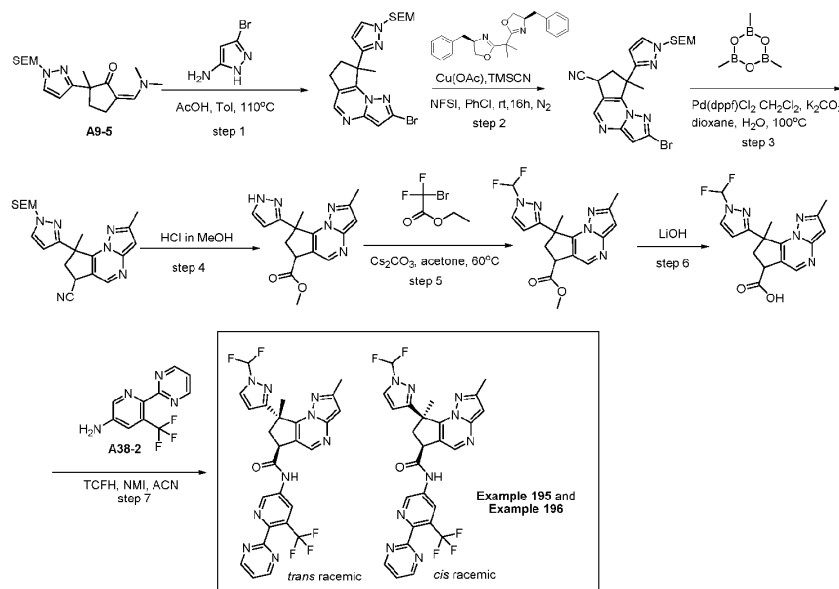
25 Step 4: **Example 193** and **Example 194**

In analogy to **Method A1 step 8** but using (8*S*)-8-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-fluoro-8-methyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid
(**A30-10-P2**, 71 mg, 202.5 μ mol) and 5-(difluoromethyl)-6-(pyrimidin-2-yl)pyridin-3-amine (45
mg, 202 μ mol), the diastereomeric title compounds were obtained: *trans* isomer **Example 193** (6.1
30 mg, 5% yield) as a white solid a *cis*-isomer **Example 194** (13.2 mg, 11% yield) as a white solid.

Example 193: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.03 (s, 1H), 9.05 (s, 1H), 8.99 (d, $J = 4.8$ Hz, 2H), 8.74 (s, 1H), 8.63 (s, 1H), 8.21 (d, $J = 2.8$ Hz, 1H), 7.44-7.88 (m, 3H), 6.63 (d, $J = 2.4$ Hz, 1H), 6.59 (d, $J = 4.8$ Hz, 1H), 4.53 (t, $J = 8.4$ Hz, 1H), 3.00-3.08 (m, 1H), 2.54-2.62 (m, 1H), 2.04 (s, 3H). LC-MS: m/z 556 $[\text{M}+\text{H}]^+$.

5 **Example 194:** ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 10.95 (s, 1H), 9.03 (s, 1H), 8.99 (d, $J = 4.8$ Hz, 2H), 8.75 (s, 1H), 8.59 (s, 1H), 8.15 (d, $J = 2.4$ Hz, 1H), 7.44-7.87 (m, 3H), 6.56 (d, $J = 4.8$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 4.59 (t, $J = 8.0$ Hz, 1H), 2.79-2.93 (m, 2H), 1.92 (s, 3H). LC-MS: m/z 556 $[\text{M}+\text{H}]^+$.

Method A55



10

Examples 195, 196: (*trans*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide; (*cis*)-8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-N-(6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxamide

15

The relative and absolute stereochemistry of each example was not determined.

Step 1: 2-bromo-8-methyl-8-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine

In analogy to **Method A6 step 6** but using 5-((dimethylamino)methylene)-2-methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)cyclopentan-1-one (5.5 g, 15.7 mmol) and 3-bromo-1H-pyrazol-5-amine (2.6 g, 15.7 mmol) and stirring at 110 °C for 16 h, the title compound was obtained as a brown oil (4.2 g, 45% yield). LC-MS: m/z 448[M+H]⁺.

