

2-AZABICYCLO[2.2.1]HEPTANE KRAS INHIBITORS

RELATED APPLICATIONS

This application is related to U.S. Provisional Application No. 63/496,859, filed April 18, 2023, U.S. Provisional Application No. 63/580,824, filed September 6, 2023, and
5 U.S. Provisional Application No. 63/557,251, filed February 23, 2024, the contents of which are incorporated in their entirety.

FIELD OF THE INVENTION

This disclosure provides compounds as well as their compositions and methods of use. The compounds modulate KRAS activity and are useful in the treatment of various
10 diseases including cancer.

BACKGROUND OF THE INVENTION

Ras proteins are part of the family of small GTPases that are activated by growth factors and various extracellular stimuli. The Ras family regulates intracellular signaling pathways responsible for growth, migration, survival and differentiation of cells. Activation of
15 Ras proteins at the cell membrane results in the binding of key effectors and initiation of a cascade of intracellular signaling pathways within the cell, including the RAF and PI3K kinase pathways. Somatic mutations in RAS may result in uncontrolled cell growth and malignant transformation while the activation of RAS proteins is tightly regulated in normal cells (D. Simanshu, *et al.*, *Cell*, **2017**, 170(1), 17-33).

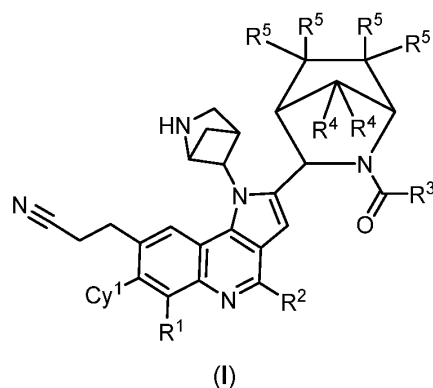
20 The Ras family is comprised of three members: KRAS, NRAS and HRAS. RAS mutant cancers account for about 25% of human cancers. KRAS is the most frequently mutated isoform accounting for 85% of all RAS mutations whereas NRAS and HRAS are found mutated in 12% and 3% of all Ras mutant cancers respectively (D. Simanshu, *et al.*, *Cell*, **2017**, 170(1), 17-33). KRAS mutations are prevalent amongst the top three most
25 deadly cancer types: pancreatic (97%), colorectal (44%), and lung (30%) (A. D. Cox, *et al.* *Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51). The majority of RAS mutations occur at amino acid residue 12, 13, and 61. The frequency of specific mutations varies between RAS gene isoforms and while G12 and Q61 mutations are predominant in KRAS and NRAS respectively, G12, G13 and Q61 mutations are most frequent in HRAS. Furthermore, the
30 spectrum of mutations in a RAS isoform differs between cancer types. For example, KRAS G12D mutations predominate in pancreatic cancers (51%), followed by colorectal adenocarcinomas (45%) and lung cancers (17%) while KRAS G12V mutations are associated with pancreatic cancers (30%), followed by colorectal adenocarcinomas (27%), and lung adenocarcinomas (23%) (A. D. Cox, *et al.* *Nat. Rev. Drug. Discov.*, **2014**, 13(11),
35 828-51). In contrast, KRAS G12C mutations predominate in non-small cell lung cancer

(NSCLC) comprising 11-16% of lung adenocarcinomas, and 2-5% of pancreatic and colorectal adenocarcinomas (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51). Genomic studies across hundreds of cancer cell lines have demonstrated that cancer cells harboring KRAS mutations are highly dependent on KRAS function for cell growth and survival (R. McDonald, *et al., Cell*, **2017**, 170(3), 577-92). The role of mutant KRAS as an oncogenic driver is further supported by extensive in vivo experimental evidence showing mutant KRAS is required for early tumor onset and maintenance in animal models (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51).

Taken together, these findings indicate that KRAS mutations play a critical role in human cancers. Development of inhibitors targeting KRAS, including mutant KRAS, will therefore be useful in the clinical treatment of diseases that are characterized by involvement of KRAS, including diseases characterized by the involvement or presence of a KRAS mutation.

SUMMARY

The present disclosure provides, *inter alia*, a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

The present disclosure further provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The present disclosure further provides methods of inhibiting KRAS activity, which comprises administering to an individual a compound of the disclosure, or a

pharmaceutically acceptable salt thereof. The present disclosure also provides uses of the compounds described herein in the manufacture of a medicament for use in therapy. The present disclosure also provides the compounds described herein for use in therapy.

The present disclosure further provides methods of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

DETAILED DESCRIPTION

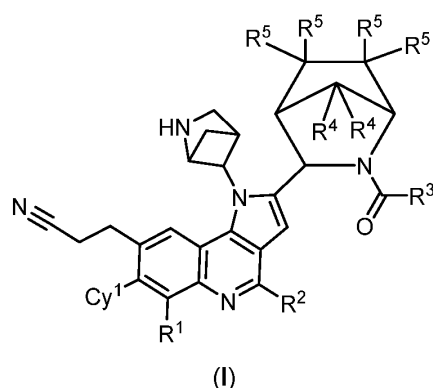
For the terms "e.g." and "such as," and grammatical equivalents thereof, the phrase "and without limitation" is understood to follow unless explicitly stated otherwise.

The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

The term "about" means "approximately" (e.g., plus or minus approximately 10% of the indicated value).

I. Compounds

In an aspect, provided herein is a compound having Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Cy¹ is phenyl optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, OH, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy;

R¹ is halogen;

R² is selected from H, D, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, C₃₋₅ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-6 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, NR^{e2}R^{e2}, and NR^{c2}C(O)R^{b2}; wherein the C₃₋₅ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-6 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene forming R² are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A};

wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, and 4-6 membered heterocycloalkyl-C₁₋₃ alkylene forming R² consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, and 4-6 membered heterocycloalkyl-C₁₋₃ alkylene forming R² is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R² are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B};

each R^{a2} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl; wherein the C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl forming R^{a2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A}; wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{a2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{a2} is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl forming R^{a2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B};

each R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl; wherein the C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl forming R^{b2}, R^{c2}, and R^{d2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A}; the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{b2}, R^{c2}, and R^{d2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{b2}, R^{c2}, and R^{d2} is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{b2}, R^{c2}, and R^{d2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B}; or

any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, or 6-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B};

each R^{e2} is independently selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl; wherein the C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl and 5-6

membered heteroaryl forming R^{e2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A} ; wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{e2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{e2} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, forming R^{e2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ; or

R^{c2} and R^{e2} attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, or 6-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ;

each R^{2A} is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, and R^{2B} , wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, forming R^{2A} are each optionally substituted with 1, 2 or 3 substituents independently selected from R^{2B} ;

each R^{2B} is independently selected from C_{3-6} cycloalkyl, 4-10 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, halo, D, CN, OR^{a2B} , $C(O)R^{b2B}$, $C(O)NR^{c2B}R^{d2B}$, $C(O)OR^{a2B}$, $NR^{c2B}R^{d2B}$, and $S(O)_2R^{b2B}$; wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2C} ;

each R^{2C} is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, halo, D, CN, OR^{a2C} , $C(O)R^{b2C}$, $C(O)NR^{c2C}R^{d2C}$, $C(O)OR^{a2C}$, $NR^{c2C}R^{d2C}$, and $S(O)_2R^{b2C}$;

each R^{a2B} , R^{b2B} , R^{c2B} and R^{d2B} is independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

each R^{a2C} , R^{b2C} , R^{c2C} and R^{d2C} is independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^3 is selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, OR^{3A} , and $NR^{3B}R^{3C}$; wherein the C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl C_{1-3} alkyl forming R^3 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D} ; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^3 consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl or 5-10 membered heteroaryl forming R^3 is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^3 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

R^{3A} is selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein the C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl C₁₋₃ alkyl forming R^{3A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3A} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl or 5-10 membered heteroaryl forming R^{3A} is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{3A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E};

R^{3B} is selected from H, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein the C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl forming R^{3B} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3B} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3B} is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{3B} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E};

R^{3B} and R^{3C}, together with the N atom to which they are both attached, optionally form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group that is optionally substituted with 1, 2, or 3 substituents independently selected from independently selected from R^{3D};

R^{3C} is selected from H, C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl; wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{3C} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E};

each R^{3D} is independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, and R^{3E}; wherein each of the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{3D} is optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E};

each R^{3E} is independently selected from D, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

R^{a3}, R^{b3}, R^{c3}, and R^{d3} are each independently selected from H, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₆₋₁₀ aryl, C₃₋₇ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered

heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl; wherein the C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3}, R^{b3}, R^{c3}, and R^{d3} are each optionally substituted with

1 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, CN, OR^{a3A}, SR^{a3A}, C(O)R^{b3A}, C(O)NR^{c3ARd3A}, C(O)OR^{a3A}, OC(O)R^{b3A}, OC(O)NR^{c3ARd3A}, NR^{c3ARd3A}, NR^{c3A}C(O)R^{b3A}, NR^{c3A}C(O)NR^{c3ARd3A}, NR^{c3A}C(O)OR^{a3A}, C(=NR^{e3A})NR^{c3ARd3A}, NR^{c3A}C(=NR^{e3A})NR^{c3ARd3A}, S(O)R^{b3A}, S(O)NR^{c3ARd3A}, S(O)₂R^{b3A}, NR^{c3A}S(O)₂R^{b3A}, and S(O)₂NR^{c3ARd3A}; wherein the ring-forming atoms of the 4-10 membered

10 heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3}, R^{b3}, R^{c3}, and R^{d3} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3},

15 R^{b3}, R^{c3}, and R^{d3} is optionally substituted by oxo to form a carbonyl group; or

R^{c3} and R^{d3} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, CN, OR^{a3A}, SR^{a3A},

20 C(O)R^{b3A}, C(O)NR^{c3ARd3A}, C(O)OR^{a3A}, OC(O)R^{b3A}, OC(O)NR^{c3ARd3A}, NR^{c3ARd3A}, NR^{c3A}C(O)R^{b3A}, NR^{c3A}C(O)NR^{c3ARd3A}, NR^{c3A}C(O)OR^{a3A}, C(=NR^{e3A})NR^{c3ARd3A}, NR^{c3A}C(=NR^{e3A})NR^{c3ARd3A}, S(O)R^{b3A}, S(O)NR^{c3ARd3A}, S(O)₂R^{b3A}, NR^{c3A}S(O)₂R^{b3A}, and S(O)₂NR^{c3ARd3A};

R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} are each independently selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, aryl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl; wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} are each optionally substituted with 1, 2, or 3 substituents

30 independently selected from OH, CN, amino, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} consist of at least one carbon atom, and 1, 2, 3, or 4 heteroatoms selected from O, N, and S;

35 and wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered

heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} is optionally substituted by oxo to form a carbonyl group; or

R^{c3A} and R^{d3A} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; R^{e3}, and R^{e3A} are each, independently, H, CN or NO₂;

each R⁴ is independently selected from H, D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, and OR^{a4};

each R^{a4} is independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OR^{a5}, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl; or, optionally, two other R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo;

R^{5A} is H, D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, OR^{a5A}, CN, or Cy²; wherein the C₁₋₃ alkyl forming R^{5A} is optionally substituted with 1, 2, 3 or 4 substituents each selected from R^{5B} and also optionally substituted with Cy², or, optionally, R^{5A} and R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo; or, optionally, R^{5A} and R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo;

each R^{5B} is independently selected from D and halo;

each R^{a5} is independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R^{a5A} is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents each selected from R^{5B} and also optionally substituted with Cy²;

Cy² is selected from C₃₋₇ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein the C₃₋₇ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl forming Cy² is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered

heteroaryl forming Cy² consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; and wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming Cy² is optionally substituted by oxo to form a carbonyl group;

- 5 each R^{Cy2} is independently selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₆ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, CN, OR^{aCy21}, SR^{aCy21}, C(O)R^{bCy21}, C(O)NR^{cCy21}R^{dCy21}, C(O)OR^{aCy21}, OC(O)R^{bCy21}, OC(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)R^{bCy21}, NR^{cCy21}C(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)OR^{aCy21}, C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, NR^{cCy21}C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, S(O)R^{bCy21}, S(O)NR^{cCy21}R^{dCy21}, S(O)₂R^{bCy21}, NR^{cCy21}S(O)₂R^{bCy21}, and S(O)₂NR^{cCy21}R^{dCy21}; wherein the C₃₋₆ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl forming R^{Cy2} are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from R^{Cy2A}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{Cy2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{Cy2} is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{Cy2} are each optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy2B};

- 20 each R^{Cy2A} is independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, and R^{Cy2B}; wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R^{Cy2A} are each optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy2B};
- each R^{Cy2B} is independently selected from D, halo, CN, OR^{aCy21}, SR^{aCy21}, C(O)R^{bCy21}, C(O)NR^{cCy21}R^{dCy21}, C(O)OR^{aCy21}, OC(O)R^{bCy21}, OC(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)R^{bCy21}, NR^{cCy21}C(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)OR^{aCy21}, C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, NR^{cCy21}C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, S(O)R^{bCy21}, S(O)NR^{cCy21}R^{dCy21}, S(O)₂R^{bCy21}, NR^{cCy21}S(O)₂R^{bCy21}, and S(O)₂NR^{cCy21}R^{dCy21};

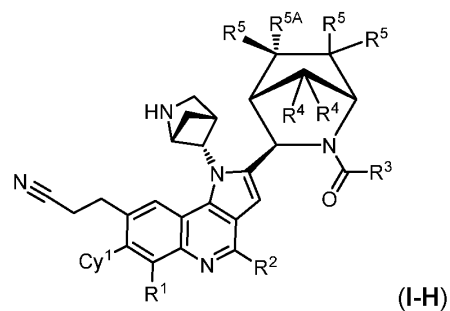
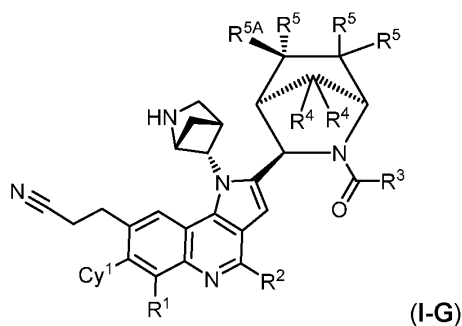
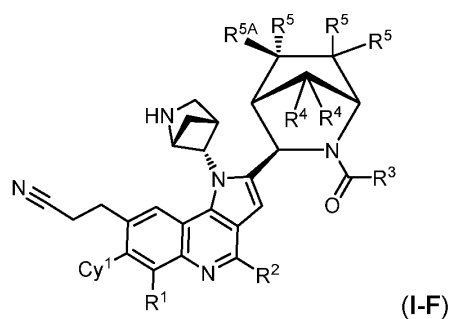
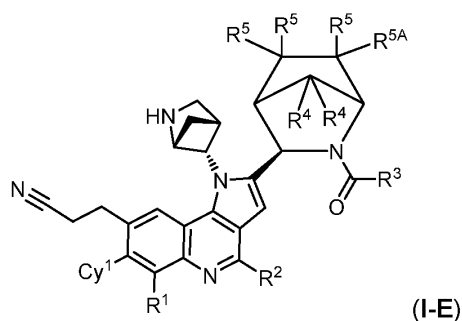
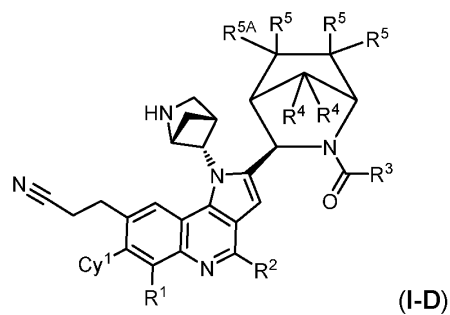
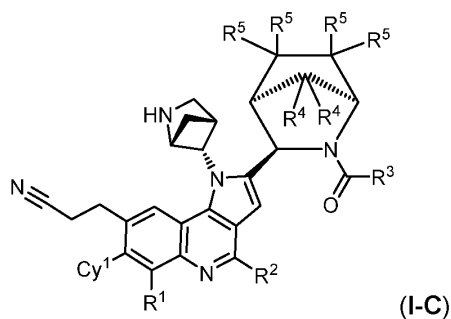
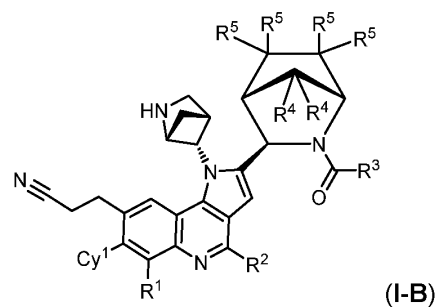
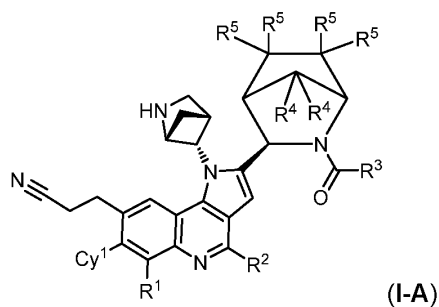
- 30 R^{aCy21}, R^{bCy21}, R^{cCy21}, and R^{dCy21} are each independently selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₆₋₁₀ aryl, C₃₋₇ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl; wherein the C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{aCy21}, R^{bCy21}, R^{cCy21}, and R^{dCy21} are each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, CN, OR^{aCy22}, SR^{aCy22}, C(O)R^{bCy22}, C(O)NR^{cCy22}R^{dCy22}, C(O)OR^{aCy22}, OC(O)R^{bCy22}, OC(O)NR^{cCy22}R^{dCy22}, NR^{cCy22}R^{dCy22},

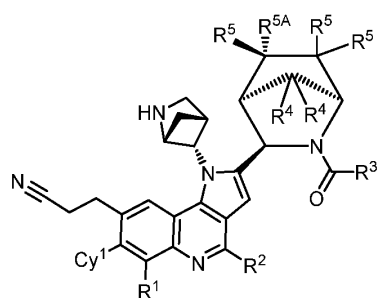
- $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{R}^{\text{bCy22}}$, $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{OR}^{\text{aCy22}}$, $\text{C}(=\text{NR}^{\text{eCy22}})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$,
 $\text{NR}^{\text{cCy22}}\text{C}(=\text{NR}^{\text{eCy22}})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{S}(\text{O})\text{R}^{\text{bCy22}}$, $\text{S}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{S}(\text{O})_2\text{R}^{\text{bCy22}}$,
 $\text{NR}^{\text{cCy22}}\text{S}(\text{O})_2\text{R}^{\text{bCy22}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, wherein the ring-forming atoms each of the 5-10
 5 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3}
 alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21}
 consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected
 from N, O, and S; and wherein a ring-forming carbon atom of the 5-10 membered heteroaryl,
 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, and 4-10 membered
 heterocycloalkyl- C_{1-3} alkyl forming R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21} is optionally substituted by
 10 oxo to form a carbonyl group;
 or R^{cCy21} and R^{dCy21} attached to the same N atom, together with the N atom to which
 they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-
 membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents
 independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, halo, CN,
 15 OR^{aCy22} , SR^{aCy22} , $\text{C}(\text{O})\text{R}^{\text{bCy22}}$, $\text{C}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{C}(\text{O})\text{OR}^{\text{aCy22}}$, $\text{OC}(\text{O})\text{R}^{\text{bCy22}}$,
 $\text{OC}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{R}^{\text{bCy22}}$, $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$,
 $\text{NR}^{\text{cCy22}}\text{C}(\text{O})\text{OR}^{\text{aCy22}}$, $\text{C}(=\text{NR}^{\text{eCy22}})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{NR}^{\text{cCy22}}\text{C}(=\text{NR}^{\text{eCy22}})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{S}(\text{O})\text{R}^{\text{bCy22}}$,
 $\text{S}(\text{O})\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$, $\text{S}(\text{O})_2\text{R}^{\text{bCy22}}$, $\text{NR}^{\text{cCy22}}\text{S}(\text{O})_2\text{R}^{\text{bCy22}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{cCy22}}\text{R}^{\text{dCy22}}$,
 R^{aCy22} , R^{bCy22} , R^{cCy22} , and R^{dCy22} are each independently selected from H, C_{1-3} alkyl,
 20 C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl-
 C_{1-3} alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl; wherein
 the C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl- C_{1-3}
 alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy22} ,
 R^{bCy22} , R^{cCy22} , and R^{dCy22} are each optionally substituted with 1, 2, or 3 substituents
 25 independently selected from OH, CN, amino, $\text{NH}(\text{C}_{1-3}$ alkyl), $\text{N}(\text{C}_{1-3}$ alkyl)₂, halo, C_{1-3} alkyl,
 C_{1-3} alkoxy, C_{1-3} haloalkyl, and C_{1-3} haloalkoxy; wherein the ring-forming atoms each of the 5-
 10 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3}
 alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy22} , R^{bCy22} , R^{cCy22} , and R^{dCy22}
 consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected
 30 from N, O, and S; and wherein a ring-forming carbon atom of the 5-10 membered heteroaryl,
 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, and 4-10 membered
 heterocycloalkyl- C_{1-3} alkyl forming R^{aCy22} , R^{bCy22} , R^{cCy22} , and R^{dCy22} is optionally substituted by
 oxo to form a carbonyl group; or
 R^{cCy22} and R^{dCy22} attached to the same N atom, together with the N atom to which
 35 they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-
 membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents

independently selected from OH, CN, amino, $\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, halo, $\text{C}_{1-3} \text{ alkyl}$, $\text{C}_{1-3} \text{ alkoxy}$, $\text{C}_{1-3} \text{ haloalkyl}$, and $\text{C}_{1-3} \text{ haloalkoxy}$; and

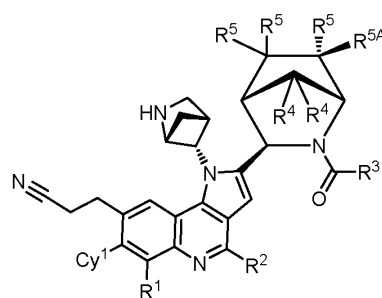
$\text{R}^{\text{eCy}21}$ and $\text{R}^{\text{eCy}22}$ are each, independently, H, CN or NO_2 .

In an embodiment, the compound of Formula (I) is a compound of any one of the
5 Formulae (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), and (I-M):

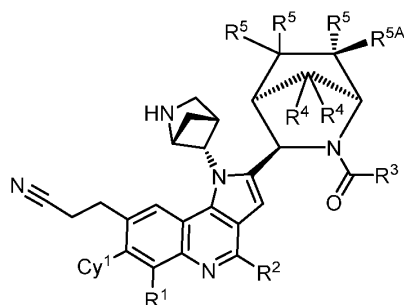




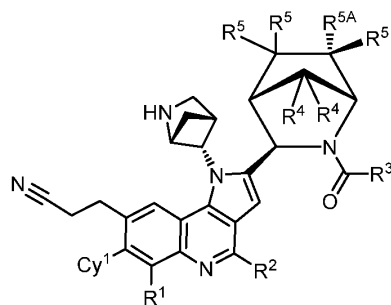
(I-I)



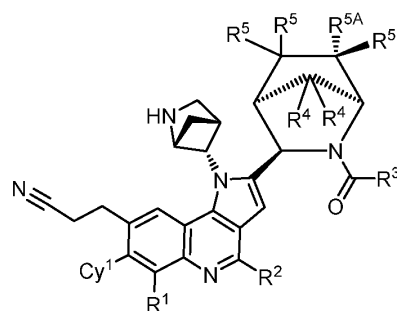
(I-J)



(I-K)



(I-L)



(I-M)

or a pharmaceutically acceptable salt thereof.

In another embodiment of the compound of Formula (I), or a pharmaceutically acceptable salt thereof:

- 5 Cy¹ is phenyl optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, and C₁₋₃ alkoxy;
- R¹ is halo;
- R² is C₁₋₃ alkyl optionally substituted with OH;
- R³ is C₃₋₁₀ cycloalkyl optionally substituted with halo;
- each R⁴ is H;
- 10 one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and
- 15 R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and Cy² is selected from C₆₋₁₀ aryl and 5-10 membered heteroaryl.

In another embodiment of the compound of Formula (I), or a pharmaceutically acceptable salt thereof:

Cy¹ is phenyl optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, and C₁₋₃ alkoxy;

R¹ is halo;

R² is C₁₋₃ alkyl optionally substituted with OH;

R³ is C₃₋₁₀ cycloalkyl optionally substituted with halo;
each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and Cy² is selected from C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl.

In yet another embodiment of the compound of Formula (I), or a pharmaceutically acceptable salt thereof:

Cy¹ is phenyl optionally substituted with 2 substituents each selected from halo;

R¹ is halo;

R² is C₁₋₃ alkyl optionally substituted with OH;

R³ is cyclopropyl optionally substituted with halo;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused cyclopropyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and Cy² is selected from phenyl and pyridinyl.

In still another embodiment of the compound of Formula (I), or a pharmaceutically acceptable salt thereof:

Cy¹ is 2,3-dichlorophenyl;

R¹ is halo;

5 R² is methyl or 1-hydroxyethyl;

R³ is cyclopropyl optionally substituted with fluoro;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms,
10 together with the carbon atoms to which they are each attached, form a fused cyclopropyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo;

R^{5A} is H, halo, OC₁₋₃ alkyl, OC₁₋₃ haloalkyl, OCD₃, O-pyridinyl, and O-benzyl; and

Cy² is selected from phenyl and pyridinyl.

15 In other embodiment of the compound of Formula (I), or a pharmaceutically acceptable salt thereof:

Cy¹ is 2,3-dichlorophenyl;

R¹ is halo;

R² is methyl or 1-hydroxyethyl;

20 R³ is cyclopropyl optionally substituted with fluoro;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused cyclopropyl
25 ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, OC₁₋₃ alkyl, OC₁₋₃ haloalkyl, OCD₃, O-pyridinyl, and O-benzyl.

In another embodiment of Formula (I), or a pharmaceutically acceptable salt thereof,

Cy¹ is 2,3-dichlorophenyl;

30 R¹ is halo;

R² is methyl or 1-hydroxyethyl;

R³ is cyclopropyl optionally substituted with fluoro;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms,
35 together with the carbon atoms to which they are each attached, form a fused cyclopropyl

ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, OC₁₋₃ alkyl, OC₁₋₃ haloalkyl, OCD₃, O-cyclopropyl, O-pyridinyl, and O-benzyl.

5 In another embodiment, Cy¹ is phenyl optionally substituted with 1, 2, or 3 substituents, (or 1 or 2 substituents, or 1 substituent) independently selected from C₁₋₃ alkyl (such as methyl), C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo (such as fluoro or chloro), OH, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy. In yet another embodiment, Cy¹ is phenyl optionally substituted with 1, 2, or 3 substituents, (or 1 or 2 substituents, or 1 substituent)
10 independently selected from , C₁₋₃ alkyl (such as methyl) and halo (such as fluoro or chloro). In still another embodiment, Cy¹ is 2-chloro-3-methylphenyl. In an embodiment, Cy¹ is 2,3-dichlorophenyl.

In another embodiment, R¹ is halo. In yet another embodiment, R¹ is fluoro. In still another embodiment, R¹ is H.

15 In another embodiment, R⁴ is H.

In an embodiment, R² is C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R² are each optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}.

In another embodiment, R² is C₁₋₃ alkyl (e.g., methyl or ethyl) optionally substituted
20 with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}. In yet another embodiment, R² is methyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}. In still another embodiment, R² is methyl. In an embodiment, R² is ethyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from
25 R^{2B}. In another embodiment, R² is ethyl. In yet another embodiment, R² is 1-hydroxyethyl.

In still another embodiment, R² is 4-6 membered heterocycloalkyl (or 4-membered, or 5-membered-, or 6-membered heterocycloalkyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A}. In an embodiment, R² is azetidin-1-yl optionally substituted with 1, 2, or 3 substituents (or 1 or 2
30 substituents, or 1 substituent) independently selected from R^{2A}. In another embodiment, R² is 2-methyl-2-(N,N-dimethylamino)-2-methylazetidin-1-yl.

In yet another embodiment, R² is 5-6 membered heteroaryl (or 5-membered or 6-membered heteroaryl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A}. In still another embodiment,
35 R² is 6 membered heteroaryl (e.g., pyridyl, such as 2-pyridyl, 3-pyridyl, or 4-pyridyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A}.

In an embodiment, R^2 is 6 membered heteroaryl (e.g., pyridyl, such as 2-pyridyl, 3-pyridyl, or 4-pyridyl) optionally substituted with 2-hydroxypropyl or with $C(O)NR^{c2B}R^{c2D}$ (such as $C(O)NH_2$, $C(O)NHMe$, or $C(O)NMe_2$). In another embodiment, R^2 is OR^{a2} .

In yet another embodiment, each R^{2A} is independently selected from C_{1-3} alkyl, $NR^{c2B}R^{c2D}$ (such as NH_2 , $NHMe$, or NMe_2), or $C(O)NR^{c2B}R^{c2D}$ (such as $C(O)NH_2$, $C(O)NHMe$, or $C(O)NMe_2$), wherein the C_{1-3} alkyl forming R^{2A} is optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) each independently selected from R^{2B} . In still another embodiment, each R^{2A} is independently selected from C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) each independently selected from R^{2B} . In an embodiment, R^{2A} is R^{2B} .

In another embodiment, R^3 is C_{1-3} alkyl (such as methyl or ethyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} .

In yet another embodiment, R^3 is C_{3-10} cycloalkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} . In still another embodiment, R^3 is C_{3-7} cycloalkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} . In an embodiment, R^3 is C_{3-6} cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} .

In another embodiment, R^3 is cyclobutyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} . In yet another embodiment, R^3 is cyclopropyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} . In still another embodiment, R^3 is cyclopropyl. In an embodiment, R^3 is 1-fluorocycloprop-1-yl. In another embodiment, R^3 is 1-methylcycloprop-1-yl.

In another embodiment, R^3 is C_{6-10} aryl (such as phenyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} . In yet another embodiment, R^3 is 5-10 membered heteroaryl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} .

In still another embodiment, R^3 is OR^{3A} . In an embodiment, R^3 is $NR^{3B}R^{3C}$.

In another embodiment, R^4 is independently selected from H, D, C_{1-3} alkyl (such as methyl or ethyl), C_{1-3} haloalkyl (such as trifluoroalkyl), and halo (such as fluoro). In yet another embodiment, each R^4 is independently selected from H, D, C_{1-3} alkyl (such as methyl or ethyl), and halo (such as fluoro). In still another embodiment, each R^4 is independently selected from H, methyl, and fluoro. In an embodiment, each R^4 is independently selected from H and methyl. In another embodiment, one R^4 is H and one R^4

is methyl. In yet another embodiment, each R^4 is H. In still another embodiment, each R^4 is methyl.

In an embodiment, one R^5 is R^{5A} ; and each other R^5 is independently selected from H, methyl, and fluoro, or, optionally, two other R^5 attached to the same carbon atom,
 5 together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl and fluoro; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as
 10 cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl and fluoro.

In another embodiment, one R^5 is R^{5A} ; and each other R^5 is independently selected from H, methyl, and fluoro. In yet another embodiment, one R^5 is R^{5A} ; and each other R^5 is independently selected from H and methyl, or, optionally, two other R^5 attached to the same
 15 carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as
 20 cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl.

In still another embodiment, one R^5 is R^{5A} ; and each other R^5 is independently selected from H and methyl. In an embodiment, one R^5 is R^{5A} ; and each other R^5 is H, or, optionally, two other R^5 attached to the same carbon atom, together with the carbon atom to
 25 which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted
 30 with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl. In another embodiment, one R^5 is R^{5A} ; and each other R^5 is H.

In yet another embodiment,

R^{5A} is H, D, C_{1-3} alkyl (such as methyl), C_{1-3} haloalkyl (such as trifluoromethyl), C_{2-3}
 35 alkenyl, C_{2-3} alkynyl, halo (such as fluoro), OR^{a5A} , and CN; or, optionally, R^{5A} and R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2,

3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from D, C₁₋₃ alkyl (such as methyl), and halo (such as fluoro); or, optionally, R^{5A} and R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from D, C₁₋₃ alkyl (such as methyl), and halo (such as fluoro); and

R^{a5A} is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B}.

In still another embodiment, R^{5A} is H, C₁₋₃ alkyl (such as methyl), or halo (such as fluoro); or, optionally, R^{5A} and R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C₁₋₃ alkyl (such as methyl) and halo (such as fluoro); or, optionally, R^{5A} and R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C₁₋₃ alkyl (such as methyl), and halo.

In an embodiment, R^{5A} is H or C₁₋₃ alkyl (such as methyl); or, optionally, R^{5A} and R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C₁₋₃ alkyl (such as methyl); or, optionally, R^{5A} and R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C₁₋₃ alkyl (such as methyl).

In another embodiment,

R^{5A} is H, D, C₁₋₃ alkyl (such as methyl), C₁₋₃ haloalkyl (such as trifluoromethyl), C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo (such as fluoro), OR^{a5A}, and CN; and

R^{a5A} is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B}.

In yet another embodiment, R^{5A} is H, C₁₋₃ alkyl (such as methyl), or halo (such as fluoro). In still another embodiment, R^{5A} is H or C₁₋₃ alkyl (such as methyl). In an

embodiment, R^{5A} is H. In another embodiment, R^{5A} is Cy^2 . In yet another embodiment, R^{5A} is C_{1-3} alkyl (such as methyl or ethyl) wherein the C_{1-3} alkyl (or methyl or ethyl) forming R^{5A} is substituted with Cy^2 and also optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B} .

5 In still another embodiment, R^{5A} is C_{1-3} alkyl (such as methyl or ethyl) wherein the C_{1-3} alkyl (or methyl or ethyl) forming R^{5A} is substituted with Cy^2 . In an embodiment, R^{5A} is CH_2Cy^2 . In an embodiment, R^{5A} is $CH_2CH_2Cy^2$. In another embodiment, R^{5A} is OR^{a5A} , and R^{a5A} is Cy^2 .

10 In yet another embodiment, R^{5A} is C_{1-3} alkyl (such as methyl or ethyl), wherein the C_{1-3} alkyl forming R^{a5A} is substituted with Cy^2 and also optionally substituted with 1, 2, 3 or 4 substituents or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B} . In still another embodiment, R^{5A} is OCH_2Cy^2 . In an embodiment, R^{5A} is $OCH_2CH_2Cy^2$.

15 In another embodiment, Cy^2 is C_{6-10} aryl (such as phenyl) optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} . In yet another embodiment, Cy^2 is phenyl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2} . In still another embodiment, Cy^2 is C_{6-10} aryl. In an embodiment, Cy^2 is phenyl.

20 In another embodiment, Cy^2 is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} . In yet another embodiment, Cy^2 is 6 membered heteroaryl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2} . In still another embodiment, Cy^2 is 6 membered heteroaryl. In an embodiment, Cy^2 is pyridinyl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2} . In 25 another embodiment, Cy^2 is pyridinyl.

30 In yet another embodiment, Cy^2 is C_{3-7} cycloalkyl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} . In still another embodiment, Cy^2 is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} .

In an embodiment, each R^{Cy2} is independently selected from D, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and halo. In another embodiment, each R^{Cy2} is independently halo.

35 In still other embodiments, the compound of Formula (I) is selected from a compound in Table 1, and pharmaceutically acceptable salts thereof.

Table 1

Entry	Compound Name
1	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
2	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
3	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
4	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> ₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
5	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
6	3-(2-(5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
7	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
8	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-(5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
9	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
10	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
11	5-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-(2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)- <i>N,N</i> -dimethylpicolinamide;
12	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
13	4-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-(2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)-2-fluoro- <i>N</i> -methylbenzamide;
14	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
15	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;

Entry	Compound Name
16	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
17	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
18	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-(5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
19	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-(5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-(1-hydroxyethyl)-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
20	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(5-chloro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(1-hydroxyethyl)-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
21	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
22	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-(5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
23	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
24	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-(5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-(1-hydroxyethyl)-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
25	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-(5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(1-hydroxyethyl)-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
26	methyl 3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
27	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-(2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
28	methyl 3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
29	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-(5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile.

In other embodiments, the compound of Formula (I) is selected from a compound in Table 2, and pharmaceutically acceptable salts thereof.

Table 2

Entry	Compound Name
1	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
2	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
3	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
4	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
5	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
6	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
7	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
8	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
9	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
10	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> ₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
11	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> ₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;

Entry	Compound Name
12	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> ₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
13	3-((<i>R</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
14	3-((<i>S</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
15	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
16	3-((<i>R</i> _a)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(Benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
17	3-((<i>S</i> _a)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(Benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
18	3-(2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(Benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
19	3-((<i>R</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
20	3-((<i>S</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
21	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
22	3-((<i>R</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
23	3-((<i>S</i> _a)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-

Entry	Compound Name
	azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
24	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
25	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
26	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
27	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
28	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
29	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
30	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
31	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
32	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
33	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
34	5-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)- <i>N</i> , <i>N</i> -dimethylpicolinamide;

Entry	Compound Name
35	5-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)- <i>N,N</i> -dimethylpicolinamide;
36	5-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)- <i>N,N</i> -dimethylpicolinamide;
37	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
38	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
39	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
40	4-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)-2-fluoro- <i>N</i> -methylbenzamide;
41	4-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)-2-fluoro- <i>N</i> -methylbenzamide;
42	4-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)-2-fluoro- <i>N</i> -methylbenzamide;
43	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
44	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
45	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
43	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-

Entry	Compound Name
	dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
44	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
45	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
46	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
47	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
48	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
49	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
50	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile
51	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
52	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
53	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;
54	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2-c]quinolin-8-yl)propanenitrile;

Entry	Compound Name
55	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
56	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
57	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
58	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
59	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
60	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
61	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> 3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
62	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> 3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
63	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy- <i>d</i> 3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
64	3-((7 <i>R_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
65	3-((7 <i>S_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
66	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-

Entry	Compound Name
	dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
67	3-((7 <i>R_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
68	3-((7 <i>S_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
69	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
70	3-((7 <i>R_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
71	3-((7 <i>S_a</i>)-1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
72	3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
73	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
74	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
75	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
76	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
77	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;

Entry	Compound Name
78	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
79	3-((7 <i>R_a</i>)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
80	3-((7 <i>S_a</i>)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
81	3-(2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
82	3-((7 <i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
83	3-((7 <i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
84	3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
85	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
86	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
87	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
88	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
89	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-

Entry	Compound Name
	azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
90	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
91	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-5-chloro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
92	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-5-chloro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
93	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-5-chloro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
94	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
95	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
96	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
97	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
98	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
99	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
100	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;

Entry	Compound Name
101	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
102	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
103	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
104	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
105	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
106	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
107	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate
108	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
109	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
110	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
111	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
112	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(1-fluorocyclopropane-1-carbonyl)-5-

Entry	Compound Name
	(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
113	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
114	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
115	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
116	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
117	methyl (1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate;
118	3-((<i>R_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
119	3-((<i>S_a</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile;
120	3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile.

In other embodiments, the compound of Formula (I) is in the form of a pharmaceutically acceptable salt. In other embodiments, the compound of Formula (I) is in the form of a free base or free acid, or other than in the form of a salt.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), or any of the embodiments thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or

in any suitable subcombination. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include
5 each and every individual subcombination of the members of such groups and ranges. For example, the term "C₁₋₆ alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl and C₆ alkyl.

The term "n-membered," where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example,
10 piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each linking substituent include both
15 the forward and backward forms of the linking substituent. For example, -NR(CR'R'')_n- includes both -NR(CR'R'')_n- and -(CR'R'')_nNR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is
20 understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The hydrogen atom is formally removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace
25 two hydrogen atoms. The term "optionally substituted" means unsubstituted or substituted. The term "substituted," unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by
30 valency. It is to be understood that substitution at a given atom results in a chemically stable molecule.

The term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons present in a chemical moiety. The term is intended to include each and every member in the indicated range. Thus, C_{n-m} includes each
35 member in the series C_n, C_{n+1}, ... C_{m-1}, and C_m. Examples include C₁₋₄ (which includes C₁, C₂, C₃, and C₄), C₁₋₆ (which includes C₁, C₂, C₃, C₄, C₅, and C₆) and the like.

The term "alkyl" employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chained or branched. The term " C_{n-m} alkyl," refers to an alkyl group having n to m carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl and the like.

The term "alkylene," employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term " C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms. Examples of alkylene groups include, but are not limited to, methylene, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-1,1-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkenyl," employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more carbon-carbon double bonds. The term " C_{n-m} alkynyl" refers to an alkenyl group having n to m carbon atoms. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. In some embodiments, the alkenyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

The term "alkynyl," employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more carbon-carbon triple bonds. The term " C_{n-m} alkynyl" refers to an alkynyl group having n to m carbon atoms. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like.

The term "alkoxy," employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term " C_{n-m} alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon

atoms. The term "C_{n-m} dialkoxy" refers to a linking group of formula -O-(C_{n-m} alkyl)-O-, the alkyl group of which has n to m carbons. Example dialkoxy groups include -OCH₂CH₂O- and OCH₂CH₂CH₂O-. In some embodiments, the two O atoms of a C_{n-m} dialkoxy group may be attached to the same B atom to form a 5- or 6- membered heterocycloalkyl group.

5 The term "amino," employed alone or in combination with other terms, refers to a group of formula -NH₂, wherein the hydrogen atoms may be substituted with a substituent described herein. For example, "alkylamino" can refer to -NH(alkyl) and -N(alkyl)₂.

 The term "carbonyl," employed alone or in combination with other terms, refers to a -C(=O)- group.

10 The terms "halo" or "halogen," used alone or in combination with other terms, refers to fluoro, chloro, bromo and iodo. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, halo groups are F.