5 Step 2: 2-bromo-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

 In analogy to **Method A1 step 6** but using 2-bromo-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (4.2 g, 9.4 mmol) in Chlorobenzene (400 mL), the title compound was obtained as a
10 light-yellow oil (2.6 g, 35% yield). LC-MS: m/z 473[M+H]⁺.

 Step 3: 2,8-dimethyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile

 To a stirred solution of 2-bromo-8-methyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (2.5 g, 5.3
15 mmol) in dioxane (80 mL) and water (20 mL) were added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (994 mg, 7.9 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (431 mg, 528 μmol) and potassium carbonate (2.2 g, 15.8 mmol). The reaction mixture was stirred at 100 °C for 4 h under nitrogen atmosphere. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was diluted with water (100 mL), and it was extracted with ethyl acetate (3x 100 mL). The
20 combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase column to afford the title compound (1.1 g, 37% yield) as a brown oil. LC-MS: m/z 409[M+H]⁺.

 Step 4: Methyl 2,8-dimethyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

25 In analogy to **Method A48 step 3** but using 2,8-dimethyl-8-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carbonitrile (1.1 g, 2.6 mmol) and purification of the product by reverse phase column chromatography, the title compound was obtained as a yellow oil (250 mg, 26% yield). LC-MS: m/z 312[M+H]⁺.

Step 5: Methyl 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate

In analogy to **Method A23 step 1** but using methyl 2,8-dimethyl-8-(1H-pyrazol-3-yl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (230 mg, 739 μ mol) and stirring at 60 °C for 2 h, the title compound was obtained as a yellow oil (80 mg, 24% yield). LC-MS: m/z 362[M+H]⁺.

Step 6: 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

In analogy to **Method A22 step 2** but using methyl 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylate (80 mg, 221 μ mol) the title compound was obtained as a yellow oil (40 mg, 41% yield). LC-MS: m/z 348[M+H]⁺.

Step 7: **Example 195** and **Example 196**

In analogy to **Method A1 step 8** but using 8-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,8-dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (40 mg, 115 μ mol) and 6-(pyrimidin-2-yl)-5-(trifluoromethyl)pyridin-3-amine (**A38-2**, 33 mg, 138 μ mol), the title compounds were obtained as racemic mixtures: *trans* isomer **Example 195** (3.2 mg, 21% yield) as an off-white solid and *cis*-isomer **Example 196** (1.6 mg, 10.4% yield) as an off-white solid.

Example 195: ¹HNMR (400 MHz, CDCl₃) δ : 9.20 (s, 1H), 8.95 (d, J = 4.8 Hz, 2H), 8.84-8.92 (m, 2H), 7.74 (s, 1H), 7.42 (t, J = 4.8 Hz, 1H), 7.08 (t, J = 60.4 Hz, 1H), 6.76 (s, 1H), 6.67 (s, 1H), 4.70-4.79 (m, 1H), 3.36-3.46 (m, 1H), 2.78-2.86 (m, 1H), 2.55 (s, 3H), 2.26 (s, 3H). LCMS (ES, m/z): 570 [M+H]⁺.

Example 196: ¹HNMR (400 MHz, CDCl₃) δ : 9.40 (s, 1H), 8.88-8.96 (m, 3H), 8.58 (s, 1H), 8.54 (s, 1H), 7.79 (d, J=2.8 Hz, 1H), 7.39-7.42 (m, 1H), 7.03 (d, J=2.4 Hz, 1H), 6.98 (t, J = 60.8 Hz, 1H), 6.58 (s, 1H), 4.52-4.58 (m, 1H), 3.38-3.45 (m, 1H), 2.83-2.93 (m, 1H), 2.51 (s, 3H), 2.19 (s, 3H). LCMS (ES, m/z): 570 [M+H]⁺.

Biological Assays

MALT1 Protease Assays

MALT1 protease activity was assessed in an *in vitro* assay using a tetrapeptide as substrate and full-length MALT1 protein His-MALT1(1-824) purified from baculovirus-infected insect

cells. The tetrapeptide substrate is Ac-LRSR-AMC (SM Biochemicals) with K_m measured at around 25 μ M.

The final assay buffer includes 1nM of MALT1 full-length protein, 25 μ M Ac-LRSR-AMC substrate, 50 mM Tris pH 7.5, 600 mM Sodium Citrate, 1 mM DTT, 1 mM EDTA, and 0.05 % BSA in 384-well plate format using black microtiter square well plates (Optiplate 384-F, Perkin Elmer).

Test compounds were dissolved in 100% DMSO stock of 10 mM, with final DMSO concentration of 0.1%. Test compounds were pre-incubated with MALT1 protein for 2 h at room temperature. Substrate was added after the pre-incubation and fluorescence signal was measured using Envision at excitation 355 nm and emission 460 nm after 8hr incubation at RT. Increase in the assay signal was linear over this period and proportional with increase in the enzyme content.

The fluorescence units were transformed to percentage of remaining activity by using the high control (HC, median of fluorescence signal from wells containing MALT1 protein, substrate, and DMSO) and low control (LC, median of fluorescence signal from wells with substrate only) with the formula below:

$$\% \text{Remaining Activity} = 100\% \times \frac{\text{Signal}_{\text{sample}} - \text{Signal}_{\text{LC}}}{\text{Signal}_{\text{HC}} - \text{Signal}_{\text{LC}}}$$

IC_{50} and Hill coefficients were obtained using Graph Pad Prism (Graph Pad software, Inc, USA) with non-linear regression analysis. MALT1 inhibition IC_{50} values of certain compounds described herein are provided in Tables A and B below.

Human IL10 Secretion Assays

IL10 is one of the cytokines that are regulated via activation of NF-kB signaling. For example, in ABC-DLBCL cell lines, the activated NF-kB signaling leads to increased IL10 secretion. Inhibition of NF-kB signaling has been shown leading to decreased IL10 secretion.

OCI-LY10 cells were seeded in IMEM supplemented with 20% fetal bovine serum at 4.8×10^5 cells per 160 μ L per well in 96-well V-bottom cell culture plates (corning, 3894), treated with 120 nL of 3-fold serial compound dilutions, starting at 4 mM. The final vehicle concentration was 0.075% DMSO in all wells. After a 24h incubation, human IL-10 pre-coated plates (Meso Scale Discovery) were washed 3 times with PBST, and 50 μ L culture medium was aspirated into the MSD plate and incubated at 4°C overnight. The supernatant was then discarded, and the wells were washed 3 times with PBST. SULFO-TAG Anti-human IL-10 Antibody (50X) was diluted

50-fold according to the Meso Scale Protocol, then 25 μ L of SULFO-TAG Anti-human IL-10 Antibody (1X) was added. After 2h of incubation at RT, the supernatant was discarded, and the well was washed 3 times with PBST. 2X read buffer was added and the signal was read on an MSD Sector S600. The effect of a particular compound on IL10 secretion is shown relative to the effect of DMSO; set as 100%. IC₅₀ values (nM) were determined using 4-parametric curve-fitting.

The biological activity of certain compounds using the assays described above are shown in Tables A and B. The MALT1 IC₅₀ and IL10 secretion cell assay IC₅₀ ranges are as follows: A denotes IC₅₀ < 10 nM; B denotes 10 nM $\leq$ IC₅₀ < 100 nM; C denotes 100 nM $\leq$ IC₅₀ < 1000 nM; D denotes IC₅₀ $\geq$ 1000 nM. NA denotes value not determined with that assay for the specified compound.

Table A. IC₅₀ Values for Selected Compounds of Formula (I)

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
1	A	C
2	D	NA
3	C	NA
4	D	NA
5	A	B
6	C	NA
7	C	NA
8	A	B
9	D	NA
10	C	NA
11	C	NA
12	A	C
13	D	NA
14	C	NA
15	C	NA
16	C	NA
17	D	NA
18	D	NA
19	D	NA