 The term "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term "C_{n-m} haloalkyl" refers to a C_{n-m} alkyl group having n to m carbon atoms and from at least one up to {2(n to m)+1} halogen atoms, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF₃, C₂F₅, CHF₂, CH₂F, CCl₃, CHCl₂, C₂Cl₅ and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

20 The term "haloalkoxy," employed alone or in combination with other terms, refers to a group of formula -O-haloalkyl, wherein the haloalkyl group is as defined above. The term "C_{n-m} haloalkoxy" refers to a haloalkoxy group, the haloalkyl group of which has n to m carbons. Example haloalkoxy groups include trifluoromethoxy and the like. In some embodiments, the haloalkoxy group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

25 The term "oxo" or "oxy" refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to carbon, or attached to a heteroatom forming a sulfoxide or sulfone group, or an N-oxide group. In some embodiments, heterocyclic groups may be optionally substituted by 1 or 2 oxo (=O) substituents.

 The term "oxidized" in reference to a ring-forming N atom refers to a ring-forming N-oxide.

30 The term "oxidized" in reference to a ring-forming S atom refers to a ring-forming sulfonyl or ring-forming sulfinyl.

 The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (*i.e.*, having (4n + 2) delocalized π (pi) electrons where n is an integer).

35 The term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (*e.g.*, having 2 fused

rings). The term “C_{n-m} aryl” refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, and the like. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. In some embodiments, aryl groups have 6 carbon atoms. In some embodiments, aryl groups have 10 carbon atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

The term “heteroaryl” or “heteroaromatic,” employed alone or in combination with other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused bicyclic heteroaryl ring. Example heteroaryl groups include, but are not limited to, pyridinyl (pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl (including 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3- and 2,6-naphthyridine), indolyl, isoindolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-*b*]thiazolyl, purinyl, and the like. In some embodiments, the heteroaryl group is pyridone (e.g., 2-pyridone).

A five-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

A six-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl, isoindolyl, and pyridazinyl.

The term “cycloalkyl,” employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon ring system (monocyclic, bicyclic or polycyclic), including cyclized

alkyl and alkenyl groups. The term "C_{n-m} cycloalkyl" refers to a cycloalkyl that has n to m ring member carbon atoms. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6 or 7 ring-forming carbons (C₃₋₇). In some embodiments, the cycloalkyl group has 3 to 6 ring members, 5 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a C₃₋₆ monocyclic cycloalkyl group. Ring-forming carbon atoms of a cycloalkyl group can be optionally oxidized to form an oxo or sulfido group. Cycloalkyl groups also include cycloalkylidenes. In some embodiments, cycloalkyl is 10 cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, e.g., benzo or thienyl derivatives of cyclopentane, cyclohexane and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of 15 cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, the cycloalkyl group is tetrahydronaphthalenyl (e.g., 1,2,3,4- 20 tetrahydronaphthalenyl).

The term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur, oxygen and phosphorus, and which 25 has 4-10 ring members, 4-7 ring members, or 4-6 ring members. Included within the term "heterocycloalkyl" are monocyclic 4-, 5-, 6- and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can include mono- or bicyclic (e.g., having two fused or bridged rings) or spirocyclic ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2 or 3 heteroatoms independently selected from nitrogen, sulfur 30 and oxygen. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido group or other oxidized linkage (e.g., C(O), S(O), C(S) or S(O)₂, *N*-oxide *etc.*) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 35 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the heterocycloalkyl ring, e.g.,

benzo or thienyl derivatives of piperidine, morpholine, azepine, *etc.* A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of heterocycloalkyl groups include 2,5-diazobicyclo[2.2.1]heptanyl; pyrrolidinyl; hexahydropyrrolo[3,4-b]pyrrol-1(2*H*)-yl; 1,6-
5 dihydropyridinyl; morpholinyl; azetidyl; piperazinyl; and 4,7-diazaspiro[2.5]octan-7-yl.

At certain places, the definitions or embodiments refer to specific rings (*e.g.*, an azetidine ring, a pyridine ring, *etc.*). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas an azetidin-3-yl ring is
10 attached at the 3-position.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on
15 how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are
20 described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic
25 acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-
30 methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

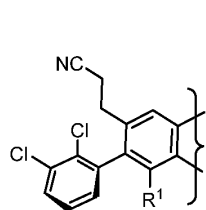
Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

When the compounds described herein contain a chiral center, unless otherwise
35 indicated, the compounds can be any of the possible stereoisomers. In some embodiments, the compounds provided herein have the (*R*)-configuration. In other embodiments, the

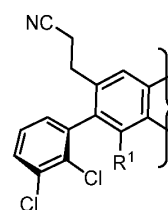
compounds have the (S)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (R) or (S), unless otherwise indicated. In compounds with a single chiral center, the stereochemistry of the chiral center can be (R) or (S). In compounds with two chiral centers, the stereochemistry of the chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R) and (R), (R) and (S); (S) and (R), or (S) and (S). In compounds with three chiral centers, the stereochemistry each of the three chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R), (R) and (R); (R), (R) and (S); (R), (S) and (R); (R), (S) and (S); (S), (R) and (R); (S), (R) and (S); (S), (S) and (R); or (S), (S) and (S).

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone–enol pairs, amide - imidic acid pairs, lactam–lactim pairs, enamine–imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, e.g., 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*- and 4*H*- 1,2,4-triazole, 1*H*- and 2*H*- isoindole and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified (e.g., in the case of purine rings, unless otherwise indicated, if a compound name or structure described the 9*H* tautomer, it would be understood that the 7*H* tautomer is also encompassed).

Compounds of the invention can exist in the form of atropisomers (*i.e.*, conformational diastereoisomers) that can be stable at ambient temperature and separable, e.g., by chromatography. For example, compounds of the invention in which Cy¹ is 2,3-dichlorophenyl, or any of the embodiments thereof, can exist in the form of atropisomers in which the conformation of the phenyl relative to the remainder of the molecule is as shown by the partial formulae Formula (II-A) or Formula (II-B) below. Reference to the compounds described herein or any of the embodiments is understood to include all such atropisomeric forms of the compounds, including, without limitation, the atropisomeric forms represented by Formula (II-A) or Formula (II-B) below. Without being limited by any theory, it is understood that, for a given compound, the atropisomer represented by Formula (II-A) is generally more potent as an inhibitor of KRAS (including G12C, G12D or G12V mutated forms of KRAS) than the atropisomer represented by Formula (II-B).



(II-A)



(II-B)

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. In the compounds provided herein, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom.

Substitution with heavier isotopes such as deuterium, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. (A. Kerekes et.al. *J. Med. Chem.* **2011**, 54, 201-210; R. Xu et.al. *J. Label Compd. Radiopharm.* **2015**, 58, 308-312). Unless otherwise stated, when a position is designated specifically as "D" or "deuterium," the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium). In embodiments, the compounds provided herein have an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

The term "compound" is intended, unless otherwise specified, to include all stereoisomers, including without limitation, geometric isomers, configurational isomers, conformational isomers, rotational isomers, and atropisomers, of the structures depicted, including each of the embodiments thereof. The term is also intended to refer to compounds

described herein regardless of how they are prepared, *e.g.*, synthetically, through biological process (*e.g.*, metabolism or enzyme conversion), or a combination thereof.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or
5 can be isolated. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

10 In some embodiments, the compounds provided herein, or salts thereof, are substantially isolated. "Substantially isolated" means that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least
15 about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

The phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment,
20 suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions "ambient temperature" and "room temperature" are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the
25 temperature of the room in which the reaction is carried out, *e.g.*, a temperature from about 20 °C to about 30 °C.

The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein, including any of the embodiments thereof. The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds
30 wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, *e.g.*,
35 from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by

reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol or butanol) or MeCN are preferred. Lists of suitable salts are found in A.R.

- 5 Gennaro (Ed.), *Remington's Pharmaceutical Sciences*, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, S. M. Berge *et al.*, *J. Pharm. Sci.*, **1977**, 66(1), 1-19, S. Gaisford in A. Adejare (Ed.), *Remington, The Science and Practice of Pharmacy*, 23rd Ed., (Elsevier, 2020), Chapter 17, pp. 307-14; S.M. Berge *et al.*, *J. Pharm. Sci.*, **1977**, 66(1), 1-19, T. S. Wiedmann, et al., *Asian J. Pharm. Sci.*, **2016**; 11, 722–34. D. Gupta et al.,
10 *Molecules*, **2018**, 23(7), 1719; P.H. Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002) and in P.H. Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, 2nd Ed. (Wiley, 2011). In some embodiments, the compounds described herein include the N-oxide forms.

II. Synthesis

- 15 Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

- The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable
20 solvents can be substantially non-reactive with the starting materials (reactants), the intermediates 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
25 reaction step can be selected by the skilled artisan.

- Preparation of compounds of the invention can involve the protection and deprotection 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 is described, e.g., in Kocienski, *Protecting Groups*,
30 (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Petursson *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, 74(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

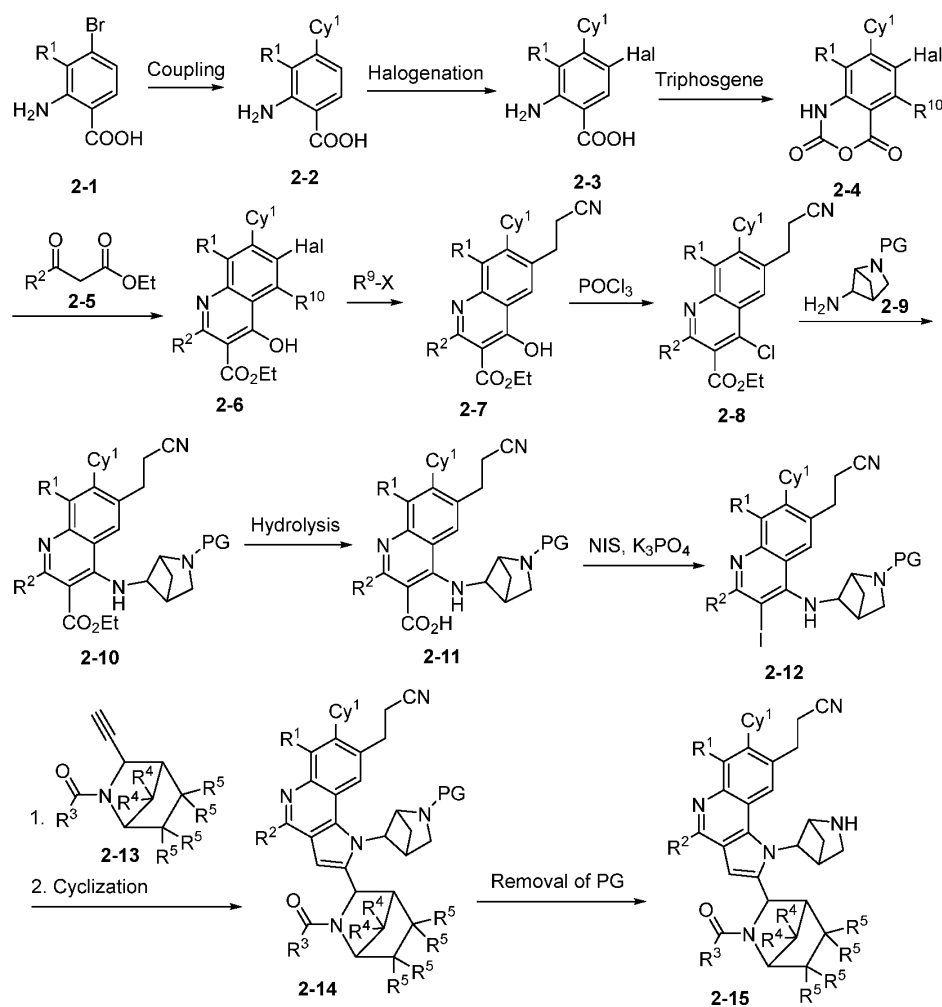
- 35 Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear

magnetic resonance spectroscopy (e.g., ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry or by chromatographic methods such as high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS), or thin layer chromatography (TLC).

5 Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) (*"Preparative LCMS Purification: Improved Compound Specific Method Optimization"* Karl F. Blom, Brian Glass, Richard Sparks, Andrew P. Combs *J. Combi. Chem.* **2004**, 6(6), 874-883) and normal phase silica chromatography.

10 The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

Scheme 1



Compounds of formula **2-15** can be prepared via the synthetic route outlined in **Scheme 1**. The bromo of **2-1** can be converted to Cy¹ via standard Suzuki Cross-Coupling conditions (e.g., in the presence of a palladium catalyst and a suitable base), standard Negishi Cross-Coupling conditions, standard Stille Cross-Coupling conditions or other suitable methods to obtain **2-2**. Halogenation of **2-2** with an appropriate reagent, such as *N*-iodosuccinimide (NIS), affords intermediate **2-3** (Hal is a halide, such as F, Cl, Br, or I). Intermediate **2-3** can be treated with reagent such as triphosgene to afford compound **2-4**. Intermediate **2-4** can then react with ketoester **2-5** and an appropriate base to deliver compound **2-6**. Coupling of halogen of **2-6** under standard Heck Cross-Coupling conditions, standard Suzuki Cross-Coupling conditions or other suitable methods gives **2-7**. Compound **2-8** can be prepared by treating **2-7** with an appropriate chlorinating reagent such as POCl₃. A S_NAr reaction of intermediate **2-8** with amine **2-9** (PG is an appropriate protecting group, such as Boc) can be carried out to generate compound **2-10**. Subsequent hydrolysis of ester of **2-10** affords **2-11**, which can then be treated with NIS and an appropriate base (eg. K₃PO₄) to afford the corresponding iodide **2-12**. Sonogashira coupling of **2-12** and compounds with formula of **2-13** followed by cyclization affords **2-14**. Compound **2-14** can optionally undergo functionalization followed by deprotection of protecting group PG to afford compound **2-15**. The order of the above described chemical reactions can be rearranged as appropriate to suite the preparation of different analogues.

For the synthesis of particular compounds, the general schemes described above and specific methods described herein for preparing particular compounds can be modified. For example, the products or intermediates can be modified to introduce particular functional groups. Alternatively, the substituents can be modified at any step of the overall synthesis by methods known to one skilled in the art, e.g., as described by R.C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations* (Wiley, 1999); R. C. Larock, *et al.*, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 3rd Ed. Vols. 1-4 (Wiley, 2018); A. R. Katritzky, *et al.* (Eds.), *Comprehensive Organic Functional Group Transformations*, Vols. 1-6 (Pergamon Press, 1995), and A. R. Katritzky *et al.* (Eds.), *Comprehensive Organic Functional Group Transformations II*, Vols. 1-6 (Elsevier, 2nd Edition, 2005).

Starting materials, reagents and intermediates whose synthesis is not described herein are either commercially available, known in the literature, or may be prepared by methods known to one skilled in the art.

It will be appreciated by one skilled in the art that the processes described are not the exclusive means by which compounds of the invention may be synthesized and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds of the invention. The person skilled in the art knows how to select

and implement appropriate synthetic routes. Suitable synthetic methods of starting materials, intermediates and products may be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic Chemistry*, Vols. 1-114 (Elsevier, 1963-2023); *Journal of Heterocyclic Chemistry* Vols. 1-60 (Journal of Heterocyclic Chemistry, 1964-2023); E. M. Carreira, *et al.* (Eds.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-4, 2013/1-4; 2014/1-4, 2015/1-2; 2016/1-3, 2017/1-3; 2018/1-4, 2019/1-3; 2020/1-3, 2021/1-3, 2022/1-3, 2023/1 (Thieme, 2001-2023); Houben-Weyl, *Methoden der Organischen Chemie*, 4th Ed. Vols. 1-67 (Thieme, 1952-1987); Houben-Weyl, *Methoden der Organischen Chemie*, E-Series. Vols. 1-23 (Thieme, 1982-2003); A. R. Katritzky, *et al.* (Eds.), *Comprehensive Organic Functional Group Transformations*, Vols. 1-6 (Pergamon Press, 1995); A. R. Katritzky *et al.* (Eds.), *Comprehensive Organic Functional Group Transformations II*, Vols. 1-6 (Elsevier, 2nd Edition, 2005); A. R. Katritzky *et al.* (Eds.); *Comprehensive Heterocyclic Chemistry*, Vols. 1-8 (Pergamon Press, 1984); A. R. Katritzky, *et al.* (Eds.); *Comprehensive Heterocyclic Chemistry II*, Vols. 1-10 (Pergamon Press, 1996); A. R. Katritzky, *et al.* (Eds.); *Comprehensive Heterocyclic Chemistry III*, Vols. 1-14 (Elsevier Science, 2008); D. St.C. Black, *et al.* (Eds.); *Comprehensive Heterocyclic Chemistry IV*, Vols. 1-14 (Elsevier Science, 2022); M.B. Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); M. B. Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 8th Ed. (Wiley, 2020); B. M. Trost *et al.* (Ed.), *Comprehensive Organic Synthesis*, Vols. 1-9 (Pergamon Press, 1991); and *Patai's Chemistry of Functional Groups*, 100 Vols. (Wiley 1964-2022).

III. Uses of the Compounds

Compounds of the present disclosure, including the compounds of Formula (I), or any of the embodiments thereof, are useful for therapy as described in further detail below. The present disclosure provides compounds of Formula (I), for use as a medicament, or for use in medicine. The present disclosure provides compounds of Formula (I), for use as a medicament, or for use in treating disease, as described in further detail below. The present disclosure also provides the use of compounds of Formula (I), or any of the embodiments thereof, as a medicament, or for treating disease, as described in further detail below. The present disclosure also provides the use of compounds of Formula (I), or any of the embodiments thereof, in the manufacture of medicament for treating disease, as described in further detail below.

Compounds of the present disclosure are KRAS inhibitors and, thus, are useful in treating diseases and disorders associated with activity of KRAS. For the uses described

herein, any of the compounds of Formula (I), including any of the embodiments thereof, may be used.

In particular, compounds of the invention are KRAS inhibitors having activity against one or more mutant forms of KRAS, and, thus, are useful in treating diseases and disorders associated with the presence or activity of mutant forms of KRAS, such as G12C, G12D, and/or the G12V mutant forms of KRAS.

The Ras family is comprised of three members: KRAS, NRAS and HRAS. RAS mutant cancers account for about 25% of human cancers. KRAS is the most frequently mutated isoform in human cancers: 85% of all RAS mutations are in KRAS, 12% in NRAS, and 3% in HRAS (D. Simanshu, *et al.*, *Cell*, **2017**, 170(1), 17-33). KRAS mutations are prevalent amongst the top three most deadly cancer types: pancreatic (97%), colorectal (44%), and lung (30%) (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51). The majority of RAS mutations occur at amino acid residues/codons 12, 13, and 61; Codon 12 mutations are most frequent in KRAS. The frequency of specific mutations varied between RAS genes and G12D mutations are most predominant in KRAS whereas Q61R and G12R mutations are most frequent in NRAS and HRAS. Furthermore, the spectrum of mutations in a RAS isoform differs between cancer types. For example, KRAS G12D mutations predominate in pancreatic cancers (51%), followed by colorectal adenocarcinomas (45%) and lung cancers (17%) (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51). In contrast, KRAS G12C mutations predominate in non-small cell lung cancer (NSCLC) comprising 11-16% of lung adenocarcinomas (nearly half of mutant KRAS is G12C), as well as 2-5% of pancreatic and colorectal adenocarcinomas, respectively (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, 13(11), 828-51). Using shRNA knockdown thousands of genes across hundreds of cancer cell lines, genomic studies have demonstrated that cancer cells exhibiting KRAS mutations are highly dependent on KRAS function for cell growth (R. McDonald, *et al.*, *Cell*, **2017**, 170(3), 577-92).

Taken together, these findings indicate that KRAS mutations play a critical role in human cancers. Development of inhibitors targeting KRAS, including mutant KRAS, will therefore be useful in the clinical treatment of diseases that are characterized by involvement of KRAS, including diseases characterized by the involvement or presence of a KRAS mutation.

Diseases that can be treated with the compounds of Formula (I) include cancers. The cancers can include adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm,

adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma,

5 atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-

10 cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma,

15 follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological

20 malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver

25 cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic

30 urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocyoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer,

35 Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion

lymphoma, primary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor,

5 signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary' s disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer,

10 urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor. In some embodiments, the cancer can be adenocarcinoma, adult T-cell leukemia/lymphoma, bladder cancer, blastoma, bone cancer, breast cancer, brain cancer, carcinoma, myeloid sarcoma, cervical cancer, colorectal

15 cancer, esophageal cancer, gastrointestinal cancer, glioblastoma multiforme, glioma, gallbladder cancer, gastric cancer, head and neck cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, intestinal cancer, kidney cancer, laryngeal cancer, leukemia, lung cancer, lymphoma, liver cancer, small cell lung cancer, non-small cell lung cancer, mesothelioma, multiple myeloma, ocular cancer, optic nerve tumor, oral cancer, ovarian

20 cancer, pituitary tumor, primary central nervous system lymphoma, prostate cancer, pancreatic cancer, pharyngeal cancer, renal cell carcinoma, rectal cancer, sarcoma, skin cancer, spinal tumor, small intestine cancer, stomach cancer, T-cell lymphoma, testicular cancer, thyroid cancer, throat cancer, urogenital cancer, urothelial carcinoma, uterine cancer, vaginal cancer, or Wilms' tumor.

25 The cancer types in which KRAS harboring G12C, G12V and G12D mutations are implicated and that can be treated using compounds of Formula (I), or any of the embodiments thereof, include, but are not limited to: carcinomas (e.g., pancreatic, colorectal, lung, bladder, gastric, esophageal, breast, head and neck, cervical skin, thyroid); hematopoietic malignancies (e.g., myeloproliferative neoplasms (MPN), myelodysplastic

30 syndrome (MDS), chronic and juvenile myelomonocytic leukemia (CMML and JMML), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and multiple myeloma (MM)); and other neoplasms (e.g., glioblastoma and sarcomas). In addition, KRAS mutations were found in acquired resistance to anti-EGFR therapy (Knickelbein, K. et al. *Genes & Cancer*, (2015): 4-12). KRAS mutations were found in immunological and inflammatory disorders

35 (Fernandez-Medarde, A. et al. *Genes & Cancer*, (2011): 344-358) such as Ras-associated lymphoproliferative disorder (RALD) or juvenile myelomonocytic leukemia (JMML) caused by somatic mutations of KRAS or NRAS.

Compounds of the present disclosure, including any of the embodiments thereof, can inhibit the activity of the KRAS protein. For example, compounds of the present disclosure can be used to inhibit activity of KRAS in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of one or more compounds of the present disclosure to the cell, individual, or patient.

As KRAS inhibitors, the compounds of the present disclosure, or any of the embodiments thereof, are useful in the treatment of various diseases associated with abnormal expression or activity of KRAS. Compounds which inhibit KRAS will be useful in providing a means of preventing the growth or inducing apoptosis in tumors, or by inhibiting angiogenesis. It is therefore anticipated that compounds of the present disclosure will prove useful in treating or preventing proliferative disorders such as cancers. In particular, tumors with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors.

In an aspect, provided herein is a method of inhibiting KRAS activity, the method comprising contacting a compound of the instant disclosure with KRAS. In an embodiment, the contacting comprises administering the compound to a patient. In an embodiment, KRAS is characterized as having a somatic mutation of G12C. In another embodiment, KRAS is characterized as having a somatic mutation of G12D. In another embodiment, KRAS is characterized as having a somatic mutation of G12V.

In an aspect, provided herein is a method of inhibiting a KRAS protein harboring a G12C mutation, the method comprising contacting a compound of Formula (I), or any of the embodiments thereof, with KRAS.

In an aspect, provided herein is a method of inhibiting a KRAS protein harboring a G12D mutation, the method comprising contacting a compound of Formula (I), or any of the embodiments thereof, with KRAS harboring a G12D mutation.

In an aspect, provided herein is a method of inhibiting a KRAS protein harboring a G12V mutation, the method comprising contacting a compound of Formula (I), or any of the embodiments thereof, with KRAS harboring a G12V mutation.

In another aspect, provided herein is a method of treating a disease or disorder associated with inhibition of KRAS interaction, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

In an embodiment, the disease or disorder is an immunological or inflammatory disorder. In another embodiment, the immunological or inflammatory disorder is Ras-associated lymphoproliferative disorder or juvenile myelomonocytic leukemia caused by somatic mutations of KRAS. In an embodiment, the immunological or inflammatory disorder is caused by a somatic mutation of KRAS.

In another embodiment, the somatic mutation of KRAS is G12C. In another embodiment, the somatic mutation of KRAS is G12D. In another embodiment, the somatic mutation of KRAS is G12V.

5 In another embodiment, the immunological or inflammatory disorder is associated with activity of KRAS having a G12C mutation. In another embodiment, the immunological or inflammatory disorder is associated with activity of KRAS having a G12D mutation. In another embodiment, the immunological or inflammatory disorder is associated with activity of KRAS having a G12V mutation.

10 In yet another aspect, provided herein is a method of treating a disease or disorder associated with inhibiting a KRAS protein harboring a G12C mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof,

15 In yet another aspect, provided herein is a method of treating a disease or disorder associated with inhibiting a KRAS protein harboring a G12D mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

20 In another aspect, provided herein is a method of treating a disease or disorder associated with inhibiting a KRAS protein harboring a G12V mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

In yet another aspect, provided herein is a method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12C mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of a compound of Formula (I), or any of the embodiments thereof,

25 In yet another aspect, provided herein is a method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12D mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

30 In another aspect, provided herein is a method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12V mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

35 In another aspect, provided herein is also a method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof.

In still another aspect, provided herein is also a method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective

amount of a compound of Formula (I), or any of the embodiments thereof, wherein the cancer is characterized by an interaction with a KRAS protein harboring a G12C mutation.

In still another aspect, provided herein is also a method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective
5 amount of a compound of Formula (I), or any of the embodiments thereof, wherein the cancer is characterized by an interaction with a KRAS protein harboring a G12D mutation.

In another aspect, provided herein is also a method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof, wherein the cancer is
10 characterized by an interaction with a KRAS protein harboring a G12V mutation.

In yet another aspect, provided herein is a method for treating a cancer in a patient, the method comprising administering to the patient a therapeutically effective amount of any one of the compounds disclosed herein, or pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method for treating a cancer in a patient
15 comprising identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12C mutation, and administering to the patient a therapeutically effective amount of any one of the compounds disclosed herein, or pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method for treating a cancer in a patient
20 comprising identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12D mutation, and administering to the patient a therapeutically effective amount of any one of the compounds disclosed herein, or pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method for treating a cancer in a patient
25 comprising identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12V mutation, and administering to the patient a therapeutically effective amount of any one of the compounds disclosed herein, or pharmaceutically acceptable salt thereof.

In an embodiment, the cancer is selected from carcinomas, hematological cancers, sarcomas, and glioblastoma. In another embodiment, the hematological cancer is selected
30 from myeloproliferative neoplasms, myelodysplastic syndrome, chronic and juvenile myelomonocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, and multiple myeloma. In yet another embodiment, the carcinoma is selected from pancreatic, colorectal, lung, bladder, gastric, esophageal, breast, head and neck, cervical, skin, and
35 thyroid. In another embodiment, the cancer is colorectal cancer, pancreatic cancer, or lung cancer. In yet another embodiment, the pancreatic cancer is pancreatic ductal

adenocarcinoma (PDAC). In still another embodiment, the cancer is non-small cell lung cancer (NSCLC).

In an embodiment, the cancer is metastatic.

In an aspect, provided herein is a method for treating a disease or disorder associated with inhibition of KRAS interaction or a mutant thereof, in a patient in need thereof, comprising the step of administering to the patient a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, in combination with another therapy or therapeutic agent as described herein.

In an aspect, provided herein is a method for treating a disease or disorder associated with activity of KRAS interaction or a mutant thereof, in a patient in need thereof, comprising the step of administering to the patient a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, in combination with another therapy or therapeutic agent as described herein.

In an embodiment, the cancer is selected from hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

In another embodiment, the lung cancer is selected from non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma, squamous cell bronchogenic carcinoma, undifferentiated small cell bronchogenic carcinoma, undifferentiated large cell bronchogenic carcinoma, adenocarcinoma, bronchogenic carcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, chondromatous hamartoma, mesothelioma, pavicellular and non-pavicellular carcinoma, bronchial adenoma, and pleuropulmonary blastoma.

In yet another embodiment, the lung cancer is non-small cell lung cancer (NSCLC). In still another embodiment, the lung cancer is adenocarcinoma.

In an embodiment, the gastrointestinal cancer is selected from esophagus squamous cell carcinoma, esophagus adenocarcinoma, esophagus leiomyosarcoma, esophagus lymphoma, stomach carcinoma, stomach lymphoma, stomach leiomyosarcoma, exocrine pancreatic carcinoma, pancreatic ductal adenocarcinoma, pancreatic insulinoma, pancreatic glucagonoma, pancreatic gastrinoma, pancreatic carcinoid tumors, pancreatic vipoma, small bowel adenocarcinoma, small bowel lymphoma, small bowel carcinoid tumors, Kaposi's sarcoma, small bowel leiomyoma, small bowel hemangioma, small bowel lipoma, small bowel neurofibroma, small bowel fibroma, large bowel adenocarcinoma, large bowel tubular adenoma, large bowel villous adenoma, large bowel hamartoma, large bowel leiomyoma, colorectal cancer, gall bladder cancer, and anal cancer.

In an embodiment, the gastrointestinal cancer is colorectal cancer.

In another embodiment, the cancer is a carcinoma. In yet another embodiment, the carcinoma is selected from pancreatic carcinoma, colorectal carcinoma, lung carcinoma, bladder carcinoma, gastric carcinoma, esophageal carcinoma, breast carcinoma, head and
5 neck carcinoma, cervical skin carcinoma, and thyroid carcinoma.

In still another embodiment, the cancer is a hematopoietic malignancy. In an embodiment, the hematopoietic malignancy is selected from multiple myeloma, acute myelogenous leukemia, and myeloproliferative neoplasms.

In another embodiment, the cancer is a neoplasm. In yet another embodiment, the
10 neoplasm is glioblastoma or sarcomas.

In certain embodiments, the disclosure provides a method for treating a KRAS-mediated disorder in a patient in need thereof, comprising the step of administering to the patient a compound according to the invention, or a pharmaceutically acceptable composition thereof.

15 In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute
20 lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV),
25 essential thrombocytosis (ET), 8p11 myeloproliferative syndrome, myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL), multiple myeloma, cutaneous T-cell lymphoma, adult T-cell leukemia, Waldenstrom's Macroglobulinemia, hairy cell lymphoma, marginal zone lymphoma, chronic myelogenous lymphoma and Burkitt's lymphoma.

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma,
30 rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, hamatoma, lymphosarcoma, leiomyosarcoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated
35 large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, mesothelioma, pavicellular and non-pavicellular carcinoma, bronchial adenoma and pleuropulmonary blastoma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (exocrine pancreatic carcinoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small
 5 bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colorectal cancer, gall bladder cancer and anal cancer.

Exemplary genitourinary tract cancers include cancers of the kidney
 10 (adenocarcinoma, Wilm's tumor [nephroblastoma], renal cell carcinoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma) and urothelial carcinoma.

15 Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant
 20 lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma,
 25 meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, neuro-ectodermal tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), neuroblastoma, Lhermitte-Duclos disease and pineal tumors.

30 Exemplary gynecological cancers include cancers of the breast (ductal carcinoma, lobular carcinoma, breast sarcoma, triple-negative breast cancer, HER2-positive breast cancer, inflammatory breast cancer, papillary carcinoma), uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma),
 35 granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma,

fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, Merkel cell skin cancer, moles dysplastic nevi, lipoma,
5 angioma, dermatofibroma, and keloids.

Exemplary head and neck cancers include glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, osteosarcoma, squamous cell carcinomas, adenocarcinomas, oral cancer, laryngeal cancer, nasopharyngeal cancer, nasal and paranasal cancers, thyroid and parathyroid cancers, tumors of the eye, tumors of the lips
10 and mouth and squamous head and neck cancer.

The compounds of the present disclosure can also be useful in the inhibition of tumor metastasis.

In addition to oncogenic neoplasms, the compounds of the invention are useful in the treatment of skeletal and chondrocyte disorders including, but not limited to,
15 achondroplasia, hypochondroplasia, dwarfism, thanatophoric dysplasia (TD) (clinical forms TD I and TD II), Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, and craniosynostosis syndromes. In some embodiments, the present disclosure provides a method for treating a patient suffering from a skeletal and chondrocyte disorder.

20 In some embodiments, compounds described herein can be used to treat Alzheimer's disease, HIV, or tuberculosis.

The term "8p11 myeloproliferative syndrome" refers to myeloid/lymphoid neoplasms associated with eosinophilia and abnormalities of FGFR1.

The term "cell" refers to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some
25 embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

The term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" KRAS with a compound
30 described herein includes the administration of a compound described herein to an individual or patient, such as a human, having KRAS, as well as, for example, introducing a compound described herein into a sample containing a cellular or purified preparation containing KRAS.

The terms "individual," "subject," or "patient," are used interchangeably, and refer to
35 any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent such as an amount of any of the solid forms or salts thereof as disclosed herein that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian,
5 medical doctor or other clinician. An appropriate “effective” amount in any individual case may be determined using techniques known to a person skilled in the art.

The phrase “pharmaceutically acceptable carrier or excipient” refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-
10 toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is “pharmaceutically acceptable” as defined herein. See, e.g., P. Beringer, *et al.*, (Eds.), *Remington: The Science and Practice of Pharmacy*, 21st Ed.; (Lippincott Williams & Wilkins: Philadelphia, Pa., 2005); A. Adejare (Ed.), *Remington, The
15 Science and Practice of Pharmacy*, 23rd Ed., (Elsevier, 2020); R. C. Rowe *et al.*, Eds., *Handbook of Pharmaceutical Excipients*, 6th Ed.; (Pharmaceutical Press, 2009); P. J. Shesky *et al.*, Eds., *Handbook of Pharmaceutical Excipients*, 9th Ed.; (The Pharmaceutical Press, 2020); M. Ash, *et al.*, (Eds.), *Handbook of Pharmaceutical Additives*, 3rd Ed.; (Gower Publishing Company: 2007); and M. Gibson (Ed.), *Pharmaceutical Preformulation and
20 Formulation*, 2nd Ed. (CRC Press LLC, 2009).

The term “treating” or “treatment” refers to inhibiting a disease; for example, inhibiting a disease, condition, or disorder in an individual who is experiencing or displaying the pathology or symptomology of the disease, condition, or disorder (*i.e.*, arresting further development of the pathology and/or symptomology) or ameliorating the disease; for
25 example, ameliorating a disease, condition, or disorder in an individual who is experiencing or displaying the pathology or symptomology of the disease, condition, or disorder (*i.e.*, reversing the pathology and/or symptomology) such as decreasing the severity of the disease.

The term “prevent,” “preventing,” or “prevention” comprises the prevention of at least
30 one symptom associated with or caused by the state, disease or disorder being prevented.

III. Combination Therapies

Compounds of the present disclosure, including the compounds of Formula (I), or any of the embodiments thereof, may be useful in therapy when used in combination with one or more additional pharmaceutical agents, as described in further detail below.

a. Cancer Therapies

Compounds of the invention, including the compounds of Formula (I), or any of the embodiments thereof, may be useful in treatment of cancer when used in combination with one or more additional pharmaceutical agents, as described in further detail below.

5 Cancer cell growth and survival can be impacted by dysfunction in multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance
10 arising in a cell population, and/or reduce the toxicity of treatment.

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, immune-oncology agents, metabolic enzyme inhibitors, chemokine receptor inhibitors, and phosphatase inhibitors, as well as targeted therapies such as Bcr-Abl, Flt-3, EGFR, HER2,
15 JAK, c-MET, VEGFR, PDGFR, c-Kit, IGF-1R, RAF, FAK, and CDK4/6 kinase inhibitors such as, for example, those described in WO 2006/056399 can be used in combination with the compounds of the present disclosure for treatment of KRAS-associated diseases, disorders or conditions. Other agents such as therapeutic antibodies can be used in combination with the compounds of the present disclosure for treatment of KRAS-associated diseases,
20 disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

In some embodiments, the KRAS inhibitor is administered or used in combination with a BCL2 inhibitor or a CDK4/6 inhibitor.

The compounds as disclosed herein can be used in combination with one or more
25 other enzyme/protein/receptor inhibitors therapies for the treatment of diseases, such as cancer and other diseases or disorders described herein. Examples of diseases and indications treatable with combination therapies include those as described herein. Examples of cancers include solid tumors and non-solid tumors, such as liquid tumors, blood cancers. Examples of infections include viral infections, bacterial infections, fungus infections
30 or parasite infections. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, BCL2, CDK4/6, TGF- β R, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IDH2, IGF-1R, IR-R, PDGF α R, PDGF β R, PI3K (alpha, beta, gamma, delta, and multiple or selective), CSF1R,
35 KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, PARP, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1,

EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following inhibitors for the treatment of cancer or infections. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancer and infections include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, *e.g.*, pemigatinib (INCB54828), INCB62079), an EGFR inhibitor (also known as Erb-1 or HER-1; *e.g.*, erlotinib, gefitinib, vandetanib, orsimertinib, cetuximab, necitumumab, or panitumumab), a VEGFR inhibitor or pathway blocker (*e.g.* bevacizumab, pazopanib, sunitinib, sorafenib, axitinib, regorafenib, ponatinib, cabozantinib, vandetanib, ramucirumab, lenvatinib, ziv-aflibercept), a PARP inhibitor (*e.g.*, olaparib, rucaparib, veliparib or niraparib), a JAK inhibitor (JAK1 and/or JAK2; *e.g.*, ruxolitinib or baricitinib; or JAK1; *e.g.*, itacitinib (INCB39110), INCB052793, or INCB054707), an IDO inhibitor (*e.g.*, epacadostat, NLG919, or BMS-986205, MK7162), an LSD1 inhibitor (*e.g.*, GSK2979552, INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (*e.g.*, 5 paraclisib (INCB50465) or INCB50797), a PI3K-gamma inhibitor such as PI3K-gamma selective inhibitor, a Pim inhibitor (*e.g.*, INCB53914), a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer; *e.g.*, INCB081776), an adenosine receptor antagonist (*e.g.*, A2a/A2b receptor antagonist), an HPK1 inhibitor, a chemokine receptor inhibitor (*e.g.*, CCR2 or CCR5 inhibitor), a SHP1/2 phosphatase inhibitor, a histone 10 deacetylase inhibitor (HDAC) such as an HDAC8 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), c-MET inhibitors (*e.g.*, capmatinib), an anti-CD19 antibody (*e.g.*, tafasitamab), an ALK2 inhibitor (*e.g.*, zilurgisertib); or combinations thereof.

25 In some embodiments, the compound or salt described herein is administered with a PI3K δ inhibitor. In some embodiments, the compound or salt described herein is administered with a JAK inhibitor. In some embodiments, the compound or salt described herein is administered with a JAK1 or JAK2 inhibitor (*e.g.*, baricitinib or ruxolitinib). In some embodiments, the compound or salt described herein is administered with a JAK1 inhibitor.

30 In some embodiments, the compound or salt described herein is administered with a JAK1 inhibitor, which is selective over JAK2.

Example antibodies for use in combination therapy include, but are not limited to, trastuzumab (*e.g.*, anti-HER2), ranibizumab (*e.g.*, anti-VEGF-A), bevacizumab (AVASTINTM, *e.g.*, anti-VEGF), panitumumab (*e.g.*, anti-EGFR), cetuximab (*e.g.*, anti-EGFR), rituxan (*e.g.*, 35 anti-CD20), and antibodies directed to c-MET.

One or more of the following agents may be used in combination with the compounds of the present disclosure and are presented as a non-limiting list: a cytostatic agent,

- cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptosar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, IRESSA™ (gefitinib), TARCEVA™ (erlotinib), antibodies to EGFR, intron, ara-C, adriamycin, cytoxan,
- 5 gemcitabine, uracil mustard, chlormethine, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, oxaliplatin, leucovorin, ELOXATIN™ (oxaliplatin), pentostatin, vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin,
- 10 doxorubicin, epirubicin, idarubicin, mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, teniposide 17.alpha.-ethinylestradiol, diethylstilbestrol, testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, testolactone, megestrolacetate, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate,
- 15 leuprolide, flutamide, toremifene, goserelin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrozole, letrozole, capecitabine, reloxafine, droloxafine, hexamethylmelamine, avastin, HERCEPTIN™ (trastuzumab), BEXXAR™ (tositumomab), VELCADE™ (bortezomib), ZEVALIN™ (ibritumomab tiuxetan), TRISENOX™ (arsenic trioxide), XELODA™ (capecitabine),
- 20 vinorelbine, porfimer, ERBITUX™ (cetuximab), thiotepa, altretamine, melphalan, trastuzumab, lerozole, fulvestrant, exemestane, ifosfomide, rituximab, C225 (cetuximab), Campath (alemtuzumab), clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.
- 25 The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, bispecific or multi-specific antibody,
- 30 antibody drug conjugate, adoptive T cell transfer, Toll receptor agonists, RIG-I agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor, PI3Kδ inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutic agent. Examples of chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab,
- 35 alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin,

cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate,

5 filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate,

10 methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine,

15 thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, and zoledronate.

Additional examples of chemotherapeutics include proteasome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

20 Example steroids include corticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include imatinib mesylate (GLEEVAC™), nilotinib, dasatinib, bosutinib, and ponatinib, and pharmaceutically acceptable salts. Other example suitable Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and

25 U.S. Pat. No. 7,745,437.

Example suitable Flt-3 inhibitors include midostaurin, lestaurtinib, linifanib, sunitinib, sunitinib maleate, sorafenib, quizartinib, crenolanib, pacritinib, tandutinib, PLX3397 and ASP2215, and their pharmaceutically acceptable salts. Other example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in

30 WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include dabrafenib, sorafenib, and vemurafenib, and their pharmaceutically acceptable salts. Other example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

35 Example suitable FAK inhibitors include VS-4718, VS-5095, VS-6062, VS-6063, BI853520, and GSK2256098, and their pharmaceutically acceptable salts. Other example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as

disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

Example suitable CDK4/6 inhibitors include palbociclib, ribociclib, trilaciclib, lerociclib, and abemaciclib, and their pharmaceutically acceptable salts. Other example suitable

5 CDK4/6 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 09/085185, WO 12/129344, WO 11/101409, WO 03/062236, WO 10/075074, and WO 12/061156.

In some embodiments, the compounds of the disclosure can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients
10 resistant to imatinib or other kinase inhibitors.

In some embodiments, the compounds of the disclosure can be used in combination with a chemotherapeutic in the treatment of cancer, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. In some embodiments, the compounds of the disclosure can
15 be used in combination with a chemotherapeutic provided herein. For example, additional pharmaceutical agents used in the treatment of multiple myeloma, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. In some embodiments, the agent is an
20 alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM). Additive or
25 synergistic effects are desirable outcomes of combining a CDK2 inhibitor of the present disclosure with an additional agent.

The agents can be combined with the present compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

30 The compounds of the present disclosure can be used in combination with one or more other inhibitors or one or more therapies for the treatment of infections. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the compounds of the disclosure where the dexamethasone is
35 administered intermittently as opposed to continuously.

The compounds of Formula (I) or any of the embodiments thereof as described herein, a compound as recited in any of the claims and described herein, or salts thereof can

be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as
5 peptides of gp100, MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds of Formula (I) or any of the embodiments thereof as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some
10 embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated
15 from tumor tissue itself. In some embodiments, the compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The compounds of the present disclosure can be used in combination with bispecific
20 macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

In some further embodiments, combinations of the compounds of the disclosure with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone
25 marrow transplant or stem cell transplant. The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used
30 in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria,
35 Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

Viruses causing infections treatable by methods of the present disclosure include, but are not limit to human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus,

poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, Ebola virus, measles virus, herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), flaviviruses, echovirus, rhinovirus, coxsackie virus, coronavirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Pathogenic bacteria causing infections treatable by methods of the disclosure include, but are not limited to, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

Pathogenic fungi causing infections treatable by methods of the disclosure include, but are not limited to, Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Pathogenic parasites causing infections treatable by methods of the disclosure include, but are not limited to, Entamoeba histolytica, Balantidium coli, Naegleria fowleri, Acanthamoeba sp., Giardia lamblia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (e.g., for more than two agents).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

b. Immune-Checkpoint Therapies

Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors for the treatment of diseases, such as cancer or infections. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CBL-B, CD20, CD28, CD40, CD70, CD122, CD96, CD73, CD47, CDK2, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, HPK1, CD137 (also known as

4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, TLR (TLR7/8), TIGIT, CD112R, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, TIGIT, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

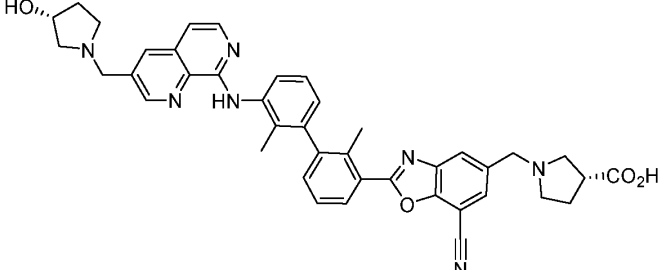
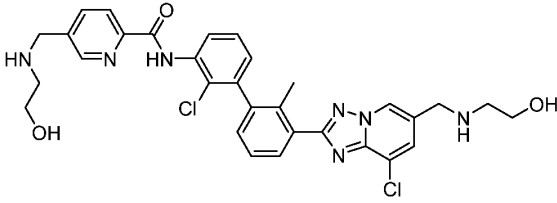
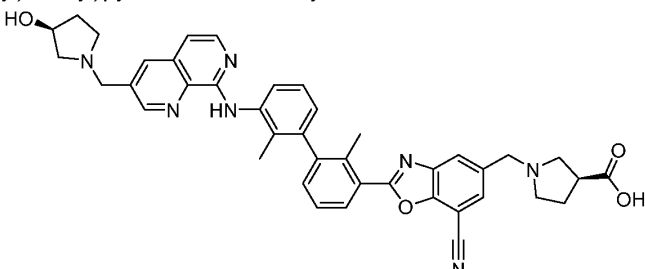
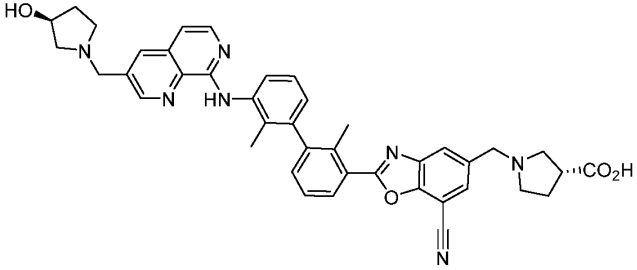
In some embodiments, the compounds provided herein can be used in combination with one or more agonists of immune checkpoint molecules, e.g., OX40, CD27, GITR, and CD137 (also known as 4-1BB).

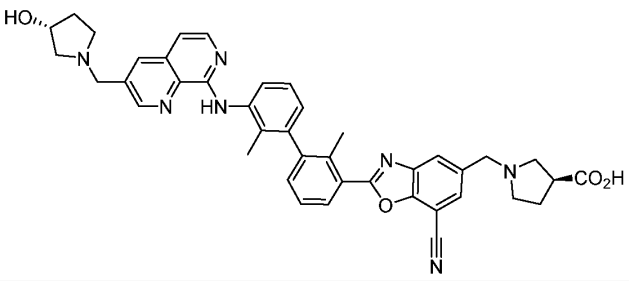
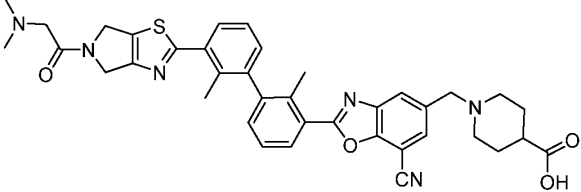
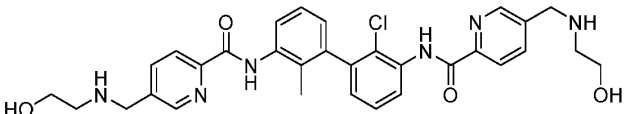
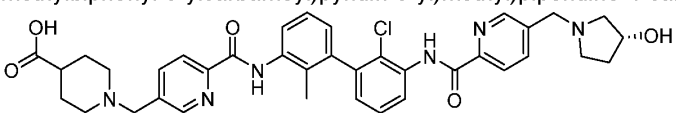
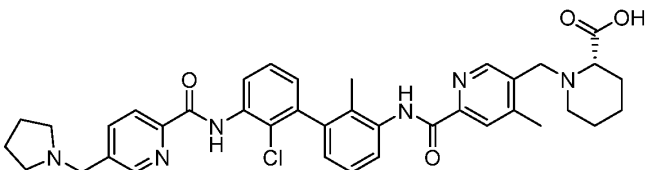
In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

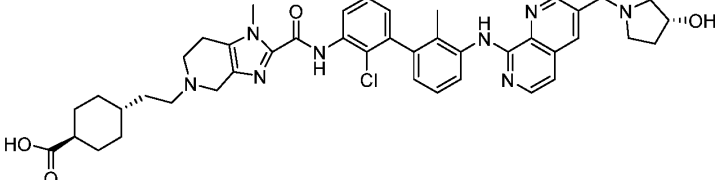
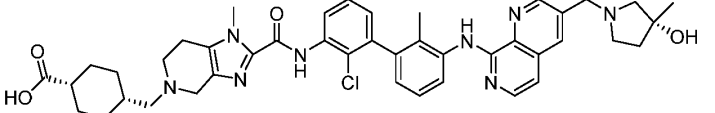
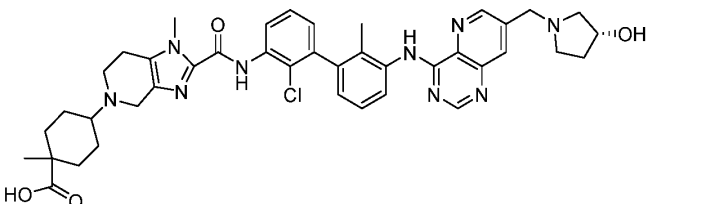
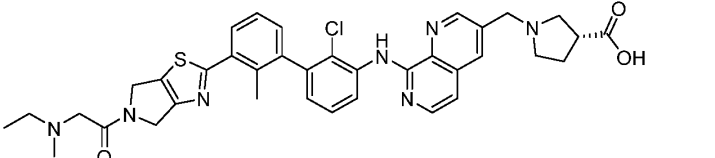
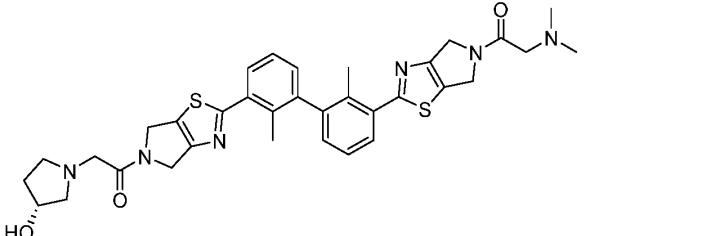
In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1 or PD-L1, e.g., an anti-PD-1 or anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-1 or anti-PD-L1 antibody is nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, atezolizumab, avelumab, tislelizumab, spartalizumab (PDR001), cetrelimab (JNJ-63723283), toripalimab (JS001), camrelizumab (SHR-1210), sintilimab (IBI308), AB122 (GLS-010), AMP-224, AMP-514/MEDI-0680, BMS936559, JTX-4014, BGB-108, SHR-1210, MEDI4736, FAZ053, BCD-100, KN035, CS1001, BAT1306, LZM009, AK105, HLX10, SHR-1316, CBT-502 (TQB2450), A167 (KL-A167), STI-A101 (ZKAB001), CK-301, BGB-A333, MSB-2311, HLX20, TSR-042, or LY3300054. In some embodiments, the inhibitor of PD-1 or PD-L1 is one disclosed in U.S. Pat. Nos. 7,488,802, 7,943,743, 8,008,449, 8,168,757, 8,217,149, or 10,308,644; U.S. Publ. Nos. 2017/0145025, 2017/0174671, 2017/0174679, 2017/0320875, 2017/0342060, 2017/0362253, 2018/0016260, 2018/0057486, 2018/0177784, 2018/0177870, 2018/0179179, 2018/0179201, 2018/0179202, 2018/0273519, 2019/0040082, 2019/0062345, 2019/0071439, 2019/0127467, 2019/0144439, 2019/0202824, 2019/0225601, 2019/0300524, or 2019/0345170; or PCT Pub. Nos. WO 03042402, WO 2008156712, WO 2010089411, WO 2010036959, WO 2011066342, WO 2011159877, WO 2011082400, or WO 2011161699, which are each incorporated herein by reference in their entirety. In some embodiments, the inhibitor of PD-L1 is INCB086550.

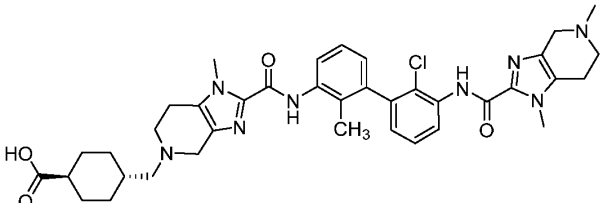
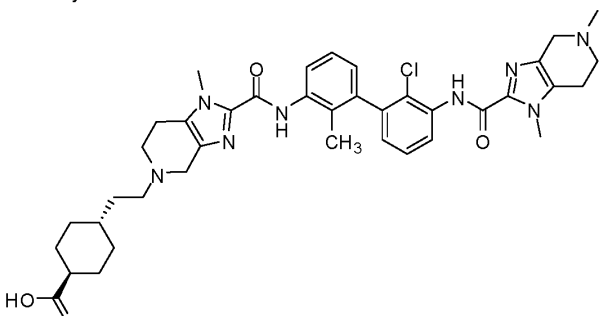
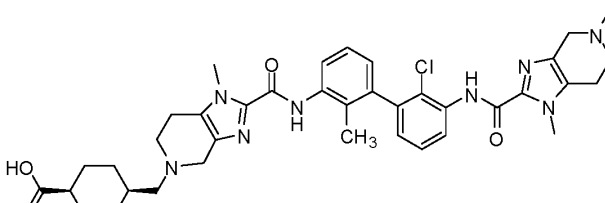
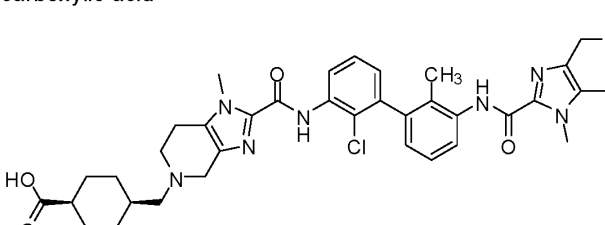
In some embodiments, the PD-L1 inhibitor is selected from the compounds in Table A, or a pharmaceutically acceptable salt thereof.

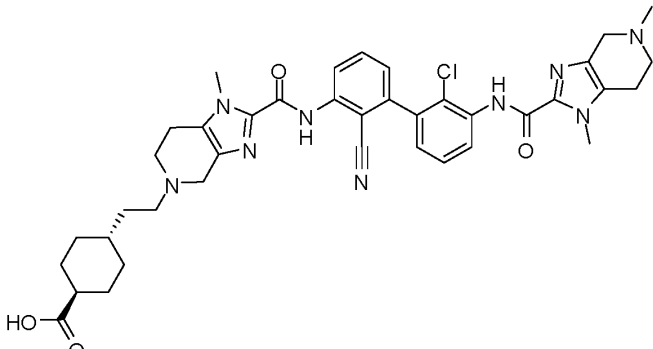
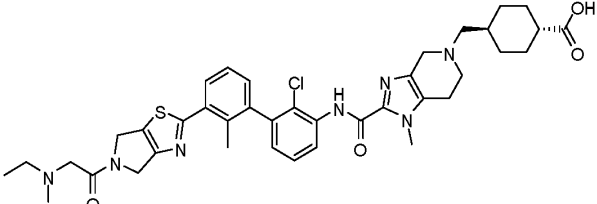
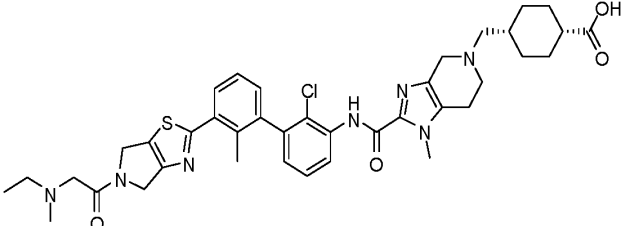
Table A

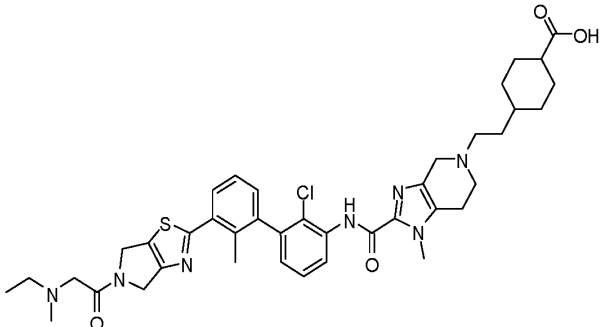
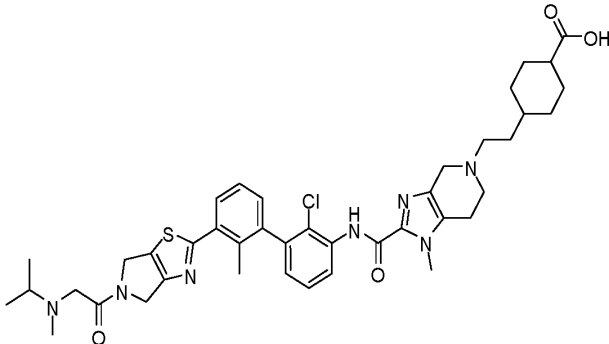
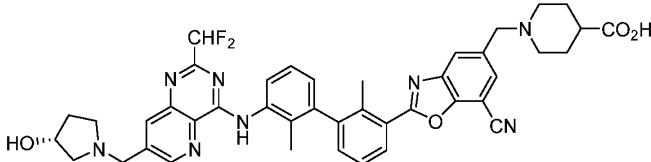
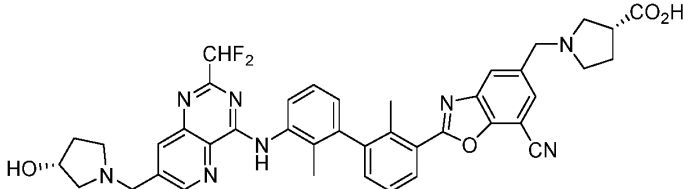
Cmpd No.	US Publication Appl. No.	Name and Structure
1	US 2018-0179197, Example #24	(<i>R</i>)-1-((7-cyano-2-(3'-(3-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid 
2	US 2018-0179201, Example #2	<i>N</i>-(2-chloro-3'-(8-chloro-6-((2-hydroxyethylamino)methyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-2'-methylbiphenyl-3-yl)-5-((2-hydroxyethylamino)methyl)picolinamide 
3	US 2018-0179197, Example #25	(<i>S</i>)-1-((7-cyano-2-(3'-(3-(((<i>S</i>)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid 
4	US 2018-0179197, Example #26	(<i>R</i>)-1-((7-cyano-2-(3'-(3-(((<i>S</i>)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid 

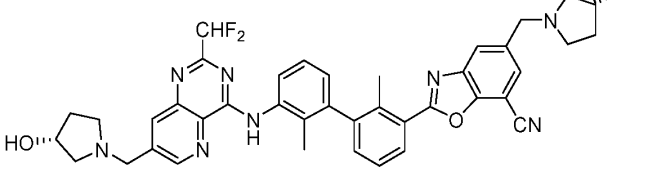
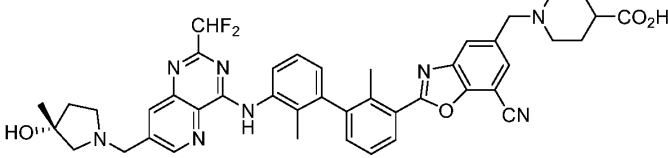
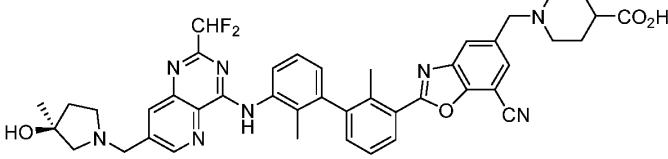
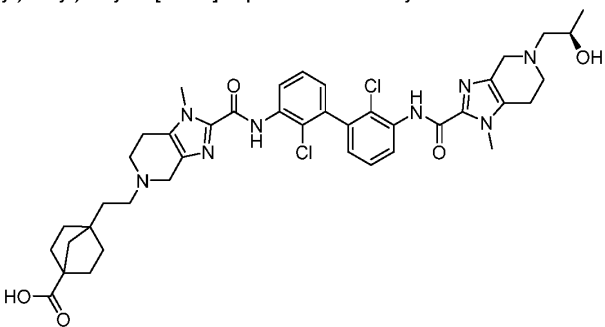
Cmpd No.	US Publication Appl. No.	Name and Structure
5	US 2018-0179197, Example #28	(S)-1-((7-cyano-2-(3'-((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methylpyrrolidine-3-carboxylic acid 
6	US 2018-0179197, Example #236	1-((7-cyano-2-(3'-(5-(2-(dimethylamino)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid 
7	US 2018-0179179, Example #1	<i>N,N'</i>-(2-chloro-2'-methylbiphenyl-3,3'-diyl)bis(5-((2-hydroxyethylamino)methyl)picolinamide) 
8	US 2018-0179179, Example #9	(<i>R</i>)-1-((6-(2'-chloro-3'-(5-((3-hydroxypyrrolidin-1-yl)methyl)picolinamido)-2-methylbiphenyl-3-ylcarbamoyl)pyridin-3-yl)methyl)piperidine-4-carboxylic acid 
9	US 2018-0179179, Example #12	(<i>S</i>)-1-((6-((2'-chloro-2-methyl-3'-(5-(pyrrolidin-1-ylmethyl)picolinamido)-[1,1'-biphenyl]-3-yl)carbamoyl)-4-methylpyridin-3-yl)methyl)piperidine-2-carboxylic acid 

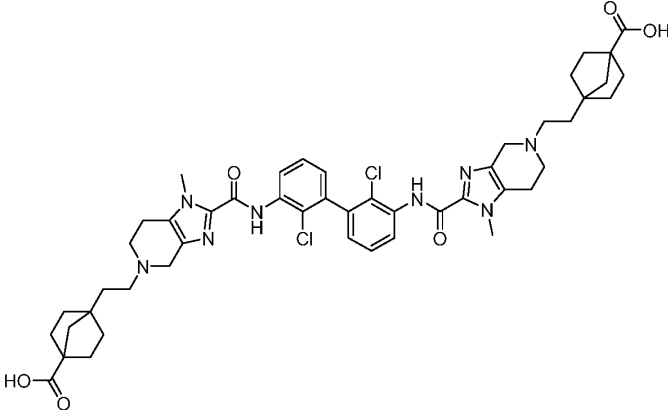
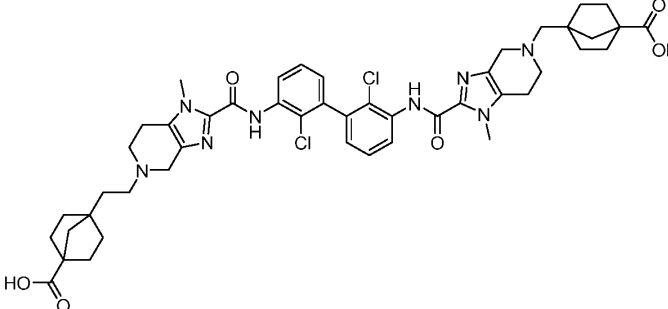
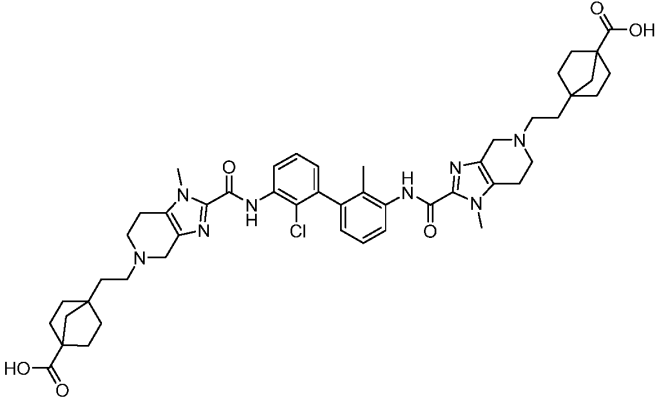
Cmpd No.	US Publication Appl. No.	Name and Structure
10	US 2018-0179202, Example #52	<i>trans</i> 4-(2-(2-(2-chloro-3'-(3-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)ethyl)cyclohexanecarboxylic acid 
11	US 2018-0179202, Example #56	<i>cis</i>-4-((2-(2-chloro-3'-(3-(((<i>R</i>)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)methyl)cyclohexanecarboxylic acid 
12	US 2018-0179202, Example #68	(<i>R</i>)-4-(2-(2-chloro-3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)-1-methylcyclohexanecarboxylic acid 
13	US 2018-0179202, Example #90	(<i>R</i>)-1-((8-((2-chloro-3'-(5-(<i>N</i>-ethyl-<i>N</i>-methylglycyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid 
14	US 2018-0177784, Example #35	(<i>R</i>)-2-(dimethylamino)-1-(2-(3'-(5-(2-(3-hydroxypyrrolidin-1-yl)acetyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2,2'-dimethylbiphenyl-3-yl)-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-5(6<i>H</i>)-yl)ethanone 

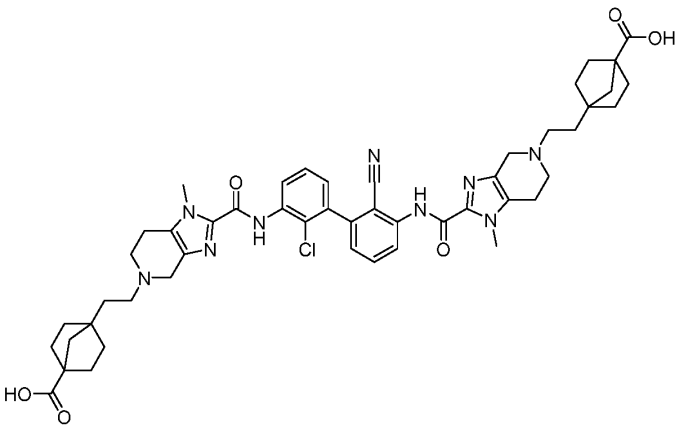
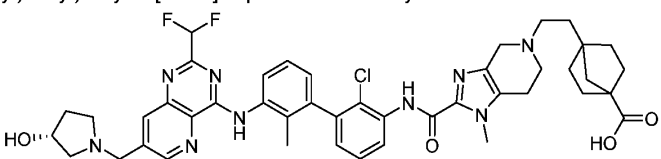
Cmpd No.	US Publication Appl. No.	Name and Structure
15	US 2018-0177870, Example #37	<i>trans</i>-4-((2-(2'-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)methyl)cyclohexane-1-carboxylic acid 
16	US 2018-0177870, Example #100	<i>trans</i>-4-(2-(2-((2'-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-2-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5-yl)ethyl)cyclohexane-1-carboxylic acid 
17	US 2018-0177870, Example #114	<i>cis</i>-4-((2-(2'-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-2-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5-yl)methyl)cyclohexane-1-carboxylic acid 
18	US 2018-0177870, Example #135	<i>cis</i>-4-((2-(2'-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5-yl)methyl)cyclohexane-1-carboxylic acid 

Cmpd No.	US Publication Appl. No.	Name and Structure
19	US 2018-0177870, Example #148	<i>trans</i>-4-((2-(2-((2'-chloro-2-cyano-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5-yl)ethyl)cyclohexane-1-carboxylic acid 
20	US 2018-0177870, Example #159	<i>trans</i>-4-((2-(2-chloro-3'-(5-(2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)methyl)cyclohexane-1-carboxylic acid 
21	US 2018-0177870, Example #160	<i>cis</i>-4-((2-(2-chloro-3'-(5-(2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)methyl)cyclohexane-1-carboxylic acid 

Cmpd No.	US Publication Appl. No.	Name and Structure
22	US 2018-0177870, Example #161	4-(2-(2-(2-chloro-3'-(5-(2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)ethyl)cyclohexane-1-carboxylic acid 
23	US 2018-0177870, Example #162	4-(2-(2-(2-chloro-3'-(5-(2-(isopropyl(methyl)amino)acetyl)-5,6-dihydro-4<i>H</i>-pyrrolo[3,4-<i>d</i>]thiazol-2-yl)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5(4<i>H</i>)-yl)ethyl)cyclohexane-1-carboxylic acid 
24	US 2019-0300524, Example #16	(<i>R</i>)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[<i>d</i>]oxazol-5-yl)methyl)piperidine-4-carboxylic acid 
25	US 2019-0300524, Example #17	(<i>R</i>)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[<i>d</i>]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid 

Cmpd No.	US Publication Appl. No.	Name and Structure
26	US 2019-0300524, Example #18	(<i>R</i>)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[<i>d</i>]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid 
27	US 2019-0300524, Example #30	(<i>R</i>)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[<i>d</i>]oxazol-5-yl)methyl)piperidine-4-carboxylic acid 
28	US 2019-0300524, Example #31	(<i>S</i>)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-<i>d</i>]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[<i>d</i>]oxazol-5-yl)methyl)piperidine-4-carboxylic acid 
29	US 2019-0345170, Example #13	(<i>R</i>)-4-(2-(2-((2,2'-dichloro-3'-(5-(2-hydroxypropyl)-1-methyl-4,5,6,7-tetrahydro-1<i>H</i>-imidazo[4,5-<i>c</i>]pyridine-2-carboxamido)-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5<i>H</i>-imidazo[4,5-<i>c</i>]pyridin-5-yl)ethyl)bicyclo[2.2.1]heptane-1-carboxylic acid 

Cmpd No.	US Publication Appl. No.	Name and Structure
30	US 2019-0345170, Example #17	4,4'-((((2,2'-dichloro-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2,5-diyl))bis(ethane-2,1-diyl))bis(bicyclo[2.2.1]heptane-1-carboxylic acid) 
31	US 2019-0345170, Example #18	4-((2-((3'-(5-(2-(4-carboxybicyclo[2.2.1]heptan-1-yl)ethyl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2,2'-dichloro-[1,1'-biphenyl]-3-yl)carbonyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)methyl)bicyclo[2.2.1]heptane-1-carboxylic acid 
32	US 2019-0345170, Example #34	4,4'-((((2-chloro-2'-methyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2,5-diyl))bis(ethane-2,1-diyl))bis(bicyclo[2.2.1]heptane-1-carboxylic acid) 

Cmpd No.	US Publication Appl. No.	Name and Structure
33	US 2019-0345170, Example #51	4,4'-((((2-chloro-2'-cyano-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2,5-diyl))bis(ethane-2,1-diyl))bis(bicyclo[2.2.1]heptane-1-carboxylic acid) 
34	US 2021-0094976, Example #1	(<i>R</i>)-4-(2-(2-((2-chloro-3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)ethyl)bicyclo[2.2.1]heptane-1-carboxylic acid 

In some embodiments, the antibody is an anti-PD-1 antibody, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, cetrelimab, toripalimab, sintilimab, AB122, AMP-224, JTX-4014, BGB-108, BCD-100, BAT1306, LZM009, AK105,

5 HLX10, or TSR-042. In some embodiments, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, cetrelimab, toripalimab, or sintilimab. In some embodiments, the anti-PD-1 antibody is pembrolizumab. In some

embodiments, the anti-PD-1 antibody is nivolumab. In some embodiments, the anti-PD-1 antibody is cemiplimab. In some embodiments, the anti-PD-1 antibody is spartalizumab. In

10 some embodiments, the anti-PD-1 antibody is camrelizumab. In some embodiments, the anti-PD-1 antibody is cetrelimab. In some embodiments, the anti-PD-1 antibody is toripalimab. In some embodiments, the anti-PD-1 antibody is sintilimab. In some

embodiments, the anti-PD-1 antibody is AB122. In some embodiments, the anti-PD-1 antibody is AMP-224. In some embodiments, the anti-PD-1 antibody is JTX-4014. In some

15 embodiments, the anti-PD-1 antibody is BGB-108. In some embodiments, the anti-PD-1

antibody is BCD-100. In some embodiments, the anti-PD-1 antibody is BAT1306. In some
embodiments, the anti-PD-1 antibody is LZM009. In some embodiments, the anti-PD-1
antibody is AK105. In some embodiments, the anti-PD-1 antibody is HLX10. In some
embodiments, the anti-PD-1 antibody is TSR-042. In some embodiments, the anti-PD-1
5 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD-1
monoclonal antibody is MGA012 (INCMGA0012; retifanlimab). In some embodiments, the
anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics
such as 4-1BB (e.g., urelumab, utomilumab). In some embodiments, the inhibitor of an
immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal
10 antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is atezolizumab,
avelumab, durvalumab, tislelizumab, BMS-935559, MEDI4736, atezolizumab
(MPDL3280A; also known as RG7446), avelumab (MSB0010718C), FAZ053, KN035,
CS1001, SHR-1316, CBT-502, A167, STI-A101, CK-301, BGB-A333, MSB-2311, HLX20, or
LY3300054. In some embodiments, the anti-PD-L1 antibody is atezolizumab, avelumab,
15 durvalumab, or tislelizumab. In some embodiments, the anti-PD-L1 antibody is
atezolizumab. In some embodiments, the anti-PD-L1 antibody is avelumab. In some
embodiments, the anti-PD-L1 antibody is durvalumab. In some embodiments, the anti-PD-L1
antibody is tislelizumab. In some embodiments, the anti-PD-L1 antibody is BMS-935559. In
some embodiments, the anti-PD-L1 antibody is MEDI4736. In some embodiments, the anti-
20 PD-L1 antibody is FAZ053. In some embodiments, the anti-PD-L1 antibody is KN035. In
some embodiments, the anti-PD-L1 antibody is CS1001. In some embodiments, the anti-PD-
L1 antibody is SHR-1316. In some embodiments, the anti-PD-L1 antibody is CBT-502. In
some embodiments, the anti-PD-L1 antibody is A167. In some embodiments, the anti-PD-L1
antibody is STI-A101. In some embodiments, the anti-PD-L1 antibody is CK-301. In some
25 embodiments, the anti-PD-L1 antibody is BGB-A333. In some embodiments, the anti-PD-L1
antibody is MSB-2311. In some embodiments, the anti-PD-L1 antibody is HLX20. In some
embodiments, the anti-PD-L1 antibody is LY3300054.

In some embodiments, the inhibitor of an immune checkpoint molecule is a small
molecule that binds to PD-L1, or a pharmaceutically acceptable salt thereof. In some
30 embodiments, the inhibitor of an immune checkpoint molecule is a small molecule that binds
to and internalizes PD-L1, or a pharmaceutically acceptable salt thereof. In some
embodiments, the inhibitor of an immune checkpoint molecule is a compound selected from
those in US 2018/0179201, US 2018/0179197, US 2018/0179179, US 2018/0179202, US
2018/0177784, US 2018/0177870, US 2019/0300524, and US 2019/0345170, or a
35 pharmaceutically acceptable salt thereof, each of which is incorporated herein by reference
in its entirety.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of KIR, TIGIT, LAIR1, CD160, 2B4 and TGFR beta.

In some embodiments, the inhibitor is MCLA-145.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab, tremelimumab, AGEN1884, or CP-675,206.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525, INCAGN2385, or eftilagimod alpha (IMP321).

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD73. In some embodiments, the inhibitor of CD73 is oleclumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIGIT. In some embodiments, the inhibitor of TIGIT is OMP-31M32.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of VISTA. In some embodiments, the inhibitor of VISTA is JNJ-61610588 or CA-170.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of B7-H3. In some embodiments, the inhibitor of B7-H3 is enoblituzumab, MGD009, or 8H9.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of KIR. In some embodiments, the inhibitor of KIR is lirilumab or IPH4102.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of A2aR. In some embodiments, the inhibitor of A2aR is CPI-444.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TGF-beta. In some embodiments, the inhibitor of TGF-beta is trabedersen, galusertinib, or M7824.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PI3K-gamma. In some embodiments, the inhibitor of PI3K-gamma is IPI-549.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD47. In some embodiments, the inhibitor of CD47 is Hu5F9-G4 or TTI-621.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD73. In some embodiments, the inhibitor of CD73 is MEDI9447.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD70. In some embodiments, the inhibitor of CD70 is cusatuzumab or BMS-936561.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD20, e.g., an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is obinutuzumab or rituximab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of OX40, CD27, CD28, GITR, ICOS, CD40, TLR7/8, and CD137 (also known as 4-1BB).

In some embodiments, the agonist of CD137 is urelumab. In some embodiments, the agonist of CD137 is utomilumab.

In some embodiments, the agonist of an immune checkpoint molecule is an inhibitor of GITR. In some embodiments, the agonist of GITR is TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, MEDI1873, or MEDI6469. In some
embodiments, the agonist of an immune checkpoint molecule is an agonist of OX40, e.g., OX40 agonist antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is INCAGN01949, MEDI0562 (tavolimab), MOXR-0916, PF-04518600, GSK3174998, BMS-986178, or 9B12. In some embodiments, the OX40L fusion protein is
MEDI6383.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD40. In some embodiments, the agonist of CD40 is CP-870893, ADC-1013, CDX-1140, SEA-CD40, RO7009789, JNJ-64457107, APX-005M, or Chi Lob 7/4.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of ICOS. In some embodiments, the agonist of ICOS is GSK-3359609, JTX-2011, or MEDI-570.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD28. In some embodiments, the agonist of CD28 is theralizumab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD27. In some embodiments, the agonist of CD27 is varlilumab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of TLR7/8. In some embodiments, the agonist of TLR7/8 is MEDI9197.

The compounds of the present disclosure can be used in combination with bispecific antibodies. In some embodiments, one of the domains of the bispecific antibody targets PD-1, PD-L1, CTLA-4, GITR, OX40, TIM3, LAG3, CD137, ICOS, CD3 or TGF β receptor. In some embodiments, the bispecific antibody binds to PD-1 and PD-L1. In some
embodiments, the bispecific antibody that binds to PD-1 and PD-L1 is MCLA-136. In some
embodiments, the bispecific antibody binds to PD-L1 and CTLA-4. In some embodiments, the bispecific antibody that binds to PD-L1 and CTLA-4 is AK104.

In some embodiments, the compounds of the disclosure can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include

epacadostat, NLG919, BMS-986205, PF-06840003, IOM2983, RG-70099 and LY338196. Inhibitors of arginase inhibitors include INCB1158.

As provided throughout, the additional compounds, inhibitors, agents, etc. can be combined with the present compound in a single or continuous dosage form, or they can be administered simultaneously or sequentially as separate dosage forms.

IV. Formulation, Dosage Forms and Administration

When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus, the present disclosure provides a composition comprising a compound of Formula (I), a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may 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. Parenteral 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 may be, e.g., by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, e.g., a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-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, e.g., up to 10% by weight of the active

compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active
5 compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other
10 formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art see, *e.g.*, WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl
15 cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient
20 by employing procedures known in the art.

In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2%
25 silicon dioxide w/w.

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some
30 embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some
35 embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and polyethylene oxide. In some embodiments, the composition further

comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (e.g., Methocel K4 M Premier™) and/or

5 hydroxypropyl methylcellulose 2208 K100LV (e.g., Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (e.g., Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the

10 composition.

The compositions 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. In some embodiments, each dosage contains about 10 mg of the active ingredient. In some embodiments, each dosage contains about 50 mg of the active

15 ingredient. In some embodiments, each dosage contains about 25 mg of the active ingredient. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The components used to formulate the pharmaceutical compositions are of high purity and are substantially free of potentially harmful contaminants (e.g., at least National Food grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Particularly for human consumption, the composition is preferably manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable

20 regulations of the U.S. Food and Drug Administration. For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

The active compound may be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the

30 amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the like.

The therapeutic dosage of a compound of the present invention can vary according to, e.g., the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a

35

pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some
5 typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its
10 route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these
15 preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, e.g., about 0.1 to about 1000 mg of the active ingredient of the present
20 invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an
25 enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

30 The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

35 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable

excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or
5 intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, *e.g.*, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and
10 the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, *e.g.*, glycerinmonostearate, PEG-glycerinmonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, *e.g.*, glycerol,
15 hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2 or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, *e.g.*, 100 g which are optionally associated with instructions for the treatment of the select indication, *e.g.*, psoriasis or other skin condition.

20 The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the
25 disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional
30 sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers or stabilizers will result in
35 the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of

the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, 5 the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of 10 progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

V. Labeled Compounds and Assay Methods

15 Another aspect of the present invention relates to labeled compounds of the disclosure (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating KRAS protein in tissue samples, including human, and for identifying KRAS ligands by inhibition binding of a labeled compound. Substitution of one or more of the atoms of the compounds 20 of the present disclosure can also be useful in generating differentiated ADME (Adsorption, Distribution, Metabolism and Excretion). Accordingly, the present invention includes KRAS binding assays that contain such labeled or substituted compounds.

The present disclosure further includes isotopically-labeled compounds of the disclosure. An "isotopically" or "radio-labeled" compound is a compound of the disclosure 25 where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). A "radio-labelled" compound can refer to an isotopically-labelled compound in which one or more atoms are replaced or substituted by an atom of an isotope that is radioactive.

30 Suitable isotopes that may be incorporated in compounds of the present disclosure include but are not limited to ²H (also written as D for deuterium), ³H (also written as T for tritium), ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁸²Br, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced by deuterium atoms (e.g., one or more hydrogen atoms of a C₁₋₆ alkyl group 35 of Formula (I) can be optionally substituted with deuterium atoms, such as –CD₃ being

substituted for $-\text{CH}_3$). In some embodiments, alkyl groups in Formula (I) can be perdeuterated.

One or more constituent atoms of the compounds presented herein can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some
5 embodiments, the compound includes at least one deuterium atom. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, or 1-6 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by deuterium atoms. For example, one or more hydrogen atoms in a compound of the present disclosure can be
10 replaced by deuterium atoms (e.g., one or more hydrogen atoms of a C_{1-6} alkyl group of Formula (I) can be optionally substituted with deuterium atoms, such as $-\text{CD}_3$ being substituted for $-\text{CH}_3$). In some embodiments, alkyl groups in Formula (I) can be perdeuterated. The symbol D included in a chemical formula or as a substituent indicates that deuterium is incorporated in the position labelled at greater than natural abundance, and
15 typically indicates an abundance of equal to or greater than 50%, preferably equal to or greater than 90% or equal to or greater than 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 99.95%, or 99.99% relative to other forms of hydrogen.

Synthetic methods for including isotopes into organic compounds are known in the art (A. F. Thomas, *Deuterium Labeling in Organic Chemistry*, (Appleton-Century-Crofts, New
20 York, N.Y., **1971**); J. Atzrodt, *et al.*, *Angew. Chem. Int. Ed.*, **2007**, 7744-65; J. R. Hanson, *The Organic Chemistry of Isotopic Labelling*, (Royal Society of Chemistry, **2011**)). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

Substitution with heavier isotopes, such as deuterium, may afford certain therapeutic
25 advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. (see e.g., A. Kerekes, *et al.*, *J. Med. Chem.* **2011**, 54(1), 201-10; R. Xu *et al.*, *J. Label. Compd. Radiopharm.* **2015**, 58, 308-12). In particular, substitution at one or more metabolism sites may afford one or more of the therapeutic advantages.