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
20	A	B
21	D	NA
22	B	NA
23	C	NA
24	A	B
25	D	NA
26	B	NA
27	D	NA
28	A	B
29	D	NA
30	B	NA
31	D	NA
32	A	C
33	D	NA
34	C	NA
35	C	NA
36	A	NA
37	D	NA
38	B	NA
39	B	NA
40	A	B
41	D	NA
42	C	NA
43	C	NA
44	B	NA
45	D	NA
46	C	NA
47	D	NA
48	A	NA
49	D	NA
50	B	NA
51	C	NA

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
52	B	NA
53	D	NA
54	C	NA
55	C	NA
56	B	NA
57	D	NA
58	D	NA
59	D	NA
60	B	NA
61	D	NA
62	D	NA
63	D	NA
64	B	NA
65	D	NA
66	C	NA
67	D	NA
68	A	C
69	D	NA
70	C	NA
71	D	NA
72	A	NA
73	D	NA
74	B	NA
75	C	NA
76	A	NA
77	D	NA
78	C	NA
79	C	NA
80	A	NA
81	D	NA
82	B	NA
83	C	NA

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
84	A	NA
85	D	NA
86	B	NA
87	C	NA
88	A	B
89	D	NA
90	B	NA
91	C	NA
92	A	C
93	D	NA
94	B	NA
95	C	NA
96	B	NA
97	D	NA
98	A	NA
99	D	NA
100	B	NA
101	C	NA
102	B	NA
103	D	NA
104	C	NA
105	C	NA
106	A	B
107	D	NA
108	C	NA
109	C	NA
110	A	B
111	D	NA
112	C	NA
113	C	NA
114	B	NA
115	C	NA

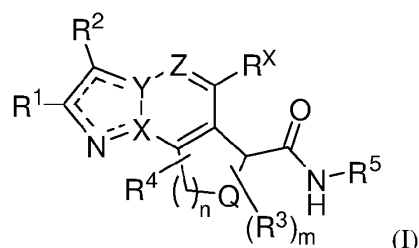
Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
116	A	C
117	C	NA
118	B	NA
119	D	NA
120	A	B
121	D	NA
122	C	NA
123	C	NA
124	A	B
125	D	NA
126	B	NA
127	B	NA
128	B	NA
129	D	NA
130	C	NA
131	D	NA
132	B	NA
133	C	NA
134	B	NA
135	C	NA
136	A	B
137	D	NA
138	C	NA
139	C	NA
140	A	B
141	D	NA
142	D	NA
143	D	NA
144	A	C
145	D	NA
146	C	NA
147	C	NA

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
148	B	C
149	D	NA
150	C	NA
151	C	NA
152	A	NA
153	D	NA
154	C	NA
155	D	NA
156	B	NA
157	D	NA
158	B	NA
159	D	NA
160	C	NA
161	D	NA
162	B	NA
163	D	NA
164	A	NA
165	D	NA
166	C	NA
167	C	NA
168	B	NA
169	D	NA
170	C	NA
171	A	NA
172	D	NA
173	B	NA
174	C	NA
175	B	NA
176	D	NA
177	A	NA
178	C	NA
179	D	NA

Example No.	MALT1 IC ₅₀ [nM]	IL-10 Secretion IC ₅₀ [nM]
180	C	NA
181	D	NA
182	D	NA
183	B	NA
184	D	NA
185	A	NA
186	D	NA
187	B	NA
188	C	NA
189	B	NA
190	D	NA
191	D	NA
192	C	NA
193	B	NA
194	D	NA
195	B	NA
196	C	NA

WHAT IS CLAIMED IS:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

- 5 each $\text{---}^{\text{***}}$ is a single or double bond;
 Q is $\text{---CH}_2\text{---}$, O, or NH;
 X is N or C;
 Y is N or C;
 Z is N or CR^6 ;
 10 wherein when one of X and Y is N, the other of X and Y is C;
 n is 1, 2, or 3;
 R^x is hydrogen or halogen;
 R^1 is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy,
 C1-C3 haloalkyl, $\text{---NR}^a\text{R}^b$, or C1-C3 alkyl optionally substituted with 1-3 substituents selected
 15 from hydroxyl and C1-C3 alkoxy;
 R^2 is hydrogen, halogen, amino, or C1-C3 alkyl;
 each R^3 is independently deuterium, halogen, C3-C6 cycloalkyl, C1-C3 alkyl,
 C1-C3 alkoxy, C1-C3 haloalkoxy, or C1-C3 haloalkyl;
 m is 0, 1, 2, or 3;
 20 R^4 is 5-10 membered heteroaryl optionally substituted with one to three substituents each
 independently selected from R^7 ;
 R^5 is phenyl or 5-9 membered heteroaryl, wherein each R^5 group is optionally substituted
 with 1-3 substituents independently selected from R^8 ;
 R^6 is hydrogen, halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy,
 25 C1-C3 haloalkyl, $\text{---NR}^c\text{R}^d$, and C1-C3 alkyl;