30 The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* adenosine receptor labeling and competition assays, compounds that incorporate ^3H , ^{14}C , ^{82}Br , ^{125}I , ^{131}I or ^{35}S can be useful. For radio-imaging applications ^{11}C , ^{18}F , ^{125}I , ^{123}I , ^{124}I , ^{131}I , ^{75}Br , ^{76}Br or ^{77}Br can be useful.

35 It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments, the radionuclide is selected from ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br .

The present disclosure can further include synthetic methods for incorporating radio-isotopes into compounds of the disclosure. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of disclosure.

5 A labeled compound of the invention can be used in a screening assay to identify and/or evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a KRAS protein by monitoring its concentration variation when contacting with the KRAS, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to
10 reduce binding of another compound which is known to bind to a KRAS protein (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the KRAS protein directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound
15 is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

VI. Kits

 The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment or prevention of diseases or disorders associated with the activity of KRAS, such
20 as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, *e.g.*, containers with one or more pharmaceutically acceptable carriers, additional containers, *etc.*, as will be readily apparent
25 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.

 The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the
30 invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to inhibit the activity of KRAS according to at least one assay described herein.

EXAMPLES

35 Experimental procedures for compounds of the invention are provided below. Preparatory LC-MS purifications of some of the compounds prepared were performed on

Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature. See e.g., K. F. Blom, *J. Combi. Chem.*, **2002**, 4(4), 295-301; K. F. Blom, *et al.*, *J. Combi. Chem.*, **2003**, 5(5), 670-683; and K. F. Blom, *et al.*, *J. Combi. Chem.* **2004**, 6(6), 874-83. The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check.

The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters SUNFIRE® C₁₈ 5 µm particle size, 2.1×5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: MeCN; gradient 2% to 80% of B in 3 min. with flow rate 2.0 mL/min.

Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

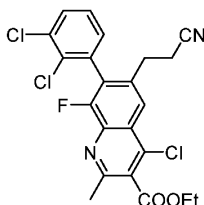
pH=2 purifications: Waters SUNFIRE® C₁₈ 5 µm particle size, 19×100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: MeCN; the flow rate was 30 mL/min., the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [see K. F. Blom, *et al.*, *J. Combi. Chem.* **2004**, 6(6), 874-83]. Typically, the flow rate used with the 30×100 mm column was 60 mL/min.

pH=10 purifications: Waters XBRIDGE® C₁₈ 5 µm particle size, 19×100 mm column, eluting with mobile phase A: 0.15% NH₄OH in water and mobile phase B: MeCN; the flow rate was 30 mL/min., the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [See K. F. Blom, *et al.*, *J. Combi. Chem.* **2004**, 6(6), 874-83]. Typically, the flow rate used with 30×100 mm column was 60 mL/min.

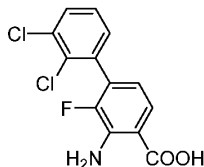
The following abbreviations may be used herein: AcOH (acetic acid); Ac₂O (acetic anhydride); aq. (aqueous); atm. (atmosphere(s)); Boc (*t*-butoxycarbonyl); Boc₂O (di-*t*-butyl dicarbonate); BOP ((benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate); br (broad); Cbz (carboxybenzyl); calc. (calculated); CO₂ (carbion dioxide); Cs₂CO₃ (cesium carbonate); CsF (cesium fluoride); d (doublet); dd (doublet of doublets); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); DCM (dichloromethane); DIAD (*N,N'*-diisopropyl azidodicarboxylate); DIPEA (*N,N*-diisopropylethylamine); DIBAL (diisobutylaluminium hydride); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); eq. (equivalent(s)); Et (ethyl); EtOH (ethanol); EtOAc (ethyl acetate); Ex. (Example); FCC

(flash column chromatography); g (gram(s)); h (hour(s)); H₂ (hydrogen); HATU (*N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate); HCl (hydrochloric acid or hydrogen chloride); HPLC (high performance liquid chromatography); Hz (hertz); J (coupling constant); K₂CO₃ (potassium carbonate); LCMS (liquid chromatography–mass spectrometry); LiBH₄ (lithium borohydride); LDA (lithium diisopropylamide); m (multiplet); M (molar); *m*CPBA (3-chloroperoxybenzoic acid); MS (Mass spectrometry); Me (methyl); MeCN (acetonitrile); MeOH (methanol); mg (milligram(s)); MgSO₄ (magnesium sulfate); min. (minutes(s)); mL (milliliter(s)); mmol (millimole(s)); N (normal); NaBH₄ (sodium borohydride); NaCl (sodium chloride); NADPH (nicotinamide adenine dinucleotide phosphate); NaHCO₃ (sodium bicarbonate); NaIO₄ (sodium metaperiodate); NaOH (sodium hydroxide); NCS (*N*-chlorosuccinimide); NEt₃ (triethylamine); NH₄OH (ammonium hydroxide); nM (nanomolar); NMP (*N*-methylpyrrolidinone); NMR (nuclear magnetic resonance spectroscopy); OTf (trifluoromethanesulfonate); Ph (phenyl); Pd(PPh₃)₄ (tetrakis(triphenylphosphine) palladium(0)); pM (picomolar); PPT (precipitate); RP-HPLC (reverse phase high performance liquid chromatography); r.t. (room temperature), s (singlet); sat. (saturated); t (triplet or tertiary); TBDPS (*tert*-butyldiphenylsilyl); TBS (*tert*-butyldimethylsilyl); tert (tertiary); tt (triplet of triplets); TFA (trifluoroacetic acid); THF (tetrahydrofuran); µg (microgram(s)); µL (microliter(s)); µM (micromolar); wt % (weight percent); xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene). Brine is sat. aq. NaCl. *In vacuo* is under vacuum.

Intermediate 1. Ethyl (*R*)-4-chloro-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylate



Step 1. 3-Amino-2',3'-dichloro-2-fluoro-[1,1'-biphenyl]-4-carboxylic acid

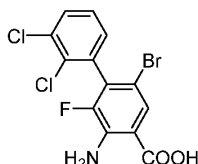


25

A mixture of 2-amino-4-bromo-3-fluorobenzoic acid (28.0 g, 120 mmol), (2,3-dichlorophenyl)boronic acid (25.1 g, 132 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (2.12 g, 3.00 mmol) and potassium phosphate (50.8 g, 239 mmol) in 1,4-dioxane (170 mL) and water (30 mL) was sparged with

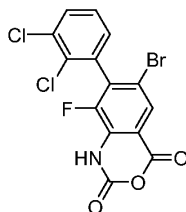
N₂ and heated at 70 °C for 1 h. Once completed, the reaction mixture was cooled down to r.t. and poured into 1 N HCl (200 mL). The mixture was stirred for another 10 min., resulting in precipitation. The solids were collected on a fritted filter, washed with water followed by hexanes and dried under reduced pressure to afford the sub-title compound in near
5 quantitative yield. The crude product was used in next step without further purification. LC-MS calc. for C₁₃H₉Cl₂FNO₂ (M+H)⁺: *m/z*=300.0; found 300.0.

Step 2. 3-Amino-6-bromo-2',3'-dichloro-2-fluoro-[1,1'-biphenyl]-4-carboxylic acid



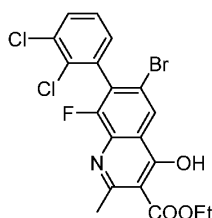
To a solution of 3-amino-2',3'-dichloro-2-fluoro-[1,1'-biphenyl]-4-carboxylic acid
10 (35.8 g, 119 mmol) in DMSO (100 mL) was added *N*-bromosuccinimide (22.3 g, 125 mmol). The resulting mixture was heated at 50 °C for 1 h. Once completed, the reaction mixture was cooled down to r.t. and poured into ice water (400 mL). To the suspension, was added 20 mL saturated Na₂S₂O₃ solution. After stirring for 15 min., the solids were collected on a
15 fritted filter, washed with water followed by hexanes and dried under reduced pressure to afford the sub-title compound (43.0 g, 95% yield). The crude product was used in next step without further purification. LC-MS calc. for C₁₃H₈BrCl₂FNO₂ (M+H)⁺: *m/z*=377.9, 379.9; found 378.0, 380.0.

Step 3. 6-Bromo-7-(2,3-dichlorophenyl)-8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione



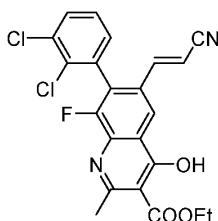
To a solution of 3-amino-6-bromo-2',3'-dichloro-2-fluoro-[1,1'-biphenyl]-4-carboxylic
20 acid (38.6 g, 102 mmol) in THF (300 mL) was added triphosgene (10.6 g, 35.6 mmol) portionwise. After addition, the mixture was heated at 60 °C for 0.5 h. Once completed, the reaction mixture was cooled down to r.t. and poured into heptane (1000 mL). After stirring for 1 h, the solids were collected on a fritted filter, washed with hexanes and dried under
25 reduced pressure to afford the sub-title compound in near quantitative yield. The crude product was used in next step without further purification.

Step 4. Ethyl 6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxy-2-methylquinoline-3-carboxylate



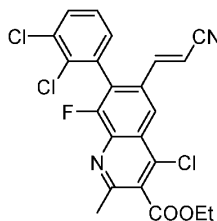
To a solution of 6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (41.5 g, 102 mmol) in DMSO (200 mL), was added (1-ethoxy-1,3-dioxobutan-2-yl)sodium (18.7 g, 123 mmol) portionwise. After addition, the mixture was heated at 80 °C for 1 h. Once completed, the reaction mixture was cooled down to r.t. and poured into 1 N HCl (400 mL). After stirring for 1 h, the solids were collected on a fritted filter, washed with water followed by hexanes and dried under reduced pressure to afford the sub-title compound (40.0 g, 83% yield). The crude product was used in next step without further purification. LC-MS calc. for C₁₉H₁₄BrCl₂FNO₃ (M+H)⁺: *m/z*=471.9, 473.9; found 471.9, 474.0.

Step 5. Ethyl (E)-6-(2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxy-2-methylquinoline-3-carboxylate



To a solution of ethyl 6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxy-2-methylquinoline-3-carboxylate (35.0 g, 74.0 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (2.62 g, 3.70 mmol) in DMF (100 mL), acrylonitrile (12.3 mL, 185 mmol) and NEt₃ (30.9 mL, 222 mmol) were added. The mixture was sparged with N₂ and heated at 85 °C for 1 h. Once completed, the reaction mixture was cooled down to r.t. and poured into 1 N HCl (500 mL). After stirring for 1 h, the solids were collected on a fritted filter, washed with water followed by hexanes and dried under reduced pressure to afford the sub-title compound (19.2 g, 58% yield). The crude product was used in next step without further purification. LC-MS calc. for C₂₂H₁₆Cl₂FN₂O₃ (M+H)⁺: *m/z*=445.0; found 445.0.

Step 6. Ethyl (E)-4-chloro-6-(2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylate

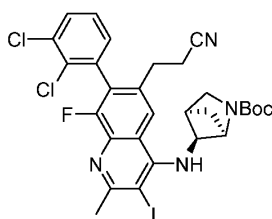


To a slurry of ethyl (E)-6-(2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxy-2-methylquinoline-3-carboxylate (30.0 g, 67.4 mmol) and benzyltriethylammonium chloride (15.4 g, 67.4 mmol) in MeCN (150 mL) at 0 °C, was added DIPEA (23.5 mL, 135 mmol). Upon stirring at 0 °C, phosphoryl chloride (12.6 mL, 135 mmol) was added dropwise into the mixture. Then the mixture was heated at 60 °C for 1 h. Upon completion, the reaction mixture was cooled to r.t. and slowly poured into ice water (1000 mL). The mixture was extracted with DCM three times, dried over Na₂SO₄, filtered and concentrated. The crude product was further purified by FCC (0-50% EtOAc/hexanes) to afford the sub-title compound (4.5 g, 14% yield). LC-MS calc. for C₂₂H₁₅Cl₃FN₂O₂ (M+H)⁺: *m/z*=463.0; found 463.0.

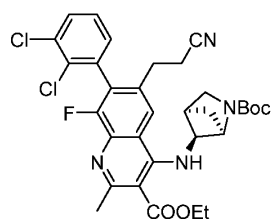
Step 7. Ethyl (R)-4-chloro-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylate

A mixture of copper(II) acetate monohydrate (0.19 g, 0.97 mmol) and Xantphos (0.56 g, 0.97 mmol) was stirred in toluene (1 mL) and *tert*-butanol (9 mL) at 60 °C for 0.5 h to afford a homogeneous solution. In a separate vial, to a mixture of ethyl (E)-4-chloro-6-(2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylate (4.5 g, 9.70 mmol) and polymethylhydrosiloxane (3.5 g, 58.2 mmol) in toluene (12 mL) at 60 °C, was added the previous copper-containing solution. The mixture was stirred at 60 °C for 0.5 h. Upon completion, the reaction mixture was filtered through diatomaceous earth and concentrated. The crude product was purified using FCC (0-40% EtOAc/DCM) to afford a mixture of two atropisomers (2.0 g, 44% yield). The title compound was separated from its atropisomer using chiral supercritical fluid chromatography (ChiralPak IJ column, eluting with 40% MeOH in CO₂ at a flow rate of 70 mL/min; the title compound eluted after its atropisomer). LC-MS calc. for C₂₂H₁₇Cl₃FN₂O₂ (M+H)⁺: *m/z*=465.0; found 465.0.

Intermediate 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(((*R*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



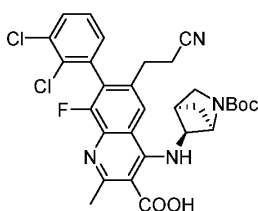
Step 1. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(((*R*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-8-fluoro-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

To a solution of ethyl (*R*)-4-chloro-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylate (**intermediate 1**, 7.2 g, 15.5 mmol) in *N*-methyl-2-pyrrolidone (21 mL), was added *tert*-butyl (1*R*,4*R*,5*S*)-5-amino-2-azabicyclo[2.1.1]hexane-2-carboxylate (5.52 g, 27.8 mmol) and DIPEA (8.1 mL, 46.4 mmol). The resulting mixture was heated at 80 °C for 18 h. Once completed, the reaction mixture was cooled down to r.t. and poured into 1 N HCl (300 mL) and ice mixture. After stirring for 0.5 h, the solids were collected on a fritted filter, washed with water followed by hexanes and dried under reduced pressure to afford white solids (8.2 g, 85% yield). The crude product was used in next step without further purification. LC-MS calc. for C₃₂H₃₄Cl₂FN₄O₄ (M+H)⁺: *m/z*=627.2; found 627.1.

Step 2. (*R*)-4-(((1*R*,4*R*,5*S*)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.1.1]hexan-5-yl)amino)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylic acid



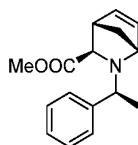
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-8-fluoro-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (4.0 g, 6.37 mmol) in MeCN (13 mL), was added 1 N NaOH (16 mL, 15.94 mmol). The mixture was heated at 50 °C for 2 h. Once completed, the reaction mixture was cooled down to r.t. and acidified to pH 5 using 1 N HCl. The organic volatiles were removed under reduced pressure. The residue aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated

under reduced pressure to give a yellow solid (3.70 g, 97% yield). The crude material was used in the next step without further purification. LC-MS calc. for $C_{30}H_{30}Cl_2FN_4O_4$ (M+H)⁺: m/z =599.2; found 599.1.

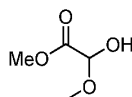
5 **Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(((*R*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate**

To a solution of (*R*)-4-(((1*R*,4*R*,5*S*)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[2.1.1]hexan-5-yl)amino)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-methylquinoline-3-carboxylic acid (3.70 g, 6.17 mmol) in MeCN (6.2 mL), was added potassium phosphate (2.62 g, 12.34 mmol) and *N*-iodosuccinimide (2.50 g, 11.1 mmol). The mixture was stirred at r.t. for 10 1 h. Once completed, the reaction mixture was poured into saturated $Na_2S_2O_3$ solution. After stirring for 10 min., the mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was further purified with FCC (0-100% EtOAc/hexanes) to afford the title compound as an off-white solid (1.95 g, 46% yield). LC-MS calc. for $C_{29}H_{29}Cl_2FIN_4O_2$ 15 (M+H)⁺: m/z =681.1; found 681.0.

Intermediate 3. Methyl (1*R*,3*R*,4*S*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate



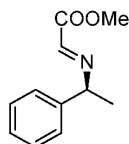
Step 1. Methyl 2-hydroxy-2-methoxyacetate



20

A solution of glyoxylic acid monohydrate (41.4 g, 450 mmol) in anhydrous MeOH (200 mL) was heated to 70 °C overnight. After cooling to r.t., the mixture was stirred with solid $NaHCO_3$ for 10 min. The resulting mixture was filtered and concentrated under reduced pressure to afford an oily residue. The residue was dissolved in CH_2Cl_2 , dried over Na_2SO_4 , 25 filtered and concentrated to afford the product (40.0 g, 82% yield). The product was used in next step without further purification.

Step 2. Methyl (*S*,*E*)-2-((1-phenylethyl)imino)acetate

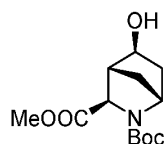


To a solution of methyl 2-hydroxy-2-methoxyacetate (40.0 g, 333 mmol) in toluene (95 mL) was added (S)-1-phenylethan-1-amine (40.4 g, 333 mmol) slowly. The mixture was stirred for 1 h at r.t. and diluted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to a yellow oil. The crude product was used in the next step without further purification.

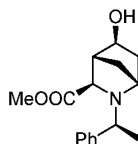
Step 3. Methyl (1R,3R,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate

To a solution of methyl (S,E)-2-((1-phenylethyl)imino)acetate (63.7 g, 333 mmol) in 2,2,2-trifluoroethanol (800 mL) at -10 °C, was added TFA (25.5 mL, 333 mmol). The reaction mixture was allowed to stir at -10 °C for 1 h before cyclopentadiene (24.2 g, 366 mmol) was added slowly. The mixture was stirred at -10 °C for another 0.5 h and then allowed to warm up to r.t. After removal of volatiles, the residue was diluted with 2 N hydrochloric acid (500 mL) and washed with diethyl ether. The organic layer was extracted with 2 N hydrochloric acid (100 mL). The combined aqueous layer was neutralized with 28% ammonium hydroxide and extracted with EtOAc three times. The combined organic layers was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-10% EtOAc/hexanes) in batches to afford the title compound as a colorless solid. LC-MS calc. for C₁₆H₂₀NO₂ (M+H)⁺: m/z=258.1; found 258.2. ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.27 (m, 2H), 7.25 (m, 2H), 7.22–7.16 (m, 1H), 6.44 (ddd, J=5.7, 3.1, 1.2 Hz, 1H), 6.29 (dd, J=5.7, 2.0 Hz, 1H), 4.33 (h, J=1.5 Hz, 1H), 3.37 (s, 3H), 3.06 (q, J=6.5 Hz, 1H), 2.93 (dq, J=3.3, 1.6 Hz, 1H), 2.24 (d, J=0.9 Hz, 1H), 2.13 (dt, J=8.4, 1.7 Hz, 1H), 1.48–1.41 (m, 4H).

Intermediate 4. 2-(tert-butyl) 3-methyl (1R,3R,4R,5S)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



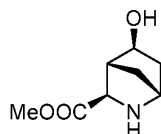
Step 1. Methyl (1R,3R,4R,5S)-5-hydroxy-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate



To a solution of methyl (1R,3R,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**intermediate 3**, 5.3 g, 20.6 mmol) in THF (70 mL) at 0 °C, was added a 0.5 N THF solution of 9-borabicyclo[3.3.1]nonane (51.5 mL, 25.7 mmol). The reaction mixture was allowed to warm up to r.t. and stirred for 18 h. Then the reaction mixture was

cooled to 0 °C and a 2 N NaOH solution (36.0 mL, 72.1 mmol) was added followed by hydrogen peroxide (30% aqueous solution, 10.5 mL, 103 mmol). The reaction mixture was allowed to warm up to r.t. and stirred for 1 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was
 5 purified by FCC (50%-70% EtOAc/hexanes) to afford the sub-title compound (2.0 g, 38% yield). LC-MS calc. for C₁₆H₂₂NO₃ (M+H)⁺: *m/z*=276.2; found 276.2.

Step 2. Methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate

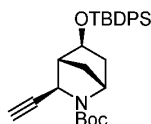


To a solution of methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (2.00 g, 7.26 mmol) in EtOH (35 mL) was added
 10 20% Pd(OH)₂/C (0.58 g). The mixture was stirred under an atmosphere of H₂ for 18 h. The resulting mixture was filtered through diatomaceous earth and concentrated to afford the sub-title compound. The crude material was used for next step without further purification. LC-MS calc. for C₈H₁₄NO₃ (M+H)⁺: *m/z*=172.1; found 172.1.

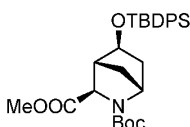
15 Step 3. 2-(*tert*-Butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate

To methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (1.24 g, 7.26 mmol) dissolved in THF (10 mL), was added DIPEA (5.10 mL, 29.1 mmol) and Boc₂O (3.96 g, 18.2 mmol). The reaction mixture was stirred at r.t. for 0.5 h and diluted with
 20 EtOAc. After washing with 0.01 N HCl and brine, the organic fraction was dried over Na₂SO₄, filtered and concentrated. The crude product was further purified by FCC (0%-100% EtOAc/hexanes) to afford the title compound (1.88 g, 95% yield). LC-MS calc. for C₉H₁₄NO₅ (M-^tBu+2H)⁺: *m/z*=216.1; found 216.1.

25 Intermediate 5. *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

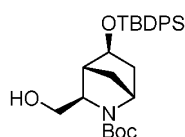


Step 1. 2-(*tert*-Butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



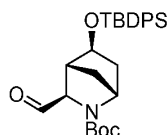
To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (**intermediate 4**, 1.88 g, 6.92 mmol) in DMF (140 mL), was added *tert*-butylchlorodiphenylsilane (2.08 g, 7.64 mmol) and imidazole (1.40 g, 20.8 mmol). The reaction mixture was stirred at r.t. for 18 h. The mixture was diluted with EtOAc, washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0%-40% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₂₅H₃₂NO₅Si (M-^tBu+2H)⁺: *m/z*=454.2; found 454.2.

Step 2. tert-Butyl (1R,3R,4R,5S)-5-((tert-butyldiphenylsilyl)oxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.53 g, 3.01 mmol) in THF (15 mL), was added a 2 N THF solution of LiBH₄ (3.8 mL, 7.52 mmol). The mixture was stirred at r.t. for 8 h and then quenched by slow addition of a saturated NH₄Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound (1.39 g, 96% yield). LC-MS calc. for C₂₄H₃₂NO₄Si (M-^tBu+2H)⁺: *m/z*=426.2; found 426.2.

Step 3. tert-Butyl (1R,3R,4R,5S)-5-((tert-butyldiphenylsilyl)oxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

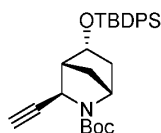


To a solution of oxalyl chloride (0.73 g, 5.76 mmol) in DCM (5.3 mL) cooled to -78 °C, was added DMSO (0.61 mL, 8.64 mmol) slowly. After stirring for 10 min., a DCM (1 mL) solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.39 g, 2.88 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h before DIPEA (1.5 mL) was added. The reaction mixture was allowed to warm up to r.t. and stirred for another 0.5 h. Then the reaction mixture was poured into a DCM (15 mL)/28% ammonium hydroxide (1.5 mL) mixture. After stirring for 10 min., the mixture was diluted with water. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for C₂₄H₃₀NO₄Si (M-^tBu+2H)⁺: *m/z*=424.2; found 424.3.

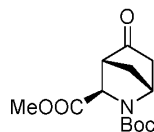
Step 4. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.38 g, 2.88 mmol) in MeOH (15 mL) was added
 5 dimethyl(1-diazo-2-oxopropyl)phosphonate (0.61 g, 3.17 mmol) and K₂CO₃ (1.19 g, 8.64 mmol). After stirring for 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-40% EtOAc/hexanes) to afford the title compound (0.20 g, 51% over 2 steps). LC-MS calc. for
 10 C₂₅H₃₀NO₃Si (M-^tBu+2H)⁺: *m/z*=420.2; found 420.2.

Intermediate 6. *tert*-butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

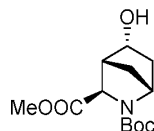


Step 1. 2-(*tert*-Butyl) 3-methyl (1*R*,3*R*,4*R*)-5-oxo-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate
 15



To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (**intermediate 4**, 1.88 g, 6.93 mmol) in DCM (35 mL) at 0 °C, was added Dess-Martin periodinane (3.32 g, 7.83 mmol) portionwise. The
 20 reaction mixture was allowed to warm up to r.t. and stirred for another 3 h. After washing with saturated Na₂S₂O₃ solution and water, the organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford an oil (1.29 g, 69% yield). LC-MS calc. for C₉H₁₂NO₅ (M-^tBu+2H)⁺: *m/z*=214.1; found 214.1.

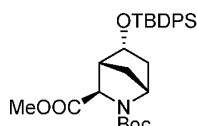
Step 2. 2-(*tert*-Butyl) 3-methyl (1*R*,3*R*,4*R*,5*R*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate
 25



To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*)-5-oxo-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.82 g, 3.04 mmol) in MeOH (15 mL) at 0 °C, was added NaBH₄ (0.29 g, 7.61 mmol) portionwise. The resulting mixture was allowed to warm up to r.t. and stirred for

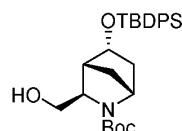
another 0.5 h. Then the reaction mixture was placed in an ice bath, and quenched by dropwise addition of saturated NH_4Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered and concentrate. The crude product was purified by FCC (30-60% EtOAc/hexanes) to afford the sub-title compound (0.47 g, 57% yield). LC-MS calc. for $\text{C}_9\text{H}_{14}\text{NO}_5$ ($\text{M}^{\text{-tBu+2H}}$)⁺: $m/z=216.1$; found 216.1.

Step 3. 2-(tert-Butyl) 3-methyl (1R,3R,4R,5R)-5-((tert-butyldiphenylsilyl)oxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



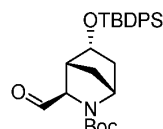
To a solution of 2-(tert-butyl) 3-methyl (1R,3R,4R,5R)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.47 g, 1.73 mmol) in DMF (3.5 mL), was added *tert*-butylchlorodiphenylsilane (0.52 g, 1.91 mmol) and imidazole (0.35 g, 5.20 mmol). The reaction mixture was stirred at r.t. for 18 h. The mixture was diluted with EtOAc, washed with brine five times, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by FCC (0-20% EtOAc/hexanes) to afford the sub-title compound (0.79 g, 89% yield). LC-MS calc. for $\text{C}_{24}\text{H}_{32}\text{NO}_3\text{Si}$ ($\text{M}^{\text{-Boc+2H}}$)⁺: $m/z=410.2$; found 410.3.

Step 4. tert-Butyl (1R,3R,4R,5R)-5-((tert-butyldiphenylsilyl)oxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of 2-(tert-butyl) 3-methyl (1R,3R,4R,5R)-5-((tert-butyldiphenylsilyl)oxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.79 g, 1.54 mmol) in THF (4 mL), was added a 2 N THF solution of LiBH_4 (1.93 mL, 3.86 mmol). The mixture was stirred at r.t. for 8 h and then quenched by slow addition of a saturated NH_4Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound (0.51 g, 69% yield). LC-MS calc. for $\text{C}_{24}\text{H}_{32}\text{NO}_4\text{Si}$ ($\text{M}^{\text{-tBu+2H}}$)⁺: $m/z=426.2$; found 426.1.

Step 5. tert-Butyl (1R,3R,4R,5R)-5-((tert-butyldiphenylsilyl)oxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

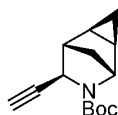


To a solution of oxalyl chloride (0.27 g, 2.12 mmol) in DCM (5.3 mL) cooled to -78°C , was added DMSO (0.23 mL, 3.18 mmol) slowly. After stirring for 10 min., a DCM (1 mL) solution of *tert*-butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.51 g, 1.06 mmol) was added. The reaction mixture was stirred at -78°C for 1 h before DIPEA (0.5 mL) was added. The reaction mixture was allowed to warm up to r.t. and stirred for another 0.5 h. Then the reaction mixture was poured into a DCM (5 mL)/28% ammonium hydroxide (0.5 mL) mixture. After stirring for 10 min., the mixture was diluted with water. The organic phase was separated, dried over Na_2SO_4 , filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for $\text{C}_{23}\text{H}_{30}\text{NO}_2\text{Si}$ ($\text{M-Boc}+2\text{H}$) $^{+}$: $m/z=380.2$; found 380.2.

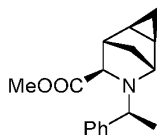
Step 6. *tert*-Butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.51 g, 1.06 mmol) in MeOH (5.3 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.22 g, 1.17 mmol) and K_2CO_3 (0.44 g, 3.18 mmol). After stirring for 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-40% EtOAc/hexanes) to afford the title compound (0.35 g, 70% yield over 2 steps). LC-MS calc. for $\text{C}_{25}\text{H}_{30}\text{NO}_3\text{Si}$ ($\text{M-}^t\text{Bu}+2\text{H}$) $^{+}$: $m/z=420.2$; found 420.2.

Intermediate 7. *tert*-butyl (1*S*,2*S*,4*R*,5*R*,7*R*)-7-ethynyl-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate



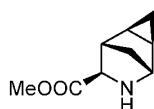
Step 1. Methyl (1*S*,2*S*,4*R*,5*R*,7*R*)-6-((*S*)-1-phenylethyl)-6-azatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate



A mixture of methyl (1*R*,3*R*,4*S*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**intermediate 3**, 0.80 g, 3.11 mmol), potassium trifluoro(iodomethyl)borate (1.16g, 4.66 mmol), *trans*-bis(acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (0.15 g, 0.155 mmol) and K_2CO_3 (0.64 g, 4.66 mmol) in DMF (13.8 mL) and water (1.7 mL)

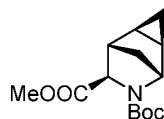
was sparged with N₂ and heated at 90°C for 8 h. Once completed, the reaction mixture was cooled down to r.t. and poured into water. The aqueous layer was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-10% EtOAc/hexanes) to afford the sub-title compound (0.34 g, 40%
 5 yield). LC-MS calc. for C₁₇H₂₂NO₂ (M+H)⁺: *m/z*=272.2; found 272.2.

Step 2. Methyl (1S,2S,4R,5R,7R)-6-azatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate



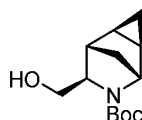
To a solution of methyl (1S,2S,4R,5R,7R)-6-((S)-1-phenylethyl)-6-azatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate (0.68 g, 2.51 mmol) in EtOH (35 mL) was added
 10 20% Pd(OH)₂/C (0.20 g). The mixture was stirred under an atmosphere of H₂ for 18 h. The resulting mixture was filtered through diatomaceous earth and concentrated to afford the sub-title compound. The crude material was used for next step without further purification. LC-MS calc. for C₉H₁₄NO₂ (M+H)⁺: *m/z*=168.1; found 168.1. ¹H NMR was collected on the TFA salt. ¹H NMR (600 MHz, DMSO-d₆) δ 9.75 (s, 1H), 8.55 (s, 1H), 4.19 (s, 1H), 4.13 (s,
 15 1H), 3.78 (s, 3H), 2.94 (s, 1H), 1.43 (d, *J*=12.7 Hz, 1H), 1.37–1.27 (m, 2H), 1.01 (d, *J*=12.6 Hz, 1H), 0.73 (dt, *J*=6.5, 3.2 Hz, 1H), 0.42 (q, *J*=7.1 Hz, 1H).

Step 3. 6-(tert-Butyl) 7-methyl (1S,2S,4R,5R,7R)-6-azatricyclo[3.2.1.0^{2,4}]octane-6,7-dicarboxylate



To methyl (1S,2S,4R,5R,7R)-6-azatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate (0.42 g, 2.51 mmol) dissolved in THF (13 mL), was added DIPEA (1.32 mL, 7.53 mmol) and Boc₂O (1.10 g, 5.02 mmol). The reaction mixture was stirred at r.t. for 0.5 h and diluted with EtOAc. After washing with brine, the organic fraction was dried over Na₂SO₄, filtered and concentrated. The crude product was further purified by FCC (0%-100% EtOAc/hexanes) to
 20 afford the sub-title compound (0.50 g, 75% yield over 2 steps). LC-MS calc. for C₁₀H₁₄NO₄ (M-^tBu+2H)⁺: *m/z*=212.1; found 212.1.

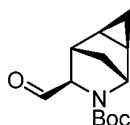
Step 4. tert-Butyl (1S,2S,4R,5R,7R)-7-(hydroxymethyl)-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate



To a solution of 6-(*tert*-butyl) 7-methyl (1*S*,2*S*,4*R*,5*R*,7*R*)-6-azatricyclo[3.2.1.0^{2,4}]octane-6,7-dicarboxylate (0.50 g, 1.87 mmol) in THF (10 mL), was added a 2 N THF solution of LiBH₄ (2.3 mL, 4.68 mmol). The mixture was stirred at r.t. for 8 h and then quenched by slow addition of a saturated NH₄Cl solution. The mixture was

5 diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₉H₁₄NO₃ (M-^{*t*}Bu+2H)⁺: *m/z*=184.1; found 184.1.

Step 5. tert-Butyl (1S,2S,4R,5R,7R)-7-formyl-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate



10 To a solution of oxalyl chloride (0.48 g, 3.76 mmol) in DCM (3.8 mL) cooled to -78 °C, was added DMSO (0.40 mL, 5.64 mmol) slowly. After stirring for 10 min., a DCM (1 mL) solution of *tert*-butyl (1*S*,2*S*,4*R*,5*R*,7*R*)-7-(hydroxymethyl)-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (0.45 g, 1.88 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h before DIPEA (1.0 mL) was added. The reaction

15 mixture was allowed to warm up to r.t. and stirred for another 0.5 h. Then the reaction mixture was poured into a DCM (10 mL)/28% ammonium hydroxide (1.0 mL) mixture. After stirring for 10 min., the mixture was diluted with water. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for C₉H₁₂NO₃ (M-^{*t*}Bu+2H)⁺: *m/z*=182.1; found 182.1.

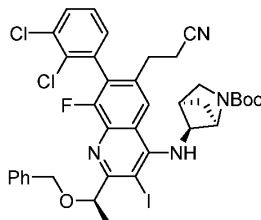
20

Step 6. tert-Butyl (1S,2S,4R,5R,7R)-7-ethynyl-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate

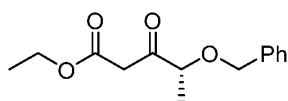
To a solution of *tert*-butyl (1*S*,2*S*,4*R*,5*R*,7*R*)-7-formyl-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (0.45 g, 1.88 mmol) in MeOH (10 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.40 g, 2.07 mmol) and K₂CO₃ (0.78 g, 5.64 mmol). After stirring for

25 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-40% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₁₀H₁₂NO₂ (M-^{*t*}Bu+2H)⁺: *m/z*=178.1; found 178.1.

Intermediate 8. *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*R*)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5 **Step 1. Ethyl (*R*)-4-(benzyloxy)-3-oxopentanoate**

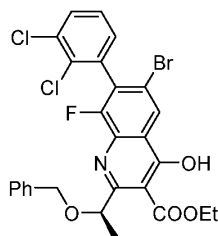


To a stirring solution of (*R*)-2-(benzyloxy)propanoic acid (8.00 g, 44.4 mmol) in EtOAc (22 mL) was slowly added 1,1'-carbonyldiimidazole (7.92 g, 48.8 mmol), resulting in gas evolving. The mixture was stirred at r.t. for 1 h to afford a clear solution.

10 To a separate reaction vessel containing magnesium chloride (10.6 g, 111 mmol) and potassium 3-ethoxy-3-oxopropanoate (15.1 g, 89.0 mmol), was added NEt₃ (19.8 mL, 142 mmol) and EtOAc (33 mL). The mixture was stirred vigorously at 60 °C for 1 h. Then the aforementioned clear solution was slowly added to the mixture. The resulting suspension was stirred at 80 °C for 3 h.

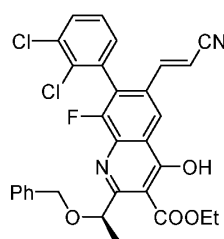
15 Upon completion, the reaction mixture was cooled to r.t. and acidified with 1 N HCl to pH<3 upon stirring. The mixture was diluted with EtOAc and water. The organic phase was separated and the aqueous phase was extracted two times with EtOAc. The combined organic layers was washed with saturated NaHCO₃ solution, water and brine, dried over Na₂SO₄, filtered and concentrated to afford the sub-title compound as an oil in near
20 quantitative yield. The crude product was used in next step without further purification. LC-MS calc. for C₁₄H₁₉O₄ (M+H)⁺: *m/z*=251.1; found 251.1.

Step 2. Ethyl 2-((*R*)-1-(benzyloxy)ethyl)-6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxyquinoline-3-carboxylate



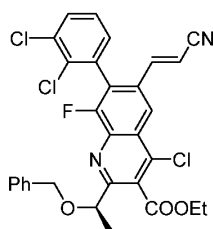
To a solution of ethyl (*R*)-4-(benzyloxy)-3-oxopentanoate (43.4 g, 173 mmol) in DMSO (220 mL) were added 6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-2*H*-benzo[d][1,3]oxazine-2,4(1*H*)-dione (**intermediate 1, step 3**, 45.0 g, 111 mmol), sodium acetate (16.4 g, 200 mmol) and NaCl (11.7 g, 200 mmol). The mixture was heated at 65 °C for 18 h. Once completed, the reaction mixture was cooled to 0 °C with ice bath, diluted with water (300 mL) and acidified to pH 3-4 using 1 N HCl, resulting in precipitation. After stirring for 1 h at 0 °C, the solids were collected on a fritted filter, washed with 1:1 mixture of MeCN and water and dried under reduced pressure to afford the sub-title compound (54.0 g, 82% yield). The crude product was used in next step without further purification. LC-MS calc. for C₂₇H₂₂BrCl₂FNO₄ (M+H)⁺: *m/z*=592.0, 594.0; found 592.0, 594.0.

Step 3. Ethyl 2-((R)-1-(benzyloxy)ethyl)-6-((E)-2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxyquinoline-3-carboxylate



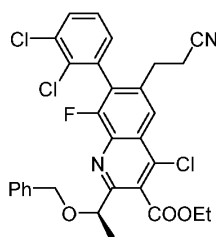
To a solution of ethyl 2-((*R*)-1-(benzyloxy)ethyl)-6-bromo-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxyquinoline-3-carboxylate (47.7 g, 80.0 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (2.28 g, 3.21 mmol) in DMF (191 mL), acrylonitrile (13.3 mL, 201 mmol) and NEt₃ (33.6 mL, 241 mmol) were added. The mixture was sparged with N₂ and heated at 85 °C for 1 h. Once completed, the reaction mixture was diluted with brine and EtOAc. The organic phase was separated and aqueous phase was extracted two more times with EtOAc. The combined organic layers was washed with brine five times and 1 N HCl, filtered and dried over Na₂SO₄. The volatiles were removed under reduced pressure to afford the sub-title compound in near quantitative yield. The crude product was used in next step without further purification. LC-MS calc. for C₃₀H₂₄Cl₂FN₂O₄ (M+H)⁺: *m/z*=565.1; found 565.1.

Step 4. Ethyl 2-((R)-1-(benzyloxy)ethyl)-4-chloro-6-((E)-2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylate



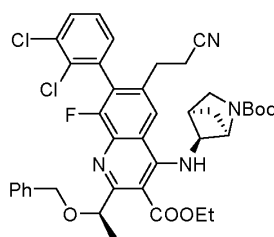
To a slurry of ethyl 2-((*R*)-1-(benzyloxy)ethyl)-6-((*E*)-2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoro-4-hydroxyquinoline-3-carboxylate (48.0 g, 85 mmol) and benzyltriethylammonium chloride (19.3 g, 85 mmol) in MeCN (210 mL) at 0 °C, was added DIPEA (29.6 mL, 170 mmol). Upon stirring at 0 °C, phosphoryl chloride (31.6 mL, 340 mmol) was added dropwise into the mixture. Then the mixture was heated at 60 °C for 2 h. Upon completion, the reaction mixture was cooled to r.t. and slowly poured into ice water (1000 mL). The mixture was extracted with EtOAc three times, dried over Na₂SO₄, filtered and concentrated to afford the sub-title compound as a light brown solid (46.9 g, 95% yield). The crude product was used in next step without further purification. LC-MS calc. for C₃₀H₂₃Cl₃FN₂O₃ (M+H)⁺: *m/z*=583.1; found 583.0.

Step 5. Ethyl 2-((R)-1-(benzyloxy)ethyl)-4-chloro-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylate



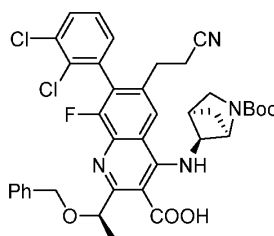
A mixture of copper(II) acetate monohydrate (1.60 g, 8.03 mmol) and Xantphos (5.58 g, 9.64 mmol) was stirred in toluene (50 mL) and *tert*-butanol (62 mL) at 60 °C for 0.5 h to afford a homogeneous solution. In a separate vessel, to a mixture of ethyl 2-((*R*)-1-(benzyloxy)ethyl)-4-chloro-6-((*E*)-2-cyanovinyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylate (46.9 g, 80.0 mmol) and polymethylhydrosiloxane (102 g, 402 mmol) in toluene (150 mL) at 50 °C, was added the previous copper-containing solution. The mixture was stirred at 50 °C for 1 h. Upon completion, the reaction mixture was filtered through diatomaceous earth and concentrated. The crude product was purified using FCC (0-40% acetone/*n*-heptane) to afford the sub-title compound (23.2 g, 49% yield). LC-MS calc. for C₃₀H₂₅Cl₃FN₂O₃ (M+H)⁺: *m/z*=585.1; found 585.1.

Step 6. tert-Butyl (1R,4R,5S)-5-((2-((R)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-8-fluoroquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



- To a solution of ethyl 2-((*R*)-1-(benzyloxy)ethyl)-4-chloro-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylate (34.3 g, 58.6 mmol) in DMSO (110 mL), was added *tert*-butyl (1*R*,4*R*,5*S*)-5-amino-2-azabicyclo[2.1.1]hexane-2-carboxylate (20.9 g, 105 mmol), lithium chloride (4.97 g, 117 mmol) and DIPEA (30.6 mL, 176 mmol). The resulting mixture was heated at 100 °C for 18 h. Once completed, the reaction mixture was diluted with water and EtOAc. The organic phase was separated and aqueous phase extracted with EtOAc two more times. The combined organic layers was washed with 1 N HCl, brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified using FCC (0-40% acetone/*n*-heptane) to afford the sub-title compound (33.6 g, 77% yield).
- LC-MS calc. for C₄₀H₄₂Cl₂FN₄O₅ (M+H)⁺: *m/z*=747.2; found 747.2.

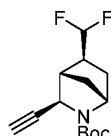
Step 7. 2-((R)-1-(Benzyloxy)ethyl)-4-(((1R,4R,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexan-5-yl)amino)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylic acid



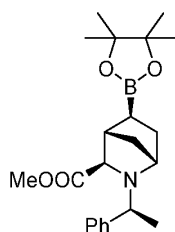
- To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*R*)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-8-fluoroquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (33.6 g, 45 mmol) in THF (100 mL) and water (100 mL), was added NaOH (10.0 g, 250 mmol). The mixture was heated at 60 °C for 3 h. Once completed, the reaction mixture was cooled down to r.t. and acidified to pH 5 using 1 N HCl. The organic volatiles were removed under reduced pressure. The residue aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the sub-title compound as a light yellow solid in near quantitative yield. The crude material was used in the next step without further purification. LC-MS calc. for C₃₈H₃₈Cl₂FN₄O₅ (M+H)⁺: *m/z*=719.2; found 719.2.
- Step 8. tert-Butyl (1R,4R,5S)-5-((2-((R)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate*
- To a solution of 2-((*R*)-1-(benzyloxy)ethyl)-4-(((1*R*,4*R*,5*S*)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexan-5-yl)amino)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoroquinoline-3-carboxylic acid (34.8 g, 48.3 mmol) in MeCN (242 mL), was added potassium phosphate (20.5 g, 97.0 mmol) and *N*-iodosuccinimide (19.6 g, 87.0 mmol). The mixture was stirred at r.t. for 1 h. Once completed, the reaction mixture was poured into

saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution. After stirring for 10 min., the mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was further purified with FCC (0-40% acetone/*n*-heptane) to afford the title compound as an light yellow solid
 5 (35.0 g, 90% yield). LC-MS calc. for $\text{C}_{37}\text{H}_{37}\text{Cl}_2\text{FIN}_4\text{O}_3$ ($\text{M}+\text{H}$)⁺: $m/z=801.1$; found 801.1.

Intermediate 9. *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

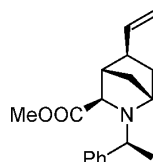


*Step 1. Methyl (1*S*,3*R*,4*S*,5*S*)-2-((*S*)-1-phenylethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.1]heptane-3-carboxylate*
 10



A mixture of methyl (1*R*,3*R*,4*S*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**intermediate 3**, 5.80 g, 22.5 mmol), bis(1,5-cyclooctadiene)diiridium(I) dichloride (0.23 g, 0.34 mmol) and 1,2-bis(diphenylphosphino)ethane (0.27 g, 0.68 mmol) in
 15 DCM (75 mL) was sparged with N_2 and cooled to 0 °C. To this mixture, was slowly added pinacolborane (3.90 mL, 27.0 mmol). After addition, the reaction mixture was allowed to warm up to r.t. and stirred for 2 h. Once completed, the volatiles were removed under reduced pressure. The crude material was purified by FCC (0-40% EtOAc/hexanes) to afford the sub-title compound (4.15 g, 48% yield). LC-MS calc. for $\text{C}_{22}\text{H}_{33}\text{BNO}_4$ ($\text{M}+\text{H}$)⁺: $m/z=386.2$;
 20 found 386.3.

*Step 2. Methyl (1*S*,3*R*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-5-vinyl-2-azabicyclo[2.2.1]heptane-3-carboxylate*

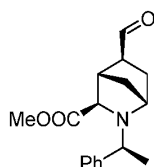


To a solution of methyl (1*S*,3*R*,4*S*,5*S*)-2-((*S*)-1-phenylethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (4.15 g, 10.8 mmol) in
 25 THF (54 mL) cooled to 0 °C, was added vinyl magnesium bromide (1 N in THF, 43.1 mL,

43.1 mmol) slowly. The resulting mixture was stirred at 0 °C for 1 h and then cooled to –78 °C. At this temperature, a solution of I₂ (10.9 g, 43.1 mmol) in MeOH (54 mL) was slowly added. After stirring at the same temperature for 0.5 h, a sodium methoxide solution (25% in MeOH, 18.6 g, 86 mmol) was added. The reaction mixture was allowed to warm up to r.t.

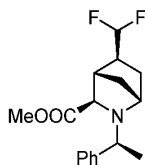
- 5 and stirred for an additional 1 h. Once completed, the mixture was diluted with EtOAc, washed with saturated Na₂S₂O₃ solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-40% EtOAc/hexanes) to afford the sub-title compound (0.86 g, 28% yield). LC-MS calc. for C₁₈H₂₄NO₂ (M+H)⁺: *m/z*=286.2; found 286.2.

- 10 *Step 3. Methyl (1R,3R,4S,5S)-5-formyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate*



- To a solution of methyl (1S,3R,4S,5R)-2-((S)-1-phenylethyl)-5-vinyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (0.86 g, 3.0 mmol) in 1,4-dioxane (12 mL) and water (4 mL), was added 2,6-lutidine (0.70 mL, 6.0 mmol), potassium osmate(VI) dihydrate (0.033 g, 0.090 mmol) and NaIO₄ (2.58 g, 12.1 mmol). The mixture was stirred at r.t. for 2 h. Once completed, the reaction mixture was diluted with EtOAc and water. The organic phase was separated and the aqueous phase extracted with EtOAc twice. The combined organic layers was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calc. for C₁₇H₂₂NO₃ (M+H)⁺: *m/z*=288.2; found 288.2.
- 15
- 20

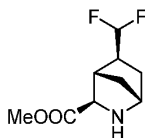
Step 4. Methyl (1R,3R,4S,5S)-5-(difluoromethyl)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate



- 25 To a solution of methyl (1R,3R,4S,5S)-5-formyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (0.86 g, 3.0 mmol) in DCM (15 mL) at 0 °C, was added diethylaminosulfur trifluoride (1.46 g, 9.0 mmol) dropwise. The resulting mixture was allowed to warm up to r.t. and stirred for 3 h. Once completed, the mixture was cooled to 0 °C and quenched by dropwise addition of sat. aq. NaHCO₃. The organic phase was
- 30 separated and the aqueous phase extracted with DCM twice. The combined organic layers

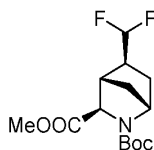
was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-20% EtOAc/hexanes) to afford the sub-title compound (0.52 g, 56% yield over 2 steps). LC-MS calc. for C₁₇H₂₂F₂NO₂ (M+H)⁺: *m/z*=310.2; found 310.1.

Step 5. Methyl (1R,3R,4S,5S)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate



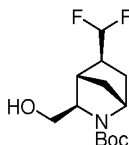
To a solution of methyl (1R,3R,4S,5S)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (0.52 g, 1.69 mmol) in EtOH (35 mL) was added 20% Pd(OH)₂/C (0.50 g). The mixture was stirred under an atmosphere of H₂ for 18 h. The resulting mixture was filtered through diatomaceous earth and concentrated to afford the sub-title compound. The crude material was used for next step without further purification. LC-MS calc. for C₉H₁₄F₂NO₂ (M+H)⁺: *m/z*=206.1; found 206.1. ¹H NMR was collected on the TFA salt. ¹H NMR (600 MHz, DMSO-d₆) δ 9.29 (br, 2H), 6.22–5.96 (td, *J*=54, 5.4 Hz, 1H), 4.29 (s, 1H), 4.14 (s, 1H), 3.79 (s, 3H), 2.93 (s, 1H), 2.49–2.38 (m, 1H), 2.03–1.95 (m, 1H), 1.82 (d, *J*=11.9 Hz, 1H), 1.73–1.61 (m, 1H), 1.53 (d, *J*=12 Hz, 1H).

Step 6. 2-(tert-Butyl) 3-methyl (1R,3R,4S,5S)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



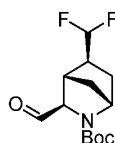
To methyl (1R,3R,4S,5S)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (0.35 g, 1.69 mmol) dissolved in THF (13 mL), was added DIPEA (0.89 mL, 5.07 mmol) and Boc₂O (0.74 g, 3.38 mmol). The reaction mixture was stirred at r.t. for 0.5 h and diluted with EtOAc. After washing with brine, the organic fraction was dried over Na₂SO₄, filtered and concentrated. The crude product was further purified by FCC (0%-20% EtOAc/hexanes) to afford the sub-title compound (0.40 g, 77% yield over 2 steps). LC-MS calc. for C₁₀H₁₄F₂NO₄ (M-^tBu+2H)⁺: *m/z*=250.1; found 250.2.

Step 7. tert-Butyl (1R,3R,4S,5S)-5-(difluoromethyl)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.40 g, 1.31 mmol) in THF (6.5 mL), was added a 2 N THF solution of LiBH₄ (1.64 mL, 3.28 mmol). The mixture was stirred at r.t. for 8 h and then quenched by slow addition of a saturated NH₄Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound (0.35 g, 95% yield). LC-MS calc. for C₉H₁₄F₂NO₃ (M-^tBu+2H)⁺: *m/z*=222.1; found 222.1.

Step 8. tert-Butyl (1R,3R,4S,5S)-5-(difluoromethyl)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

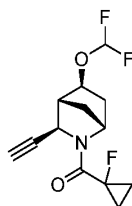


To a solution of *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.35 g, 1.25 mmol) in DCM (6.2 mL), was added Dess-Martin periodinane (0.79 g, 1.87 mmol) portionwise. The resulting mixture was stirred at r.t. for 1 h. Once completed, a saturated Na₂S₂O₃ solution (5 mL) was added to the reaction mixture. The mixture was stirred for an additional 0.5 h. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for C₉H₁₂F₂NO₃ (M-^tBu+2H)⁺: *m/z*=220.1; found 220.0.

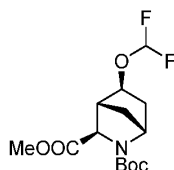
Step 9. tert-Butyl (1R,3R,4S,5S)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.34 g, 1.25 mmol) in MeOH (6 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.36 g, 1.88 mmol) and K₂CO₃ (0.52 g, 3.75 mmol). After stirring for 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-30% EtOAc/hexanes) to afford the title compound (0.080 g, 23% yield over 2 steps). LC-MS calc. for C₁₀H₁₂F₂NO₂ (M-^tBu+2H)⁺: *m/z*=216.1; found 216.1.

Intermediate 10. ((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone

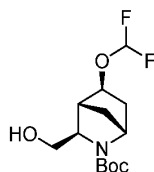


Step 1. 2-(*tert*-Butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



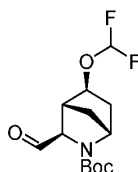
A flask containing 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (**intermediate 4**, 5.30 g, 19.5 mmol) and copper(I) iodide (0.744 g, 3.91 mmol) was charged with MeCN (98 mL). The mixture was stirred at 50 °C before an MeCN solution (10 mL) containing 2-(fluorosulfonyl)difluoroacetic acid (5.22 g, 29.3 mmol) was added slowly. The reaction mixture was stirred at 50 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM, washed with saturated NaHCO₃ solution and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0%-40% EtOAc/hexanes) to afford the sub-title compound (3.12 g, 50% yield). LC-MS calc. for C₁₀H₁₄F₂NO₅ (M-^{*t*}Bu+2H)⁺: *m/z*=266.1; found 266.0.

Step 2. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate



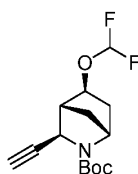
To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (3.12 g, 9.71 mmol) in THF (49 mL), was added LiBH₄ (2 M in THF, 12.1 mL, 24.27 mmol). The mixture was stirred at r.t. for 8 h and then quenched by slow addition of a saturated aqueous NH₄Cl solution at 0 °C. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound (1.62 g, 57% yield). LC-MS calc. for C₉H₁₄F₂NO₄ (M-^{*t*}Bu+2H)⁺: *m/z*=238.1; found 238.1.

Step 3. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.62 g, 5.52 mmol) in DCM (28 mL), was added Dess-Martin periodinane (3.51 g, 8.28 mmol) portionwise. The resulting mixture was stirred at r.t. for 1 h. Once completed, a saturated Na₂S₂O₃ solution (5 mL) was added to the reaction mixture. The mixture was stirred for an additional 0.5 h. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for C₉H₁₂F₂NO₄ (M-^tBu+2H)⁺: *m/z*=236.1; found 236.0.

Step 4. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.61 g, 5.52 mmol) in MeOH (28 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (1.59 g, 8.28 mmol) and K₂CO₃ (2.29 g, 16.6 mmol). After stirring for 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the sub-title compound (0.71 g, 45% yield over 2 steps). LC-MS calc. for C₁₀H₁₂F₂NO₃ (M-^tBu+2H)⁺: *m/z*=232.1; found 232.1.

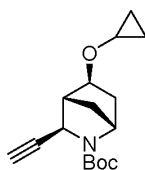
Step 5. ((1*R*,3*R*,4*R*,5*S*)-5-(Difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone

To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.71 g, 2.49 mmol) in 1,4-dioxane (7 mL), was added 4 N HCl in 1,4-dioxane (7 mL). The reaction mixture was stirred at r.t. for 1 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DMF (0.5 mL).

To a separate vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.52 g, 5.00 mmol) in DMF (12 mL), was added DIPEA (1.30 mL, 7.46 mmol) followed by HATU (1.89 g, 5.00 mmol). The mixture was stirred for 15 min. before the above solution was added. The resulting mixture was stirred for 0.5 h. Once completed, the reaction mixture was

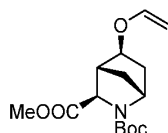
5 diluted with EtOAc, washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was further purified with FCC (0-30% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₁₃H₁₅F₃NO₂ (M+H)⁺: *m/z*=274.1; found 274.1.

Intermediate 11. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate



10

*Step 1. 2-(tert-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(vinylloxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate*

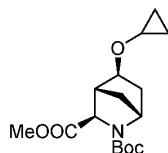


15

A mixture of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (**intermediate 4**, 0.94 g, 3.46 mmol), palladium(II) acetate (0.16 g, 0.69 mmol), 1,10-phenanthroline (0.13 g, 0.69 mmol), NEt₃ (0.95 mL, 6.93 mmol) and *n*-butyl vinyl ether (13.5 mL, 104 mmol) was sparged with N₂ and heated at 90°C for 18 h. Once completed, the reaction mixture was cooled down to r.t. and poured into water. The aqueous layer was extracted with EtOAc, washed with brine, dried

20 over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-30% EtOAc/hexanes) to afford the sub-title compound (0.86 g, 83% yield). LC-MS calc. for C₁₁H₁₆NO₅ (M-^tBu+2H)⁺: *m/z*=242.1; found 242.1.

*Step 2. 2-(tert-Butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate*

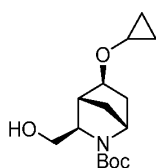


25

To a flask containing DCM (15 mL) at 0 °C, was added diethyl zinc (1 N in hexanes, 11.6 mL, 11.6 mmol) followed by slow addition of a DCM solution (3 mL) containing

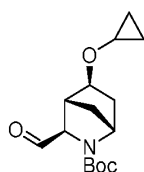
methylene iodide (3.10 g, 11.6 mmol). The mixture was stirred at 0 °C for 0.5 h before a DCM solution (3 mL) containing 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(vinylloxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.86 g, 2.89 mmol) was added. The resulting mixture was stirred at 0 °C for 8 h. Upon completion, the reaction mixture was quenched by
 5 slow addition of NaHCO₃ solution. The mixture was filtered through diatomaceous earth. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-30% EtOAc/hexanes) to afford the sub-title compound (0.70 g, 77% yield). LC-MS calc. for C₁₂H₁₈NO₅ (M-^tBu+2H)⁺: *m/z*=256.1; found 256.1.

Step 3. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-(hydroxymethyl)-2-
 10 azabicyclo[2.2.1]heptane-2-carboxylate



To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (0.70 g, 2.23 mmol) in THF (11 mL), was added LiBH₄ (2 M in THF, 2.8 mL, 5.58 mmol). The mixture was stirred at r.t. for 16 h and then
 15 quenched by slow addition of a saturated aqueous NH₄Cl solution at 0 °C. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound (0.47 g, 74% yield). LC-MS calc. for C₁₁H₁₈NO₄ (M-^tBu+2H)⁺: *m/z*=228.1; found 228.1.

Step 4. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-formyl-2-azabicyclo[2.2.1]heptane-2-
 20 carboxylate

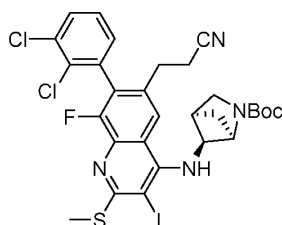


To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.47 g, 1.65 mmol) in DCM (8 mL), was added Dess-Martin periodinane (1.05 g, 2.48 mmol) portionwise. The resulting mixture was stirred
 25 at r.t. for 0.5 h. Once completed, a saturated Na₂S₂O₃ solution (5 mL) was added to the reaction mixture. The mixture was stirred for an additional 0.5 h. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product, which was used in the next step without further purification. LC-MS calc. for C₁₁H₁₆NO₄ (M-^tBu+2H)⁺:
 30 *m/z*=226.1; found 226.0.

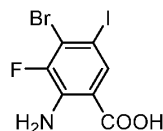
Step 5. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-formyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.47 g, 1.65 mmol) in MeOH (8 mL) was added
 5 dimethyl(1-diazo-2-oxopropyl)phosphonate (0.48 g, 2.48 mmol) and K₂CO₃ (0.69 g, 4.96 mmol). After stirring for 18 h, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated. The residue was extracted with EtOAc, filtered through diatomaceous earth and concentrated. The crude product was purified by FCC (0-60% EtOAc/hexanes) to afford the title compound (0.30 g, 65% yield over 2 steps). LC-MS calc.
 10 for C₁₂H₁₆NO₃ (M-^tBu+2H)⁺: *m/z*=222.1; found 222.1.

Intermediate 12. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-(methylthio)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate

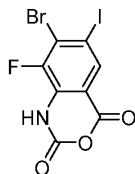


Step 1. 2-Amino-4-bromo-3-fluoro-5-iodobenzoic acid



To a DMF solution (200 mL) containing 2-amino-4-bromo-3-fluorobenzoic acid (20 g, 85 mmol) was added 1-iodopyrrolidine-2,5-dione (21 g, 94 mmol) portionwise. After stirring at 80 °C for 3 h, the mixture was cooled to 0 °C. Water (500 mL) was added to the stirring
 20 mixture, resulting in precipitation. The solids were collected on a fritted filter, washed with cold water and dried under reduced pressure to afford the sub-title compound (28 g, 90% yield).

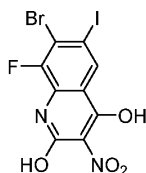
Step 2. 7-Bromo-8-fluoro-6-iodo-2*H*-benzo[d][1,3]oxazine-2,4(1*H*)-dione



To a 1,4-dioxane solution (200 mL) containing 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid (28 g, 78 mmol) was added triphosgene (11.5 g, 39 mmol). After stirring at

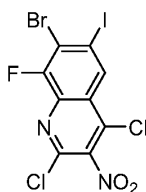
80 °C for 2 h, the reaction mixture was cooled to 0 °C and filtered. To the filtrate upon vigorous stirring was added 1 N HCl (100 mL) resulting in precipitation. The solids were collected on a fritted filter, washed with EtOAc to afford the sub-title compound (19 g, 63% yield).

5 *Step 3. 7-Bromo-8-fluoro-6-iodo-3-nitroquinoline-2,4-diol*



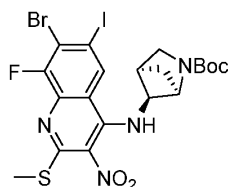
To a toluene solution (200 mL) containing 7-bromo-8-fluoro-6-iodo-2*H*-benzo[d][1,3]oxazine-2,4(1*H*)-dione (19 g, 49 mmol) and ethyl 2-nitroacetate (13 g, 98 mmol) was added DIPEA (17 mL, 98 mmol). The reaction mixture was stirred at 95 °C for 3 h. Upon completion, the reaction mixture was cooled to 0 °C. The precipitation was collected on a fritted filter, washed with small amount of hexanes to afford the sub-title compound (10 g, 47% yield).

Step 4. 7-Bromo-2,4-dichloro-8-fluoro-6-iodo-3-nitroquinoline



DIPEA (8.1 mL, 47 mmol) was added to a mixture of 7-bromo-8-fluoro-6-iodo-3-nitroquinoline-2,4-diol (10 g, 23 mmol) in POCl₃ (11 mL) and then the reaction mixture was stirred at 100 °C for 2 h. The solvent was removed under vacuum and then azeotroped with toluene 3 times to provide the crude material which can be further purified with FCC.

20 *Step 5. tert-Butyl (1R,4R,5S)-5-((7-bromo-8-fluoro-6-iodo-2-(methylthio)-3-nitroquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate*

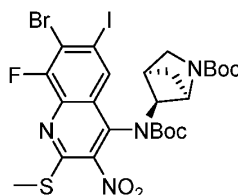


To a solution of 7-bromo-2,4-dichloro-8-fluoro-6-iodo-3-nitroquinoline (25.0 g, 53.7 mmol) and *tert*-butyl (1*R*,4*R*,5*S*)-5-amino-2-azabicyclo[2.1.1]hexane-2-carboxylate (11.2 g, 56.4 mmol) in DMF (107 mL) was added DIPEA (28.1 mL, 161 mmol) and the reaction mixture was heated to 60 °C for 0.5 h. The mixture was cooled to 0 °C and a

solution of sodium thiomethoxide (11.3 g, 161 mmol) in MeOH (30 mL) was slowly added and the reaction mixture was stirred at this temperature for 1 h. Ice and water were added, and the solid was filtered. The filtrate was extracted with EtOAc and combined with the solid. The combined solids were dried on a weighing paper to afford the sub-title compound

5 (20.0 g, 58% yield). LC-MS calc. for $C_{20}H_{22}BrFIN_4O_4S^+$ ($M+H$) $^+$: $m/z=639.0$; found 638.9.

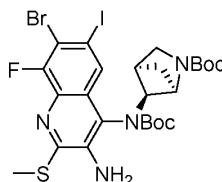
Step 6. tert-Butyl (1R,4R,5S)-5-((7-bromo-8-fluoro-6-iodo-2-(methylthio)-3-nitroquinolin-4-yl)(tert-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



To a stirred solution of *tert*-butyl (1R,4R,5S)-5-((7-bromo-8-fluoro-6-iodo-2-(methylthio)-3-nitroquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (20.0 g, 31.3 mmol) in THF (63 mL), NEt_3 (12.8 mL, 94 mmol), DMAP (0.38 g, 3.13 mmol), and Boc_2O (13.7 g, 62.6 mmol) were added sequentially at r.t., and stirring was continued for 16 h. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude

15 product was used without purification. LC-MS calc. for $C_{21}H_{22}BrFIN_4O_6S^+$ ($M-tBu+2H$) $^+$: $m/z=683.0$; found 682.9.

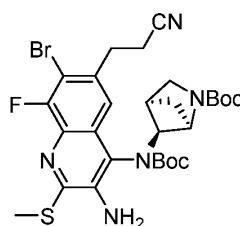
Step 7. tert-Butyl (1R,4R,5S)-5-((3-amino-7-bromo-8-fluoro-6-iodo-2-(methylthio)quinolin-4-yl)(tert-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A flask equipped with a mechanical stirrer was charged with *tert*-butyl (1R,4R,5S)-5-((7-bromo-8-fluoro-6-iodo-2-(methylthio)-3-nitroquinolin-4-yl)(tert-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (23.1 g, 31.3 mmol), MeOH (52 mL), water (52 mL), and THF (52 mL). Iron (17.5 g, 313 mmol) and ammonium chloride (16.7 g, 313 mmol) were added, and the reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was

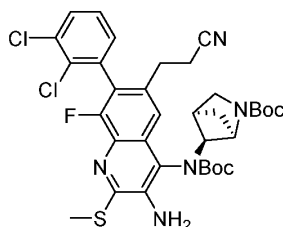
25 diluted with EtOAc and filtered through diatomaceous earth. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The product was used without purification. LC-MS calc. for $C_{25}H_{32}BrFIN_4O_4S^+$ ($M+H$) $^+$: $m/z=709.0$; found 709.0.

Step 8. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((3-amino-7-bromo-6-(2-cyanoethyl)-8-fluoro-2-(methylthio)-quinolin-4-yl)(*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



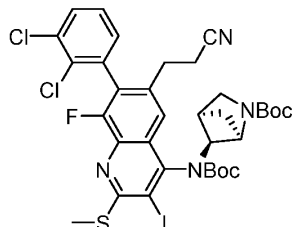
To a DMF solution (78 mL) containing *tert*-butyl (1*R*,4*R*,5*S*)-5-((3-amino-7-bromo-8-fluoro-6-iodo-2-(methylthio)quinolin-4-yl)(*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (20.3 g, 31.0 mmol) and Pd(PPh₃)₄ (7.2 g, 6.2 mmol) was added acrylonitrile (20.3 mL, 310 mmol), DIPEA (8.1 mL, 46.5 mmol) and tetramethylammonium formate (25% solution in water, 29.6 mL, 62.0 mmol). The headspace was purged with nitrogen and the reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled to r.t. and diluted with EtOAc. The resulting mixture was washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-70% EtOAc/hexanes) to afford the sub-title compound (10.3 g, 57% yield over 3 steps). LC-MS calc. for C₂₄H₂₈BrFN₅O₄S⁺ (M-^tBu+2H)⁺: *m/z*=580.1; found 580.1.

Step 9. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((3-amino-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-(methylthio)quinolin-4-yl)(*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((3-amino-7-bromo-6-(2-cyanoethyl)-8-fluoro-2-(methylthio)-quinolin-4-yl)(*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (10.3 g, 16.2 mmol), (2,3-dichlorophenyl)boronic acid (3.70 g, 19.42 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (1.15 g, 1.62 mmol) and potassium fluoride (3.76 g, 64.7 mmol) in 1,4-dioxane (74 mL) and water (7.4 mL) was sparged with N₂ and heated at 100 °C for 2 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound (10.0 g, 88% yield). LC-MS calc. for C₃₀H₃₁Cl₂FN₅O₄S (M-^tBu+2H)⁺: *m/z*=646.1; found 646.1.

Step 10. tert-Butyl (1R,4R,5S)-5-((tert-butoxycarbonyl)(6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-(methylthio)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



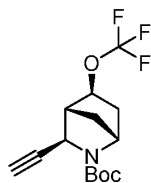
5 To an MeCN solution (240 mL) of *tert*-butyl (1*R*,4*R*,5*S*)-5-((3-amino-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-(methylthio)quinolin-4-yl)(*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (10.0 g, 14.2 mmol) cooled to -20°C was added H_2SO_4 (1.5 mL, 28.5 mmol) in 4 mL water followed by sodium nitrite (2.46 g, 35.6 mmol) in 4 mL water. The resulting mixture gradually turned red and was let to stir for additional
10 10 min. with internal temperature $<-10^{\circ}\text{C}$. To the mixture was added potassium iodide (9.45 g, 56.9 mmol) portionwise resulting in vigorous bubbling. After addition, the reaction mixture was stirred for additional 0.5 h at -10°C and then allowed to warm up to r.t. The reaction mixture was poured into sodium thiosulfate solution and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The
15 crude product was used in next step without purification. LC-MS calc. for $\text{C}_{30}\text{H}_{29}\text{Cl}_2\text{FIN}_4\text{O}_4\text{S}^+$ ($\text{M}-t\text{Bu}+2\text{H}$) $^+$: $m/z=757.0$; found 757.0.

Step 11. tert-Butyl (1R,4R,5S)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-(methylthio)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate

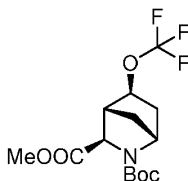
To *tert*-butyl (1*R*,4*R*,5*S*)-5-((*tert*-butoxycarbonyl)(6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-(methylthio)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (11.6 g, 14.2 mmol) dissolved in MeCN (19 mL) was added TFA (76 mL). The mixture was stirred at r.t. for 5 h and concentrated.
20

To the residue dissolved in THF (29 mL) was added DIPEA (12.4 mL, 71.2 mmol) and Boc_2O (6.21 g, 28.5 mmol). The mixture was stirred at r.t. for 0.5 h. Upon completion,
25 the mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the title compound (3.05 g, 30% yield over 2 steps). LC-MS calc. for $\text{C}_{29}\text{H}_{29}\text{Cl}_2\text{FIN}_4\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$: $m/z=713.0$; found 713.0.

Intermediate 13. *tert*-Butyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate
30

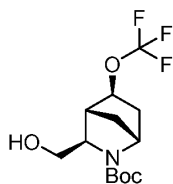


Step 1. 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate



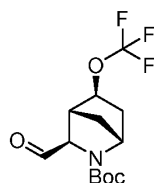
- 5 To a flask containing 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (**intermediate 4**, 4.53 g, 16.7 mmol), potassium fluoride (2.91 g, 50.1 mmol), silver trifluoromethanesulfonate (8.58 g, 33.4 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (8.87 g, 25.1 mmol) under N₂, was added anhydrous ethyl acetate (167 mL), trifluoromethyltrimethylsilane (4.9 mL, 33.4 mmol) and 2-fluoropyridine (2.9 mL, 33.4 mmol). The reaction mixture was covered with aluminum foil and stirred at room temperature for 12 h. Upon completion, the mixture was filtered through Celite and concentrated. The crude product was further purified by silica chromatography (0%-20% EtOAc/hexanes) to afford the title compound as a colorless oil (2.74 g, 48% yield). LC-MS calc. for C₁₀H₁₃F₃NO₅ (M-^tBu+2H)⁺: m/z = 284.1; found 284.1.

Step 2. *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-(hydroxymethyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate



- To a solution of 2-(*tert*-butyl) 3-methyl (1*R*,3*R*,4*R*,5*S*)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (2.74 g, 8.08 mmol) in THF (40 mL), was added lithium borohydride (2 M in THF, 10.1 mL, 20.2 mmol). The mixture was stirred at room temperature for 16 h and then quenched by slow addition of a saturated aq. NH₄Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica chromatography (0-60% EtOAc/hexanes) to afford title compound as a colorless oil (2.10 g, 84% yield). LC-MS calc. for C₉H₁₃F₃NO₄ (M-^tBu+2H)⁺: m/z = 256.1; found 256.1.

Step 3. *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-formyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

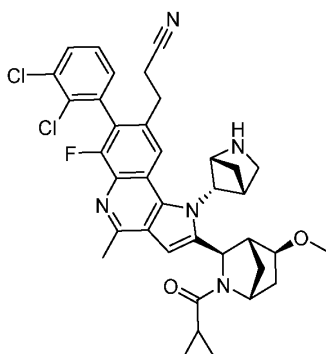


To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-(hydroxymethyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (2.10 g, 6.75 mmol) in DCM (34 mL), was added Dess-Martin periodinane (4.29 g, 10.1 mmol) portionwise. The resulting mixture was stirred at room temperature for 1 h. Once completed, a saturated aq. Na₂S₂O₃ solution (5 mL) was added to the reaction mixture. The mixture was stirred for an additional 0.5 h. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated to give crude product. The crude product was used in the next step without further purification. LC-MS calculated for C₉H₁₁F₃NO₄ (M-^tBu+2H)⁺: m/z = 254.1; found 254.1.

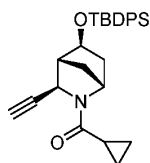
Step 4. *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-formyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (2.09 g, 6.75 mmol) in methanol (34 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (1.95 g, 10.1 mmol) and potassium carbonate (2.80 g, 20.3 mmol). After stirring for 16 h, the reaction mixture was filtered through Celite. The filtrate was concentrated. The residue was extracted with ethyl acetate, filtered through Celite and concentrated. The crude product was purified by silica chromatography (0-20% ethyl acetate/hexanes) to afford title compound (1.40 g, 68% yield over 2 steps). LC-MS calculated for C₁₀H₁₁F₃NO₃ (M-^tBu+2H)⁺: m/z = 250.1; found 250.1.

Example 1. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

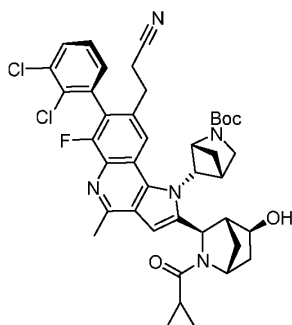


Step 1. ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone



To a solution of *tert*-butyl ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 5**, 0.95 g, 2.00 mmol) in DCM (5 mL), was added TFA (5 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (10 mL). Upon stirring, DIPEA (1.7 mL, 10.0 mmol) was added followed by cyclopropanecarbonyl chloride (0.26 g, 2.50 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude product was used directly for next step without further purification. LC-MS calc. for C₂₈H₃₄NO₂Si (M+H)⁺: *m/z*=444.2; found 444.2.

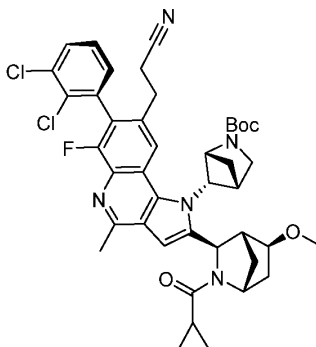
Step 2. *tert*-Butyl ((1*R*,4*R*,5*S*)-5-(((*R*_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of *tert*-butyl ((1*R*,4*R*,5*S*)-5-(((*R*_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.76 g, 1.11 mmol), ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone (0.84 g, 1.89 mmol), copper(I) iodide (0.085 g, 0.444 mmol), Pd(PPh₃)₄ (0.26 g, 0.222 mmol), CsF (0.51 g, 3.33 mmol) and DIPEA (1.9 mL, 11.1 mmol) in DMF (13.8 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (1.09 g, 3.33 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100%

EtOAc/hexanes) to afford the sub-title compound (0.50 g, 45% yield). LC-MS calc. for $C_{41}H_{43}Cl_2FN_5O_4$ (M+H)⁺: $m/z=758.3$; found 758.2.

Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.50 g, 0.66 mmol) in DMF (3.5 mL), was added sodium hydride (60% dispersion in mineral oil, 0.079 g, 1.98 mmol) portionwise. After stirring at r.t. for 0.5 h, a 2 N *tert*-butyl methyl ether solution of iodomethane (0.99 mL, 1.98 mmol) was added slowly. The resulting mixture was stirred for another 15 min. and quenched by dropwise addition of saturated NH_4Cl solution. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was further purified using FCC (0-100% EtOAc/hexanes). LC-MS calc. for $C_{42}H_{45}Cl_2FN_5O_4$ (M+H)⁺: $m/z=772.3$; found 772.2.

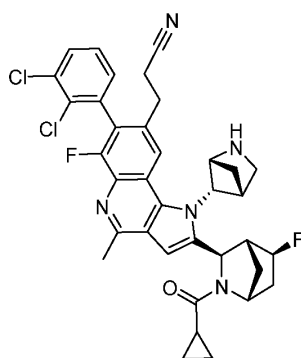
Step 4. 3-((*R*_a)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.030 g, 0.038 mmol) in DCM (1 mL), was added MeCN (0.1 mL) and TFA (1.1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS XBRIDGE® C_{18} column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for $C_{37}H_{37}Cl_2FN_5O_2$ (M+H)⁺: $m/z=672.2$; found 672.2. 1H NMR was collected on the TFA salt. 1H NMR (600 MHz, $DMSO-d_6$) δ 9.26 (s, 1H), 8.12 (s, 1H), 8.07 (s, 1H), 7.85 (dd, $J=8.2, 1.5$ Hz,

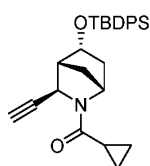
1H), 7.59 (t, $J=7.8$ Hz, 1H), 7.46 (dd, $J=7.6$, 1.5 Hz, 1H), 6.70 (s, 1H), 5.76–5.73 (m, 1H), 4.86 (d, $J=6.0$ Hz, 1H), 4.78 (s, 1H), 4.50 (s, 1H), 3.97 (dd, $J=7.2$, 2.7 Hz, 1H), 3.87 (dt, $J=6.2$, 3.0 Hz, 1H), 3.75 (s, 1H), 3.39 (dd, $J=7.4$, 3.8 Hz, 1H), 3.34 (s, 3H), 3.03 (dt, $J=14.0$, 6.5 Hz, 1H), 2.88–2.78 (m, 5H), 2.72–2.63 (m, 2H), 2.36 (d, $J=9.1$ Hz, 1H), 2.11 (m, 2H),
 5 1.69–1.52 (m, 4H), 0.95–0.82 (m, 3H), 0.79–0.73 (m, 1H).

The alternative atropisomer 3-((S_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above
 10 starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((S_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((R_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 2. 3-((R_a)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile
 15



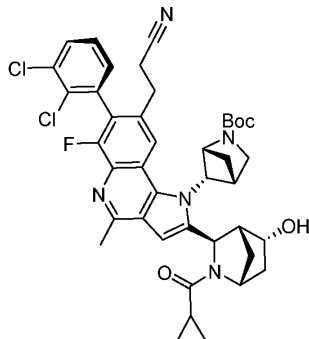
Step 1. ((1*R*,3*R*,4*R*,5*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone



20

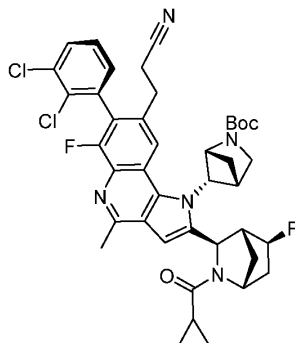
The sub-title compound was prepared in an analogous fashion to **Example 1, Step 1**, with *tert*-butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 6**) replacing *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 5**). LC-MS calc. for $C_{28}H_{34}NO_2Si$ ($M+H$)⁺: $m/z=444.2$; found 444.2.
 25

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*R*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5 The sub-title compound was prepared in an analogous fashion to **Example 1, Step 2**, with ((1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone replacing ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone. LC-MS calc. for $C_{41}H_{43}Cl_2FN_5O_4$ ($M+H$)⁺: m/z =758.3; found 758.2.

10 Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



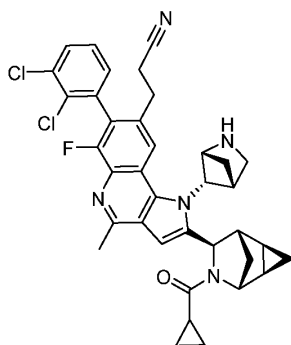
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*R*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.015 g, 0.020 mmol) in DCM (0.2 mL) was added diethylaminosulfur trifluoride (6.4 mg, 0.040 mmol). The reaction mixture was stirred for 0.5 h at r.t. and quenched with saturated NaHCO₃ solution at 0 °C. The resulting mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calc. for $C_{41}H_{42}Cl_2F_2N_5O_3$ ($M+H$)⁺: m/z =760.3; found 760.4.

Step 4. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

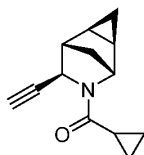
The title compound was prepared in an analogous fashion to **Example 1, Step 4**,
 5 with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-
 10 MS calc. for C₃₆H₃₄Cl₂F₂N₅O (M+H)⁺: *m/z*=660.2; found 660.2.

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be
 15 prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*S_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

20 **Example 3.** 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*S*,2*S*,4*R*,5*R*,7*R*)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



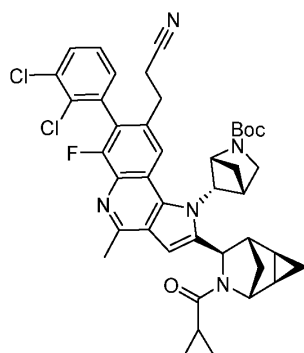
Step 1. Cyclopropyl((1*S*,2*S*,4*R*,5*R*,7*R*)-7-ethynyl-6-azatricyclo[3.2.1.0^{2,4}]octan-6-yl)methanone
 25



The sub-title compound was prepared in an analogous fashion to **Example 1, Step 1**, with *tert*-butyl (1*S*,2*S*,4*R*,5*R*,7*R*)-7-ethynyl-6-azatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (**intermediate 7**) replacing *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 5**). LC-MS calc. for C₁₃H₁₆NO

(M+H)⁺: *m/z*=202.1; found 202.1.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*S*,2*S*,4*R*,5*R*,7*R*)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.015 g, 0.022 mmol), cyclopropyl((1*S*,2*S*,4*R*,5*R*,7*R*)-7-ethynyl-6-azatricyclo[3.2.1.0^{2,4}]octan-6-yl)methanone (0.009 g, 0.044 mmol), copper(I) iodide (0.002 g, 0.009 mmol), Pd(PPh₃)₄ (0.005 g, 0.004 mmol) and DIPEA (39 μL, 0.220 mmol) in DMF (0.2 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (0.022 g, 0.066 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calc. for C₄₂H₄₃Cl₂FN₅O₃ (M+H)⁺: *m/z*=754.3; found 754.3.