each R^7 is independently selected from the group consisting of halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 haloalkyl, oxetanyl, $-NR^C R^D$, C1-C3 alkyl optionally substituted with one cyclopropyl; and C3-C7 cycloalkyl optionally substituted with one C1-C3 alkyl;

5 each R^8 is independently selected from halogen; cyano; amino; $-N=(S=O)(C1-C3 \text{ alkyl})_2$; $-S(=O)_p(C1-C3 \text{ alkyl})$; 1-imino-1-lambda⁶-thietanyl 1-oxide, $-(C=O)NR^E R^F$; C1-C3 alkoxy; C1-C3 haloalkyl optionally substituted with hydroxyl; C1-C3 haloalkoxy; 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, amino, C1-C3 haloalkyl, 4-6 membered heterocyclyl, or C1-C3 alkyl
 10 optionally substituted with hydroxyl or $-NR^E R^F$; C1-C4 alkyl optionally substituted with hydroxyl, $-NR^E R^F$, or C1-C3 alkoxy; 3-8 membered heterocyclyl; and C3-C6 cycloalkoxy;

p is 1 or 2; and

R^A , R^B , R^C , R^D , R^E , and R^F , are independently hydrogen, C1-C3 alkyl, C3-C6 cycloalkyl, or R^A and R^B , or R^C and R^D , or R^E and R^F , together with the nitrogen atom to which they are attached
 15 come together to form a 4-6 membered heterocyclyl optionally substituted with 1-2 halogens.

2. The compound of claim 1, wherein X is N and Y is C.

3. The compound of claim 1 or 2, wherein Z is N.

4. The compound of any one of claims 1-3, wherein R^X is hydrogen.

5. The compound of any one of claims 1-4, wherein Q is $-\text{CH}_2-$.

20 6. The compound of any one of claims 1-5, wherein R^1 is halogen.

7. The compound of any one of claims 1-6, wherein R^2 is hydrogen.

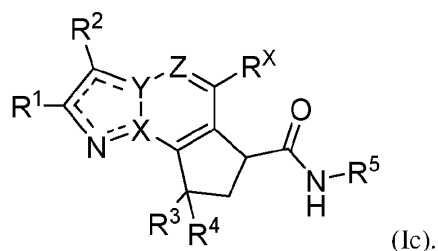
8. The compound of any one of claims 1-7, wherein n is 1.

9. The compound of any one of claims 1-8, wherein m is 1.

10. The compound of any one of claims 1-9, wherein each R^3 is independently halogen,
 25 C3-C6 cycloalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

11. The compound of any one of claims 1-10, wherein m is 1 and R³ is methyl or trifluoromethyl.

12. A compound according to anyone of claims 1-11, which is a compound according to formula (Ic), or a pharmaceutically acceptable salt thereof



13. The compound of any one of claims 1-12, wherein R⁴ is a 5 or 6 membered heteroaryl optionally substituted with one to three substituents each independently selected from R⁷.