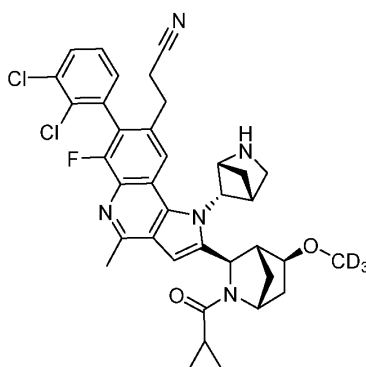
Step 3. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*S*,2*S*,4*R*,5*R*,7*R*)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

The title compound was prepared in an analogous fashion to **Example 1, Step 4**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*S*,2*S*,4*R*,5*R*,7*R*)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-

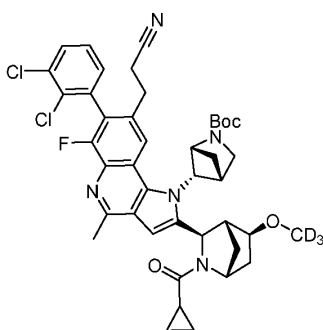
methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for $C_{37}H_{35}Cl_2F_2N_5O$ (M+H)⁺: $m/z=654.2$; found 654.2.

The alternative atropisomer 3-((S_a)-1-((1R,4R,5S)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1S,2S,4R,5R,7R)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1R,4R,5S)-5-(((S_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1R,4R,5S)-5-(((R_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 4. 3-((R_a)-1-((1R,4R,5S)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1R,3R,4R,5S)-2-(cyclopropanecarbonyl)-5-(methoxy-*d*₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile



Step 1. *tert*-Butyl (1R,4R,5S)-5-((R_a)-8-(2-cyanoethyl)-2-((1R,3R,4R,5S)-2-(cyclopropanecarbonyl)-5-(methoxy-*d*₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



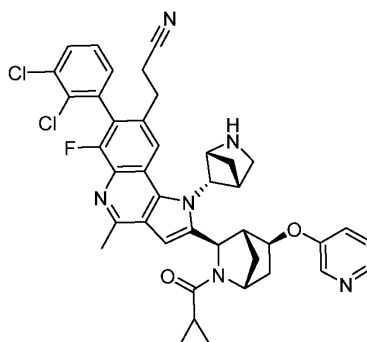
The sub-title compound was prepared in an analogous fashion to **Example 1, Step 3**, with iodomethane- d_3 replacing iodomethane. LC-MS calc. for $C_{42}H_{42}D_3Cl_2FN_5O_4$ ($M+H$)⁺: $m/z=775.3$; found 775.2.

Step 2. 3-((R_a)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(methoxy- d_3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

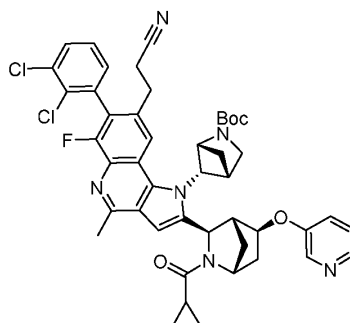
The title compound was prepared in an analogous fashion to **Example 1, Step 4**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-((R_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(methoxy- d_3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((R)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for $C_{37}H_{34}D_3Cl_2F_2N_5O_2$ ($M+H$)⁺: $m/z=675.2$; found 675.3.

The alternative atropisomer 3-((S_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(methoxy- d_3)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((S_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((R_a)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 5. 3-((R_a)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



Step 1. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**Example 1, Step 2**, 0.035 g, 0.046 mmol), copper(I) iodide (0.007 g, 0.035 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.016 g, 0.069 mmol), Cs₂CO₃ (0.113 g, 0.346 mmol) and 3-iodopyridine (0.047 g, 0.231 mmol) in toluene (0.5 mL) was sparged with N₂ and heated at 130 °C for 18 h. Upon completion, the mixture was cooled down to r.t. and diluted with EtOAc and saturated NH₄Cl solution. The organic layer was separated. The aqueous solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calc. for C₄₆H₄₆Cl₂FN₆O₄ (M+H)⁺: *m/z*=835.3; found 835.2.

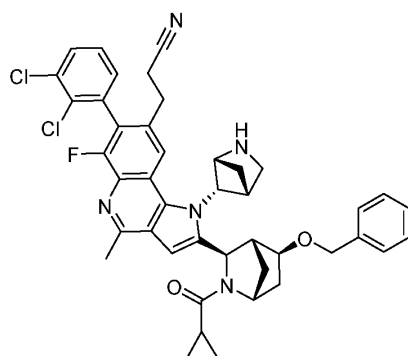
Step 2. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

The title compound was prepared in an analogous fashion to **Example 1, Step 4**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for C₄₁H₃₈Cl₂FN₆O₂ (M+H)⁺: *m/z*=735.2; found 735.2.

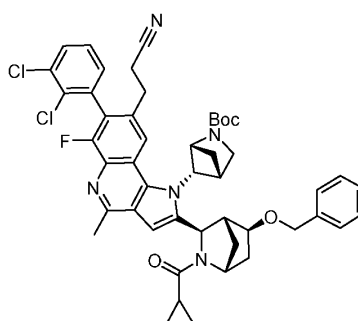
25

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above
 5 starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((*S_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate.
 10

Example 6. 3-((*R_a*)-2-((1*R*,3*R*,4*R*,5*S*)-5-(Benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



15 **Step 1.** *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-2-((1*R*,3*R*,4*R*,5*S*)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



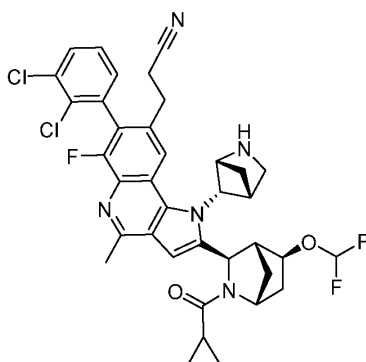
20 The sub-title compound was prepared in an analogous fashion to **Example 1, Step 3**, with benzyl bromide replacing iodomethane. LC-MS calc. for C₄₈H₄₉Cl₂FN₅O₄ (M+H)⁺: *m/z*=848.3; found 848.2.

Step 2. 3-((*R_a*)-2-((1*R*,3*R*,4*R*,5*S*)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

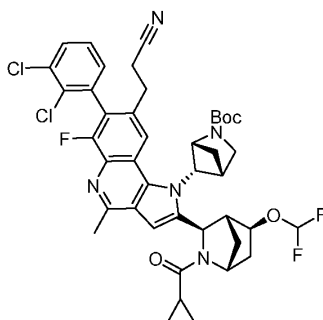
The title compound was prepared in an analogous fashion to **Example 1, Step 4**,
 5 with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-2-((1*R*,3*R*,4*R*,5*S*)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-
 10 *c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for C₄₃H₄₁Cl₂FN₅O₂ (M+H)⁺: *m/z*=748.3; found 748.2.

The alternative atropisomer 3-((*S_a*)-2-((1*R*,3*R*,4*R*,5*S*)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-
 15 *c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((*S_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-
 20 *c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-
 25 *c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 7. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



Step 1. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

To mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**Example 1, Step 2**, 0.014 g, 0.018 mmol) and copper iodide (0.001 g, 0.005 mmol) in MeCN (0.1 mL) heated at 50 °C, was added an MeCN solution (0.1 mL) of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.005 g, 0.027 mmol). The mixture was stirred at the same temperature for 1 h. Upon completion, the mixture was cooled down to r.t. and diluted with EtOAc and saturated NH₄Cl solution. The organic layer was separated. The aqueous solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calc. for C₄₂H₄₃Cl₂F₃N₅O₄ (M+H)⁺: *m/z*=808.3; found 808.2.

Step 2. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

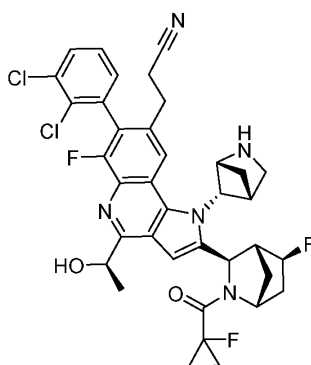
The title compound was prepared in an analogous fashion to **Example 1, Step 4**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for C₃₇H₃₅Cl₂F₃N₅O₂ (M+H)⁺: *m/z*=708.2; found 708.2.

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-

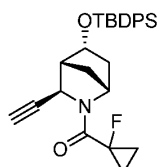
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yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((*S_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 8. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



Step 1. ((1*R*,3*R*,4*R*,5*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone

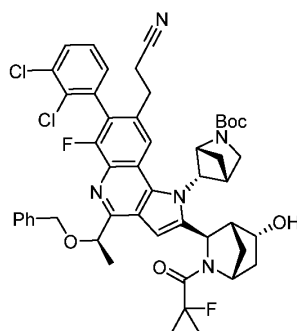


To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 6**, 0.250 g, 0.53 mmol) in 1,4-dioxane (2 mL), was added 4 N HCl in 1,4-dioxane (2 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DMF (0.5 mL).

To a separated vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.129 g, 1.05 mmol) in DMF (2 mL), was added DIPEA (0.46 mL, 2.63 mmol) followed by HATU (0.400 g, 1.05 mmol). The mixture was stirred for 15 min. before the aforementioned residue was added as a DMF solution. The resulting mixture was stirred for 0.5 h. Once completed,

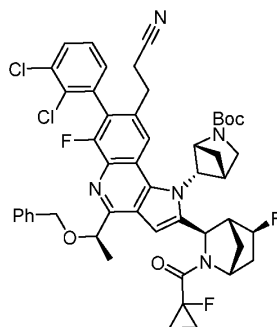
the reaction mixture was diluted with EtOAc, washed with brine five times, dried over Na_2SO_4 , filtered and concentrated. The crude product was further purified with FCC (0-40% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for $\text{C}_{28}\text{H}_{33}\text{FNO}_2\text{Si}$ ($\text{M}+\text{H}$)⁺: $m/z=462.2$; found 462.2.

- 5 **Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(4-((*R*_a)-1-(benzyloxy)ethyl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*R*)-2-(1-fluorocyclopropane-1-carbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate**



- 10 The sub-title compound was prepared in an analogous fashion to **Example 1, Step 2**, with ((1*R*,3*R*,4*R*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone replacing ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone and *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*R*_a)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 8**) replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R*_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**). LC-MS calc. for $\text{C}_{49}\text{H}_{50}\text{Cl}_2\text{F}_2\text{N}_5\text{O}_5$ ($\text{M}+\text{H}$)⁺: $m/z=896.3$; found 896.2.

- 15 **Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(4-((*R*_a)-1-(benzyloxy)ethyl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate**



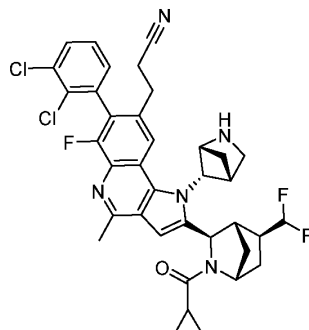
The sub-title compound was prepared in an analogous fashion to **Example 3, Step 3**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-(4-((*R_a*)-1-(benzyloxy)ethyl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*R*)-2-(1-fluorocyclopropane-1-carbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*R*)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for C₄₉H₄₉Cl₂F₃N₅O₄ (M+H)⁺: *m/z*=898.3; found 898.2.

Step 4. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

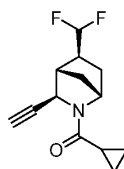
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(4-((*R_a*)-1-(benzyloxy)ethyl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.060 g, 0.067 mmol) in DCM (1.4 mL) cooled to -78 °C, was added BCl₃ (1 N in DCM, 0.34 mL, 0.34 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm up to r.t. Upon completion, the mixture was cooled to 0 °C and saturated NaHCO₃ solution (2 mL) was added. The mixture was extracted with DCM three times and concentrated. The residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS (XBRIDGE® C₁₈ column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford a pair of atropisomers. The title compound was isolated as peak 1 of the two atropisomers. LC-MS calc. for C₃₇H₃₅Cl₂F₃N₅O₂ (M+H)⁺: *m/z*=708.2; found 708.2.

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*S_a*)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*R_a*)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 9. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*S*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

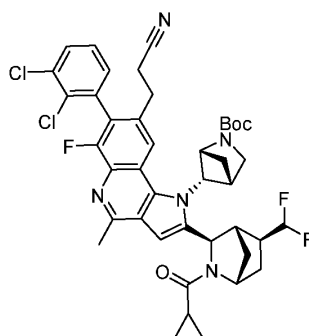


- 5 *Step 1.* Cyclopropyl((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)methanone



- The sub-title compound was prepared in an analogous fashion to **Example 1, Step 1**, with *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 9**) replacing *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 5**).
 10 LC-MS calc. for C₁₃H₁₆F₂NO (M+H)⁺: *m/z*=240.1; found 240.1.

- Step 2.* *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*S*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate
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The sub-title compound was prepared in an analogous fashion to **Example 1, Step 2**, with cyclopropyl((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-

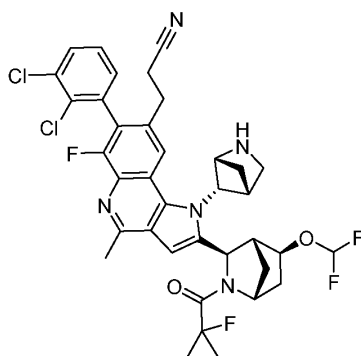
yl)methanone replacing ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone. LC-MS calc. for C₄₂H₄₃Cl₂F₃N₅O₃ (M+H)⁺: *m/z*=792.3; found 792.2.

Step 3. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*S*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

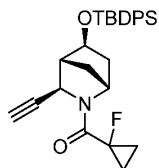
The title compound was prepared in an analogous fashion to **Example 1, Step 4**, with *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*S*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate replacing *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. LC-MS calc. for C₃₇H₃₅Cl₂F₃N₅O (M+H)⁺: *m/z*=692.2; found 692.1.

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*S*,5*S*)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-((*S_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 10. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



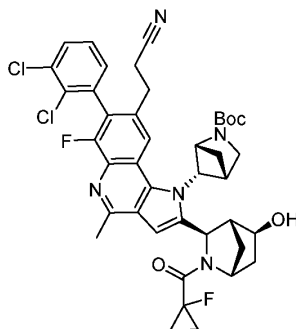
Step 1. ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone



To a solution of *tert*-butyl ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-carboxylate (**intermediate 5**, 0.17 g, 0.36 mmol) in 1,4-dioxane (2 mL), was added 4 N HCl in 1,4-dioxane (2 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DMF (0.5 mL).

To a separate reaction vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.074 g, 0.72 mmol) in DMF (2 mL), was added DIPEA (0.31 mL, 1.79 mmol) followed by HATU (0.27 g, 0.72 mmol). The mixture was stirred for 15 min. before the aforementioned residue was added as a DMF solution. The resulting mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with EtOAc, washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified with FCC (0-40% EtOAc/hexanes) to afford the sub-title compound (0.073 g, 54% yield). LC-MS calc. for C₂₈H₃₃FN₂O₂Si (M+H)⁺: *m/z*=462.2; found 462.2.

Step 2. *tert*-Butyl ((1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



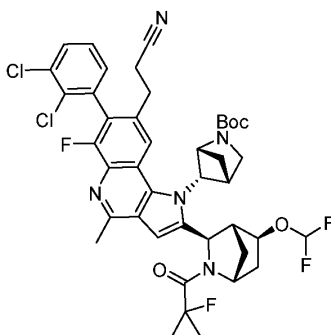
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A mixture of *tert*-butyl ((1*R*,4*R*,5*S*)-5-((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.070 g, 0.103 mmol), ((1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone (0.071 g, 0.154 mmol), copper(I) iodide (0.008 g, 0.041 mmol), Pd(PPh₃)₄ (0.024 g, 0.021 mmol), CsF (0.047 g, 0.308 mmol) and DIPEA (0.18 mL, 1.03 mmol) in DMF (0.5 mL) was sparged with

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N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (0.100 g, 0.308 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried
 5 over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound (0.073 g, 70% yield). LC-MS calc. for C₄₁H₄₂Cl₂F₂N₅O₄ (M+H)⁺: *m/z*=776.3; found 776.2.

Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-
 ((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-
 10 azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-
 azabicyclo[2.1.1]hexane-2-carboxylate



To mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-
 fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-hydroxy-2-
 15 azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-
 azabicyclo[2.1.1]hexane-2-carboxylate (0.035 g, 0.045 mmol) and copper iodide (0.002 g,
 0.009 mmol) in MeCN (0.1 mL) heated at 50 °C, was added an MeCN solution (0.1 mL) of
 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.012 g, 0.068 mmol). The mixture was stirred at
 the same temperature for 1 h. Upon completion, the mixture was cooled down to r.t. and
 20 diluted with EtOAc and saturated NH₄Cl solution. The organic layer was separated. The
 aqueous solution was extracted with EtOAc twice. Then the combined organic layers were
 washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was
 used for next step without further purification. LC-MS calc. for C₄₂H₄₂Cl₂F₄N₅O₄ (M+H)⁺:
m/z=826.3; found 826.2.

Step 4. 3-((*R*_a)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-
 ((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-
 azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-
 2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-

azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.037 g, 0.045 mmol) in DCM (1 mL), was added MeCN (0.1 mL) and TFA (1.1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS (XBRIDGE® C₁₈ column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for C₃₇H₃₄Cl₂F₄N₅O₂ (M+H)⁺: *m/z*=726.2; found 726.2.

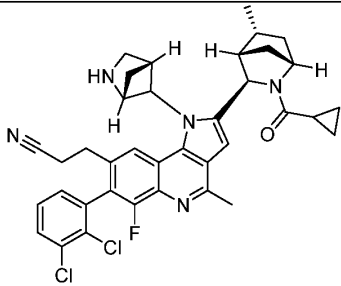
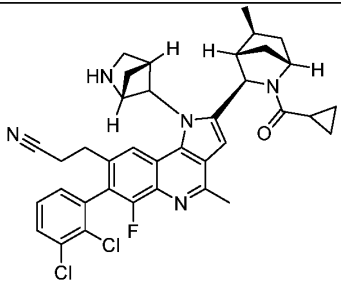
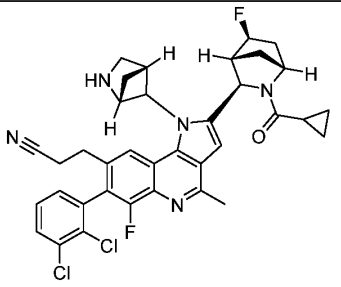
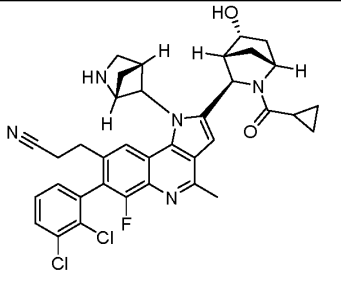
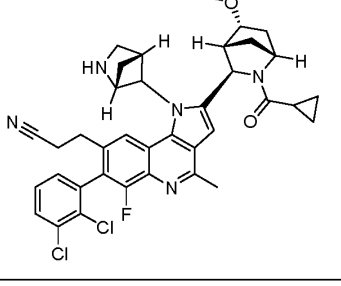
The alternative atropisomer 3-((S_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-c]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((S_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((R_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

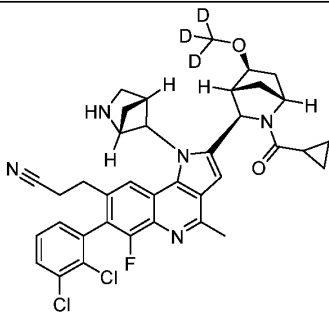
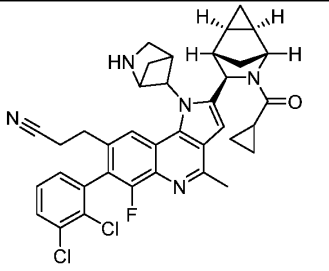
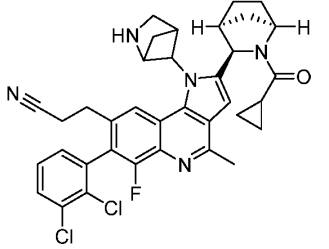
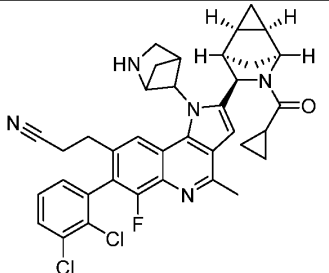
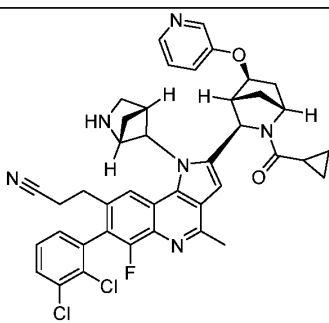
Additional Example compounds within the scope of the present disclosure were also prepared and are listed in Table B below.

Table B. Examples 11-34

Ex. No.	Structure	Name
11		3-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2-c]quinolin-8-yl)propanenitrile
12		5-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2-c]quinolin-4-yl)- <i>N,N</i> -dimethylpicolinamide

Ex. No.	Structure	Name
13		3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
14		4-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-4-yl)-2-fluoro- <i>N</i> -methylbenzamide
15		3-(1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
16		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
17		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile

Ex. No.	Structure	Name
18		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
19		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-methyl-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
20		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-fluoro-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
21		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-hydroxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
22		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(cyclopropanecarbonyl)-5-methoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile

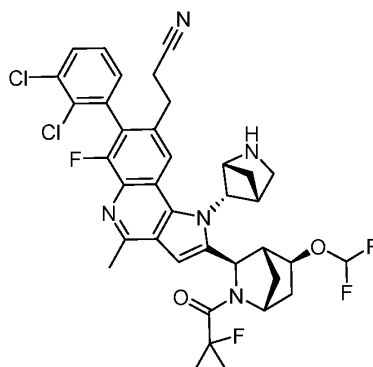
Ex. No.	Structure	Name
23		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(methoxy-d ₃)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
24		3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
25		3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
26		3-(1-(2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>R</i>)-6-(cyclopropanecarbonyl)-6-azatricyclo[3.2.1.0 ^{2,4}]octan-7-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
27		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile

Ex. No.	Structure	Name
28		3-(1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
29		3-(2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-(benzyloxy)-2-(cyclopropanecarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
30		3-((7 <i>R</i>)-1-((1 <i>R</i> ,4 <i>R</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
31		3-((<i>R</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile

Ex. No.	Structure	Name
32		3-((<i>R</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-5-fluoro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
33		3-((<i>R</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-5-chloro-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((<i>R</i>)-1-hydroxyethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile
34		3-((<i>R</i>)-1-((1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i>)-2-(cyclopropanecarbonyl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]quinolin-8-yl)propanenitrile

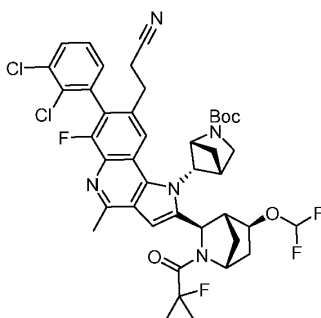
The alternative atropisomers of the compounds in the table above can be prepared by an analogous route by performing processes analogous to the steps above starting from intermediates of the alternative atropisomer (*S_a*).

Example 35. 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



5

Step 1. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate

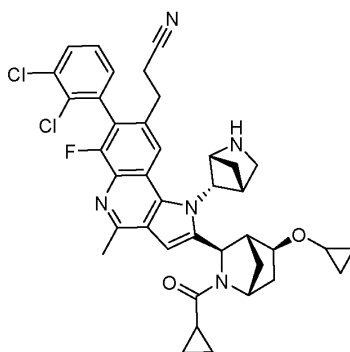


10 A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.81 g, 1.18 mmol), ((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone (**intermediate 10**, 0.39 g, 1.42 mmol), copper(I) iodide (0.090 g, 0.474 mmol), Pd(PPh₃)₄ (0.27 g, 0.237 mmol) and
15 DIPEA (2.1 mL, 11.8 mmol) in DMF (5.9 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (1.09 g, 3.33 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and
20 concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₄₂H₄₂Cl₂F₄N₅O₄ (M+H)⁺: *m/z*=826.3; found 826.2.

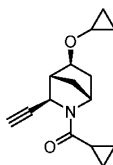
Step 2. 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.500 g, 0.60 mmol) in DCM (10 mL), was added MeCN (0.5 mL) and TFA (10 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (20 mL) and water (5 mL) and purified by preparative LC-MS (XBRIDGE® C₁₈ column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound as the corresponding TFA salt. LC-MS calc. for C₃₇H₃₄Cl₂F₄N₅O₂ (M+H)⁺: *m/z*=726.2; found 726.1. ¹H NMR was collected on the TFA salt. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.35 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.85 (dd, *J*=8.0, 1.5 Hz, 1H), 7.59 (t, *J*=7.9 Hz, 1H), 7.49–7.44 (m, 1H), 6.84 (t, *J*=7.5 Hz, 1H), 6.76 (s, 1H), 5.72 (m, 1H), 4.98 (d, *J*=6.8 Hz, 1H), 4.94 (s, 1H), 4.87 (d, *J*=6.1 Hz, 1H), 4.81 (s, 1H), 3.92 (m, 1H), 3.69 (m, 1H), 3.40 (m, 1H), 3.04 (m, 1H), 2.94–2.77 (m, 5H), 2.73–2.64 (m, 2H), 2.39–2.29 (m, 2H), 1.88 (dd, *J*=13.7, 3.1 Hz, 1H), 1.75 (d, *J*=10.8 Hz, 1H), 1.69–1.59 (m, 2H), 1.52–1.36 (m, 3H), 1.32–1.22 (m, 1H).

Example 36. 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

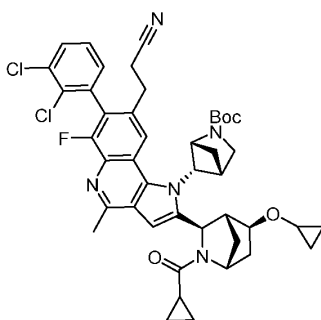


Step 1. ((1*R*,3*R*,4*R*,5*S*)-5-Cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone



To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 11**, 0.014 g, 0.050 mmol) in 1,4-dioxane (1 mL), was added 4 N HCl in 1,4-dioxane (1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (0.25 mL). DIPEA (0.044 mL, 0.25 mmol) was added with stirring followed by cyclopropanecarbonyl chloride (0.006 g, 0.060 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude product was used directly for next step without further purification. LC-MS calc. for C₁₅H₂₀NO₂ (M+H)⁺: *m/z*=246.1; found 246.1.

Step 2. tert-Butyl (1R,4R,5S)-5-(8-(2-cyanoethyl)-2-((1R,3R,4R,5S)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate

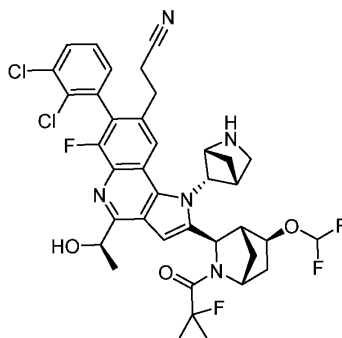


A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.020 g, 0.029 mmol), ((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(cyclopropyl)methanone (0.012 g, 0.050 mmol), copper(I) iodide (0.002 g, 0.012 mmol), Pd(PPh₃)₄ (0.007 g, 0.006 mmol) and DIPEA (0.051 mL, 0.29 mmol) in DMF (0.15 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (0.029 g, 0.088 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₄₄H₄₇Cl₂FN₅O₄ (M+H)⁺: *m/z*=798.3; found 798.2.

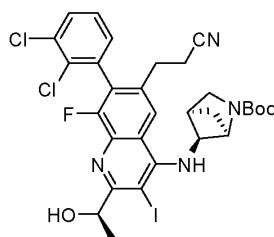
Step 3. 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-cyclopropoxy-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.023 g, 0.029 mmol) in DCM (1 mL), was added MeCN (0.1 mL) and TFA (1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS (XBRIDGE® C₁₈ column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound as the corresponding TFA salt. LC-MS calc. for C₃₉H₃₉Cl₂FN₅O₂ (M+H)⁺: *m/z*=698.2; found 698.2.

Example 37. 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



Step 1. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-((*R*)-1-hydroxyethyl)-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate

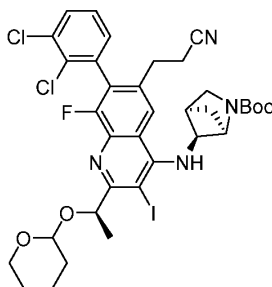


To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((2-((*R*)-1-(benzyloxy)ethyl)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 8**, 0.070 g, 0.087 mmol) in DCM (8.7 mL) cooled to -78 °C, was

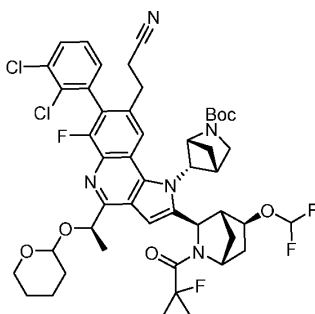
added BCl_3 (1 N in DCM, 0.44 mL, 0.44 mmol) dropwise. The reaction mixture was stirred at -78°C for 1 h and then allowed to warm up to r.t. Upon completion, the mixture was cooled to 0°C and saturated NaHCO_3 solution (3 mL) was added. The mixture was extracted with DCM three times and concentrated.

- 5 To the residue dissolved in THF (1 mL) was added DIPEA (0.046 mL, 0.26 mmol) and Boc_2O (0.038 g, 0.18 mmol). The resulting mixture was stirred at r.t. for 0.5 h. Upon completion, the reaction mixture was diluted with EtOAc and washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for $\text{C}_{30}\text{H}_{31}\text{Cl}_2\text{FIN}_4\text{O}_3$ ($\text{M}+\text{H}$) $^+$: $m/z=711.1$; found 711.0.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-((1*R*)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate



- 15 To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-2-((*R*)-1-hydroxyethyl)-3-iodoquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.507 g, 0.713 mmol) in 3,4-dihydro-2*H*-pyran (2 mL) and DCM (1 mL) was added pyridinium *p*-toluenesulfonate (0.068 g, 0.356 mmol) in one portion. The reaction was stirred at room temperature for 1 h. Upon completion, the mixture was quenched with
- 20 saturated NaHCO_3 solution and diluted with DCM. The organic layer was separated and aqueous layer extracted with DCM three times. The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (0-60% ethyl acetate/hexanes) to afford the title compound as a colorless oil (0.070 g, 64% yield). LC-MS calc. for $\text{C}_{35}\text{H}_{39}\text{Cl}_2\text{FIN}_4\text{O}_4$ ($\text{M}+\text{H}$) $^+$: $m/z=795.1$; found 795.1.
- 25 Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((1*R*)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



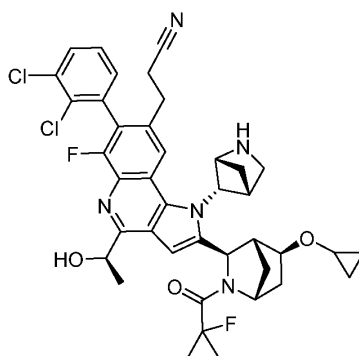
A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-((1*R*)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.365 g, 0.459 mmol), **Intermediate 10** (0.138 g, 0.505 mmol), copper(I) iodide (0.035 g, 0.184 mmol), tetrakis(triphenylphosphine) palladium(0) (0.106 g, 0.092 mmol) and *N,N*-diisopropylethylamine (0.80 mL, 4.59 mmol) in DMF (2.3 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, Cs₂CO₃ (0.447 g, 1.38 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 10 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₄₈H₅₂Cl₂F₄N₅O₆ (M+H)⁺: *m/z*=940.3; found 940.2.

Step 4. 3-((*R*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

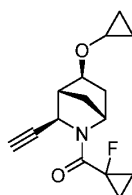
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-((1*R*)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.049 g, 0.057 mmol) in DCM (1 mL), was added MeCN (0.1 mL) and TFA (1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS (XBRIDGE® C₁₈ column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford a pair of atropisomers. The title compound was isolated as peak 1 of the two atropisomers. LC-MS calc. for C₃₈H₃₆Cl₂F₄N₅O₃ (M+H)⁺: *m/z*=756.2; found 756.2. ¹H NMR was collected on the TFA salt. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.26 (s, 1H), 8.20–8.08 (m, 2H), 7.84 (dd, *J*=8.1, 1.5 Hz, 1H), 7.58 (t, *J*=7.9 Hz, 1H), 7.47 (dd, *J*=7.7, 1.6 Hz, 1H), 6.86 (s, 1H), 6.84 (t, *J*=75 Hz, 1H), 5.68 (m, 1H), 5.17 (q, *J*=6.6 Hz, 1H), 4.97 (dd,

$J=7.3$, 2.6 Hz, 1H), 4.94 (s, 1H), 4.87 (d, $J=6.1$ Hz, 1H), 4.81 (s, 1H), 3.90 (dt, $J=6.3$, 3.0 Hz, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 3.09–2.97 (m, 1H), 2.93–2.77 (m, 2H), 2.71–2.62 (m, 2H), 2.38–2.28 (m, 2H), 1.88 (dt, $J=13.3$, 2.8 Hz, 1H), 1.74–1.59 (m, 3H), 1.52 (d, $J=6.6$ Hz, 3H), 1.52–1.39 (m, 2H), 1.39–1.23 (m, 2H).

- 5 **Example 38.** 3-(1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



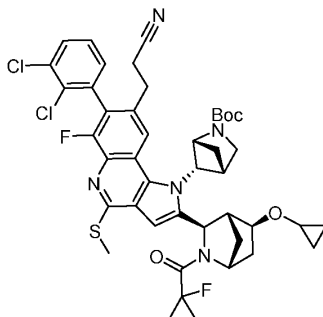
- 10 **Step 1.** ((1*R*,3*R*,4*R*,5*S*)-5-Cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone



- To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 11**, 0.21 g, 0.74 mmol) in 1,4-dioxane (2 mL), was added 4 N HCl in 1,4-dioxane (2 mL). The reaction mixture was stirred at r.t. for 1 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DMF (0.5 mL).

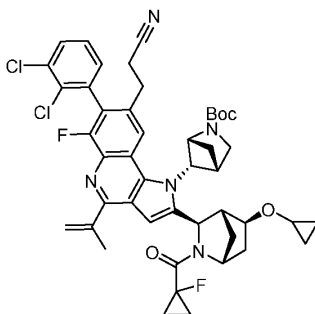
- To a separated vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.16 g, 1.49 mmol) in DMF (1.0 mL), was added DIPEA (0.65 mL, 3.71 mmol) followed by HATU (0.57 g, 1.49 mmol). The mixture was stirred for 15 min. then the above solution was added. The resulting mixture was stirred for 0.5 h at r.t. Once completed, the reaction mixture was diluted with EtOAc, washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was further purified with FCC (0-30% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₁₅H₁₉FN₂O₂ (M+H)⁺: $m/z=264.1$; found 264.1.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(methylthio)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



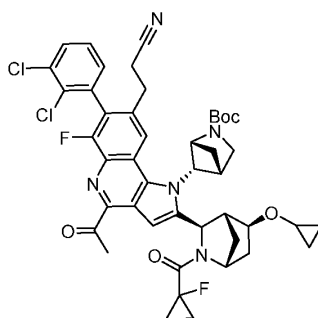
- 5 A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-((6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-(methylthio)quinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (intermediate 12, 0.085 g, 0.12 mmol), ((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone (0.41 g, 0.16 mmol), copper(I) iodide (0.009 g, 0.048 mmol), Pd(PPh₃)₄ (0.028 g, 0.024 mmol) and DIPEA (0.21 mL, 1.19 mmol) in DMF (0.6 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, c
- 10 Cs₂CO₃ (0.12 g, 0.36 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to r.t. and poured into water. The solution was extracted with EtOAc twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The
- 15 crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound (0.060 g, 59% yield). LC-MS calc. for C₄₄H₄₆Cl₂F₂N₅O₄S (M+H)⁺: *m/z*=848.3; found 848.2.

- Step 3. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(prop-1-en-2-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate
- 20



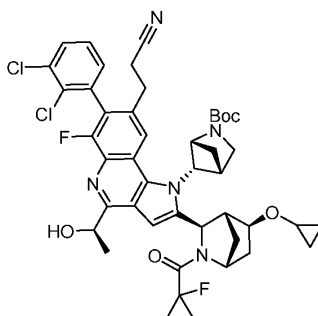
A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(methylthio)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.060 g, 0.071 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.095 g, 0.57 mmol), copper(I) 3-methylsalicylate (0.053 g, 0.25 mmol) and Pd(PPh₃)₄ (0.016 g, 0.014 mmol) in 1,4-dioxane (0.7 mL) was sparged with N₂ and heated at 100 °C for 3 h. Upon completion, the mixture was cooled down and diluted with EtOAc. The mixture was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound. LC-MS calc. for C₄₆H₄₈Cl₂F₂N₅O₄ (M+H)⁺: *m/z*=842.3; found 842.2.

Step 4. tert-Butyl (1R,4R,5S)-5-(4-acetyl-8-(2-cyanoethyl)-2-((1R,3R,4R,5S)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



To *tert*-butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-(prop-1-en-2-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.059 g, 0.070 mmol) dissolved in a mixture of THF (0.56 mL) and water (0.14 mL), was added NaIO₄ (0.075 mg, 0.35 mmol) followed by potassium osmate(VI) dihydrate (0.001 g, 0.003 mmol). After stirring for 1 h, the mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by FCC (0-100% EtOAc/hexanes) to afford the sub-title compound (0.040 g, 68% over 2 steps). LC-MS calc. for C₄₅H₄₆Cl₂F₂N₅O₅ (M+H)⁺: *m/z*=844.3; found 844.2.

Step 5. *tert*-Butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

To *tert*-butyl (1*R*,4*R*,5*S*)-5-(4-acetyl-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.040 g, 0.047 mmol) dissolved in DCM (0.66 mL) was added formic acid/ NEt_3 5:2 complex (0.13 mL) followed by $\text{RuCl}_2(p\text{-cymene})[(R,R)\text{-Ts-DPEN}]$ (0.003 g, 0.005 mmol). The resulting mixture was stirred at 40 °C for 16 h. Upon completion, the mixture was cooled down to r.t. and diluted with DCM, washed with saturated NaHCO_3 solution, dried over Na_2SO_4 , filtered and concentrated. The crude product was used in the next step without further purification. LC-MS calc. for $\text{C}_{45}\text{H}_{48}\text{Cl}_2\text{F}_2\text{N}_5\text{O}_5$ ($\text{M}+\text{H}^+$): $m/z=846.3$; found 846.2.

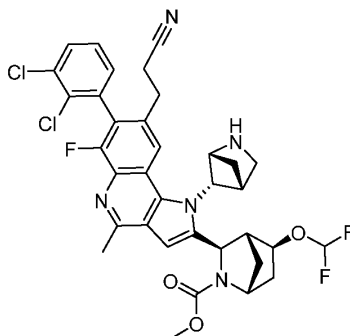
Step 6. 3-(1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-5-cyclopropoxy-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-((*R*)-1-hydroxyethyl)-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.040 g, 0.047 mmol) in DCM (1 mL), was added MeCN (0.1 mL) and TFA (1 mL). The reaction mixture was stirred at r.t. for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in MeCN (4 mL) and water (1 mL) and purified by preparative LC-MS (XBRIDGE® C_{18} column, eluting with a gradient of MeCN/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford a pair of atropisomers. The title compound was isolated as the earlier eluting peak in the separation. LC-MS calc. for $\text{C}_{40}\text{H}_{40}\text{Cl}_2\text{F}_2\text{N}_5\text{O}_3$ ($\text{M}+\text{H}^+$): $m/z=746.2$; found 746.1. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.25 (s, 1H), 8.17 (s, 1H), 8.11 (s, 1H), 7.84 (dd, $J=8.2, 1.5$ Hz, 1H), 7.58 (t, $J=7.9$ Hz, 1H), 7.46 (dd, $J=7.6, 1.6$ Hz, 1H), 6.83 (s, 1H), 5.71 (d, $J=2.9$ Hz, 1H), 5.16 (q, $J=6.6$ Hz, 1H), 4.92–4.85 (m, 2H), 4.68 (s, 1H), 4.22 (dd, $J=7.1, 2.8$ Hz, 1H), 3.86 (m, 1H),

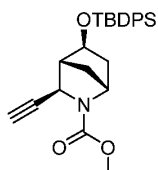
30

3.71 (m, 1H), 3.49 (m, 1H), 3.42 (m, 1H), 3.09–2.98 (m, 1H), 2.92–2.76 (m, 3H), 2.71–2.60 (m, 1H), 2.38 (d, $J=9.1$ Hz, 1H), 2.16 (dd, $J=13.1, 7.3$ Hz, 1H), 1.70 (dt, $J=13.1, 3.0$ Hz, 1H), 1.66–1.54 (m, 3H), 1.52 (d, $J=6.6$ Hz, 3H), 1.48–1.40 (m, 2H), 1.40–1.31 (m, 1H), 1.29–1.20 (m, 1H), 0.66–0.49 (m, 4H).

- 5 **Example 39. Methyl (1*R*,3*R*,4*R*,5*S*)-3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate**

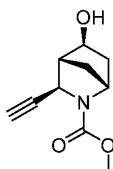


- 10 **Step 1. Methyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate**



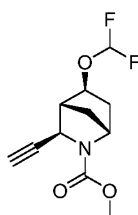
- To a solution of **Intermediate 5** (1.85 g, 3.89 mmol) in dioxane (10 mL) was added HCl (4 N in dioxane, 10 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (20 mL). Upon stirring, *N,N*-diisopropylethylamine (2.0 mL, 11.7 mmol) was added followed by methyl chloroformate (0.6 mL, 7.78 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-50% ethyl acetate/hexanes) to afford the title compound. LC-MS calc. for C₂₆H₃₂NO₃Si (M+H)⁺: $m/z=434.2$; found 434.2.

Step 2. Methyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate



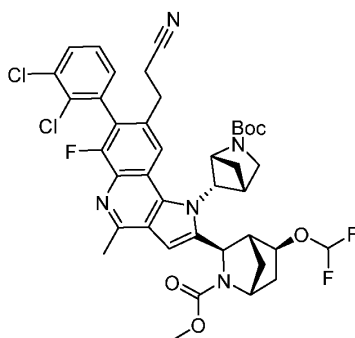
To a solution of methyl (1*R*,3*R*,4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.43 g, 3.30 mmol) in THF (11 mL) was added TBAF (1 N in THF, 4.0 mL, 3.96 mmol). The reaction was stirred at room temperature for 16 h. Upon completion, the volatiles were removed. The crude was purified by flash chromatography (0-10% methanol/DCM) to afford the title compound. LC-MS calc. for C₁₀H₁₄NO₃ (M+H)⁺: m/z=196.1; found 196.1.

Step 3. Methyl (1R,3R,4R,5S)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate



To a flask containing methyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.514 g, 2.63 mmol) and copper(I) iodide (0.100 g, 0.527 mmol) was charged acetonitrile (13 mL). The mixture was stirred at 50 °C before an acetonitrile solution (2 mL) containing 2-(fluorosulfonyl)difluoroacetic acid (0.703 g, 3.95 mmol) was added slowly. The reaction mixture was stirred at 50 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM, washed with saturated NaHCO₃ solution and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica chromatography (0-50% ethyl acetate/hexanes) to afford title compound (0.467 g, 72% yield). LC-MS calc. for C₁₁H₁₄F₂NO₃ (M+H)⁺: m/z=246.1; found 246.1.

Step 4. tert-Butyl (1R,4R,5S)-5-((R_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1R,3R,4R,5S)-5-(difluoromethoxy)-2-(methoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of **Intermediate 2** (0.500 g, 0.734 mmol), methyl (1*R*,3*R*,4*R*,5*S*)-5-(difluoromethoxy)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.270 g, 1.10 mmol), copper(I) iodide (0.056 g, 0.294 mmol), tetrakis(triphenylphosphine)palladium(0) (0.170 g,

0.147 mmol) and *N,N*-diisopropylethylamine (1.3 mL, 7.34 mmol) in DMF (4.6 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.717 g, 2.20 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water.

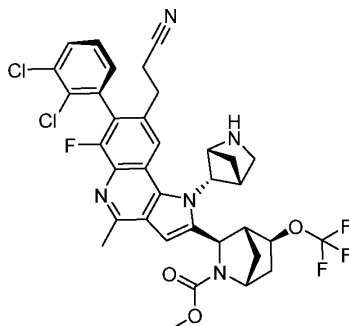
5 The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₄₀H₄₁Cl₂F₃N₅O₅ (M+H)⁺: m/z=798.2; found 798.3.

10 *Step 4. Methyl (1R,3R,4R,5S)-3-((R_a)-1-((1R,4R,5S)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate*

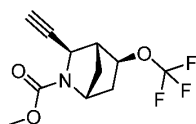
To a solution of *tert*-butyl (1R,4R,5S)-5-((R_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1R,3R,4R,5S)-5-(difluoromethoxy)-2-(methoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.350 g, 0.439 mmol) in DCM (7 mL), was added acetonitrile (0.7 mL) and TFA (7 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for C₃₅H₃₃Cl₂F₃N₅O₃ (M+H)⁺: m/z=698.2; found 698.2. ¹H NMR was collected on the TFA salt. ¹H NMR (500 MHz, DMSO-d₆) δ 9.53 (s, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 7.86 (dd, *J*=8.1, 1.5 Hz, 1H), 7.59 (t, *J*=7.9 Hz, 1H), 7.47 (td, *J*=7.8, 1.6 Hz, 1H), 6.97 (s, 1H), 6.83 (t, *J*=7.5 Hz, 1H), 5.73 (s, 1H), 4.96 (m, 1H), 4.88 (m, 1H), 4.59 (s, 1H), 4.32 (s, 1H), 3.92 (m, 1H), 3.74 (s, 3H), 3.53 (m, 1H), 3.44 (m, 1H), 3.12–2.99 (m, 1H), 2.97–2.78 (m, 5H), 2.76–2.62 (m, 2H), 2.39–2.32 (m, 1H), 2.32–2.19 (m, 1H), 1.76–1.59 (m, 3H), 1.57–1.47 (m, 1H).

The alternative atropisomer methyl (1R,3R,4R,5S)-3-((S_a)-1-((1R,4R,5S)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(difluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1R,4R,5S)-5-((S_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1R,3R,4R,5S)-5-(difluoromethoxy)-2-(methoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1R,4R,5S)-5-((R_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1R,3R,4R,5S)-5-(difluoromethoxy)-2-(methoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 40. Methyl (1*R*,3*R*,4*R*,5*S*)-3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

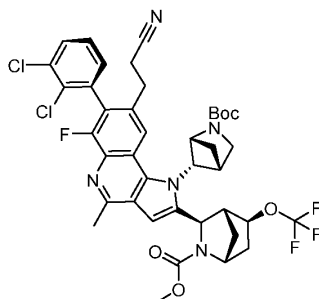


- 5 **Step 1. Methyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate**



- To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 13**, 0.100 g, 0.33 mmol) in DCM (2 mL), was added TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (2 mL). Upon stirring, *N,N*-diisopropylethylamine (0.29 mL, 1.64 mmol) was added followed by methyl chloroformate (0.038 mL, 0.49 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude was used directly for next step without further purification. LC-MS calculated for C₁₁H₁₃F₃NO₃ (M+H)⁺: m/z = 264.1; found 264.1.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(methoxycarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (intermediate 2, 0.200 g, 0.29 mmol), methyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.087 g, 0.33 mmol), copper(I) iodide (0.022 g, 0.12 mmol), tetrakis(triphenylphosphine)palladium(0) (0.068 g, 0.059 mmol) and *N,N*-diisopropylethylamine (0.51 mL, 2.94 mmol) in DMF (1.5 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.287 g, 0.88 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water. The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₄₀H₄₀Cl₂F₄N₅O₅ (M+H)⁺: m/z = 816.2; found 816.4.

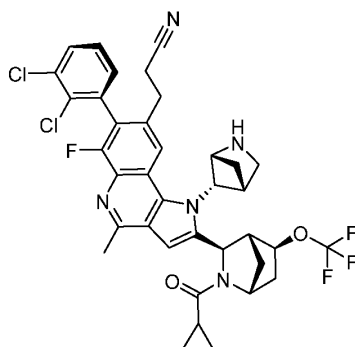
Step 3. Methyl (1R,3R,4R,5S)-3-((R_a)-1-((1R,4R,5S)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(methoxycarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.120 g, 0.15 mmol) in DCM (2 mL), was added acetonitrile (0.2 mL) and TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for C₃₅H₃₂Cl₂F₄N₅O₃ (M+H)⁺: m/z = 716.2; found 716.2. ¹H NMR was collected on the TFA salt. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.28 (br, 1H), 8.31 – 8.10 (m, 2H), 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.49 – 7.43 (m, 1H), 6.99 – 6.83 (m, 1H), 5.73 – 5.69 (m, 1H), 5.30 (m, 1H), 4.88 (m, 1H), 4.73 – 4.63 (m, 1H), 4.37 – 4.28 (m, 1H), 3.92 – 3.76 (m, 1H), 3.74 (s, 2H), 3.65 (m, 1H), 3.54 (m, 1H), 3.41 (s, 1H), 3.07 – 2.97 (m, 1H), 2.95 – 2.78 (m, 5H), 2.76 (m, 1H), 2.72 – 2.62 (m, 1H), 2.38 – 2.26 (m, 2H), 1.90 – 1.78 (m, 1H), 1.70 – 1.49 (m, 3H).

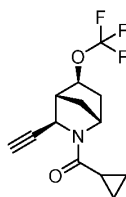
The alternative atropisomer methyl (1*R*,3*R*,4*R*,5*S*)-3-(((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-2-yl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*S_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-

fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 41. 3-(((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-(((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



Step 1. Cyclopropyl((1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

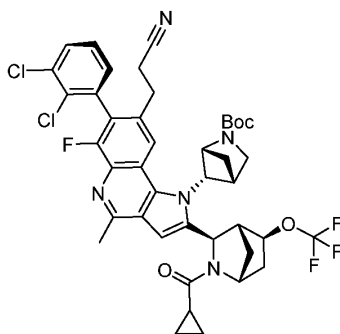


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To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 13**, 0.100 g, 0.33 mmol) in DCM (2 mL), was added TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (2 mL). Upon stirring, *N,N*-diisopropylethylamine (0.29 mL, 1.64 mmol) was added followed by cyclopropanecarbonyl chloride (0.045 mL, 0.49 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude was used directly for next step without further purification. LC-MS calculated for C₁₃H₁₅F₃NO₂ (M+H)⁺: m/z = 274.1; found 274.2.

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Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.200 g, 0.29 mmol), cyclopropyl((1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone (0.090 g, 0.33 mmol), copper(I) iodide (0.022 g, 0.12 mmol), tetrakis(triphenylphosphine)palladium(0) (0.068 g, 0.059 mmol) and *N,N*-diisopropylethylamine (0.51 mL, 2.94 mmol) in DMF (1.5 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.287 g, 0.88 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water. The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₄₂H₄₂Cl₂F₄N₅O₄ (M+H)⁺: m/z = 826.3; found 826.4.

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Step 3. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

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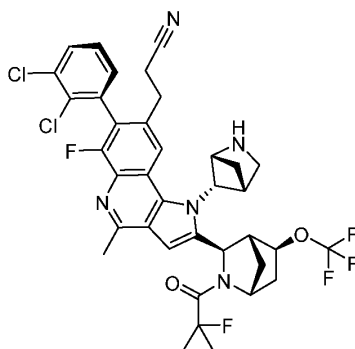
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.110 g, 0.13 mmol) in DCM (2 mL), was added acetonitrile (0.2 mL) and TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the

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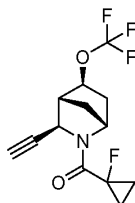
title compound. LC-MS calc. for $C_{37}H_{34}Cl_2F_4N_5O_2$ ($M+H$)⁺: m/z = 726.2; found 726.2. 1H NMR was collected on the TFA salt. 1H NMR (500 MHz, DMSO- d_6) δ 9.18 (br, 1H), 8.12 (s, 1H), 8.05 (br, 1H), 7.85 (dd, J = 8.0, 1.5 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 7.8, 1.6 Hz, 1H), 6.70 (s, 1H), 5.69 (m, 1H), 5.35 – 5.29 (m, 1H), 4.88 (m, 1H), 4.87 – 4.82 (m, 1H), 4.76 (m, 1H), 3.89 (m, 1H), 3.74 (m, 1H), 3.36 (m, 1H), 3.06 – 2.96 (m, 1H), 2.95 – 2.85 (m, 1H), 2.85 – 2.77 (m, 4H), 2.75 (s, 1H), 2.72 – 2.62 (m, 1H), 2.38 – 2.30 (m, 2H), 2.12 (tt, J = 8.0, 4.7 Hz, 1H), 1.96 (d, J = 13.7 Hz, 1H), 1.77 (d, J = 11.0 Hz, 1H), 1.66 (d, J = 10.7 Hz, 1H), 1.60 (d, J = 9.3 Hz, 1H), 0.96 – 0.76 (m, 4H).

The alternative atropisomer 3-((S_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,4*R*,5*S*)-2-(cyclopropanecarbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((S_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((R_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 42. 3-((R_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



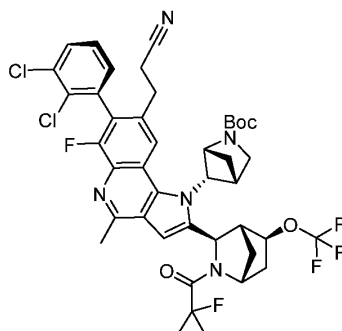
Step 1. ((1*R*,3*R*,4*R*,5*S*)-3-Ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone



To a solution of *tert*-butyl (1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 13**, 0.150 g, 0.33 mmol) in DCM (2 mL), was added TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure.

- 5 To a separated vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.102 g, 0.98 mmol) in DMF (2.5 mL), was added *N,N*-diisopropylethylamine (0.43 mL, 2.46 mmol) followed by HATU (0.374 g, 0.98 mmol). The mixture was stirred for 15 mins before the deprotected intermediate above was added as a DMF solution. The resulting mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with ethyl acetate,
- 10 washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude was further purified with silica chromatography (0-30% ethyl acetate/hexanes) to afford the title compound (0.125 g, 87% yield). LC-MS calculated for C₁₃H₁₄F₄NO₂ (M+H)⁺: m/z = 292.0; found 292.1.

- Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate
- 15



- A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.250 g, 0.37 mmol), ((1*R*,3*R*,4*R*,5*S*)-3-ethynyl-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone (0.118 g, 0.40 mmol), copper(I) iodide (0.028 g, 0.15 mmol), tetrakis(triphenylphosphine)palladium(0) (0.085 g, 0.073 mmol) and *N,N*-diisopropylethylamine (0.64 mL, 3.67 mmol) in DMF (1.8 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.359 g, 1.10 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water. The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by
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- 25

flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for $C_{42}H_{41}Cl_2F_5N_5O_4$ ($M+H$)⁺: m/z = 844.2; found 844.4.

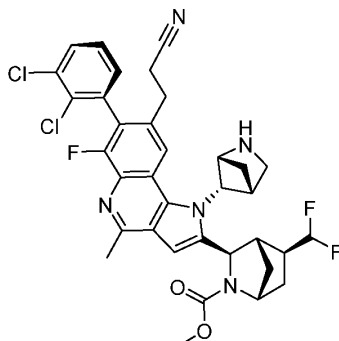
Step 3. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-

5 azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

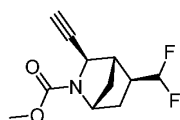
To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.110 g, 0.13 mmol) in DCM (2 mL), was added
10 acetonitrile (0.2 mL) and TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for $C_{37}H_{33}Cl_2F_5N_5O_2$
15 ($M+H$)⁺: m/z = 744.2; found 744.2. ¹H NMR was collected on the TFA salt. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.29 (s, 1H), 8.19 – 8.08 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 6.76 (s, 1H), 5.73 (m, 1H), 5.37 – 5.33 (m, 1H), 4.97 (m, 1H), 4.91 (s, 1H), 4.87 (d, *J* = 6.2 Hz, 1H), 3.89 (m, 1H), 3.69 (m, 1H), 3.38 (m, 1H), 3.09 – 2.96 (m, 1H), 2.94 – 2.76 (m, 6H), 2.74 – 2.60 (m, 1H), 2.42 – 2.30 (m, 2H), 2.02 (d, *J* = 13.6
20 Hz, 1H), 1.79 (d, *J* = 11.0 Hz, 1H), 1.68 (d, *J* = 10.9 Hz, 1H), 1.63 (d, *J* = 9.2 Hz, 1H), 1.54 – 1.22 (m, 4H).

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous
25 to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*S_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 43. Methyl (1*R*,3*R*,4*S*,5*S*)-3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

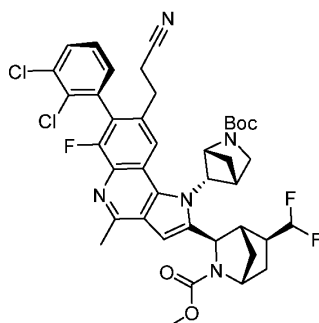


- 5 **Step 1. Methyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate**



- To a solution of *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 9**, 0.080 g, 0.30 mmol) in DCM (2 mL), was added TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (2 mL). Upon stirring, *N,N*-diisopropylethylamine (0.26 mL, 1.47 mmol) was added followed by methyl chloroformate (0.034 mL, 0.44 mmol). The mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over Na₂SO₄, filtered and concentrated. The crude was used directly for next step without further purification. LC-MS calculated for C₁₁H₁₄F₂NO₂ (M+H)⁺: *m/z* = 230.1; found 230.1.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R*_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (intermediate 2, 0.180 g, 0.26 mmol), methyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.068 g, 0.30 mmol), copper(I) iodide (0.020 g, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (0.061 g, 0.053 mmol) and *N,N*-diisopropylethylamine (0.46 mL, 2.64 mmol) in DMF (1.3 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.258 g, 0.79 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water. The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₄₀H₄₁Cl₂F₃N₅O₄ (M+H)⁺: m/z = 782.2; found 782.4.

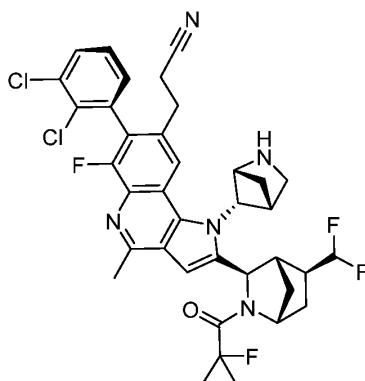
Step 3. Methyl (1R,3R,4S,5S)-3-((R_a)-1-((1R,4R,5S)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1H-pyrrolo[3,2-c]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R*_a)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-(methoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.083 g, 0.11 mmol) in DCM (2 mL), was added acetonitrile (0.2 mL) and TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for C₃₅H₃₃Cl₂F₃N₅O₂ (M+H)⁺: m/z = 682.2; found 682.3. ¹H NMR was collected on the TFA salt. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.25 (br, 1H), 8.26 – 8.08 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.49 – 7.42 (m, 1H), 6.97 – 6.76 (m, 1H), 6.87 (td, *J* = 57, 6.0 Hz, 1H), 5.69 (m, 1H), 4.90 – 4.84 (m, 1H), 4.68 – 4.62 (m, 1H), 4.35 – 4.26 (m, 1H), 3.86 – 3.76 (m, 1H), 3.75 (s, 2H), 3.66 (s, 1H), 3.52 (m, 1H), 3.44 – 3.40 (m, 1H), 3.05 – 2.98 (m, 1H), 2.96 – 2.72 (m, 6H), 2.72 – 2.65 (m, 1H), 2.62 – 2.57 (m, 1H), 2.35 (d, *J* = 9.0 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.73 – 1.40 (m, 4H).

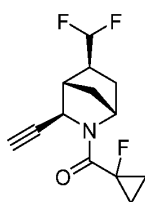
The alternative atropisomer methyl (1*R*,3*R*,4*S*,5*S*)-3-(((*R*_a)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-2-yl)-5-(difluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*S*_a)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-

3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example 44. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile



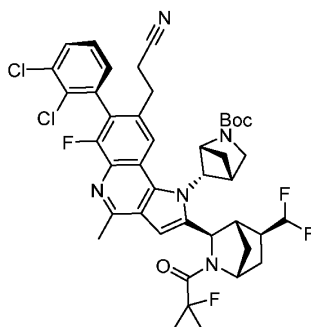
Step 1. ((1*R*,3*R*,4*S*,5*S*)-5-(Difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone



To a solution of *tert*-butyl (1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (**intermediate 9**, 0.100 g, 0.37 mmol) in DCM (2 mL), was added TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, the volatiles were removed under reduced pressure.

To a separated vessel containing 1-fluorocyclopropane-1-carboxylic acid (0.077 g, 0.74 mmol) in DMF (1.8 mL), was added *N,N*-diisopropylethylamine (0.32 mL, 1.84 mmol) followed by HATU (0.280 g, 0.74 mmol). The mixture was stirred for 15 mins before the aforementioned residue was added as a DMF solution. The resulting mixture was stirred for 0.5 h. Once completed, the reaction mixture was diluted with ethyl acetate, washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude was further purified with silica chromatography (0-100% ethyl acetate/hexanes) to afford the title compound (0.070 g, 74% yield). LC-MS calculated for C₁₃H₁₅F₃NO (M+H)⁺: m/z = 258.1; found 258.2.

Step 2. *tert*-Butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



5

A mixture of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate (**intermediate 2**, 0.170 g, 0.25 mmol), ((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-3-ethynyl-2-azabicyclo[2.2.1]heptan-2-yl)(1-fluorocyclopropyl)methanone (0.070 g, 0.27 mmol), copper(I) iodide (0.019 g, 0.10 mmol), tetrakis(triphenylphosphine)palladium(0) (0.058 g, 0.050 mmol) and *N,N*-diisopropylethylamine (0.44 mL, 2.50 mmol) in DMF (1.2 mL) was sparged with N₂ and heated at 70 °C for 1 h. Then, cesium carbonate (0.244 g, 0.75 mmol) was added to the reaction mixture. The resulting slurry was stirred at 90 °C for another 18 h. Upon completion, the mixture was cooled down to room temperature and poured into water. The solution was extracted with ethyl acetate twice. Then the combined organic layers were washed with brine five times, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC-MS calc. for C₄₂H₄₂Cl₂F₄N₅O₃ (M+H)⁺: *m/z* = 810.3; found 810.4.

15

Step 3. 3-((*R_a*)-1-((1*R*,4*R*,5*S*)-2-Azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile

20

To a solution of *tert*-butyl (1*R*,4*R*,5*S*)-5-((*R_a*)-8-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-6-fluoro-2-((1*R*,3*R*,4*R*,5*S*)-2-(1-fluorocyclopropane-1-carbonyl)-5-(trifluoromethoxy)-2-azabicyclo[2.2.1]heptan-3-yl)-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (0.73 g, 0.09 mmol) in DCM (2 mL), was added acetonitrile (0.2 mL) and TFA (2 mL). The reaction was stirred at room temperature for 0.5 h. Upon completion, volatiles were removed under reduced pressure and the residue was dissolved in acetonitrile (4 mL) and water (1 mL) and purified by preparative LC-MS (XBridge® C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the title compound. LC-MS calc. for C₃₇H₃₄Cl₂F₄N₅O (M+H)⁺:

25

30

m/z = 710.2; found 710.3. ¹H NMR was collected on the TFA salt. ¹H NMR (500 MHz, DMSO-d₆) δ 9.22 (br, 1H), 8.12 (s, 1H), 8.07 (br, 1H), 7.84 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.67 (s, 1H), 6.14 (td, *J* = 5.7, 5.5 Hz, 1H), 5.69 (m, 1H), 4.93 (s, 1H), 4.89 (s, 1H), 4.86 (d, *J* = 6.1 Hz, 1H), 3.85 (dt, *J* = 6.2, 3.2 Hz, 1H), 3.68 (m, 1H), 3.38 (m, 1H), 3.07 – 2.97 (m, 1H), 2.94 – 2.86 (m, 1H), 2.85 – 2.74 (m, 5H), 2.73 – 2.58 (m, 2H), 2.35 (m, 1H), 2.03 – 1.93 (m, 1H), 1.87 – 1.79 (m, 1H), 1.68 (d, *J* = 10.8 Hz, 1H), 1.64 – 1.56 (m, 2H), 1.54 – 1.21 (m, 4H).

The alternative atropisomer 3-((*S_a*)-1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-7-(2,3-dichlorophenyl)-2-((1*R*,3*R*,4*S*,5*S*)-5-(difluoromethyl)-2-(1-fluorocyclopropane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile can be prepared by an analogous route by performing processes analogous to the steps above starting from *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*S_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate instead of *tert*-butyl (1*R*,4*R*,5*S*)-5-(((*R_a*)-6-(2-cyanoethyl)-7-(2,3-dichlorophenyl)-8-fluoro-3-iodo-2-methylquinolin-4-yl)amino)-2-azabicyclo[2.1.1]hexane-2-carboxylate.

Example A. GDP-GTP exchange assay.

The inhibitor potency of the exemplified compounds was determined in a fluorescence based guanine nucleotide exchange assay, which measures the exchange of bodipy-GDP (fluorescently labeled GDP) for GppNHp (Non-hydrolyzable GTP analog) to generate the active state of KRAS in the presence of SOS1 (guanine nucleotide exchange factor). Inhibitors were serially diluted in DMSO and a volume of 0.1 μL was transferred to the wells of a black low volume 384-well plate. 5 μL/well volume of bodipy-loaded KRAS G12D diluted to 2.5 nM in assay buffer (25 mM Hepes pH 7.5, 50 mM NaCl, 10 mM MgCl₂ and 0.01% Brij-35) was added to the plate and pre-incubated with inhibitor for 4 h at r.t. Appropriate controls (enzyme with no inhibitor or with a G12D inhibitor) were included on the plate. The exchange was initiated by the addition of a 5 μL/well volume containing 1 mM GppNHp and 300 nM SOS1 in assay buffer. The 10 μL/well reaction concentration of the bodipy-loaded KRAS G12D, GppNHp, and SOS1 were 2.5 nM, 500 μM, and 150 nM, respectively. The reaction plates were incubated at r.t. for 2 h, a time estimated for complete GDP-GTP exchange in the absence of inhibitor. For the KRAS G12V mutant, similar guanine nucleotide exchange assays were used with 2.5 nM as final concentration for the bodipy loaded KRAS proteins and 3 h incubation after adding GppNHp-SOS1 mixture. A cyclic peptide described to selectively bind G12D mutant (Sakamoto *et al.*, BBRC 484.3 (2017), 605-611) or internal compounds with confirmed binding were used as positive controls in the assay plates. Fluorescence intensities were measured on a PheraStar plate reader instrument (BMG Labtech) with excitation at 485 nm and emission at 520 nm.

Either GraphPad prism or Genedata Screener SmartFit was used to analyze the data. The IC₅₀ values were derived by fitting the data to a four parameter logistic equation producing a sigmoidal dose-response curve with a variable Hill coefficient.

- The KRAS_G12D and KRAS_G12V exchange assay IC₅₀ data are provided in
- 5 Table C below. The symbol “†” indicates IC₅₀ ≤ 100 nM, “††” indicates IC₅₀ > 100 nM but ≤ 1 μM; and “†††” indicates IC₅₀ is >1 μM but ≤ 5 μM, “††††” indicates IC₅₀ is >5 μM but ≤ 10 μM. “NA” indicates IC₅₀ not available. For certain compounds that were isolated as more atropisomers and/or diastereoisomers, the value for the most potent isomer is quoted.

Table C

Ex. No.	G12D	G12V	Ex. No.	G12D	G12V
1	†	†	23	†	†
2	†	†	24	†	†
3	†	†	25	†††	††††
4	†	†	26	††††	††††
5	†	†	27	†	†
6	†	†	28	†	†
7	†	†	29	†	†
8	†	†	30	†	†
9	†	†	31	†	†
10	†	†	32	†	†
11	†	†	33	†	†
12	†	†	34	†	†
13	†	†	35	†	†
14	†	†	36	†	†
15	†	†	37	†	†
16	†	†	38	†	†
17	†	†	39	†	†
18	†	†	40	†	†
19	†	†	41	†	†
20	†	†	42	†	†
21	††	††	43	†	†
22	††	††	44	†	†

10 **Example B: Luminescent Viability Assay**

- MIA PaCa-2 (KRAS G12C; ATCC® CRL-1420), NCI-H358 (KRAS G12C; ATCC® CRL-5807), A427 (KRAS G12D; ATCC® HTB53), HPAFII (KRAS G12D; ATCC® CRL-1997), YAPC (KRAS G12V; DSMZ ACC382), SW480 (KRAS G12V; ATCC® CRL-228) and NCI-H838 (KRAS WT; ATCC® CRL-5844) cells are cultured in RPMI 1640 media
- 15 supplemented with 10% FBS (Gibco/Life Technologies). Eight hundred cells per well in RPMI 1640 media supplemented with 2% FBS are seeded into white, clear bottomed 384-well Costar tissue culture plates containing 50nL dots of test compounds (final concentration is a 1:500 dilution, with a final concentration in 0.2% DMSO). Plates are incubated for 3 days

at 37 °C, 5% CO₂. At the end of the assay, 25 µL/well of CellTiter-Glo reagent (Promega) is added. Luminescence is read after 15 min. with a PHERAstar (BMG). Data are analyzed in Genedata Screener using SmartFit for IC₅₀ values.

Example C: Cellular pERK HTRF Assay

- 5 MIA PaCa-2 (KRAS G12C; ATCC® CRL-1420), NCI-H358 (KRAS G12C; ATCC® CRL-5807), A427 (KRAS G12D; ATCC® HTB53), HPAFII (KRAS G12D; ATCC® CRL-1997), YAPC (KRAS G12V; DSMZ ACC382), SW480 (KRAS G12V; ATCC® CRL-228) and NCI-H838 (KRAS WT; ATCC® CRL-5844) cells are purchased from ATCC and maintained in RPMI 1640 media supplemented with 10% FBS (Gibco/Life Technologies). The cells are
- 10 plated at 5000 cells per well (8 µL) into Greiner 384-well low volume, flat-bottom, and tissue culture treated white plates and incubated overnight at 37 °C, 5% CO₂. The next morning, test compound stock solutions are diluted in media at 3× the final concentration and 4 µL are added to the cells, with a final concentration of 0.1% of DMSO. The cells are incubated with the test compounds for 4 h (G12C and G12V) or 2 h (G12D) at 37°C, 5% CO₂. 4 µL of 4×
- 15 lysis buffer with blocking reagent (Cisbio) are added to each well and plates are rotated gently (300 rpm) for 30 min. at room temperature. 4 µL per well of Cisbio anti Phospho-ERK 1/2 d2 is mixed with anti Phospho-ERK 1/2 Cryptate (1:1), and added to each well, incubated overnight in the dark at room temperature. Plates are read on the Pherastar plate reader at 665 nm and 620 nm wavelengths. Data are analyzed in Genedata Screener using
- 20 SmartFit for IC₅₀ values.

Example D: Whole Blood pERK1/2 HTRF Assay

- MIA PaCa-2 cells (KRAS G12C; ATCC® CRL-1420), HPAF-II (KRAS G12D; ATCC® CRL-1997) and YAPC (KRAS G12V; DSMZ ACC382) are maintained in RPMI 1640 with 10% FBS (Gibco/Life Technologies). For MIA PaCa-2 assay, cells are seeded into 96 well
- 25 tissue culture plates (Corning #3596) at 25000 cells per well in 100 µL media and cultured for 2 days at 37 °C, 5% CO₂ before the assay. For HPAF-II and YAPC assay, cells are seeded in 96 well tissue culture plates at 50000 cells per well in 100 µL media and cultured for 1 day before the assay. Whole Blood are added to the 1 µL dots of compounds (prepared in DMSO) in 96 well plates and mixed gently by pipetting up and down so that the
- 30 concentration of the compound in blood is 1× of desired concentration, in 0.5% DMSO. The media is aspirated from the cells and 50 µL per well of whole blood with test compound is added and incubated for 4 h for MIA PaCa and YAPC assay; or 2 h for HPAF-II assay, respectively at 37 °C, 5% CO₂. After dumping the blood, the plates are gently washed twice by adding PBS to the side of the wells and dumping the PBS from the plate onto a paper
- 35 towel, tapping the plate to drain well. 50 µL/well of 1× lysis buffer #1 (Cisbio) with blocking reagent (Cisbio) and Benzonase nuclease (Sigma Cat # E1014-5KU, 1: 10000 final

concentration) is then added and incubated at room temperature for 30 min. with shaking (250 rpm). Following lysis, 16 µL of lysate is transferred into 384-well Greiner small volume white plate using an Assist Plus (Integra Biosciences, NH). 4 µL of 1:1 mixture of anti Phospho-ERK 1/2 d2 and anti Phospho-ERK 1/2 Cryptate (Cisbio) is added to the wells
5 using the Assist Plus and incubated at room temperature overnight in the dark. Plates are read on the Pherastar plate reader at 665 nm and 620 nm wavelengths. Data are analyzed in Genedata Screener using SmartFit for IC₅₀ values.

Example E: Ras Activation Elisa

The 96-Well Ras Activation ELISA Kit (Cell Biolabs Inc; #STA441) uses the
10 Raf1 RBD (Rho binding domain) bound to a 96-well plate to selectively pull down the active form of Ras from cell lysates. The captured GTP-Ras is then detected by a pan-Ras antibody and HRP-conjugated secondary antibody.

MIA PaCa-2 (KRAS G12C; ATCC® CRL-1420), NCI-H358 (KRAS G12C; ATCC® CRL-5807), A427 (KRAS G12D; ATCC® HTB53), HPAFII (KRAS G12D; ATCC® CRL-1997), YAPC (KRAS G12V; DSMZ ACC382), SW480 (KRAS G12V; ATCC® CRL-228) and
15 NCI-H838 (KRAS WT; ATCC® CRL-5844) cells are maintained in RPMI 1640 with 10% FBS (Gibco/Life Technologies). The cells are seeded into 96 well tissue culture plates (Corning #3596) at 25000 cells per well in 100 µL media and cultured for 2 days at 37 °C, 5% CO₂ so that they are approximately 80% confluent at the start of the assay. The cells are treated
20 with compounds for either 4 h or overnight at 37 °C, 5% CO₂. At the time of harvesting, the cells are washed with PBS, drained well and then lysed with 50 µL of the 1× Lysis buffer (provided by the kit) plus added Halt Protease and Phosphatase inhibitors (1:100) for 1 h on ice.

The Raf-1 RBD is diluted 1:500 in Assay Diluent (provided in kit) and 100 µL of the
25 diluted Raf-1 RBD is added to each well of the Raf-1 RBD Capture Plate. The plate is covered with a plate sealing film and incubated at room temperature for 1 h on an orbital shaker. The plate is washed 3 times with 250 µL 1X Wash Buffer per well with thorough aspiration between each wash. 50 µL of Ras lysate sample (10-100 µg) is added per well in duplicate. A “no cell lysate” control is added in a couple of wells for background
30 determination. 50 µL of Assay Diluent is added to all wells immediately to each well and the plate is incubated at room temperature for 1 h on an orbital shaker. The plate is washed 5 times with 250 µL 1X Wash Buffer per well with thorough aspiration between each wash. 100 µL of the diluted Anti-pan-Ras Antibody is added to each well and the plate is incubated at room temperature for 1 h on an orbital shaker. The plate is washed 5 times as previously.
35 100 µL of the diluted Secondary Antibody, HRP Conjugate is added to each well and the plate is incubated at room temperature for 1 h on an orbital shaker. The plate is washed 5

times as previously and drained well. 100 μ L of Chemiluminescent Reagent (provided in the kit) is added to each well, including the blank wells. The plate is incubated at room temperature for 5 min. on an orbital shaker before the luminescence of each microwell is read on a plate luminometer. The % inhibition is calculated relative to the DMSO control wells after a background level of the “no lysate control” is subtracted from all the values. IC₅₀ determination is performed by fitting the curve of inhibitor percent inhibition versus the log of the inhibitor concentration using the GraphPad Prism 7 software.

Example F: Inhibition of RAS-RAF and PI3K-AKT Pathways

The cellular potency of compounds is determined by measuring phosphorylation of KRAS downstream effectors extracellular-signal-regulated kinase (ERK), ribosomal S6 kinase (RSK), AKT (also known as protein kinase B, PKB) and downstream substrate S6 ribosomal protein.

To measure phosphorylated extracellular-signal-regulated kinase (ERK), ribosomal S6 kinase (RSK), AKT and S6 ribosomal protein, cells (details regarding the cell lines and types of data produced are further detailed in Table D) are seeded overnight in Corning 96-well tissue culture treated plates in RPMI medium with 10% FBS at 4×10⁴ cells/well. The following day, cells are incubated in the presence or absence of a concentration range of test compounds for 4 h at 37 °C, 5% CO₂. Cells are washed with PBS and lysed with 1× lysis buffer (Cisbio) with protease and phosphatase inhibitors (Thermo Fisher, 78446). 10 or 20 μ g of total protein lysates is subjected to SDS-PAGE and immunoblot analysis using following antibodies: phospho-ERK1/2-Thr202/Tyr204 (#9101L), total-ERK1/2 (#9102L), phospho-AKT-Ser473 (#4060L), phospho-p90RSK-Ser380 (#11989S) and phospho-S6 ribosomal protein-Ser235/Ser236 (#2211S) are from Cell Signaling Technologies (Danvers, MA).

Table D

Cell Line	Histology	KRAS alteration	Readout
H358	Lung	G12C	pERK, pAKT, p-S6, p-p90RSK
MIA PaCa-2	Pancreas	G12C	pERK, pAKT, p-S6, p-p90RSK
HPAF II	Pancreas	G12D	pERK, pAKT, p-S6, p-p90RSK
A427	Lung	G12D	pERK, pAKT, p-S6, p-p90RSK
AGS	Stomach	G12D	pERK, pAKT, p-S6, p-p90RSK
PaTu 8988s	Pancreas	G12V	pERK, pAKT, p-S6, p-p90RSK
H441	Lung	G12V	pERK, pAKT, p-S6, p-p90RSK
YAPC	Pancreas	G12V	pERK, pAKT, p-S6, p-p90RSK
SW480	Colorectal	G12V	pERK, pAKT, p-S6, p-p90RSK

Example G: *In Vivo* Efficacy Studies

MIA-PaCa-2 (KRAS G12C), H358 (KRAS G12C), HPAF-II (KRAS G12D), AGS (KRAS G12D), SW480 (KRAS G12V) or YAPC(KRAS G12V) human cancer cells are obtained from the American Type Culture Collection and maintained in RPMI media supplemented with 10% FBS. For efficacy studies experiments, 5×10^6 cells are inoculated subcutaneously into the right hind flank of 6- to 8-week-old BALB/c nude mice (Charles River Laboratories, Wilmington, MA, USA). When tumor volumes are approximately 150–250 mm³, mice are randomized by tumor volume and compounds are orally administered. Tumor volume is calculated using the formula $(L \times W^2)/2$, where L and W refer to the length and width dimensions, respectively. Tumor growth inhibition is calculated using the formula $(1 - (VT/VC)) \times 100$, where VT is the tumor volume of the treatment group on the last day of treatment, and VC is the tumor volume of the control group on the last day of treatment. Two-way analysis of variance with Dunnett's multiple comparisons test is used to determine statistical differences between treatment groups (GraphPad Prism). Mice are housed at 10–12 animals per cage, and are provided enrichment and exposed to 12 h light/dark cycles. Mice whose tumor volumes exceeded limits (10% of body weight) are humanely euthanized by CO₂ inhalation. Animals are maintained in a barrier facility fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. All of the procedures are conducted in accordance with the US Public Service Policy on Human Care and Use of Laboratory Animals and with Incyte Animal Care and Use Committee Guidelines.

Example H: Caco2 Assay

Caco-2 cells are grown at 37 °C in an atmosphere of 5% CO₂ in DMEM growth medium supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) nonessential amino acids, penicillin (100 U/mL), and streptomycin (100 µg/mL). Confluent cell monolayers are subcultured every 7 days or 4 days for Caco-2 by treatment with 0.05% trypsin containing 1 µM EDTA. Caco-2 cells are seeded in 96-well Transwell plates. The seeding density for Caco-2 cells is 14,000 cells/well. DMEM growth medium is replaced every other day after seeding. Cell monolayers are used for transport assays between 22 and 25 days for Caco-2 cells.

Cell culture medium is removed and replaced with HBSS. To measure the TEER, the HBSS is added into the donor compartment (apical side) and receiver compartment (basolateral side). The TEER is measured by using a REMS Autosampler to ensure the integrity of the cell monolayers. Caco-2 cell monolayers with TEER values $\geq 300 \Omega \cdot \text{cm}^2$ are used for transport experiments. To determine the P_{app} in the absorptive direction (A-B), solution of test compound (50 µM) in HBSS is added to the donor compartment (apical

side), while HBSS solution with 4% BSA is added to the receiver compartment (basolateral side). The apical volume was 0.075 mL, and the basolateral volume is 0.25 mL. The incubation period is 120 min. at 37 °C in an atmosphere of 5% CO₂. At the end of the incubation period, samples from the donor and receiver sides are removed and an equal volume of MeCN is added for protein precipitation. The supernatants are collected after centrifugation (3000 rpm, Allegra X-14R Centrifuge from Beckman Coulter, Indianapolis, IN) for LCMS analysis. The permeability value is determined according to the equation:

$$P_{app} \text{ (cm/s)} = (F * VD) / (SA * MD),$$

where the flux rate (F, mass/time) is calculated from the slope of cumulative amounts of compound of interest on the receiver side, SA is the surface area of the cell membrane, VD is the donor volume, and MD is the initial amount of the solution in the donor chamber.

The Caco-2 data are provided in Tables G and H below. The symbol "+" indicates a Caco-2 value of ≤0.5, "++" indicates a Caco-2 value of >0.5 but ≤1; and "+++" indicates a Caco-2 value of >1. "NA" indicates IC₅₀ not available.