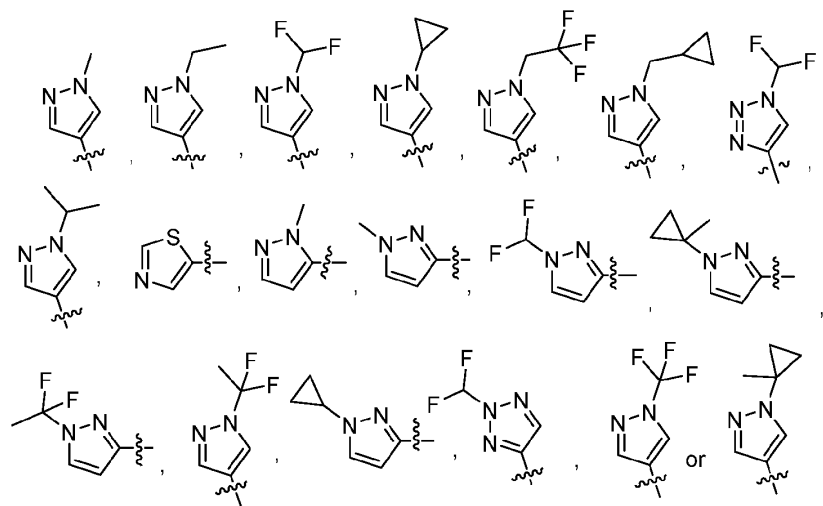
14. The compound of any one of claims 1-13, wherein R⁴ is a 6 membered heteroaryl optionally substituted with one to three substituents each independently selected from R⁷.

15 15. The compound of any one of claims 1-13, wherein R⁴ is a 5 membered heteroaryl optionally substituted with one to three substituents each independently selected from R⁷.

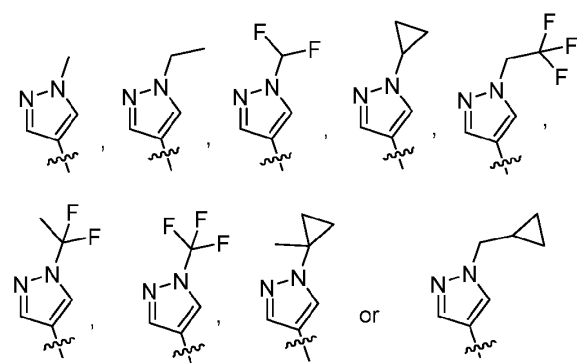
16. The compound of any one of claims 1-13 and 15, wherein R⁴ is 4H-pyrazolyl, 3H-pyrazolyl, triazolyl, or thiazolyl optionally substituted with one to three substituents each independently selected from R⁷.

15 17. The compound of any one of claims 1-16, wherein each R⁷ is independently selected from the group consisting of C1-C3 haloalkyl, C1-C3 alkyl optionally substituted with one cyclopropyl, and C3-C7 cycloalkyl optionally substituted with one C1-C3 alkyl.

18. The compound of any one of claims 1-13 and 15-17 wherein R^4 is:

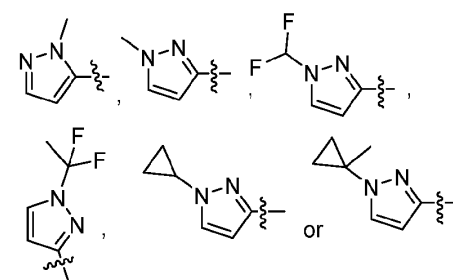


19. The compound of any one of claims 1-13, and 15-18 wherein R^4 is:

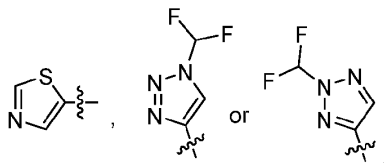


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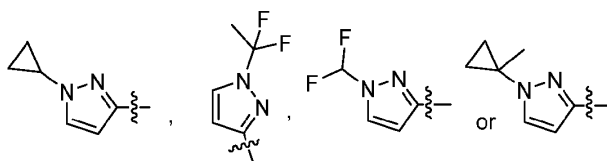
20. The compound of any one of claims 1-13 and 15-18 wherein R^4 is:



21. The compound of any one of claims 1-13 and 15-18 wherein R^4 is:



22. The compound of any one of claims 1-13, 15-18 and 20 wherein R^4 is:



5 23. The compound of any one of claims 1-22, wherein R^5 is phenyl optionally substituted with 1-3 independently selected R^8 .

24. The compound of any one of claims 1-22, wherein R^5 is 5-9 membered heteroaryl optionally substituted with 1-3 independently selected R^8 .