Table G

Ex. No.	Caco-2	Ex. No.	Caco-2	Ex. No.	Caco-2
1	+++	6	NA	36	+++
2	++	7	+	37	++
3	+++	8	+++	38	+++
4	++	9	NA	39	+++
5	+	35	+++		

Example I: Human Whole Blood Stability

The whole blood stability of the exemplified compounds is determined by LC-MS/MS. The 96-Well Flexi-Tier™ Block (Analytical Sales & Services, Inc, Flanders, NJ) is used for the incubation plate containing 1.0 mL glass vials with 0.5 mL of blood per vial (pooled gender, human whole blood sourced from BIOIVT, Hicksville, NY or similar). Blood is pre-warmed in water bath to 37 °C for 30 min. A 96-deep well analysis plate is prepared with the addition of 100 µL ultrapure water/well. 50 µL chilled ultrapure water/well is added to 96-deep well sample collection plate and covered with a sealing mat. 1 µL of 0.5 µM compound working solution (DMSO:water) is added to the blood in incubation plate to reach final concentrations of 1 µM, mixed by pipetting thoroughly and 50 µL is transferred into the T=0 wells of the sample collection plate. Blood is allowed to sit in the water for 2 min. and then 400 µL stop solution/well is added (MeCN containing an internal standard). The incubation plate is placed in the Incu-Shaker CO₂ Mini incubator (Benchmark Scientific, Sayreville, NJ) at 37 °C with shaking at 150 rpm. At 1, 2 and 4 h, the blood samples are mixed thoroughly by pipetting and 50 µL is transferred into the corresponding wells of the sample collection plate. Blood is allowed to sit in the water for 2 min. and then 400 µL of stop

solution/well is added. The collection plate is sealed and vortexed at 1700 rpm for 3 min. (VX-2500 Multi-Tube Vortexer, VWR International, Radnor, PA), and samples are then centrifuged in the collection plate at 3500 rpm for 10 min. (Allegra X-14R Centrifuge Beckman Coulter, Indianapolis, IN). 100 μ L of supernatant/well is transferred from the sample collection plate into the corresponding wells of the analysis plate. The final plate is vortexed at 1700 rpm for 1 min. and analyze samples by LC-MS/MS. The peak area ratio of the 1, 2, and 4 h samples relative to T=0 is used to determine the percent remaining. The natural log of the percent remaining versus time is used to determine a slope to calculate the compounds half-life in blood ($t_{1/2}=0.693/\text{slope}$).

10 **Example J: *In Vitro* Intrinsic Clearance Protocol**

For *in vitro* metabolic stability experiments, test compounds are incubated with human liver microsomes at 37 °C. The incubation mixture contains test compounds (1 μ M), NADPH (2 mM), and human liver microsomes (0.5 mg protein/mL) in 100 mM phosphate buffer (pH 7.4). The mixture is pre-incubated for 2 min. at 37 °C before the addition of NADPH. Reactions are commenced upon the addition of NADPH and quenched with ice-cold MeOH at 0, 10, 20, and 30 min. Terminated incubation mixtures are analyzed using LC-MS/MS system. The analytical system consisted of a Shimadzu LC-30AD binary pump system and SIL-30AC autosampler (Shimadzu Scientific Instruments, Columbia, MD) coupled with a Sciex Triple Quad 6500+ mass spectrometer from Applied Biosystems (Foster City, CA). Chromatographic separation of test compounds and internal standard is achieved using a Hypersil Gold C₁₈ column (50 $\times$ 2.1 mm, 5 μ M, 175 Å) from ThermoFisher Scientific (Waltham, MA). Mobile phase A consists of 0.1% formic acid in water, and mobile phase B consists of 0.1% formic acid in MeCN. The total LC-MS/MS runtime can be 2.75 min. with a flow rate of 0.75 mL/min. Peak area integrations and peak area ratio calculations are performed using Analyst software (version 1.6.3) from Applied Biosystems.

The *in vitro* intrinsic clearance, $CL_{\text{int, in vitro}}$, is calculated from the $t_{1/2}$ of test compound disappearance as $CL_{\text{int, in vitro}}=(0.693/ t_{1/2})\times(1/C_{\text{protein}})$, where C_{protein} is the protein concentration during the incubation, and $t_{1/2}$ is determined by the slope (k) of the log-linear regression analysis of the concentration versus time profiles; thus, $t_{1/2}=\ln 2/k$. The $CL_{\text{int, in vitro}}$ values are scaled to the *in vivo* values for human by using physiologically based scaling factors, hepatic microsomal protein concentrations (45 mg protein/g liver), and liver weights (21 g/kg body weight). The equation $CL_{\text{int}}=CL_{\text{int, in vitro}}\times(\text{mg protein/g liver weight})\times(\text{g liver weight/kg body weight})$ is used. The *in vivo* hepatic clearance (CL_H) is then calculated by using CL_{int} and hepatic blood flow, Q (20 mL $\cdot$ min⁻¹ $\cdot$ kg⁻¹ in humans) in the well-stirred liver model disregarding all binding from $CL_H=(Q\times CL_{\text{int}})/(Q+CL_{\text{int}})$. The hepatic extraction ratio was calculated as CL_H divided by Q.

Example K: *In Vivo* Pharmacokinetics Protocol

For *in vivo* pharmacokinetic experiments, test compounds are administered to male Sprague Dawley rats or male and female Cynomolgus monkeys intravenously or *via* oral gavage. For intravenous (IV) dosing, test compounds are dosed at 0.5 to 1 mg/kg using a formulation of 10% dimethylacetamide (DMAC) in acidified saline *via* IV bolus for rat and 5 min. or 10 min. IV infusion for monkey. For oral (PO) dosing, test compounds are dosed at 1.0 to 3.0 mg/kg using 5% DMAC in 0.5% methylcellulose in citrate buffer (pH 2.5). Blood samples are collected at predose and various time points up to 24 h postdose. All blood samples are collected using EDTA as the anticoagulant and centrifuged to obtain plasma samples. The plasma concentrations of test compounds are determined by LC-MS methods. The measured plasma concentrations are used to calculate PK parameters by standard noncompartmental methods using Phoenix® WinNonlin software program (version 8.0, Pharsight Corporation).

In rats and monkeys, cassette dosing of test compounds are conducted to obtain preliminary PK parameters.

In vivo pharmacokinetic experiments with male beagle dogs may be performed under the conditions described above.

Example L: Time Dependent Inhibition (TDI) of CYP Protocol

This assay is designed to characterize an increase in CYP inhibition as a test compounds is metabolized over time. Potential mechanisms for this include the formation of a tight-binding, quasi-irreversible inhibitory metabolite complex or the inactivation of P450 enzymes by covalent adduct formation of metabolites. While this experiment employs a 10-fold dilution to diminish metabolite concentrations and therefore effects of reversible inhibition, it is possible (but not common) that a metabolite that is an extremely potent CYP inhibitor could result in a positive result.

The results are from a cocktail of CYP specific probe substrates at 4 times their Km concentrations for CYP2C9, 2C19, 2D6 and 3A4 (midazolam) using human liver microsomes (HLM). The HLMs can be pre-incubated with test compounds at a concentration 10 µM for 30 min. in the presence (+N) or absence (-N) of a NADPH regenerating system, diluted 10-fold, and incubated for 8.min in the presence of the substrate cocktail with the addition of a fresh aliquot of NADPH regenerating system. A calibration curve of metabolite standards can be used to quantitatively measure the enzyme activity using LC-MS/MS. In addition, incubations with known time dependent inhibitors, tienilic acid (CYP2C9), ticlopidine (CYP2C19), paroxetine (CYP2D6), and troleandomycin (CYP3A4), used as positive controls are pre-incubated 30 min. with or without a NADPH regenerating system.

The analytical system consists of a Shimadzu LC-30AD binary pump system and SIL-30AC autosampler (Shimadzu Scientific Instruments, Columbia, MD) coupled with a Sciex Triple Quad 6500+ mass spectrometer from Applied Biosystems (Foster City, CA). Chromatographic separation of test compounds and internal standard can be achieved using
5 an ACQUITY UPLC BEH 130A, 2.1×50 mm, 1.7 μm HPLC column (Waters Corp, Milford, MA). Mobile phase A consists of 0.1% formic acid in water, and mobile phase B consists of 0.1% formic acid in MeCN. The total LC-MS/MS runtime will be 2.50 min. with a flow rate of 0.9 mL/min. Peak area integrations and peak area ratio calculations are performed using Analyst software (version 1.6.3) from Applied Biosystems.

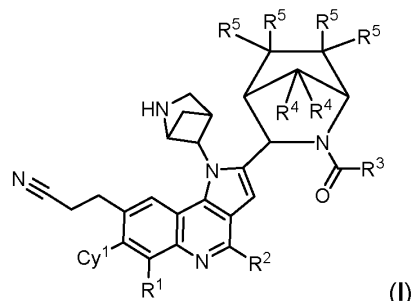
10 The percentage of control CYP2C9, CYP2C19, CYP2D6, and CYP3A4 activity remaining following preincubation of the compounds with NADPH is corrected for the corresponding control vehicle activity and then calculated based on 0 min. as 100%. A linear regression plot of the natural log of % activity remaining versus time for each isozyme is used to calculate the slope. The –slope is equal to the rate of enzyme loss, or the K_{obs} .

15 Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

20

What is claimed is:

1. A compound having Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Cy¹ is phenyl optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, OH, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy;

R¹ is halogen;

R² is selected from H, D, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, C₃₋₅ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-6 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{e2}, and NR^{c2}C(O)R^{b2}; wherein the C₃₋₅ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-6 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene forming R² are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A}; wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, and 4-6 membered heterocycloalkyl-C₁₋₃ alkylene forming R² consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, and 4-6 membered heterocycloalkyl-C₁₋₃ alkylene forming R² is optionally substituted by oxo to form a carbonyl group; and wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R² are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B};

each R^{a2} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl; wherein the C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl forming R^{a2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A}; wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{a2} consist of at least one carbon

atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{a2} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl forming R^{a2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ;

each R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl; wherein the C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl forming R^{b2} , R^{c2} , and R^{d2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A} ; the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{b2} , R^{c2} , and R^{d2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{b2} , R^{c2} , and R^{d2} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{b2} , R^{c2} , and R^{d2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ; or

any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, or 6-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ;

each R^{e2} is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl; wherein the C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl forming R^{e2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2A} ; wherein the ring-forming atoms of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{e2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-6 membered heterocycloalkyl and 5-6 membered heteroaryl forming R^{e2} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, forming R^{e2} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ; or

R^{c2} and R^{e2} attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, or 6-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from R^{2B} ;

each R^{2A} is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, and R^{2B} , wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, forming R^{2A} are each optionally substituted with 1, 2 or 3 substituents independently selected from R^{2B} ;

each R^{2B} is independently selected from C_{3-6} cycloalkyl, 4-10 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, halo, D, CN, OR^{a2B} , $C(O)R^{b2B}$, $C(O)NR^{c2B}R^{d2B}$, $C(O)OR^{a2B}$, $NR^{c2B}R^{d2B}$, and $S(O)_2R^{b2B}$; wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, and 5-6 membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{2C} ;

each R^{2C} is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, halo, D, CN, OR^{a2C} , $C(O)R^{b2C}$, $C(O)NR^{c2C}R^{d2C}$, $C(O)OR^{a2C}$, $NR^{c2C}R^{d2C}$, and $S(O)_2R^{b2C}$;

each R^{a2B} , R^{b2B} , R^{c2B} and R^{d2B} is independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

each R^{a2C} , R^{b2C} , R^{c2C} and R^{d2C} is independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^3 is selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, OR^{3A} , and $NR^{3B}R^{3C}$; wherein the C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl C_{1-3} alkyl forming R^3 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D} ; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^3 consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl or 5-10 membered heteroaryl forming R^3 is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^3 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

R^{3A} is selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein the C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl C_{1-3} alkyl forming R^{3A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D} ; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3A} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl or 5-10 membered heteroaryl forming R^{3A} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{3A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

R^{3B} is selected from H, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein the C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl

forming R^{3B} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3D} ; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3B} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{3B} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{3B} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

R^{3B} and R^{3C} , together with the N atom to which they are both attached, optionally form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group that is optionally substituted with 1, 2, or 3 substituents independently selected from independently selected from R^{3D} ;

R^{3C} is selected from H, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl; wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{3C} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

each R^{3D} is independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and R^{3E} ; wherein each of the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{3D} is optionally substituted with 1, 2, or 3 substituents independently selected from R^{3E} ;

each R^{3E} is independently selected from D, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$;

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are each independently selected from H, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl; wherein the C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{a3} , R^{b3} , R^{c3} , and R^{d3} are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, halo, CN, OR^{a3A} , SR^{a3A} , $C(O)R^{b3A}$, $C(O)NR^{c3A}R^{d3A}$, $C(O)OR^{a3A}$, $OC(O)R^{b3A}$, $OC(O)NR^{c3A}R^{d3A}$, $NR^{c3A}R^{d3A}$, $NR^{c3A}C(O)R^{b3A}$, $NR^{c3A}C(O)NR^{c3A}R^{d3A}$, $NR^{c3A}C(O)OR^{a3A}$, $C(=NR^{e3A})NR^{c3A}R^{d3A}$, $NR^{c3A}C(=NR^{e3A})NR^{c3A}R^{d3A}$, $S(O)R^{b3A}$, $S(O)NR^{c3A}R^{d3A}$, $S(O)_2R^{b3A}$, $NR^{c3A}S(O)_2R^{b3A}$, and $S(O)_2NR^{c3A}R^{d3A}$; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{a3} , R^{b3} , R^{c3} , and R^{d3} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10

membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3}, R^{b3}, R^{c3}, and R^{d3} is optionally substituted by oxo to form a carbonyl group; or

R^{c3} and R^{d3} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, CN, OR^{a3A}, SR^{a3A}, C(O)R^{b3A}, C(O)NR^{c3A}R^{d3A}, C(O)OR^{a3A}, OC(O)R^{b3A}, OC(O)NR^{c3A}R^{d3A}, NR^{c3A}R^{d3A}, NR^{c3A}C(O)R^{b3A}, NR^{c3A}C(O)NR^{c3A}R^{d3A}, NR^{c3A}C(O)OR^{a3A}, C(=NR^{e3A})NR^{c3A}R^{d3A}, NR^{c3A}C(=NR^{e3A})NR^{c3A}R^{d3A}, S(O)R^{b3A}, S(O)NR^{c3A}R^{d3A}, S(O)₂R^{b3A}, NR^{c3A}S(O)₂R^{b3A}, and S(O)₂NR^{c3A}R^{d3A};

R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} are each independently selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, aryl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl; wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} are each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} consist of at least one carbon atom, and 1, 2, 3, or 4 heteroatoms selected from O, N, and S; and wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{a3A}, R^{b3A}, R^{c3A}, and R^{d3A} is optionally substituted by oxo to form a carbonyl group; or

R^{c3A} and R^{d3A} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; R^{e3}, and R^{e3A} are each, independently, H, CN or NO₂;

each R⁴ is independently selected from H, D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, and OR^{a4};

each R^{a4} is independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OR^{a5}, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl; or, optionally, two other R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each

selected from D, C₁₋₃ alkyl, and halo; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo;

R^{5A} is H, D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo, OR^{a5A}, CN, or Cy²; wherein the C₁₋₃ alkyl forming R^{5A} is optionally substituted with 1, 2, 3 or 4 substituents each selected from R^{5B} and also optionally substituted with Cy², or, optionally, R^{5A} and R⁵ attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo; or, optionally, R^{5A} and R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1, 2, 3, or 4 substituents each selected from D, C₁₋₃ alkyl, and halo;

each R^{5B} is independently selected from D and halo;

each R^{a5} is independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R^{a5A} is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents each selected from R^{5B} and also optionally substituted with Cy²;

Cy² is selected from C₃₋₇ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein the C₃₋₇ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl forming Cy² is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming Cy² consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; and wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming Cy² is optionally substituted by oxo to form a carbonyl group;

each R^{Cy2} is independently selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₆ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, CN, OR^{aCy21}, SR^{aCy21}, C(O)R^{bCy21}, C(O)NR^{cCy21}R^{dCy21}, C(O)OR^{aCy21}, OC(O)R^{bCy21}, OC(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)R^{bCy21}, NR^{cCy21}C(O)NR^{cCy21}R^{dCy21}, NR^{cCy21}C(O)OR^{aCy21}, C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, NR^{cCy21}C(=NR^{eCy21})NR^{cCy21}R^{dCy21}, S(O)R^{bCy21}, S(O)NR^{cCy21}R^{dCy21}, S(O)₂R^{bCy21}, NR^{cCy21}S(O)₂R^{bCy21}, and S(O)₂NR^{cCy21}R^{dCy21}; wherein the C₃₋₆ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl forming R^{Cy2} are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from R^{Cy2A}; wherein the ring-forming atoms of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl

forming R^{Cy2} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl forming R^{Cy2} is optionally substituted by oxo to form a carbonyl group; and wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{Cy2} are each optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy2B} ;

each R^{Cy2A} is independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and R^{Cy2B} ; wherein the C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl forming R^{Cy2A} are each optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy2B} ,

each R^{Cy2B} is independently selected from D, halo, CN, OR^{aCy21} , SR^{aCy21} , $C(O)R^{bCy21}$, $C(O)NR^{cCy21}R^{dCy21}$, $C(O)OR^{aCy21}$, $OC(O)R^{bCy21}$, $OC(O)NR^{cCy21}R^{dCy21}$, $NR^{cCy21}R^{dCy21}$, $NR^{cCy21}C(O)R^{bCy21}$, $NR^{cCy21}C(O)NR^{cCy21}R^{dCy21}$, $NR^{cCy21}C(O)OR^{aCy21}$, $C(=NR^{eCy21})NR^{cCy21}R^{dCy21}$, $NR^{cCy21}C(=NR^{eCy21})NR^{cCy21}R^{dCy21}$, $S(O)R^{bCy21}$, $S(O)NR^{cCy21}R^{dCy21}$, $S(O)_2R^{bCy21}$, $NR^{cCy21}S(O)_2R^{bCy21}$, and $S(O)_2NR^{cCy21}R^{dCy21}$,

R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21} are each independently selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl; wherein the C_{6-10} aryl- C_{1-3} alkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, C_{3-7} cycloalkyl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21} are each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, halo, CN, OR^{aCy22} , SR^{aCy22} , $C(O)R^{bCy22}$, $C(O)NR^{cCy22}R^{dCy22}$, $C(O)OR^{aCy22}$, $OC(O)R^{bCy22}$, $OC(O)NR^{cCy22}R^{dCy22}$, $NR^{cCy22}R^{dCy22}$, $NR^{cCy22}C(O)R^{bCy22}$, $NR^{cCy22}C(O)NR^{cCy22}R^{dCy22}$, $NR^{cCy22}C(O)OR^{aCy22}$, $C(=NR^{eCy22})NR^{cCy22}R^{dCy22}$, $NR^{cCy22}C(=NR^{eCy22})NR^{cCy22}R^{dCy22}$, $S(O)R^{bCy22}$, $S(O)NR^{cCy22}R^{dCy22}$, $S(O)_2R^{bCy22}$, $NR^{cCy22}S(O)_2R^{bCy22}$, and $S(O)_2NR^{cCy22}R^{dCy22}$; wherein the ring-forming atoms each of the 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; and wherein a ring-forming carbon atom of the 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl- C_{1-3} alkyl, and 4-10 membered heterocycloalkyl- C_{1-3} alkyl forming R^{aCy21} , R^{bCy21} , R^{cCy21} , and R^{dCy21} is optionally substituted by oxo to form a carbonyl group;

or R^{cCy21} and R^{dCy21} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, halo, CN,

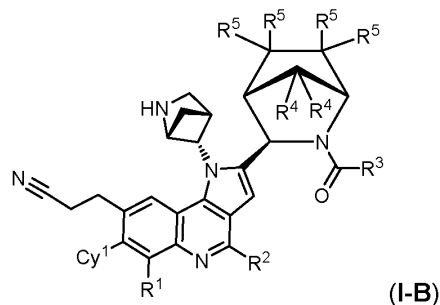
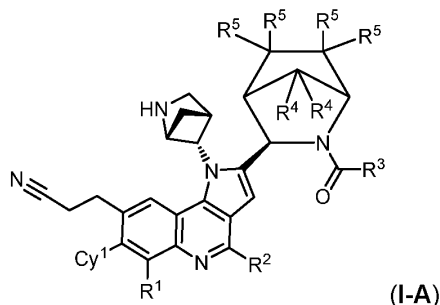
OR^{aCy22}, SR^{aCy22}, C(O)R^{bCy22}, C(O)NR^{cCy22}R^{dCy22}, C(O)OR^{aCy22}, OC(O)R^{bCy22}, OC(O)NR^{cCy22}R^{dCy22}, NR^{cCy22}R^{dCy22}, NR^{cCy22}C(O)R^{bCy22}, NR^{cCy22}C(O)NR^{cCy22}R^{dCy22}, NR^{cCy22}C(O)OR^{aCy22}, C(=NR^{eCy22})NR^{cCy22}R^{dCy22}, NR^{cCy22}C(=NR^{eCy22})NR^{cCy22}R^{dCy22}, S(O)R^{bCy22}, S(O)NR^{cCy22}R^{dCy22}, S(O)₂R^{bCy22}, NR^{cCy22}S(O)₂R^{bCy22}, and S(O)₂NR^{cCy22}R^{dCy22},

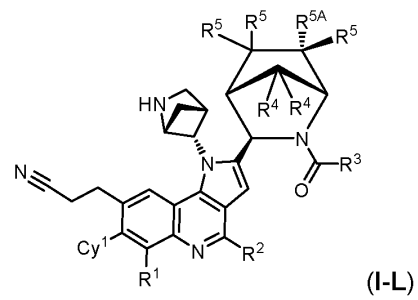
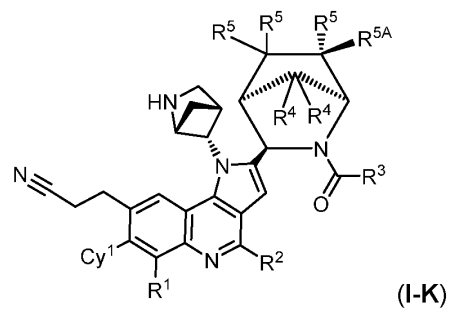
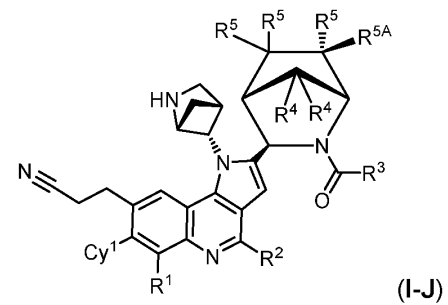
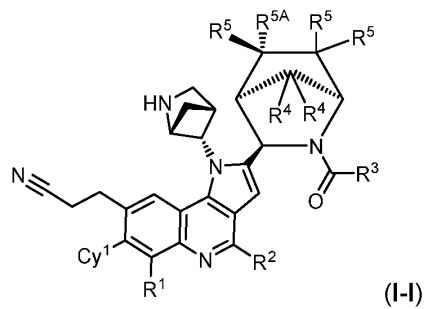
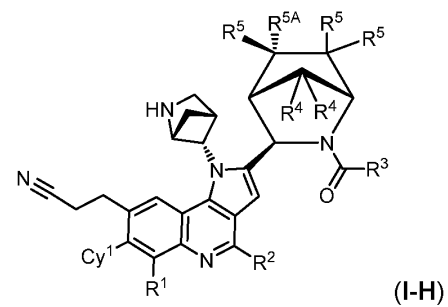
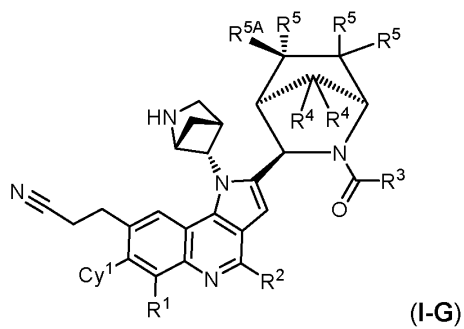
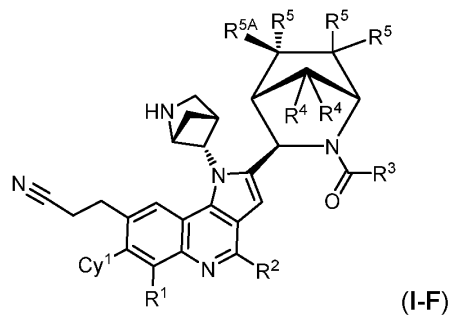
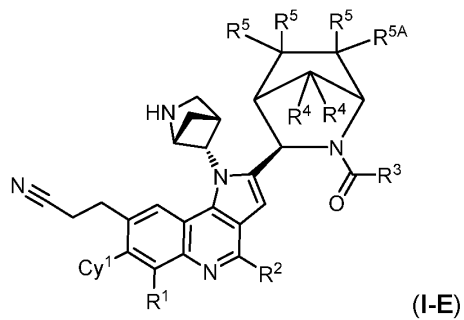
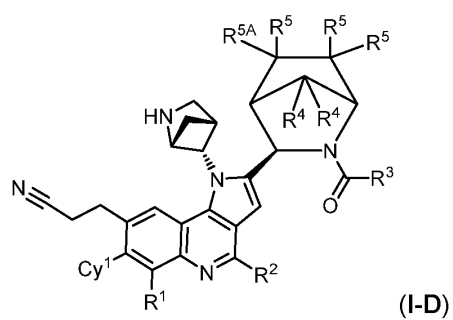
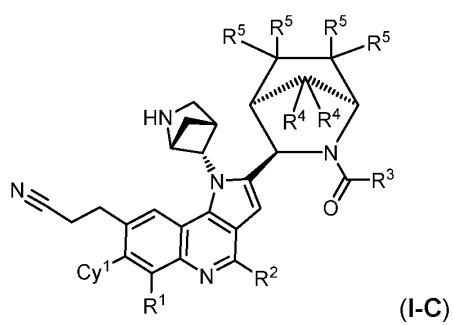
R^{aCy22}, R^{bCy22}, R^{cCy22}, and R^{dCy22} are each independently selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, aryl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl; wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₆₋₁₀ aryl-C₁₋₃ alkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{aCy22}, R^{bCy22}, R^{cCy22}, and R^{dCy22} are each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, halo, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ haloalkoxy; wherein the ring-forming atoms each of the 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{aCy22}, R^{bCy22}, R^{cCy22}, and R^{dCy22} consist of at least one carbon atom and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; and wherein a ring-forming carbon atom of the 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C₁₋₃ alkyl, and 4-10 membered heterocycloalkyl-C₁₋₃ alkyl forming R^{aCy22}, R^{bCy22}, R^{cCy22}, and R^{dCy22} is optionally substituted by oxo to form a carbonyl group; or

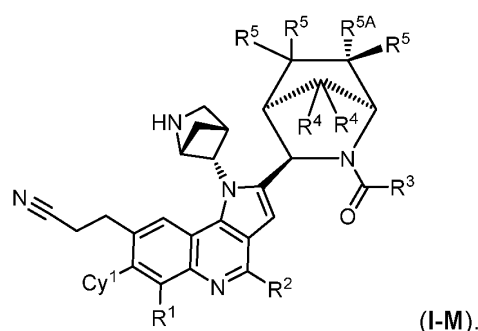
R^{cCy22} and R^{dCy22} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, halo, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ haloalkoxy; and

R^{eCy21} and R^{eCy22} are each, independently, H, CN or NO₂.

2. A compound or pharmaceutically acceptable salt thereof according to claim 1 having any one of the Formulae (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), and (I-M):







3. A compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

Cy¹ is phenyl optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, and C₁₋₃ alkoxy;

R¹ is halo;

R² is C₁₋₃ alkyl optionally substituted with OH;

R³ is C₃₋₁₀ cycloalkyl optionally substituted with halo;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and

Cy² is selected from C₆₋₁₀ aryl and 5-10 membered heteroaryl.

4. A compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

Cy¹ is phenyl optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, and C₁₋₃ alkoxy;

R¹ is halo;

R² is C₁₋₃ alkyl optionally substituted with OH;

R³ is C₃₋₁₀ cycloalkyl optionally substituted with halo;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, D, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C₃₋₆ cycloalkyl

ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and

Cy² is selected from C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl.

5. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein

Cy¹ is phenyl optionally substituted with 2 substituents each selected from halo;

R¹ is halo;

R² is C₁₋₃ alkyl optionally substituted with OH;

R³ is cyclopropyl optionally substituted with halo;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused cyclopropyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, or OR^{a5A};

R^{a5A} is selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, or 3 D, and also optionally substituted with Cy²; and

Cy² is selected from phenyl and pyridinyl.

6. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein

Cy¹ is 2,3-dichlorophenyl;

R¹ is halo;

R² is methyl or 1-hydroxyethyl;

R³ is cyclopropyl optionally substituted with fluoro;

each R⁴ is H;

one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused cyclopropyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and

R^{5A} is H, halo, OC₁₋₃ alkyl, OC₁₋₃ haloalkyl, OCD₃, O-pyridinyl, and O-benzyl.

7. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein
- Cy¹ is 2,3-dichlorophenyl;
 - R¹ is halo;
 - R² is methyl or 1-hydroxyethyl;
 - R³ is cyclopropyl optionally substituted with fluoro;
 - each R⁴ is H;
 - one R⁵ is R^{5A}; and each other R⁵ is independently selected from H, halo, C₁₋₃ alkyl, OC₁₋₃ alkyl, C₁₋₃ haloalkyl; or, optionally, two other R⁵ attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused cyclopropyl ring that is optionally substituted with 1 or 2 substituents each selected from D, C₁₋₃ alkyl, and halo; and
 - R^{5A} is H, halo, OC₁₋₃ alkyl, OC₁₋₃ haloalkyl, OCD₃, O-cyclopropyl, O-pyridinyl, and O-benzyl.
8. A compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein Cy¹ is phenyl optionally substituted with 1, 2, or 3 substituents, (or 1 or 2 substituents, or 1 substituent) independently selected from C₁₋₃ alkyl (such as methyl), C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo (such as fluoro or such as chloro), OH, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy.
9. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8, wherein Cy¹ is phenyl optionally substituted with 1, 2, or 3 substituents, (or 1 or 2 substituents, or 1 substituent) independently selected from C₁₋₃ alkyl (such as methyl) and halo (such as fluoro or such as chloro).
10. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, 8, and 9, wherein Cy¹ is 2-chloro-3-methylphenyl.
11. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, 8, and 9, wherein Cy¹ is 2,3-dichlorophenyl
12. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 11, wherein R¹ is halo.
13. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, wherein R¹ is fluoro.

14. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 13, wherein R⁴ is H.
15. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 14, wherein R² is C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, wherein the C₁₋₃ alkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl forming R² are each optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}.
16. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 15, wherein R² is C₁₋₃ alkyl (e.g., methyl or ethyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}.
17. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 16, wherein R² is methyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}.
18. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 17, wherein R² is methyl.
19. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5 and 8 to 16, wherein R² is ethyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2B}.
20. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, 8 to 16, and 19, wherein R² is ethyl.
21. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, 8 to 16, and 19, wherein R² is 1-hydroxyethyl.
22. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 14, wherein R² is 4-6 membered heterocycloalkyl (or 4-membered, or 5-membered-, or 6-membered heterocycloalkyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A}.
23. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, and 22, wherein R² is azetidin-1-yl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A}.

24. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, 22, and 23, wherein R^2 is 2-methyl-2-(*N,N*-dimethylamino)-2-methylazetidin-1-yl.
25. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 14, wherein R^2 is 5-6 membered heteroaryl (or 5-membered or 6-membered heteroaryl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A} .
26. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, and 25, wherein R^2 is 6 membered heteroaryl (e.g., pyridyl, such as 2-pyridyl, 3-pyridyl, or 4-pyridyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) independently selected from R^{2A} .
27. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, 25, and 26, wherein R^2 is 6 membered heteroaryl (e.g., pyridyl, such as 2-pyridyl, 3-pyridyl, or 4-pyridyl) optionally substituted with 2-hydroxypropyl or with $C(O)NR^{c2B}R^{c2D}$ (such as $C(O)NH_2$, $C(O)NHMe$, or $C(O)NMe_2$).
28. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 14, wherein R^2 is OR^{a2} .
29. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, 22, 23, 25, and 26, wherein each R^{2A} is independently selected from C_{1-3} alkyl, $NR^{c2B}R^{c2D}$ (such as NH_2 , $NHMe$, or NMe_2), or $C(O)NR^{c2B}R^{c2D}$ (such as $C(O)NH_2$, $C(O)NHMe$, or $C(O)NMe_2$), wherein the C_{1-3} alkyl forming R^{2A} is optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) each independently selected from R^{2B} .
30. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, 22, 23, 25, 26, and 29, wherein each R^{2A} is independently selected from C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents, or 1 substituent) each independently selected from R^{2B} .
31. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 14, 22, 23, 25, and 26, wherein each R^{2A} is R^{2B} .
32. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R^3 is C_{1-3} alkyl (such as methyl or ethyl) optionally

substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

33. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R³ is C₃₋₁₀ cycloalkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

34. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 31, and 33, wherein R³ is C₃₋₇ cycloalkyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

35. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 31, 33, and 34, wherein R³ is C₃₋₆ cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

36. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 31, and 33 to 35, wherein R³ is cyclobutyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

37. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 31, and 33 to 35, wherein R³ is cyclopropyl optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

38. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 31 and 33 to 37, wherein R³ is cyclopropyl.

39. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 31 and 33 to 37, wherein R³ is 1-fluorocycloprop-1-yl.

40. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 31 and 33 to 37, wherein R³ is 1-methylcycloprop-1-yl.

41. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R³ is C₆₋₁₀ aryl (such as phenyl) optionally substituted with 1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E}.

42. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R³ is 5-10 membered heteroaryl optionally substituted with

1, 2, or 3 substituents (or 1 or 2 substituents or 1 substituent) independently selected from R^{3E} .

43. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R^3 is OR^{3A} .

44. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 31, wherein R^3 is $NR^{3B}R^{3C}$.

45. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 44, wherein each R^4 is independently selected from H, D, C_{1-3} alkyl (such as methyl or ethyl), C_{1-3} haloalkyl (such as trifluoroalkyl), and halo (such as fluoro).

46. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 45, wherein each R^4 is independently selected from H, D, C_{1-3} alkyl (such as methyl or ethyl), and halo (such as fluoro).

47. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 46, wherein each R^4 is independently selected from H, methyl, and fluoro.

48. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 47, wherein each R^4 is independently selected from H and methyl.

49. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 48, wherein one R^4 is H and one R^4 is methyl.

50. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 48, wherein each R^4 is H.

51. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 12, and 14 to 48, wherein each R^4 is methyl.

52. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 51, wherein one R^5 is R^{5A} , and each other R^5 is independently selected from H, methyl, and fluoro, or, optionally, two other R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2,

or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl and fluoro; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl and fluoro.

53. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 52, wherein one R^5 is R^{5A} ; and each other R^5 is independently selected from H, methyl, and fluoro.

54. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 52, wherein one R^5 is R^{5A} ; and each other R^5 is independently selected from H and methyl, or, optionally, two other R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl.

55. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 54, wherein one R^5 is R^{5A} ; and each other R^5 is independently selected from H and methyl.

56. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 54, wherein one R^5 is R^{5A} ; and each other R^5 is H, or, optionally, two other R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl; or, optionally, two other R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from methyl.

57. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 56, wherein one R^5 is R^{5A} ; and each other R^5 is H.

58. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein

R^{5A} is H, D, C_{1-3} alkyl (such as methyl), C_{1-3} haloalkyl (such as trifluoromethyl), C_{2-3} alkenyl, C_{2-3} alkynyl, halo (such as fluoro), OR^{5A} , and CN; or, optionally, R^{5A} and R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from D, C_{1-3} alkyl (such as methyl), and halo (such as fluoro); or, optionally, R^{5A} and R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from D, C_{1-3} alkyl (such as methyl), and halo (such as fluoro); and

R^{a5A} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, and Cy^2 , wherein the C_{1-3} alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B} .

59. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 58, wherein R^{5A} is H, C_{1-3} alkyl (such as methyl), or halo (such as fluoro); or, optionally, R^{5A} and R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C_{1-3} alkyl (such as methyl) and halo (such as fluoro); or, optionally, R^{5A} and R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C_{1-3} alkyl (such as methyl), and halo.

60. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 59, wherein R^{5A} is H or C_{1-3} alkyl (such as methyl); or, optionally, R^{5A} and R^5 attached to the same carbon atom, together with the carbon atom to which they are both attached, form a spiro C_{3-6} cycloalkyl ring, such as cyclopropyl, that is optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C_{1-3} alkyl (such as methyl); or, optionally, R^{5A} and R^5 attached to adjacent carbon atoms, together with the carbon atoms to which they are each attached, form a fused C_{3-6} cycloalkyl ring (such as cyclopropyl) that is optionally substituted

with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from C₁₋₃ alkyl (such as methyl).

61. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 58, wherein

R^{5A} is H, D, C₁₋₃ alkyl (such as methyl), C₁₋₃ haloalkyl (such as trifluoromethyl), C₂₋₃ alkenyl, C₂₋₃ alkynyl, halo (such as fluoro), OR^{a5A}, and CN; and

R^{a5A} is selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and Cy², wherein the C₁₋₃ alkyl forming R^{a5A} is optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B}.

62. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 61, wherein R^{5A} is H, C₁₋₃ alkyl (such as methyl), or halo (such as fluoro).

63. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 62, wherein R^{5A} is H or C₁₋₃ alkyl (such as methyl).

64. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 63, wherein R^{5A} is H.

65. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is Cy².

66. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is C₁₋₃ alkyl (such as methyl or ethyl) wherein the C₁₋₃ alkyl (or methyl or ethyl) forming R^{5A} is substituted with Cy² and also optionally substituted with 1, 2, 3 or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B}.

67. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is C₁₋₃ alkyl (such as methyl or ethyl) wherein the C₁₋₃ alkyl (or methyl or ethyl) forming R^{5A} is substituted with Cy².

68. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 57, and 67, wherein R^{5A} is CH₂Cy².

69. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 57, and 67, wherein R^{5A} is CH₂CH₂Cy².

70. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is OR^{a5A} ; and R^{a5A} is Cy^2 .
71. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is C_{1-3} alkyl (such as methyl or ethyl), wherein the C_{1-3} alkyl forming R^{a5A} is substituted with Cy^2 and also optionally substituted with 1, 2, 3 or 4 substituents or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) each selected from R^{5B} .
72. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is OCH_2Cy^2 .
73. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 57, wherein R^{5A} is $OCH_2CH_2Cy^2$.
74. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 73, wherein Cy^2 is C_{6-10} aryl (such as phenyl) optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} .
75. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 74, wherein Cy^2 is phenyl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2} .
76. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 75, wherein Cy^2 is C_{6-10} aryl.
77. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 76, wherein Cy^2 is phenyl.
78. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 73, wherein Cy^2 is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2} .
79. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 73, and 78, wherein Cy^2 is 6 membered heteroaryl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2} .

80. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 73, 78, and 79, wherein Cy² is 6 membered heteroaryl.
81. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 73, and 78 to 80, wherein Cy² is pyridinyl optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2}.
82. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 73, and 78 to 81, wherein Cy² is pyridinyl.
83. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 73, wherein Cy² is C₃₋₇ cycloalkyl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2}.
84. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 8 to 73, wherein Cy² is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents (or 1, 2, or 3 substituents, or 1 or 2 substituents, or 1 substituent) independently selected from R^{Cy2}.
85. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 75, 78, 79, 81, 83 and 84, wherein each R^{Cy2} is independently selected from D, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, and halo.
86. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, 8 to 75, 78, 79, 81, and 83 to 85, wherein each R^{Cy2} is independently halo.
87. A compound selected from the compounds listed in Tables 1 and 2, and pharmaceutically acceptable salts thereof.
88. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, and at least one pharmaceutically acceptable carrier or excipient.
89. A method of inhibiting KRAS activity, the method comprising contacting the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88, with KRAS.
90. The method of claim 89, wherein the contacting comprises administering the compound to a patient.

91. The method of claim 89 or 90, wherein KRAS is characterized as having a somatic mutation of G12C.
92. The method of claim 89 or 90, wherein KRAS is characterized as having a somatic mutation of G12D.
93. The method of claim 89 or 90, wherein KRAS is characterized as having a somatic mutation of G12V.
94. A method of treating a disease or disorder associated with activity of KRAS, the method comprising administering to a patient in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.
95. A method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12C mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.
96. A method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12D mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.
97. A method of treating a disease or disorder associated with activity of a KRAS protein harboring a G12V mutation, the method comprising administering to a patient in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.
98. A method for treating a cancer in a patient, the method comprising administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.
99. The method of claim 98, wherein the cancer is selected from carcinomas, hematological cancers, sarcomas, and glioblastoma.
100. The method of claim 98, wherein the cancer is a hematological cancer selected from myeloproliferative neoplasms, myelodysplastic syndrome, chronic and juvenile

myelomonocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, and multiple myeloma.

101. The method of claim 98, wherein the cancer is a carcinoma selected from pancreatic, colorectal, lung, bladder, gastric, esophageal, breast, head and neck, cervical, skin, and thyroid cancers.

102. The method of any one of claims 98 to 101, wherein abnormally proliferating cells of the cancer comprise KRAS having a G12C mutation.

103. The method of any one of claims 98 to 101, wherein abnormally proliferating cells of the cancer comprise KRAS having a G12D mutation.

104. The method of any one of claims 98 to 101, wherein abnormally proliferating cells of the cancer comprise KRAS having a G12V mutation.

105. A method of treating an immunological or inflammatory disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.

106. The method of claim 105, wherein the immunological or inflammatory disorder is associated with activity of KRAS.

107. The method of claim 105, wherein the immunological or inflammatory disorder is associated with activity of KRAS having a G12C mutation.

108. The method of claim 105, wherein the immunological or inflammatory disorder is associated with activity of KRAS having a G12D mutation.

109. The method of claim 105, wherein the immunological or inflammatory disorder is associated with activity of KRAS having a G12V mutation.

110. The method of claim 105, wherein the immunological or inflammatory disorder is Ras-associated lymphoproliferative disorder or juvenile myelomonocytic leukemia caused by a somatic mutation of KRAS.

111. The method of claim 110, wherein the somatic mutation of KRAS is G12C.

112. The method of claim 110, wherein the somatic mutation of KRAS is G12D.

113. The method of claim 110, wherein the somatic mutation of KRAS is G12V.

114. A method of treating a cancer in a patient comprising:
identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12C mutation;

administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.

115. A method of treating a cancer in a patient comprising:

identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12D mutation;

administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.

116. A method of treating a cancer in a patient comprising:

identifying that the patient is in need of treatment of a cancer and that abnormally proliferating cells of the cancer comprise KRAS having a G12V mutation;

administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 87, or the pharmaceutical composition of claim 88.