10 25. The compound of any one of claims 1-22 and 24, wherein R^5 is 5-6 membered heteroaryl substituted with 1-3 independently selected R^8 .

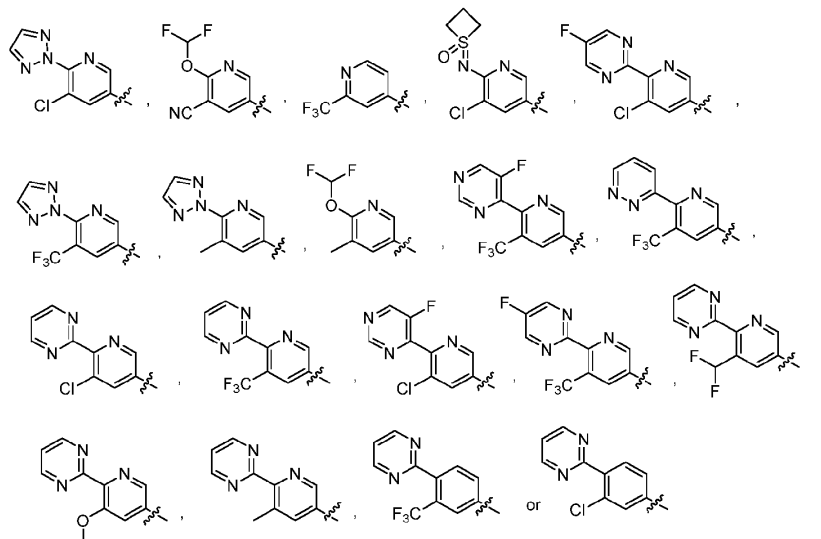
26. The compound of any one of claims 1-22, 24 and 25 wherein R^5 is 3-pyridyl or 4-pyridyl optionally substituted with 1-3 independently selected R^8 .

27. The compound of any one of claims 1-26, wherein at least one of R^8 is halogen.

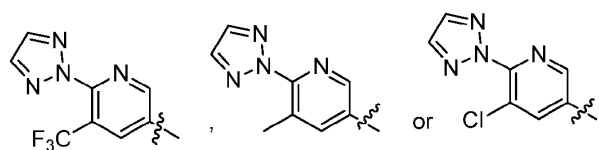
15 28. The compound of any one of claims 1-27, wherein at least one of R^8 is 5-6 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$, amino, or C1-C3 haloalkyl.

20 29. The compound of any one of claims 1-28, wherein at least one of R^8 is 5 membered heteroaryl optionally substituted with halogen, cyano, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C1-C3 alkyl optionally substituted with hydroxyl or $-NR^E R^F$, amino, or C1-C3 haloalkyl.

30. The compound of any one of claims 1-26 wherein R⁵ is:

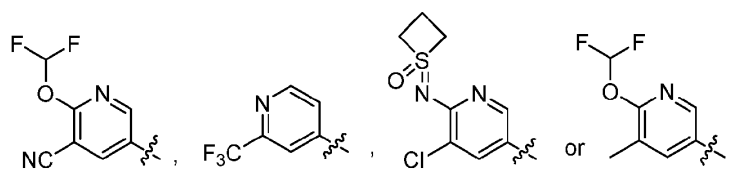


31. The compound of any one of claims 1-26, and 30 wherein R⁵ is:

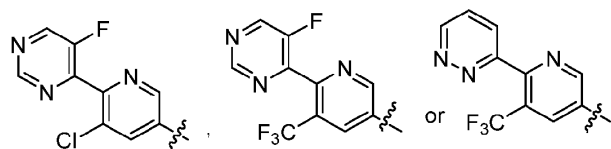


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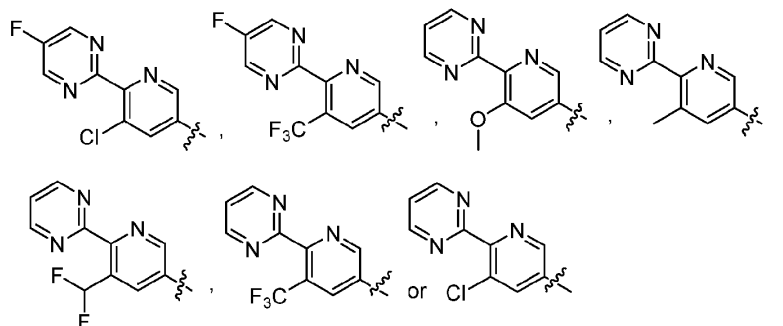
32. The compound of any one of claims 1-26 and 30 wherein R⁵ is:



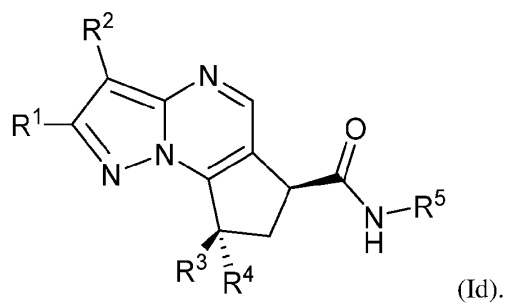
33. The compound of any one of claims 1-26 and 30 wherein R⁵ is:



34. The compound of any one of claims 1-26 and 30 wherein R⁵ is:

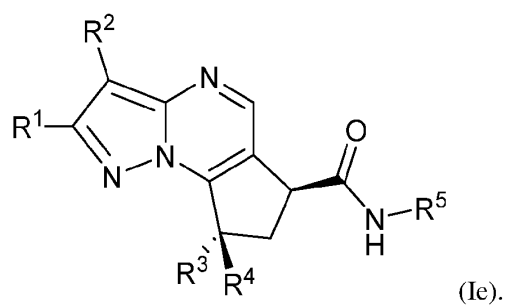


35. A compound according to anyone of claims 1-34, which is a compound according to formula (Id), or a pharmaceutically acceptable salt thereof

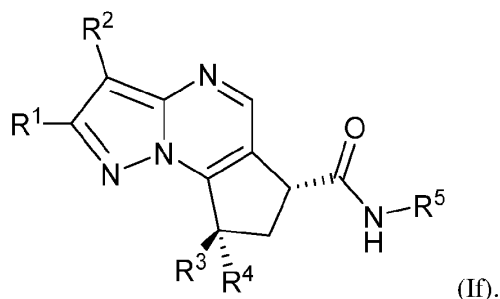


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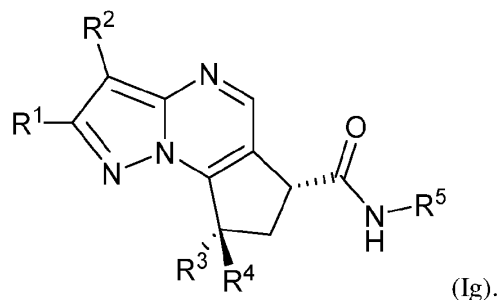
36. A compound according to anyone of claims 1-34, which is a compound according to formula (Ie), or a pharmaceutically acceptable salt thereof



37. A compound according to anyone of claims 1-34, which is a compound according to formula (If), or a pharmaceutically acceptable salt thereof



38. A compound according to anyone of claims 1-34, which is a compound according to
5 formula (Ig), or a pharmaceutically acceptable salt thereof



39. A compound according to claim 1, selected from Table 1, or a pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition comprising a compound according to any one of
10 claims 1-39, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients.

41. A method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 40.

15 42. The method of claim 41 wherein the cancer is a MALT1-associated cancer.

43. The method of claims 41 or 42 wherein the cancer is lymphoma.

44. The method of claim 43 wherein the lymphoma is non-Hodgkin lymphoma, DLBCL, refractory DLBCL, (ABC) subtype of DLBCL, mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL).

45. The method of claims 41 or 42 wherein the cancer is leukemia.

5 46. The method of claim 45 where in the leukemia is chronic lymphocytic leukemia (CLL).

47. The method of claim 41 or 42 wherein the cancer is a solid tumor.

48. A method of treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 40.

10 49. The method according to claim 48 wherein the autoimmune disorder is chronic graft versus host disease.

50. The method of any one of claims 41-49, further comprising administering an additional therapy or therapeutic agent to the subject.